Universidade Federal do Rio Grande do Sul

Programa de Pós-Graduação Ciências Médicas: Endocrinologia

Cristine Dieter

O papel de RNAs não-codificantes no desenvolvimento do diabetes mellitus e da doença renal do diabetes

Porto Alegre

2023

Cristine Dieter

O papel de RNAs não-codificantes no desenvolvimento do diabetes mellitus e da doença renal do diabetes

Tese apresentada como requisito parcial à obtenção do título de doutora em Endocrinologia pelo Programa de Pós-graduação em Ciências Médicas: Endocrinologia da Faculdade de Medicina da Universidade Federal do Rio Grande do Sul.

Orientador: Profª Drª Daisy Crispim Moreira

Co-orientador: Profª Drª Taís Silveira Assmann

Porto Alegre

2023

CIP - Catalogação na Publicação

Dieter, Cristine
O papel de RNAs não-codificantes no desenvolvimento do diabetes mellitus e da doença renal do diabetes / Cristine Dieter. -- 2023.
485 f.
Orientadora: Daisy Crispim Moreira.

Coorientadora: Taís Silveira Assmann.

Tese (Doutorado) -- Universidade Federal do Rio Grande do Sul, Faculdade de Medicina, Programa de Pós-Graduação em Ciências Médicas: Endocrinologia, Porto Alegre, BR-RS, 2023.

1. Diabetes Mellitus. 2. Nefropatias. 3. MicroRNAs. 4. RNA não codificante longo. I. Moreira, Daisy Crispim, orient. II. Assmann, Taís Silveira, coorient. III. Título.

Elaborada pelo Sistema de Geração Automática de Ficha Catalográfica da UFRGS com os dados fornecidos pelo(a) autor(a).

AGRADECIMENTOS

Eu não poderia escrever essa tese sem agradecer aqueles que fizeram parte desta caminhada.

À minha mãe, Noeli Scherer, que sempre foi uma inspiração pra mim e me fazer querer chegar até aqui. Obrigada por sempre me incentivar e aplaudir todas as minhas conquistas. Obrigada não medir esforços para nos ajudar e cuidar de nós, inclusive ficando sem carro nesses últimos anos pós-pandemia em que precisei dele pra ir a Porto Alegre para fazer o doutorado. Essa conquista é nossa! Amo você!

À minha irmã, Daiane Dieter, por sempre me aconselhar, estar do meu lado e comemorar e vibrar comigo todas as minhas conquistas! Obrigada pelo teu olhar mais razão e menos emoção. Obrigada pela compressão quando precisei do teu celular pra gravar para a disciplina do doutorado e da Semana Científica do HCPA. E obrigada por trazer o Leonardo Diehl pra fazer parte da nossa família. Todas as vezes que precisei, vocês dois sempre me ajudaram. Jamais vou esquecer o quanto vocês dois comemoraram as minhas conquistas ao longo desses anos. Amo vocês!

Ao Guilherme Scartezzini Zagonel, por ser simplesmente você e me dar todo o apoio que precisei, especialmente nesta reta final. Obrigada por sempre me incentivar, por acreditar em mim, comemorar minhas conquistas e pelo melhor abraço e colo do mundo. Obrigada por toda compreensão neste período, sei o quanto abri mão de momentos contigo porque precisava terminar um artigo, escrever a tese e preparar uma apresentação. Sem dúvidas, tudo isso ficou mais leve e fácil com você do meu lado. Tu és o acaso mais incrível da minha vida e sou imensamente grata por te ter comigo. Obrigada por nunca soltar a minha mão. Te amo!

À minha super orientadora, Daisy Crispim Moreira, por sempre acreditar em mim e me incentivar como aluna/pesquisadora. Tu com toda a certeza és um exemplo de professora e pesquisadora pra mim e tenho a sorte de ter entrado no teu grupo de pesquisa em 2014. Obrigada por sempre confiar nos meus projetos e nas minhas ideias. Obrigada pela troca de conhecimentos que tivemos ao longo desses anos. Sou muito grata por tudo que aprendi contigo.

À Taís Silveira Assmann, minha coorientadora, por desde a época do mestrado me auxiliar e ensinar sobre os RNAs não codificantes e as análises de bioinformática. Com certeza tu foste uma das pessoas que me inspiraram como pesquisadora. Obrigada pelo apoio, aprendizado, conhecimento compartilhado e auxilio no desenvolvimento desta tese.

À Dra Andrea Carla Bauer, Dr. Luís Henrique Canani, Dra Márcia Puñales, Dr. César Geremias e Dr. Balduíno Tscheidel pelas fundamentais colaborações e contribuições que enriqueceram este trabalho.

À Natália Emerim Lemos, minha mãe cientifica, por ser minha colega de laboratório, mas também um grande presente que o mundo da pesquisa me deu. Obrigada por dividir todo esse período comigo, pela ajuda nos experimentos, pela amizade que construímos ao longo desses anos, pelas idas e vindas à Porto Alegre, por sempre me auxiliar em todos os desafios que surgiram (ensaiar apresentações, processos seletivos) e por ser você! Obrigada por, mesmo estando em SP, comemorar muito e vibrar com as minhas conquistas! Como sempre te falei, sou muito grata por ter te encontrado em 2014 e aprendido tanto contigo. Se eu estou terminando o doutorado hoje, saibas que tu tens um papel muito importante nisso. Gratidão pela nossa amizade. Conta sempre comigo! Te amo!

Aos colegas e amigos do Serviço de Endocrinologia, pela troca de conhecimento, incentivo e amizades construídas ao longo desses anos.

Às alunas de iniciação cientifica Nathalia Rodrigues de Faria Corrêa, Denise Taurino Ramos e Eliandra Girardi, sem vocês essa tese não teria acontecido. Obrigada por estarem comigo ao longo deste período, pela contribuição nos experimentos no laboratório e principalmente pelas coletas no ICD. Se temos o nosso banco de amostras hoje, é porque vocês passaram muitas manhãs no ICD coletando e esperando os pacientes. Vocês foram fundamentais para a construção dessa tese de doutorado.

À Unidade de Pesquisa Experimental, em especial à Dra. Marina Siebert, pela ajuda nos experimentos de *microarray*.

Ao Núcleo de Bioinformática do Hospital de Clínicas de Porto Alegre, em especial à Thayne Woycinck Kowalski, Mariana Recamonde Mendoza e Giovanna Câmara Guidecelli, pelas análises de bioinformática e colaboração na presente tese.

Ao Instituto da Criança com Diabetes por confiar e acreditar em mais um projeto de pesquisa, seguindo com a parceira construída ao longo dos últimos anos.

Aos pacientes dos ambulatórios de endocrinologia do Hospital de Clínicas de Porto Alegre e do Instituto da Criança com Diabetes por aceitarem participar desse trabalho.

A Cristiane Dias, por cuidar da minha saúde mental nesses últimos anos. Se eu consegui curtir essa reta final de uma forma leve e tranquila, com certeza é porque você esteve comigo. Gratidão! Gratidão! Gratidão!

A todos os amigos e familiares que me apoiaram e incentivaram no decorrer desta caminhada.

A CAPES, CNPq, FAPERGS e FIPE-HCPA pelo apoio financeiro.

Por fim, agradeço a todos que de alguma forma contribuíram para a realização desse trabalho.

Esta tese de doutorado segue o formato proposto pelo Programa de Pós-Graduação em Ciências Médicas: Endocrinologia, Metabolismo e Nutrição da Faculdade de Medicina, Universidade Federal do Rio Grande do Sul, sendo apresentada na forma de uma breve introdução sobre o assunto, seguida dos manuscritos originais sobre o tema da tese.

Artigo 1: "Urinary microRNAs are associated with progression to end-stage renal disease in type 1 diabetes patients"

Artigo 2: "The impact of lncRNAs in diabetes mellitus: A systematic review and *in silico* analyses"

Artigo 3: "Expressions of lncRNAs *MALAT1*, *MEG3*, and *TUG1* are upregulated in recently diagnosed type 1 diabetes patients"

Artigo 4: "The lncRNA *MALAT1* is upregulated in urine of type 1 diabetes mellitus patients with diabetic kidney disease"

Artigo 5: "The rs3931283/*PVT1* and rs7158663/*MEG3* polymorphisms are associated with diabetic kidney disease and markers of renal function in patients with type 2 diabetes mellitus"

Que os nossos esforços desafiem as impossibilidades.

Lembrai-vos de que as grandes proezas da história foram

conquistas daquilo que parecia impossível.

Charles Chaplin

RESUMO

Os RNAs não codificantes (ncRNAs) são um grande grupo de RNAs que não têm funções aparentes de codificação de proteínas, mas desempenham papéis importantes em diversos processos biológicos, incluindo a patogênese de doenças. Dentre os ncRNAs, duas classes vêm sendo amplamente estudadas, os microRNAs (miRNAs) e os RNAs não-codificantes longos (lncRNAs).

Os miRNAs são pequenos ncRNAs que regulam a expressão gênica. Mudanças na expressão de miRNAs foram observadas em diversas situações patológicas, incluindo no diabetes mellitus (DM) e suas complicações crônicas. Os estudos que relacionaram miRNAs circulantes, urinários ou renais com a doença renal do diabetes (DRD) sugerem que um perfil de miRNAs parece se alterar nas diferentes fases desta complicação. Entretanto, os resultados desses estudos ainda são inconclusivos. Sendo assim, estudos ainda são necessários para identificar um perfil alterado de expressão de miRNAs em pacientes com DRD.

Os miRNAs encontrados em fluidos biológicos, tais como no sangue e na urina, são de especial interesse como potenciais biomarcadores, pois podem ser coletados facilmente e são estáveis sob diferentes condições de estocagem. Nesse sentido, os miRNAs urinários podem ser possíveis candidatos a biomarcadores da DRD, especialmente porque não são eliminados durante o processo de hemodiálise, não sofrem filtração glomerular e podem refletir mais diretamente alterações renais ao contrário de miRNAs circulantes no plasma ou soro, os quais podem estar marcando alterações em outros tecidos. Além disso, a coleta de urina aleatória é fácil de ser realizada, não necessita jejum e pode ser realizada a qualquer momento do dia.

Dessa forma, realizou-se uma análise do miRNoma urinário (análise de todos os miRNAs maduros conhecidos) em pacientes com DRD [progressores *vs*. não-progressores para declínio rápido na taxa de filtração glomerular estimada (TFGe)] e em pacientes sem essa complicação com o objetivo de identificar um perfil de miRNAs urinários envolvidos no desenvolvimento e progressão da DRD em pacientes com DM tipo 1 (DM1). Para isso, realizamos uma fase de *screening*, onde foi feita a análise do miRNoma urinário em pacientes com DM1, sendo 6 sem DRD e 14 com DRD [divididos em progressores (n= 7) e não-progressores (n= 7) em relação à diminuição rápida na TFGe (declínio ≥ 3,5 mL/min/1,73m^2/ano) durante o período de seguimento do estudo (média de 11.6 ± 3.6 anos)]. O *microarray* foi realizado utilizando o GeneChip miRNA 4.0 arrays (Thermo Fisher Scientific). Como resultado, identificamos 79 miRNAs diferencialmente expressos entre os grupos. Entre esses, 63 diferiram entre progressores *vs*. pacientes com TFGe normal; 12 entre não-progressores *vs*. pacientes com TFGe normal; e 15 entre progressores *vs*. não-progressores. Análises de bioinformática mostraram que esses miRNAs estão envolvidos em vias associadas com o DM e a DRD. Após a análise do miRNoma, 2 miRNAs diferencialmente expressos entre os grupos da amostra *screening* foram selecionados para validação individual por real-time PCR. Isso foi feito em uma amostra independente de 46 pacientes com DM1: 18 sem DRD e 28 com DRD, também divididos entre progressores (n = 12) e não-progressores (n = 16) para diminuição rápida na TFGe. Confirmamos que o hsa-miR-30a-5p está aumentado em pacientes progressores *vs*. não-progressores e pacientes sem DRD. O hsa-miR-210-3p não teve seu resultado confirmado nesta amostra de validação. Além disso, realizamos uma segunda validação comparando os nossos dados do miRNoma com dados de um estudo de transcriptômica disponível no banco de dados público GEO (GSE121221). Esta análise confirmou que os hsa-miR-212-5p, hsa-miR-4484 e hsa-miR-4487 apresentam níveis de expressão diminuídos em pacientes com DRD em comparação

aos pacientes sem esta complicação. Como conclusão desse primeiro artigo, os hsa-miR-30a-5p, hsa-miR-212-5p, hsa-miR-4484 e hsa-miR-4487 foram validados como potenciais biomarcadores para a progressão da DRD em pacientes com DM1.

Além de investigar o papel dos miRNAs na DRD, também avaliamos o envolvimento de lncRNAs no desenvolvimento do DM e da DRD. Os lncRNAs são moléculas de RNA longas (> 200 nucleotídeos) que estruturalmente se assemelham ao mRNA, mas não codificam proteínas. Essa classe de RNA não codificante já foi associada com funções como de regulação da expressão gênica, controle do ciclo celular, transcrição, regulação do *splicing*, diferenciação celular, inativação do cromossomo X e *imprinting* gênico. Interessantemente, lncRNAs têm sido identificados em condições normais e patológicas, podendo funcionar como biomarcadores de diversas doenças, tais como o DM e suas complicações crônicas. Desta forma, visando proporcionar um melhor entendimento do papel do lncRNAs no desenvolvimento do DM, realizamos uma revisão sistemática e um estudo de caso-controle, seguido de análises de bioinformática, com o objetivo de encontrar lncRNAs associados ao DM.

A revisão sistemática incluiu 53 estudos que investigaram a expressão de lncRNAs em pacientes com DM1 ou DM tipo 2 (DM2). Como resultado, encontramos 6 lncRNAs consistentemente desregulados em pacientes com DM (*ANRIL*, *HOTAIR*, *MALAT1*, *MIAT*, *KCNQ1OT1* e *MEG3*) em comparação ao grupo controle. Análises de bioinformática demonstraram que esses lncRNAs estão envolvidos em vias relacionadas ao DM, tais como PI3K/Akt, MAPK, apoptose e FoxO. No estudo de caso-controle, investigamos a expressão dos lncRNAs *MALAT1*, *MEG3*, *MIAT*, *PVT1* e *TUG1* em células mononucleares de 27 pacientes com DM1 (casos) e 13 indivíduos saudáveis (controles). O grupo caso foi dividido em: 14 pacientes com <5 anos de diagnóstico de DM1 e 13 pacientes com ≥5 anos de diagnóstico. As expressões dos lncRNAs *MALAT1* e *TUG1* foram aumentadas em pacientes

com <5 anos de DM1 em comparação ao grupo controle e pacientes com ≥5 anos de diagnóstico. A expressão de *MEG3* também estava aumentada nos pacientes <5 anos de DM1 *vs*. controles. Interessantemente, os níveis de expressão de *MALAT1* e *TUG1* foram negativamente correlacionados com o tempo de DM1 e os níveis de *MEG3* e *TUG1* foram positivamente correlacionados com os valores de hemoglobina glicada.

Além dos estudos em relação ao papel dos lncRNAs no contexto do DM, também avaliamos o envolvimento dessa classe de RNAs no desenvolvimento da DRD. Assim, em um primeiro estudo, avaliamos as expressões dos lncRNAs *MALAT1* e *TUG1* na urina de pacientes com DM1 categorizados em: 18 pacientes com DRD (casos) e 9 pacientes sem esta complicação (controles). A expressão do lncRNA *MALAT1* foi aumentada na urina dos pacientes com DRD em comparação ao grupo controle. Análises de bioinformática mostraram que esses dois lncRNAs estão envolvidos em vias relacionadas ao DM e a DRD, tais como glicólise/gliconeogênese, PI3K-Akt, AMPK e a via do DM1.

Num segundo estudo relacionado à associação de lncRNAs com DRD, comparamos as frequências dos polimorfismos rs3200401/*MALAT1*, rs1894720/*MIAT*, rs3931283/*PVT1*, rs11993333/*PVT1*, rs5749201/*TUG1* e rs7158663/*MEG3* entre 902 pacientes com DM2 com DRD (casos) e 394 pacientes com DM2 sem DRD (controles). Como resultado, o genótipo G/G do polimorfismo rs3931283/*PVT1* foi associado com risco para DRD após ajuste para covariáveis. Em concordância, os pacientes com o genótipo G/G também apresentaram níveis maiores de excreção urinária de albumina (EUA) em comparação aos pacientes com o genótipo A/A. Interessantemente, pacientes com o genótipo G/G do polimorfismo rs7158663/*MEG3* tiveram níveis diminuídos de creatinina e valores aumentados de TFGe comparado aos portadores do alelo A. Além disso, o alelo G deste polimorfismo no gene *MEG3* foi associado com proteção para DRD severa.

Em conclusão, os estudos incluídos nesta tese evidenciaram o papel de ncRNAs no DM e na DRD, demonstrando a contribuição de fatores epigenéticos no desenvolvimento dessas patologias. Um perfil de miRNAs associados com o desenvolvimento e progressão de DRD em pacientes com DM1 foi identificado. Além disso, nossos estudos indicam o envolvimento dos lncRNAs na patogênese do DM e da DRD, através de alterações nos seus níveis de expressão como também por meio da presença de polimorfismos genéticos nesses lncRNAs.

Palavras-chave: MicroRNAs. LncRNAs. Diabetes mellitus. Doença renal do diabetes. Biomarcadores.

ABSTRACT

Non-coding RNAs (ncRNAs) are a large group of RNAs that have no apparent protein-coding functions, but play important roles in diverse biological processes, including in the pathogenesis of diseases. Among ncRNAs, two classes have been widely studied, microRNAs (miRNAs) and long non-coding RNAs (lncRNAs).

MiRNAs are small non-coding RNAs that negatively regulate gene expression. Changes in miRNA expressions have been observed in several pathological situations, including in diabetes mellitus (DM) and its chronic complications. The studies that have associated circulating, urinary, or renal miRNAs with diabetic kidney disease (DKD) suggest that a miRNA profile seems to be altered in the different stages of this disease. However, the results of these studies are still inconclusive. Therefore, additional studies are necessary to identify an altered profile of miRNA expression in patients with DKD.

MiRNAs found in biological fluids, such as circulating and urinary miRNAs, are of special interest as potential biomarkers since they can be collected easily and are stable under different storage conditions. In this context, urinary miRNAs could be potential biomarkers of DKD, specially because they are not eliminated during the hemodialysis process, do not undergo glomerular filtration, and may more directly reflect renal changes as opposed to circulating miRNAs in plasma or serum, which may be marking changes in other tissues. Moreover, a random urine collection is easy to perform, does not require fasting, and can be performed at any time of the day.

Therefore, a urinary miRNoma analysis (analysis of all known mature miRNAs) was performed in patients with DKD [progressors *vs*. non-progressors for a rapid decline in the estimated glomerular filtration rate (eGFR)] and patients without this complication, aiming to identify a profile of urinary miRNAs involved in the development and progression of

DKD in patients with type 1 DM (T1DM). For this, in a screening phase, the urinary miRNoma was analyzed in 6 patients with T1DM without DKD and 14 with T1DM and DKD [divided into progressors (n= 7) and non-progressors (n= 7) in relation to a rapid decline in eGFR (≥ 3.5 mL/min/1.73 m^2/year) during the study follow-up (mean of 11.6 ± 3.6 years)]. The miRNoma was performed with the microarray technique, using the GeneChip miRNA 4.0 arrays (Thermo Fisher Scientific). As a result, we identified 79 differentially expressed miRNAs between groups. Of these, 63 differed between progressors *vs*. patients with normal eGFR; 12 between non-progressors *vs*. patients with normal eGFR; and 15 between progressor *vs*. non-progressor groups. Bioinformatics analyses showed that these miRNAs are involved in pathways associated with DM and DKD. After miRNoma analysis, 2 differentially expressed miRNAs between groups of the screening sample were selected for individual validation by real-time PCR. This was done in an independent sample of 46 T1DM patients: 18 without DKD and 28 with DKD, also divided into progressors (n= 12) and non-progressors (n= 16) for a rapid decrease in eGFR. We confirmed that hsa-miR-30a-5p is increased in progressors *vs*. non-progressor patients and patients without DKD. Hsa-miR-210-3p was not confirmed in the validation sample. In addition, we performed a second validation comparing our miRNoma data with data from a transcriptomic study available in the public GEO database (GSE121221). This analysis confirmed that hsa-miR-212-5p, hsa-miR-4484 and hsa-miR-4487 show decreased expression levels in patients with DKD compared to patients without this complication. As a conclusion of this first paper, hsa-miR-30a-5p, hsa-miR-212-5p, hsa-miR-4484, and hsa-miR-4487 were validated as potential biomarkers of DKD progression in T1DM patients.

In addition to the study of the role of miRNAs in DKD, we also evaluated the involvement of lncRNAs in the development of DM and DKD. LncRNAs are RNAs with >200 nucleotides that structurally resemble mRNAs but are unable to encode proteins. This

class of non-coding RNAs has already been associated with functions such as regulation of gene expression, cell cycle control, transcription, splicing regulation, cell differentiation, X chromosome inactivation, and gene imprinting. Interestingly, lncRNAs have a key role in many physiological and pathological processes and, therefore, can be biomarkers of several diseases, including DM and DKD. Thus, to provide a better understanding of the role of lncRNAs in the development of DM, we carried out both a systematic review and a case-control study, followed by bioinformatics analysis, to find lncRNAs associated with DM.

The systematic review included 53 studies that investigated lncRNA expressions in patients with T1DM or type 2 DM (T2DM). As a result, we found 6 lncRNAs consistently dysregulated in patients with DM (*ANRIL*, *HOTAIR*, *MALAT1*, *MIAT*, *KCNQ1OT1*, and *MEG3*) compared to the control group. Bioinformatics analyses demonstrated that these lncRNAs are involved in DM-related pathways, such as PI3K/Akt, MAPK, apoptosis, and FoxO. In the case-control study, we investigated the expression of lncRNAs *MALAT1*, *MEG3*, *MIAT*, *PVT1*, and *TUG1* in mononuclear cells from 27 T1DM patients (cases) and 13 healthy individuals (controls). The case group was divided into 14 patients with <5 years of diagnosis of T1DM and 13 patients with ≥5 years of diagnosis. LncRNAs *MALAT1* and *TUG1* expressions were increased in patients with <5 years of T1DM compared to the control group and patients with ≥5 years of diagnosis. *MEG3* expression was also increased in T1DM patients <5 years of diagnosis *vs*. controls. Interestingly, *MALAT1* and *TUG1* expressions were negatively correlated with T1DM duration, and *MEG3* and *TUG1* levels were positively correlated with glycated hemoglobin values.

Besides the studies about the role of lncRNAs in the DM context, we also evaluated the involvement of this type of RNAs in the development of DKD. Thus, in a first study, we evaluated the expressions of lncRNAs *MALAT1* and *TUG1* in the urine of patients with T1DM categorized into 18 patients with DKD (cases) and 9 patients without this

complication (controls). LncRNA *MALAT1* expression was increased in the urine from DKD patients compared to the control group. Bioinformatics analyses showed that these two lncRNAs are involved in pathways related to DM and DKD, such as glycolysis/gluconeogenesis, PI3K-Akt, AMPK, and the T1DM pathway.

In a second study related to the association of lncRNAs with DKD, we compared the frequencies of rs3200401/*MALAT1*, rs1894720/*MIAT*, rs3931283/*PVT1*, rs11993333/*PVT1*, rs5749201/*TUG1*, and rs7158663/*MEG3* polymorphisms between 902 T2DM patients with DKD (cases) and 394 T2DM patients without DKD (controls). As a result, we demonstrated that the G/G genotype of the rs3931283/*PVT1* polymorphism was associated with risk for DKD after adjusting for covariates. Accordingly, patients with the G/G genotype of this polymorphism also had higher levels of urinary albumin excretion (UAE) compared to patients with the A/A genotype. Interestingly, patients carrying the G/G genotype of the rs7158663/*MEG3* polymorphism had decreased creatinine levels and increased eGFR values compared to A allele carriers. Furthermore, the G allele of the *MEG3* polymorphism was associated with protection against severe DKD.

In conclusion, the studies included here showed the role of ncRNAs in DM and DKD, demonstrating the contribution of epigenetic factors in the development of these pathologies. A profile of miRNAs associated with the development and progression of DKD was identified in T1DM patients. Furthermore, our studies indicate the involvement of lncRNAs in the pathogenesis of DM and DKD through alterations in their expression levels as well as the presence of genetic polymorphisms in these lncRNAs.

Keywords: MicroRNAs. LncRNAs. Diabetes mellitus. Diabetes kidney disease. Biomarkers.

LISTA DE ILUSTRAÇÕES

Figura 1. Número de indivíduos com DM (adultos de 20-79 anos, dados de 2021)..... 22
Figura 2. Hiperglicemia crônica e desenvolvimento de complicações do DM..... 24
Figura 3. Lesões histopatológicas da Doença Renal do Diabetes.. 26
Figura 4. Valores para a classificação dos diferentes graus de doença renal crônica, considerando-se a albuminúria e a taxa de filtração glomerular estimada (TFGe), de acordo com as diretrizes da *Kidney Disease/Improving Global Outcomes* (KDIGO)..... 28
Figura 5. Biogênese de miRNAs.. 31
Figura 6. Classificação dos lncRNAs de acordo com sua localização genômica. 35
Figura 7. Principais funções dos lncRNAs no núcleo e no citoplasma. 36

LISTA DE ABREVIATURAS E SIGLAS

1. INTRODUÇÃO

CKD-EPI: *Chronic Kidney Disease Epidemiology Collaboration*

DM: Diabetes mellitus

DM1: diabetes mellitus tipo 1

DM2: diabetes mellitus tipo 2

DRC: doença renal crônica

DRCT: doença renal crônica terminal

DRD: doença renal do diabetes

EROs: espécies reativas de oxigênio

EUA: excreção urinária de albumina

HAS: hipertensão arterial sistêmica

IDF: *International Diabetes Federation*

KDIGO: *Kidney Disease/Improving Global Outcomes*

LncRNAs: RNAs não-codificantes longos

MALAT1: *metastasis associated lung adenocarcinoma transcript 1*

MEG3: *maternally expressed gene 3*

MIAT: *myocardial infarction associated transcript*

miRNAs: microRNAs

ncRNAs: RNAs não-codificantes

PARP1: poli(ADP ribose) polimerase 1

PVT1: *plasmacytoma variant translocation 1*

RD: retinopatia diabética

RI: resistência à insulina

RISC: complexo de silenciamento induzido por RNA

TFG: taxa de filtração glomerular

TGFe: taxa de filtração glomerular estimada

TGF-β1: *transforming growth fator beta 1*

TUG1*: taurine upregulated 1*

2. ARTIGOS

CKD-EPI - Chronic Kidney Disease Epidemiology Collaboration

DCCT - Diabetes Control and Complications Trial

DEG - differential gene expression

DKD – diabetic kidney disease

DM – diabetes mellitus

DR – diabetic retinopathy

ECM - extracellular matrix

eGFR - estimated Glomerular Filtration Rate

EGR1 - early growth response factor 1

EMT - epithelial-mesenchymal transition

ESRD - end-stage renal disease

FC - fold changes

FDR - false discovery rate

GEO - gene expression omnibus

GFR - glomerular filtration rate

GO – gene ontology

HbA1c - Glycated hemoglobin

HG - high glucose

HGNC - HUGO gene nomenclature committee

HK-2 - human renal tubular epithelial cells

HRECs - human retinal endothelial cells

HUVECs - human umbilical vein endothelial cells

HWE - Hardy–Weinberg equilibrium

KDIGO - Kidney Disease Improving Global Outcomes

LncRNAs - long non-coding RNAs

MALAT1 - metastasis-associated ling adenocarcinoma transcript 1

MCs - mesangial cells

MEG3 - Maternally expressed gene 3

MIAT - Myocardial infarction-associated transcript

MIN6 - murine beta-cell line

miRNAs - microRNAs

MtRNA - mitochondrial RNA

ncRNAS - non-coding RNAs

NPDR - nonproliferative diabetic retinopathy

PBMC - peripheral blood mononuclear cells

PBMCs - peripheral blood mononuclear cells

PDR – proliferative diabetic retinopathy

PVT1 - Plasmacytoma variant translocation 1

RMA - robust multiaveraging

RT-qPCR - real-time quantitative PCR

SNP - single nucleotide polymorphism

snRNAS - small nuclear RNAs

STROBE - Strengthening the Reporting of Observational studies in Epidemiology

STZ – streptozotocin

T1DM – type 1 diabetes mellitus

T2DM – type 2 diabetes mellitus

TGF-β1 - Transforming growth factor-β1

TUG1 - taurine-upregulated gene 1

UAE - urinary albumin excretion

SUMÁRIO

1 INTRODUÇÃO 23
1.1 DOENÇA RENAL DO DIABETES (DRD) 26
1.2 MECANISMOS EPIGENÉTICOS 30
1.2.1 MicroRNAs e a doença renal do diabetes 31
1.2.2 LncRNAs no contexto do DM e da DRD 35
2 OBJETIVOS 49
2.1 OBJETIVOS GERAIS 49
2.2 OBJETIVOS ESPECÍFICOS 49
CAPÍTULO 1 51
ARTIGO 1 52
CAPÍTULO 2 147
ARTIGO 2 148
ARTIGO 3 236
CAPÍTULO 3 352
ARTIGO 4 353
ARTIGO 5 421
CONCLUSÕES GERAIS 462
OUTRAS PRODUÇÕES NO PERÍODO 465
PREMIAÇÕES NO PERÍODO DO DOUTORADO 485

1 INTRODUÇÃO

O diabetes mellitus (DM) é um conjunto de distúrbios metabólicos que apresentam em comum à hiperglicemia, a qual pode ser resultante de defeitos na secreção de insulina, ação da insulina, ou ambos (1). De acordo com a Federação Internacional de Diabetes (*International Diabetes Federation* - IDF) (2), 537 milhões de indivíduos em todo o mundo apresentam algum tipo de diabetes mellitus (DM). Estatísticas mostram que o número de indivíduos afetados continua a aumentar e que providências se fazem necessárias para modificar a trajetória dessa epidemia. Caso isso não ocorra, a prevalência poderá chegar a 783 milhões de indivíduos com DM em 2045 (**Figura 1**) (2). No Brasil, mais de 12 milhões de indivíduos vivem hoje com algum tipo de DM (9% da população) (3).

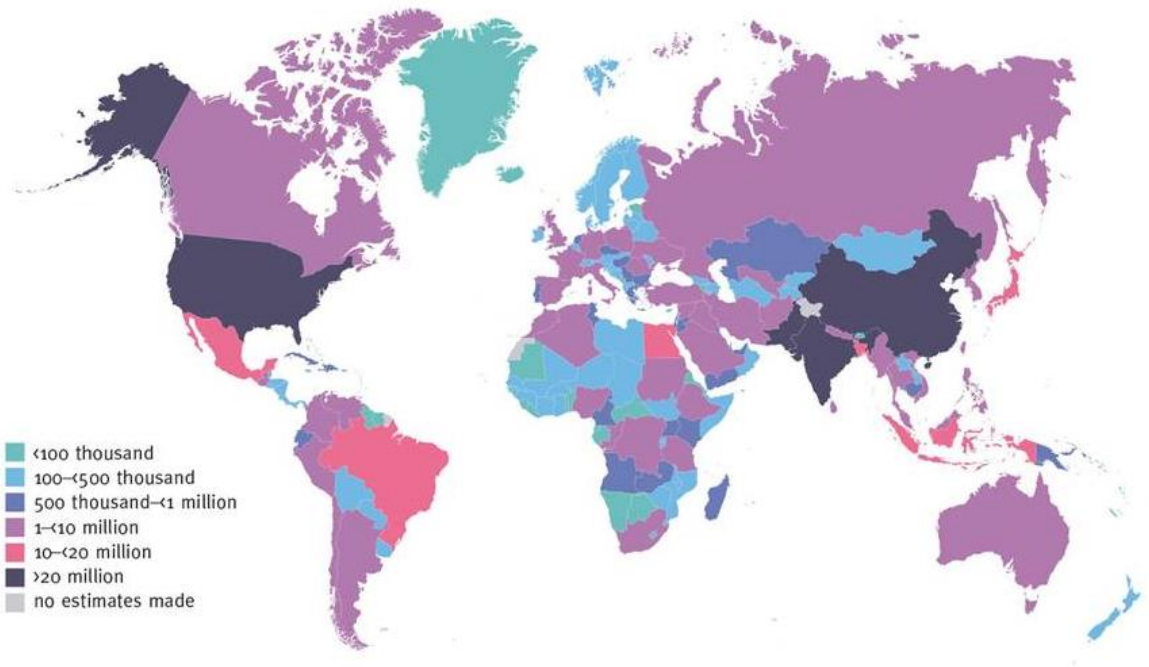

Figura 1. Número de indivíduos com DM (adultos de 20-79 anos, dados de 2021). Fonte: Federação Internacional de Diabetes (Atlas IDF 2021) (2).

O DM tipo 1 (DM1) é uma doença autoimune de etiologia múltipla causada pela complexa associação de fatores de risco genéticos, ambientais, imunológicos e epigenéticos (4-6). Essa doença é causada pela destruição autoimune das células-beta pancreáticas mediada por linfócitos T e macrófagos, o que leva a uma deficiência total na secreção de insulina e faz com que os indivíduos necessitem de tratamento com insulina para a sobrevivência (4-7).

O DM tipo 2 (DM2) é caracterizado por uma hiperglicemia crônica causada por um desbalanço entre ação e secreção de insulina e ocorre principalmente em indivíduos com mais de 30 anos de idade e com obesidade (4, 8). Na maioria dos casos, a anormalidade inicial detectável é uma diminuição na sensibilidade das células-alvo à ação da insulina (resistência à insulina - RI). Como processo fisiológico compensatório a RI, ocorre um aumento na secreção de insulina pelas células-beta (hiperinsulinemia), resultando na manutenção de uma glicemia temporariamente normal. Entretanto, com o passar do tempo, ocorre uma "exaustão" na capacidade secretória das células-beta, fazendo com que a homeostase glicêmica no jejum não possa mais ser mantida e a forma clínica dessa doença se estabeleça, podendo ser então detectada (4, 8, 9). O DM2 também parece ser desencadeado por fatores ambientais em indivíduos com predisposição genética (10). Entre esses fatores ambientais podemos citar: a obesidade e o sobrepeso, excesso de gordura abdominal, sedentarismo, tabagismo, dieta hipercalórica, hipertensão arterial sistêmica (HAS), colesterol LDL e triglicerídeos elevados, diabetes gestacional e uso de corticoides (10).

A hiperglicemia crônica em pacientes com DM leva à geração de intermediários tóxicos, como as espécies reativas de oxigênio (EROs) (11). O fluxo excessivo de glicose pode gerar EROs de várias maneiras diferentes. O aumento da oxidação do substrato mitocondrial com consequente aumento do potencial de membrana mitocondrial leva à

superprodução de superóxido. Ao mesmo tempo, o aumento do fluxo de glicose leva à ativação da NADPH oxidase e ao desacoplamento da óxido nítrico sintase. Os danos no DNA mediados pelo aumento de EROs no núcleo ativam os mecanismos de reparo do DNA, incluindo a enzima poli (ADP ribose) polimerase 1 (PARP1), que inibe a principal enzima da via glicolítica, a gliceraldeído-3-fosfato desidrogenase (GAPDH), por poliADP-ribosilação. A inibição da atividade de GAPDH causa um bloqueio no processo de glicólise, resultando no acúmulo de intermediários glicolíticos, e consequentemente leva à disfunção celular, inflamação, apoptose e fibrose em células expostas ao fluxo excessivo de glicose (**Figura 2**) (11).

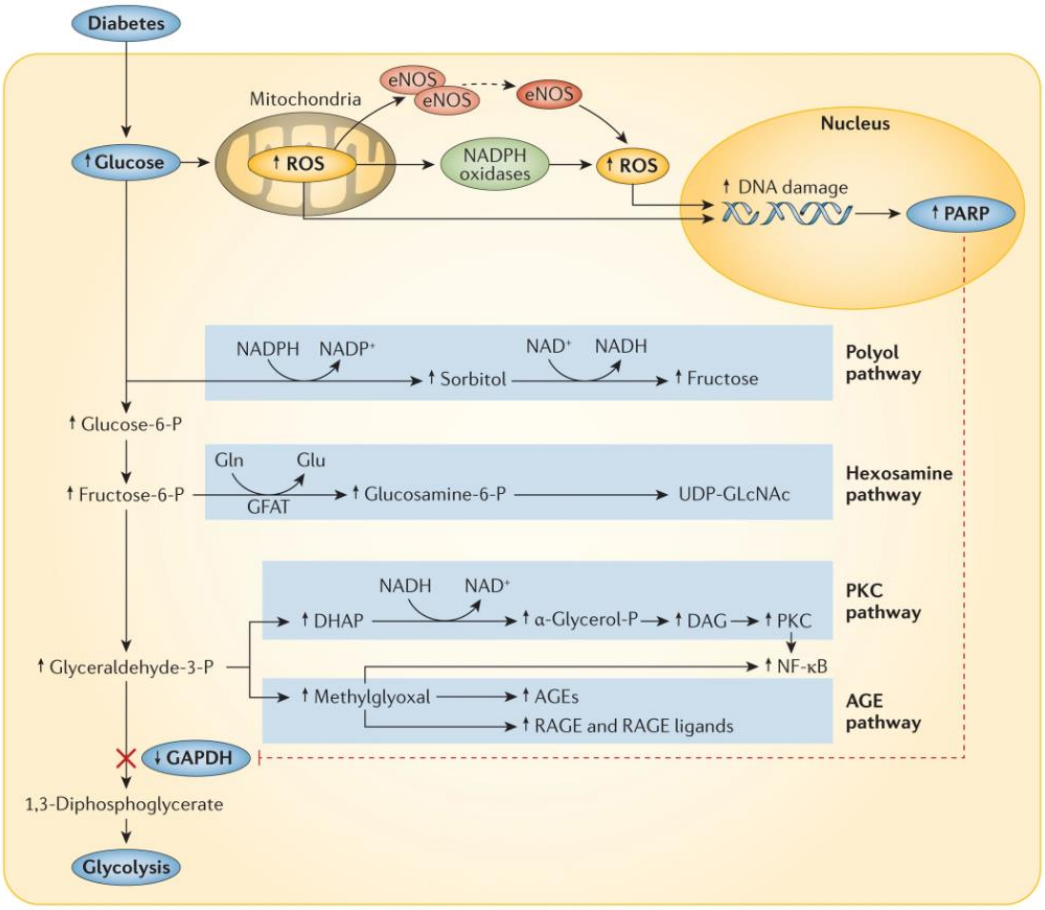

Figura 2. Hiperglicemia crônica e desenvolvimento de complicações do DM. A hiperglicemia crônica leva ao acúmulo de substrato de várias vias relacionadas ao processo de glicólise, tais como: vias de glicação avançada, poliol, hexosamina e proteína quinase C. Esse aumento de

substrato dessas vias leva a disfunção células e danos nessas células, resultando no desenvolvimento das complicações do DM. Fonte: (11).

Desta forma, a hiperglicemia crônica pode provocar lesões estruturais que causam danos, disfunções e falhas de vários órgãos e tecidos, levando ao aparecimento das complicações crônicas do DM (4). Estas complicações crônicas são divididas em microvasculares [doença renal do diabetes (DRD), retinopatia diabética (RD) e neuropatia diabética] e macro vasculares (doença arterial coronariana, doença vascular periférica e acidente vascular cerebral) (4). Seu desenvolvimento associa-se com elevada morbimortalidade e também à piora da qualidade de vida (12). De uma forma geral, a presença destas complicações depende do tempo de DM, idade do paciente, presença de HAS, dislipidemia, suscetibilidade genética do paciente ao tipo de complicação e da intensidade e persistência da hiperglicemia (13, 14).

1.1 DOENÇA RENAL DO DIABETES (DRD)

A DRD é a maior causa de doença renal crônica (DRC) e de doença renal crônica terminal (DRCT) a qual requer tratamento dialítico ou transplante renal (14, 15). Entre 25-40% dos pacientes com DM desenvolvem DRD até 25 anos de doença (16, 17). No Brasil, no ano de 2020, mais de 144 mil indivíduos estavam em tratamento com hemodiálise, sendo que 31% desses pacientes tinha como doença base o DM (18). Entre os pacientes diabéticos com DRD, o aumento do risco absoluto de mortalidade por todas as causas em relação ao grupo controle foi de 23,4% e o aumento correspondente no subgrupo sem DRD foi de apenas 3,4% (19). Isto sugere que entre os pacientes com diabetes, os portadores de DRD constituem um subgrupo de maior morbimortalidade, concentrando grande parte do risco hoje atribuído à presença de DM.

Normalmente a DRD é uma doença progressiva, caracterizada por alterações fisiopatológicas decorrentes do ambiente diabético, que começam por hiperfiltração renal e hipertrofia glomerular, podendo progredir para proteinúria e uma diminuição gradual da taxa de filtração glomerular (TFG) (14, 20). Com relação às alterações fisiopatológicas da DRD, o início é evidenciado pelo espessamento da membrana basal glomerular e aumento da deposição de colágeno na matriz extracelular, obliteração de pedicelos secundários e diminuição da quantidade de podócitos. Esses fatores contribuem para que ocorra a excreção de proteínas de alto peso molecular, como a albumina. Além disso, outras regiões do rim são afetadas, como, por exemplo, no túbulo proximal ocorre a atrofia do epitélio tubular com a perda de micro vilosidades, diminuição da quantidade de capilares e a infiltração inflamatória (21, 22) (**Figura 3**).

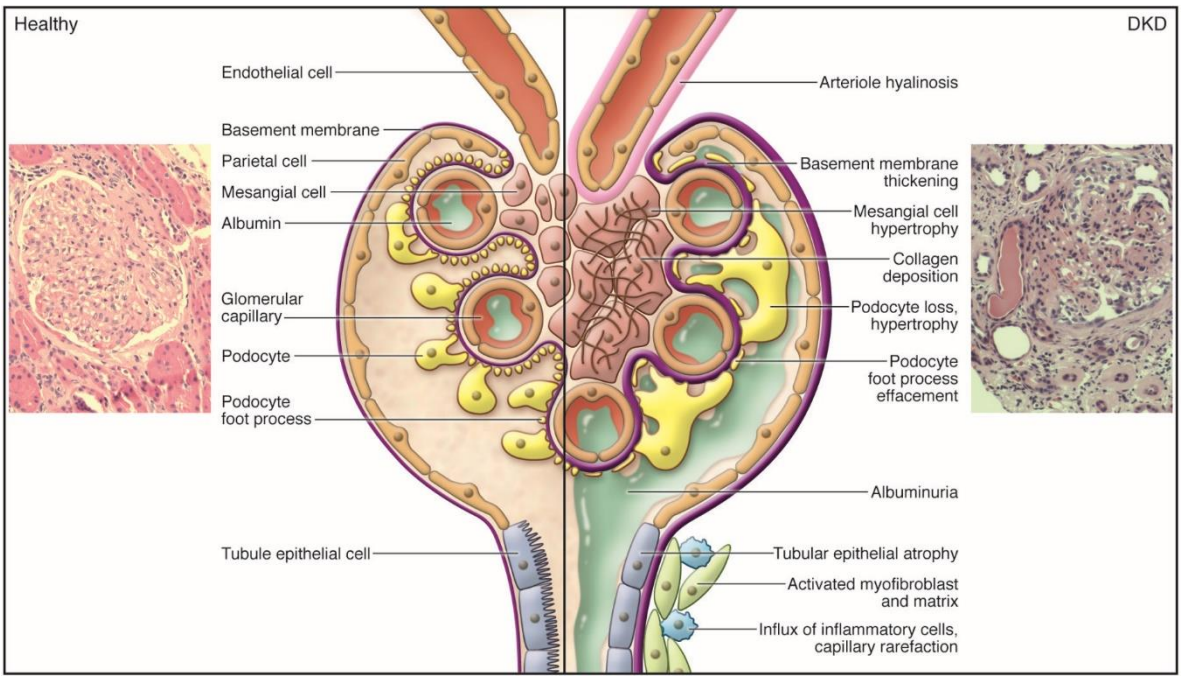

Figura 3. Lesões histopatológicas da Doença Renal do Diabetes. O glomérulo de um paciente saudável inclui arteríola aferente, capilares glomerulares, células endoteliais, membrana basal, podócitos, células epiteliais parietais, células túbulo-epiteliais e é impermeável à albumina. Em contraste, o glomérulo de um paciente com diabetes apresenta hialinose arteriolar, expansão mesangial, deposição de colágeno, espessamento da membrana basal, perda e hipertrofia de

podócitos, albuminúria, atrofia do epitélio tubular, acúmulo de matriz e mio fibroblastos ativados, influxo de células inflamatórias e rarefação de capilares. Também é mostrado tecido renal de glomérulo saudável e de paciente com DRD (corado com ácido periódico de Schiff). Fonte: Reidy e colaboradores (23).

Os processos envolvidos no desenvolvimento nas lesões e alterações renais são complexos e pouco conhecidos. Sem dúvida a hiperglicemia está muito relacionada ao desenvolvimento e progressão da DRD, afetando diversas células, como por exemplo, células endoteliais e mesangiais renais, células inflamatórias, podócitos, além do sistema tubular renal e ductos coletores. Como consequência da hiperglicemia, ocorre o aumento da produção de EROs pela mitocôndria, as quais ativam fatores de transcrição e moléculas de sinalização, aumentando assim a expressão de citocinas, fatores de crescimento e proteínas de matriz extracelular. Além disso, a hiperglicemia também aumenta a expressão celular de *transforming growth fator beta 1* (TGF-β1), que estimula a produção de matriz extracelular, contribuindo para a hipertrofia celular e síntese de colágeno (24).

Para avaliação da gravidade da disfunção renal utilizam-se atualmente os valores de albuminúria juntamente com a estimativa da TFG (TFGe). A albuminúria reflete a gravidade do dano renal, podendo ser classificada de acordo com os níveis de excreção urinária de albumina (EUA): 1) albuminúria normal ou levemente aumentada; 2) albuminúria moderadamente aumentada (anteriormente conhecida como microalbuminúria) ou, 3) albuminúria severamente aumentada (anteriormente chamada de macroalbuminúria) (25). Além disso, recomenda-se a TFGe para o rastreamento da DRD, uma vez que alguns pacientes com valores normais de albumina já podem apresentar uma diminuição na TFG (TFGe < 60 mL/min/1,73m^2) (26). Atualmente, a fórmula matemática mais utilizada para o cálculo da TFGe é a fórmula CKD-EPI (*Chronic Kidney Disease Epidemiology Collaboration*) (27), por ter sido validada em uma coorte que compreendia indivíduos saudáveis e indivíduos com DRC, e, por isso, apresentar melhor desempenho.

Dessa forma, segundo as diretrizes da *Kidney Disease/Improving Global Outcomes* (KDIGO) (25), a classificação dos estágios da DRC deve basear-se tanto na EUA quanto na TFGe, conforme a **Figura 4**.

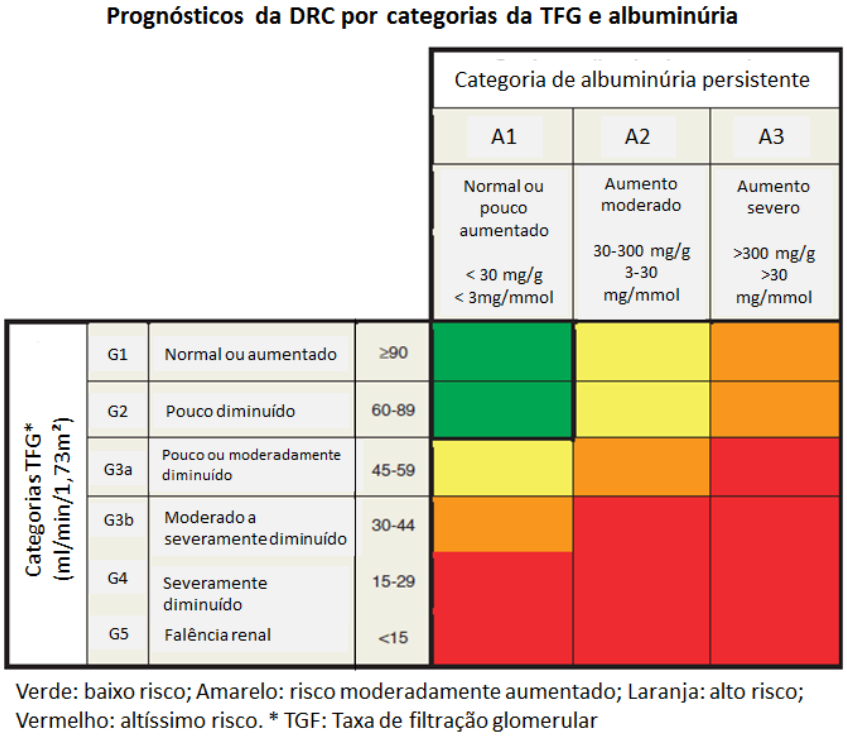

Figura 4. Valores para a classificação dos diferentes graus de doença renal crônica, considerando-se a albuminúria e a taxa de filtração glomerular estimada (TFGe), de acordo com as diretrizes da *Kidney Disease/Improving Global Outcomes* (KDIGO), 2012 (25).

Contudo, as equações utilizadas para determinar a TFG subestimam a TFG no DM e não permitem avaliar com precisão o curso da função renal (28, 29). Além disso, a EUA carece de sensibilidade e especificidade, pois estudos recentes mostram que há pacientes que desenvolvem a DRD antes que um aumento na EUA seja detectado. Dessa forma, novos biomarcadores estão sendo extensivamente investigados como indicadores mais precoces de DRD e são alvos de estudos para melhor compreensão do desenvolvimento da

doença, como por exemplo, fatores epigenéticos, incluindo os RNAs não-codificantes de proteínas.

1.2 MECANISMOS EPIGENÉTICOS

O termo epigenética significa “em adição à informação genética codificada no DNA” (30). Segundo Tang e Ho (31), a epigenética é definida como mudanças herdáveis na expressão gênica que não alteram a sequência do DNA. Os fatores epigenéticos regulam a expressão gênica de forma tecido-específica e tem sido demonstrado que alterações epigenéticas podem ser os principais causadores de doenças humanas (32, 33), como o DM e suas complicações crônicas. Além disso, modificações epigenéticas têm sido identificadas como um dos mecanismos pelos quais o meio ambiente interage com o genoma e modifica o risco para o desenvolvimento do DM1 e do DM2, bem como de suas complicações crônicas, como a DRD (34-36).

A exposição de células endoteliais do tecido microvascular à hiperglicemia é capaz de induzir alterações nos mecanismos epigenéticos, alterando a expressão gênica e, consequentemente, induzindo a ativação de diversas vias pró-inflamatórias associadas com as complicações do DM (36, 37). No entanto, a hiperglicemia não é o único fator que leva a alterações epigenéticas em pacientes com DM. A formação de EROs, hipóxia, inflamação, produção de citocinas, fatores de crescimento, medicamentos, nutrição e atividade física também podem causar modificações epigenéticas que influenciarão o desenvolvimento do DM e de suas complicações crônicas (38, 39).

As três maiores classes de mecanismos epigenéticos são as alterações nas histonas, metilação do DNA e regulação gênica por RNAs não-codificantes (ncRNAs) (36, 40). Entre os ncRNAs, os microRNAs (miRNAs) e os RNAs não-codificantes de proteínas

longos (lncRNAs) estão duas classes de ncRNAs mais descritas e estão associados com o desenvolvimento de diversas patologias (41-43), incluindo DM e DRD (43-48).

1.2.1 MicroRNAs e a doença renal do diabetes

Os miRNAs são uma classe de pequenos ncRNAs fita simples, de aproximadamente 19–25 nucleotídeos, que agem como potentes reguladores pós-transcricionais da expressão de mais de 60% dos genes codificantes de proteínas (41, 42). No núcleo, a maioria dos transcritos primários de miRNAs (pri-miRNAs) são transcritos pela RNA polimerase II (RNA pol II). Um complexo formado pela ribonuclease DROSHA e a proteína DGCR8 cliva o pri-miRNA para gerar miRNAs precursores (pré-miRNAs), que então são exportados do núcleo pela exportina 5. No citoplasma, os pré-miRNAs são clivados por Dicer para formar um miRNA duplex, de aproximadamente 22 nucleotídeos, que interage com as proteínas Argonautas (AGO1-4) para formar o complexo de silenciamento induzido por RNA (RISC) (49). O RISC carregado com miRNA se liga a sequências complementares no seus mRNAs alvos. Essa ligação resulta no silenciamento do gene por repressão da tradução do mRNA ou por desestabilização ou degradação do mRNA. Além disso, os miRNAs maduros também podem ser alvo de RNAs longos não-codificantes (lncRNAs), que atuam como esponjas de miRNA (**Figura 5**) (49).

Na maioria dos casos, os miRNAs exercem seus efeitos regulatórios ligando-se à região 3’UTR de seus mRNA alvos. No entanto, a interação de miRNAs com outras regiões, incluindo as regiões 5’UTR e promotora, também já foi relatada (50). Além disso, foi demonstrado que os miRNAs podem ativar a expressão gênica sob certas condições (51). Um único miRNA pode ter até 100 mRNAs alvos e vários miRNAs podem ter como alvo o mesmo mRNA (52).

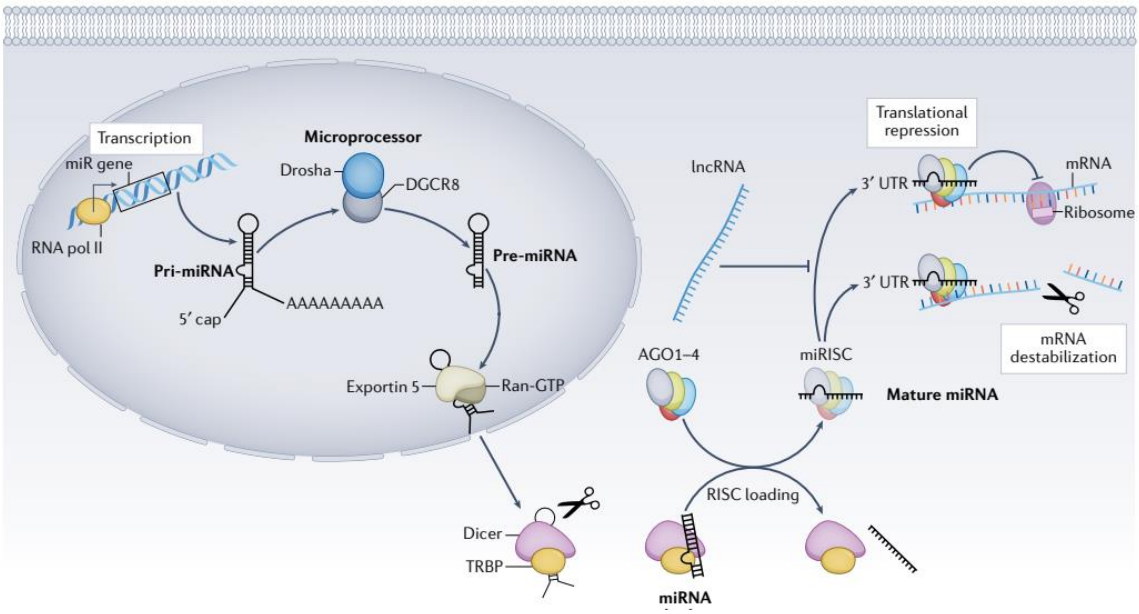

Figura 5. Biogênese de miRNAs. Fonte: Mahtal e colaboradores (49).

Estudos recentes demonstraram alterações na expressão de miRNAs em diversas patologias humanas, incluindo o DM e suas complicações crônicas (44, 48, 53, 54), o que enfatiza a importância dessas moléculas em processos fisiológicos e patológicos. Os miRNAs podem ser transportados de uma célula para outra, bem como podem circular nos diferentes fluidos biológicos de forma estável, constituindo uma nova forma de comunicação célula-célula (55, 56). Um perfil de expressão de miRNAs circulantes nos fluidos biológicos usualmente reflete um dano tecidual específico (57). Sendo assim, miRNAs circulantes são considerados bons biomarcadores não-invasivos para monitorar alterações fisiopatológicas e a progressão de diversas doenças (58). Consequentemente, miRNAs circulantes também são biomarcadores atraentes para o DM e suas complicações crônicas uma vez que podem ser facilmente coletados, são estáveis em diferentes condições de estocagem e podem ser quantificados usando-se *assays* específicos (44, 48). No contexto da DRD, o uso de miRNAs circulantes no plasma/soro ou miRNA urinários representa uma alternativa viável para o monitoramento do desenvolvimento e progressão

da doença, uma vez que eles não são eliminados durante a hemodiálise e não parecem ser afetados pela filtração glomerular, pois circulam nos fluídos biológicos complexados a proteínas, como a Argonauta-2, ou dentro de microvesículas, exossomos ou corpos apoptóticos (59, 60).

A associação entre miRNAs e disfunção renal foi inicialmente sugerida por estudos experimentais que demonstraram que a deleção específica da Dicer (uma enzima necessária para a produção dos miRNAs maduros) nos podócitos causou proteinúria, apoptose dos podócitos, glomeruloesclerose e fibrose (61). A hiperglicemia induziu a expressão de diversos miRNAs em células renais tanto em modelos *in vivo* quanto *in vitro*, promovendo o acúmulo de proteínas na matriz extracelular relacionadas com a fibrose e disfunção glomerular (61, 62). Além disso, alguns estudos usando células renais e modelos animais de DRD demonstraram relações funcionais entre a expressão aberrante de alguns miRNAs (miR-192, miR200b/c, miR-216 e miR-217) e processos relacionados à fibrose renal e DRD (63-66).

Em humanos, nos últimos anos, diversos estudos investigaram a expressão de diferentes miRNAs em pacientes com e sem DRD, buscando possíveis marcadores dos diferentes estágios dessa complicação (62, 67-74). Entretanto, os resultados desses estudos são variados e inconclusivos e podem ser específicos para uma dada população ou etnia. Dessa forma, visando sintetizar os resultados desses estudos, em 2018, nosso grupo realizou uma revisão sistemática da literatura sobre os 27 estudos que investigaram a expressão de miRNAs em pacientes com DRD e em indivíduos controles (48). Esses estudos avaliaram a expressão de um miRNA até 1066 miRNAs no plasma, soro, urina, exossomos urinários ou biópsias renais de pacientes diabéticos (DM1 ou DM2) com DRD e de indivíduos controles (DM sem DRD ou indivíduos saudáveis). A DRD foi diagnosticada usando-se diferentes critérios diagnósticos (EUA, TFGe, biópsia renal ou

razão EUA/creatinina). Como resultado, mostramos que 6 miRNAs estavam consistentemente desregulados em pacientes com diferentes graus de DRD comparados aos controles; isto é, eram diferencialmente expressos entre casos e controles em pelo menos 3 estudos da literatura. Entre esses miRNAs, miR-21-5p, miR-29a-3p, miR-126, miR-214 e miR-342 tinham a expressão aumentada, enquanto que o miR-192 tinha a expressão diminuída em pacientes com DRD comparado aos controles (48). Ainda, entre os 27 estudos revisados, 6 estudos mostraram perfis de expressão de miRNAs alterados na urina de pacientes com DRD comparado aos controles, demonstrando que miRNAs urinários também são possíveis biomarcadores do desenvolvimento da DRD.

Pezzolesi e colaboradores (68) investigaram a expressão de alguns miRNAs regulados por TGF-β1 no plasma de uma coorte de pacientes com DM1 proteinúricos, mas com TFGe normal. O TGF-β1 é um fator de crescimento que tem um papel chave na regulação da fibrose e inflamação e, consequentemente, na patogênese da DRD (48). Esses autores mostraram que os miRNAs let-7c-5p e miR-29a-3p foram associados com proteção contra progressão rápida para DRCT (medida pela diminuição na TFGe), enquanto let-7b-5p e miR-21-5p foram associados com risco de progressão rápida para DRCT (68). Esse estudo sugere que alguns miRNAs também tem o potencial de serem usados como biomarcadores da progressão de DRD para suas formas mais severas.

Recentemente, investigamos um perfil de expressão de 48 miRNAs no plasma de 23 pacientes com DM1 sem DRD (controles) e 35 pacientes com diferentes graus de DRD (casos) através de análise de *macroarray* (47). Nossos resultados demonstraram que 9 miRNAs foram diferencialmente expressos em pacientes com DRD comparados aos controles. Entre eles, 5 miRNAs foram escolhidos para validação em uma amostra independente de 19 casos e 10 controles por análise de real-time PCR (qPCR): miR-21-3p e miR-378a-5p tiveram a expressão aumentada, enquanto miR-16-5p e miR-29a-3p

tiveram a expressão diminuída nos pacientes com DRD severa comparado aos controles. A expressão do miR-503-3p não foi validada, isto é, esse miRNA não se confirmou como estando associado com DRD (47).

1.2.2 LncRNAs no contexto do DM e da DRD

LncRNAs são moléculas de RNA longas (> 200 nucleotídeos) que estruturalmente se assemelham ao mRNA, mas não codificam proteínas (75). A maioria dos lncRNAs ainda não é bem descrita, no entanto, algumas características já são conhecidas: a) possuem os promotores, regiões de *splicing*, éxons, posição no genoma e expressão bem conservadas (76); b) expressão dinâmica e *splicing* alternativo durante o processo de diferenciação celular (77); c) associação com conformações específicas da cromatina que são indicativos da transcrição de genes (78); e d) regulação dos lncRNAs por fatores de transcrição, pseudogenes e hormônios (79).

Com base na posição cromossômica dos lncRNAs, eles podem ser classificados em 5 principais tipos: *sense* lncRNAs – localizado sobre múltiplos íntrons ou éxons de um gene codificador de proteínas; *intronic* lncRNAs – dentro de um dos íntrons de um gene codificador de proteínas na fita 5'-3'; *antisense* lncRNAs – transcrito da fita oposta do gene codificador de proteínas; *bidirectional* lncRNAs – situados na fita oposta, mas dentro de 1kb do promotor na fita 5'-3'; e *intergenic* lncRNAs – localizados entre dois genes codificadores de proteínas (**Figura 6**) (80).

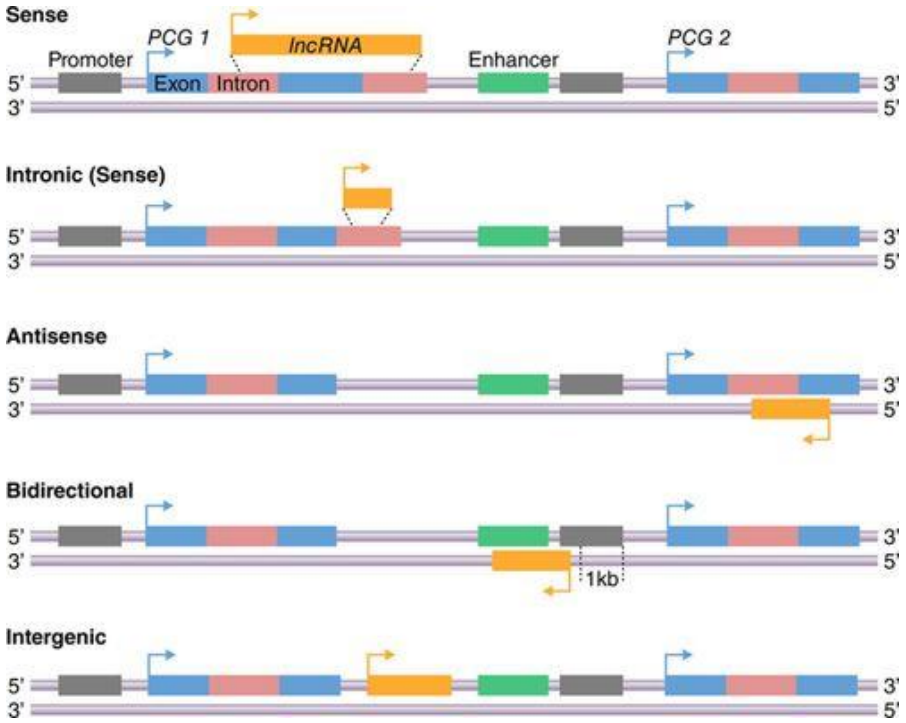

Figura 6. Classificação dos lncRNAs de acordo com sua localização genômica. Fonte: Bär e colaboradores (80).

Os lncRNAs estão localizados no núcleo ou no citoplasma, onde podem regular a expressão gênica em níveis transcricionais ou pós-transcricionais (80). Os lncRNAs localizados na região nuclear regulam a expressão gênica de vários modos, como: resposta a estímulos, sequestrando fatores de transcrição/complexo proteico, reunindo complexos multiproteicos ou guiando fatores de transcrição/complexo proteico para seu local alvo específico e induzindo o *looping* cromossômico para aumentar a associação entre o intensificador e a região promotora (80). Os lncRNAs citoplasmáticos (lineares ou circulares) podem estabilizar complexos de ribonucleoproteínas, regular a estabilidade de mRNA ou miRNAs, controlando assim a tradução (**Figura 7**) (80). Devido a seus importantes papéis como reguladores da expressão gênica, os lncRNAs já foram associados com funções como controle do ciclo celular, transcrição, regulação do *splicing*, diferenciação celular, inativação do cromossomo X e *imprinting* gênico (81).

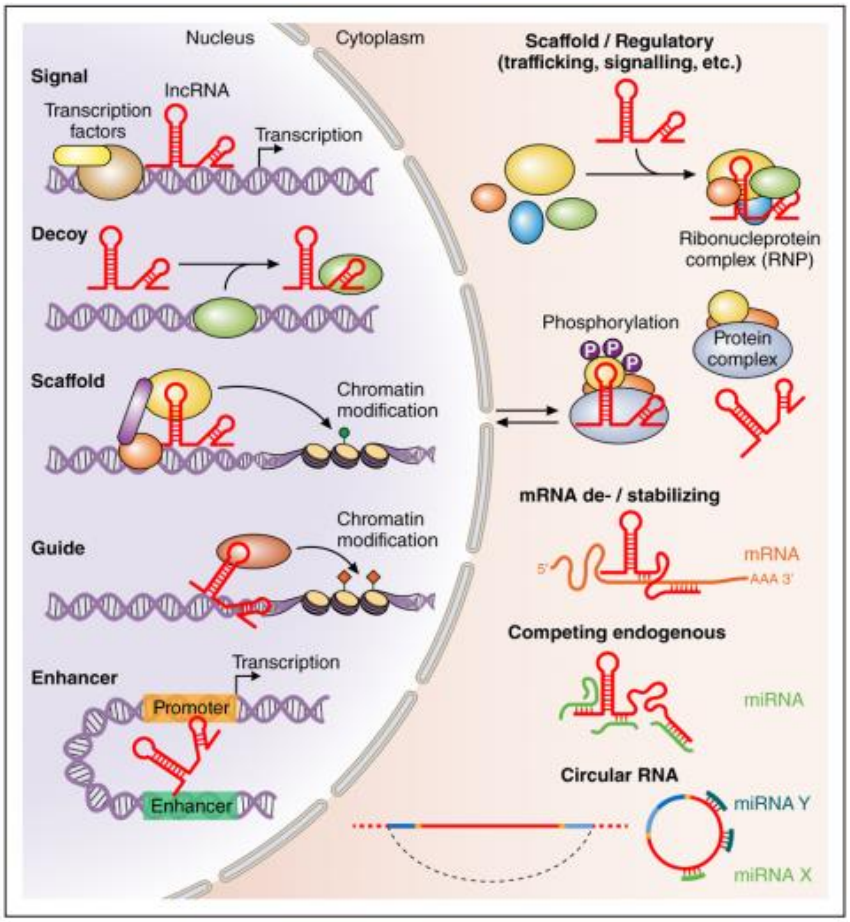

Figura 7. Principais funções dos lncRNAs no núcleo e no citoplasma. Fonte: Bär e colaboradores (80).

Nos últimos anos, vários estudos vêm demonstrando um papel importante dessa classe de ncRNAs no desenvolvimento de doenças, incluindo o DM e a DRD. Neste contexto, o lncRNA *metastasis associated lung adenocarcinoma transcript 1* (*MALAT1*), um dos mais estudados até o momento, vem sendo descrito como tendo a sua expressão aumentada em pacientes com DM em comparação ao grupo controle. Juntamente com o *MALAT1*, os lncRNAs *HOTAIR*, *MEG3*, *LET*, *MIAT*, *CDKN2BAS1/ANRIL*, *XIST*, *PANDA*, *GAS5*, *Linc-p21*, *ENST00000550337.1*, *PLUTO*, *THRIL*, *SALRNA1* e *NBR2* estavam desregulados em pacientes com DM2 em comparação ao grupo (82). Interessantemente, os lncRNAs *SALRNA1* e *THRIL* foram negativamente correlacionados com o controle glicêmico e RI (82).

Em estudos experimentais, a regulação positiva do lncRNA *maternally expressed gene 3* (*MEG3*) demonstrou aumentar a taxa de gliconeogênese e prejudicar a síntese de glicogênio estimulada pela insulina por meio do aumento da expressão de *FoxO1* em hepatócitos primários, promovendo resistência hepática à insulina (83). Além disso, You e colaboradores (84) demonstraram que a expressão de *Meg3* foi relativamente maior no pâncreas de camundongos do que em qualquer outro órgão, incluindo fígado, baço, pulmão e rim. A supressão da expressão de *Meg3 in vitro* e o *knockdown* de *Meg3 in vivo* podem afetar a síntese e secreção de insulina diminuindo a expressão de *Pdx-1* e *MafA* (84).

No contexto da DRD, uma revisão sistemática realizada por Zhao e colaboradores (85), que incluiu 28 artigos que avaliaram a expressão de lncRNAs em pacientes com e sem DRD, identificou 8 lncRNAs desregulados na DRD (*MALAT1*, *GAS5*, *MIAT*, *CASC2*, *NEAT1*, *NR_033515*, *ARAP1-AS2* e *ARAP1-AS1*). Análises de bioinformática mostraram que esses lncRNAs participam de vias relacionadas à DRD, tais como PI3K/Akt, TNF, HIF-1, AGE/RAGE, apoptose e FoxO (85). Estudos experimentais também vêm descrevendo o envolvimento de lncRNAs na DRD. Puthsnveetil e colaboradores (86) demonstraram que a expressão do lncRNA *MALAT1* estava aumentada em células epiteliais tratadas com altas doses de glicose. O aumento na expressão do lncRNA *MALAT1* correlacionou-se com o aumento na expressão de genes que regulam a inflamação, como *tumor necrosis factor* (*TNF*), *serum amyloid A* (*SAA3*) e *interleukin-6* (*IL-6*). O silenciamento do lncRNA *MALAT1* em células endoteliais normalizou os níveis de expressão de *SAA3*, *IL-6* e *TNF*. Esses resultados indicam que certos lncRNAs podem interferir no processo de inflamação relacionado com a DRD, sugerindo que a sua modulação terapêutica poderia melhorar as complicações crônicas do DM. Interessantemente, os lncRNAs *MALAT1* e *myocardial infarction associated transcript* (*MIAT*) foram demonstrados como reguladores da inflamação nas complicações do DM,

incluindo a DRD (86-89). A expressão de *MIAT* estava diminuída em túbulos renais de ratos com DM e foi negativamente correlacionada com os níveis de creatinina (89). Além disso, esse ncRNA regula diversas vias de sinalização relacionadas a função celulares, tais como proliferação e apoptose (90).

Outro lncRNA que parece estar associado com doenças renais é o lncRNA intergênico *plasmacytoma variant translocation 1* (*PVT1*). O PVT1 foi identificado através dos estudos de varredura de genoma conduzidos para identificar variantes genéticas que contribuem para DRCT em pacientes com DM2 (40). O tratamento com altos níveis de glicose induziu a expressão de *PVT1*, assim como de fibronectina 1 (*FN1*), *colágeno tipo IV α1*, *TGF-β1* e inibidor do ativador de plasminogênio 1 (*PAI-1*; anteriormente conhecido como *SERPINE1*) em células renais humanas (32). O silenciamento do lncRNA *PVT1* resultou na diminuição da expressão desses fatores. Outro estudo demonstrou que um miRNA derivado de *PVT1*, miR-1207-5p, é altamente expresso no rim e é regulado pelos níveis de glicose e TGF-β1 (91). Consistentemente, *PVT1* é expresso em todos os tipos celulares presentes no rim. Com o objetivo de investigar quais os mecanismos pelos quais o lncRNA *PVT1* contribui para o desenvolvimento da DRD, Alvarez e colaboradores (92) analisaram células mesangiais expostas a altos níveis de glicose e encontraram que esse lncRNA parece mediar o desenvolvimento e progressão da DRD através de mecanismos envolvendo acúmulo de matriz extracelular.

Do mesmo modo, o lncRNA *taurine upregulated 1* (*TUG1*) também parece atuar no contexto renal (93, 94). Zang e colaboradores (93) demonstraram que esse lncRNA tinha sua expressão diminuída em ratos diabéticos e células mesangiais expostas a alta concentração de glicose. Ainda, a superexpressão de *TUG1* inibiu a taxa de proliferação das células mesangiais e diminuiu a expressão de genes relacionados com o acúmulo de matriz extracelular, sugerindo assim, que esse lncRNA possa ter um papel protetor na

DRD (93). De acordo com esses achados, um estudo realizado por Xu e colaboradores (94) demonstrou que *TUG1* é capaz de proteger células HK-2, uma linhagem de célula renal, contra danos inflamatórios causados pela exposição a lipopolissacarídeo (LPS) (94).

O lncRNA *MEG3* foi demonstrado como estando desregulado em pacientes com DM (95-97). Além disso, esse lncRNA também parece ter um papel importante no desenvolvimento das complicações crônicas, tais como a DRD (98). Em ratos diabéticos e células mesangiais, a expressão de *MEG3* estava aumentada em comparação ao grupo controle. Além disso, a superexpressão de *MEG3* foi capaz de promover fibrose e respostas inflamatórias no contexto da DRD, através da via miR181a/Egr-1/TLR4, *in vivo* e *in vitro* (98).

REFERÊNCIAS DA INTRODUÇÃO

1. American Diabetes Association Professional Practice C. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2022. Diabetes Care. 2022;45(Suppl 1):S17-S38.
2. Sun H, Saeedi P, Karuranga S, Pinkepank M, Ogurtsova K, Duncan BB, et al. IDF Diabetes Atlas: Global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. Diabetes research and clinical practice. 2022;183:109119.
3. Reis R, Duncan BB, Malta DC, Iser BPM, Schmidt MI. Evolution of diabetes in Brazil: prevalence data from the 2013 and 2019 Brazilian National Health Survey. Cadernos de saude publica. 2022;38Suppl 1(Suppl 1):e00149321.
4. American Diabetes A. 2. Classification and Diagnosis of Diabetes. Diabetes care. 2017;40(Suppl 1):S11-S24.
5. Pirot P, Cardozo AK, Eizirik DL. Mediators and mechanisms of pancreatic beta-cell death in type 1 diabetes. Arquivos brasileiros de endocrinologia e metabologia. 2008;52(2):156-65.
6. Eizirik DL, Colli ML, Ortis F. The role of inflammation in insulitis and beta-cell loss in type 1 diabetes. Nat Rev Endocrinol. 2009;5(4):219-26.
7. Eizirik DL, Mandrup-Poulsen T. A choice of death--the signal-transduction of immune-mediated beta-cell apoptosis. Diabetologia. 2001;44(12):2115-33.
8. Association AD. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2014;37 Suppl 1:S81-90.
9. Skyler JS, Bakris GL, Bonifacio E, Darsow T, Eckel RH, Groop L, et al. Differentiation of Diabetes by Pathophysiology, Natural History, and Prognosis. Diabetes. 2017;66(2):241-55.
10. Dendup T, Feng X, Clingan S, Astell-Burt T. Environmental Risk Factors for Developing Type 2 Diabetes Mellitus: A Systematic Review. Int J Environ Res Public Health. 2018;15(1).
11. Thomas MC, Brownlee M, Susztak K, Sharma K, Jandeleit-Dahm KA, Zoungas S, et al. Diabetic kidney disease. Nature reviews Disease primers. 2015;1:15018.
12. Strong K, Mathers C, Leeder S, Beaglehole R. Preventing chronic diseases: how many lives can we save? Lancet. 2005;366(9496):1578-82.
13. Correa-Giannella ML, Vieira SM. [Genetic susceptibility to microangiopathy development in Type 1 diabetes mellitus]. Arquivos brasileiros de endocrinologia e metabologia. 2008;52(2):375-86.
14. Carpena M, Rados D, Sortica D, Souza B, Reis A, Canani L, et al. Genetics of diabetic nephropathy. Arquivos brasileiros de endocrinologia e metabologia. 2010;54(3):253-61.
15. Gross JL, de Azevedo MJ, Silveiro SP, Canani LH, Caramori ML, Zelmanovitz T. Diabetic nephropathy: diagnosis, prevention, and treatment. Diabetes Care. 2005;28(1):164-76.
16. Molitch ME, DeFronzo RA, Franz MJ, Keane WF, Mogensen CE, Parving HH, et al. Nephropathy in diabetes. Diabetes care. 2004;27 Suppl 1:S79-83.
17. Sortica DA, Crispim D, Zaffari GP, Friedman R, Canani LH. The role of ecto-nucleotide pyrophosphatase/phosphodiesterase 1 in diabetic nephropathy. Arq Bras Endocrinol Metabol. 2011;55(9):677-85.

18. Nerbass FB, Lima HDN, Thome FS, Vieira Neto OM, Lugon JR, Sesso R. Brazilian Dialysis Survey 2020. Jornal brasileiro de nefrologia : 'orgao oficial de Sociedades Brasileira e Latino-Americana de Nefrologia. 2022;44(3):349-57.
19. Afkarian M, Sachs MC, Kestenbaum B, Hirsch IB, Tuttle KR, Himmelfarb J, et al. Kidney disease and increased mortality risk in type 2 diabetes. J Am Soc Nephrol. 2013;24(2):302-8.
20. Ritz E, Zeng XX, Rychlik I. Clinical manifestation and natural history of diabetic nephropathy. Contrib Nephrol. 2011;170:19-27.
21. Macisaac RJ, Jerums G. Diabetic kidney disease with and without albuminuria. Curr Opin Nephrol Hypertens. 2011;20(3):246-57.
22. Tuttle KR, Bakris GL, Bilous RW, Chiang JL, de Boer IH, Goldstein-Fuchs J, et al. Diabetic kidney disease: a report from an ADA Consensus Conference. Am J Kidney Dis. 2014;64(4):510-33.
23. Reidy K, Kang HM, Hostetter T, Susztak K. Molecular mechanisms of diabetic kidney disease. The Journal of clinical investigation. 2014;124(6):2333-40.
24. Lemos NE, Dieter C, Dorfman LE, Assmann TS, Duarte GCK, Canani LH, et al. The rs2292239 polymorphism in ERBB3 gene is associated with risk for type 1 diabetes mellitus in a Brazilian population. Gene. 2018;644:122-8.
25. Group KDIGOKCW. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney international. 2013;Suppl. 3:1-150.
26. Zelmanovitz T, Gerchman F, Balthazar AP, Thomazelli FC, Matos JD, Canani LH. Diabetic nephropathy. Diabetology & metabolic syndrome. 2009;1(1):10.
27. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604-12.
28. Camargo EG, Soares AA, Detanico AB, Weinert LS, Veronese FV, Gomes EC, et al. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation is less accurate in patients with Type 2 diabetes when compared with healthy individuals. Diabetic medicine : a journal of the British Diabetic Association. 2011;28(1):90-5.
29. Soares AA, Eyff TF, Campani RB, Ritter L, Weinert LS, Camargo JL, et al. Performance of the CKD Epidemiology Collaboration (CKD-EPI) and the Modification of Diet in Renal Disease (MDRD) Study equations in healthy South Brazilians. Am J Kidney Dis. 2010;55(6):1162-3.
30. Feinberg AP, Tycko B. The history of cancer epigenetics. Nature reviews Cancer. 2004;4(2):143-53.
31. Tang WY, Ho SM. Epigenetic reprogramming and imprinting in origins of disease. Reviews in endocrine & metabolic disorders. 2007;8(2):173-82.
32. Jirtle RL, Skinner MK. Environmental epigenomics and disease susceptibility. Nature reviews Genetics. 2007;8(4):253-62.
33. Jiang YH, Bressler J, Beaudet AL. Epigenetics and human disease. Annual review of genomics and human genetics. 2004;5:479-510.
34. Dang MN, Buzzetti R, Pozzilli P. Epigenetics in autoimmune diseases with focus on type 1 diabetes. Diabetes/metabolism research and reviews. 2013;29(1):8-18.
35. Ling C, Groop L. Epigenetics: a molecular link between environmental factors and type 2 diabetes. Diabetes. 2009;58(12):2718-25.
36. Reddy MA, Zhang E, Natarajan R. Epigenetic mechanisms in diabetic complications and metabolic memory. Diabetologia. 2015;58(3):443-55.
37. Pirola L, Balcerczyk A, Tothill RW, Haviv I, Kaspi A, Lunke S, et al. Genome-wide analysis distinguishes hyperglycemia regulated epigenetic signatures of primary vascular cells. Genome research. 2011;21(10):1601-15.

38. Horsburgh S, Robson-Ansley P, Adams R, Smith C. Exercise and inflammation-related epigenetic modifications: focus on DNA methylation. Exercise immunology review. 2015;21:26-41.
39. Milagro FI, Mansego ML, De Miguel C, Martinez JA. Dietary factors, epigenetic modifications and obesity outcomes: progresses and perspectives. Molecular aspects of medicine. 2013;34(4):782-812.
40. Reddy MA, Tak Park J, Natarajan R. Epigenetic modifications in the pathogenesis of diabetic nephropathy. Semin Nephrol. 2013;33(4):341-53.
41. Butz H, Kinga N, Racz K, Patocs A. Circulating miRNAs as biomarkers for endocrine disorders. Journal of endocrinological investigation. 2016;39(1):1-10.
42. Esteller M. Non-coding RNAs in human disease. Nature reviews Genetics. 2011;12(12):861-74.
43. Feng F, Jiao P, Wang J, Li Y, Bao B, Luoreng Z, et al. Role of Long Noncoding RNAs in the Regulation of Cellular Immune Response and Inflammatory Diseases. Cells. 2022;11(22).
44. Assmann TS, Recamonde-Mendoza M, de Souza BM, Crispim D. MicroRNA expression profiles and type 1 diabetes mellitus: systematic review and bioinformatics analysis. Endocr Connect. 2017.
45. Nielsen LB, Wang C, Sorensen K, Bang-Berthelsen CH, Hansen L, Andersen ML, et al. Circulating levels of microRNA from children with newly diagnosed type 1 diabetes and healthy controls: evidence that miR-25 associates to residual beta-cell function and glycaemic control during disease progression. Exp Diabetes Res. 2012;2012:896362.
46. Pandey A, Ajgaonkar S, Jadhav N, Saha P, Gurav P, Panda S, et al. Current Insights into miRNA and lncRNA Dysregulation in Diabetes: Signal Transduction, Clinical Trials and Biomarker Discovery. Pharmaceuticals. 2022;15(10).
47. Assmann TS, Recamonde-Mendoza M, Costa AR, Punales M, Tschiedel B, Canani LH, et al. Circulating miRNAs in diabetic kidney disease: case-control study and in silico analyses. Acta Diabetol. 2019;56(1):55-65.
48. Assmann TS, Recamonde-Mendoza M, de Souza BM, Bauer AC, Crispim D. MicroRNAs and diabetic kidney disease: Systematic review and bioinformatic analysis. Molecular and cellular endocrinology. 2018.
49. Mahtal N, Lenoir O, Tinel C, Anglicheau D, Tharaux PL. MicroRNAs in kidney injury and disease. Nature reviews Nephrology. 2022;18(10):643-62.
50. Broughton JP, Lovci MT, Huang JL, Yeo GW, Pasquinelli AE. Pairing beyond the Seed Supports MicroRNA Targeting Specificity. Molecular cell. 2016;64(2):320-33.
51. Vasudevan S. Posttranscriptional upregulation by microRNAs. Wiley interdisciplinary reviews RNA. 2012;3(3):311-30.
52. Selbach M, Schwanhausser B, Thierfelder N, Fang Z, Khanin R, Rajewsky N. Widespread changes in protein synthesis induced by microRNAs. Nature. 2008;455(7209):58-63.
53. Assmann TS, Recamonde-Mendoza M, Punales M, Tschiedel B, Canani LH, Crispim D. MicroRNA expression profile in plasma from type 1 diabetic patients: Case-control study and bioinformatic analysis. Diabetes research and clinical practice. 2018;141:35-46.
54. Dieter C, Assmann TS, Costa AR, Canani LH, de Souza BM, Bauer AC, et al. MiR-30e-5p and MiR-15a-5p Expressions in Plasma and Urine of Type 1 Diabetic Patients With Diabetic Kidney Disease. Frontiers in genetics. 2019;10:563.
55. Guay C, Regazzi R. Circulating microRNAs as novel biomarkers for diabetes mellitus. Nature reviews Endocrinology. 2013;9(9):513-21.

56. Weber JA, Baxter DH, Zhang S, Huang DY, Huang KH, Lee MJ, et al. The microRNA spectrum in 12 body fluids. Clinical chemistry. 2010;56(11):1733-41.
57. Seyhan AA, Nunez Lopez YO, Xie H, Yi F, Mathews C, Pasarica M, et al. Pancreas-enriched miRNAs are altered in the circulation of subjects with diabetes: a pilot cross-sectional study. Sci Rep. 2016;6:31479.
58. Mitchell PS, Parkin RK, Kroh EM, Fritz BR, Wyman SK, Pogosova-Agadjanyan EL, et al. Circulating microRNAs as stable blood-based markers for cancer detection. Proceedings of the National Academy of Sciences of the United States of America. 2008;105(30):10513-8.
59. Martino F, Lorenzen J, Schmidt J, Schmidt M, Broll M, Gorzig Y, et al. Circulating microRNAs are not eliminated by hemodialysis. PloS one. 2012;7(6):e38269.
60. Lorenzen JM, Thum T. Circulating and urinary microRNAs in kidney disease. Clinical journal of the American Society of Nephrology : CJASN. 2012;7(9):1528-33.
61. Harvey SJ, Jarad G, Cunningham J, Goldberg S, Schermer B, Harfe BD, et al. Podocyte-specific deletion of dicer alters cytoskeletal dynamics and causes glomerular disease. Journal of the American Society of Nephrology : JASN. 2008;19(11):2150-8.
62. Kato M, Natarajan R. MicroRNAs in diabetic nephropathy: functions, biomarkers, and therapeutic targets. Annals of the New York Academy of Sciences. 2015;1353:72-88.
63. Kato M, Arce L, Wang M, Putta S, Lanting L, Natarajan R. A microRNA circuit mediates transforming growth factor-beta1 autoregulation in renal glomerular mesangial cells. Kidney Int. 2011;80(4):358-68.
64. Kato M, Natarajan R. Diabetic nephropathy--emerging epigenetic mechanisms. Nature reviews Nephrology. 2014;10(9):517-30.
65. Park JT, Kato M, Yuan H, Castro N, Lanting L, Wang M, et al. FOG2 protein down-regulation by transforming growth factor-beta1-induced microRNA-200b/c leads to Akt kinase activation and glomerular mesangial hypertrophy related to diabetic nephropathy. The Journal of biological chemistry. 2013;288(31):22469-80.
66. Kato M, Wang L, Putta S, Wang M, Yuan H, Sun G, et al. Post-transcriptional up-regulation of Tsc-22 by Ybx1, a target of miR-216a, mediates TGF-{beta}-induced collagen expression in kidney cells. The Journal of biological chemistry. 2010;285(44):34004-15.
67. Argyropoulos C, Wang K, McClarty S, Huang D, Bernardo J, Ellis D, et al. Urinary microRNA profiling in the nephropathy of type 1 diabetes. PloS one. 2013;8(1):e54662.
68. Pezzolesi MG, Satake E, McDonnell KP, Major M, Smiles AM, Krolewski AS. Circulating TGF-beta1-Regulated miRNAs and the Risk of Rapid Progression to ESRD in Type 1 Diabetes. Diabetes. 2015;64(9):3285-93.
69. Chung AC, Yu X, Lan HY. MicroRNA and nephropathy: emerging concepts. International journal of nephrology and renovascular disease. 2013;6:169-79.
70. Argyropoulos C, Wang K, Bernardo J, Ellis D, Orchard T, Galas D, et al. Urinary MicroRNA Profiling Predicts the Development of Microalbuminuria in Patients with Type 1 Diabetes. J Clin Med. 2015;4(7):1498-517.
71. Du B, Ma LM, Huang MB, Zhou H, Huang HL, Shao P, et al. High glucose down-regulates miR-29a to increase collagen IV production in HK-2 cells. FEBS Lett. 2010;584(4):811-6.
72. Peng H, Zhong M, Zhao W, Wang C, Zhang J, Liu X, et al. Urinary miR-29 correlates with albuminuria and carotid intima-media thickness in type 2 diabetes patients. PloS one. 2013;8(12):e82607.
73. Barutta F, Tricarico M, Corbelli A, Annaratone L, Pinach S, Grimaldi S, et al. Urinary exosomal microRNAs in incipient diabetic nephropathy. PloS one. 2013;8(11):e73798.

74. Bijkerk R, Duijs JM, Khairoun M, Ter Horst CJ, van der Pol P, Mallat MJ, et al. Circulating microRNAs associate with diabetic nephropathy and systemic microvascular damage and normalize after simultaneous pancreas-kidney transplantation. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2015;15(4):1081-90.
75. Yan B, Wang Z. Long noncoding RNA: its physiological and pathological roles. DNA and cell biology. 2012;31 Suppl 1:S34-41.
76. Pang KC, Frith MC, Mattick JS. Rapid evolution of noncoding RNAs: lack of conservation does not mean lack of function. Trends Genet. 2006;22(1):1-5.
77. Dinger ME, Amaral PP, Mercer TR, Pang KC, Bruce SJ, Gardiner BB, et al. Long noncoding RNAs in mouse embryonic stem cell pluripotency and differentiation. Genome Res. 2008;18(9):1433-45.
78. Guttman M, Amit I, Garber M, French C, Lin MF, Feldser D, et al. Chromatin signature reveals over a thousand highly conserved large non-coding RNAs in mammals. Nature. 2009;458(7235):223-7.
79. Koshimizu TA, Fujiwara Y, Sakai N, Shibata K, Tsuchiya H. Oxytocin stimulates expression of a noncoding RNA tumor marker in a human neuroblastoma cell line. Life Sci. 2010;86(11-12):455-60.
80. Bar C, Chatterjee S, Thum T. Long Noncoding RNAs in Cardiovascular Pathology, Diagnosis, and Therapy. Circulation. 2016;134(19):1484-99.
81. Wapinski O, Chang HY. Long noncoding RNAs and human disease. Trends in cell biology. 2011;21(6):354-61.
82. Sathishkumar C, Prabu P, Mohan V, Balasubramanyam M. Linking a role of lncRNAs (long non-coding RNAs) with insulin resistance, accelerated senescence, and inflammation in patients with type 2 diabetes. Human genomics. 2018;12(1):41.
83. Zhu X, Wu YB, Zhou J, Kang DM. Upregulation of lncRNA MEG3 promotes hepatic insulin resistance via increasing FoxO1 expression. Biochemical and biophysical research communications. 2016;469(2):319-25.
84. You L, Wang N, Yin D, Wang L, Jin F, Zhu Y, et al. Downregulation of Long Noncoding RNA Meg3 Affects Insulin Synthesis and Secretion in Mouse Pancreatic Beta Cells. Journal of cellular physiology. 2016;231(4):852-62.
85. Zhao Y, Yan G, Mi J, Wang G, Yu M, Jin D, et al. The Impact of lncRNA on Diabetic Kidney Disease: Systematic Review and In Silico Analyses. Computational intelligence and neuroscience. 2022;2022:8400106.
86. Puthanveetil P, Chen S, Feng B, Gautam A, Chakrabarti S. Long non-coding RNA MALAT1 regulates hyperglycaemia induced inflammatory process in the endothelial cells. Journal of cellular and molecular medicine. 2015;19(6):1418-25.
87. Liu JY, Yao J, Li XM, Song YC, Wang XQ, Li YJ, et al. Pathogenic role of lncRNA-MALAT1 in endothelial cell dysfunction in diabetes mellitus. Cell death & disease. 2014;5:e1506.
88. Jae N, Dimmeler S. Long noncoding RNAs in diabetic retinopathy. Circulation research. 2015;116(7):1104-6.
89. Zhou L, Xu DY, Sha WG, Shen L, Lu GY, Yin X. Long non-coding MIAT mediates high glucose-induced renal tubular epithelial injury. Biochemical and biophysical research communications. 2015;468(4):726-32.
90. Sun C, Huang L, Li Z, Leng K, Xu Y, Jiang X, et al. Long non-coding RNA MIAT in development and disease: a new player in an old game. J Biomed Sci. 2018;25(1):23.
91. Simmons R. Epigenetics and maternal nutrition: nature v. nurture. The Proceedings of the Nutrition Society. 2011;70(1):73-81.

92. Alvarez ML, DiStefano JK. Functional characterization of the plasmacytoma variant translocation 1 gene (PVT1) in diabetic nephropathy. PLoS One. 2011;6(4):e18671.
93. Zang XJ, Li L, Du X, Yang B, Mei CL. LncRNA TUG1 inhibits the proliferation and fibrosis of mesangial cells in diabetic nephropathy via inhibiting the PI3K/AKT pathway. European review for medical and pharmacological sciences. 2019;23(17):7519-25.
94. Xu Y, Deng W, Zhang W. Long non-coding RNA TUG1 protects renal tubular epithelial cells against injury induced by lipopolysaccharide via regulating microRNA-223. Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie. 2018;104:509-19.
95. Luo L, Ji LD, Cai JJ, Feng M, Zhou M, Hu SP, et al. Microarray Analysis of Long Noncoding RNAs in Female Diabetic Peripheral Neuropathy Patients. Cellular Physiology and Biochemistry. 2018;46(3):1209-17.
96. Kameswaran V, Golson ML, Ramos-Rodriguez M, Ou K, Wang YJ, Zhang J, et al. The Dysregulation of the DLK1-MEG3 Locus in Islets From Patients With Type 2 Diabetes Is Mimicked by Targeted Epimutation of Its Promoter With TALE-DNMT Constructs. 2018;67(9):1807-15.
97. Zhang D, Qin H, Leng Y, Li X, Zhang L, Bai D, et al. LncRNA MEG3 overexpression inhibits the development of diabetic retinopathy by regulating TGF-β1 and VEGF. Experimental and Therapeutic Medicine. 2018;16(3):2337-42.
98. Zha F, Qu X, Tang B, Li J, Wang Y, Zheng P, et al. Long non-coding RNA MEG3 promotes fibrosis and inflammatory response in diabetic nephropathy via miR-181a/Egr-1/TLR4 axis. Aging (Albany NY). 2019;11(11):3716-30.

JUSTIFICATIVA

O DM é uma doença complexa que caracteriza um grave problema de saúde pública, pois possui acentuada morbidade e mortalidade bem como devido a repercussões econômicas e sociais decorrentes do impacto de suas complicações crônicas, as quais comprometem a qualidade de vida e a produtividade dos indivíduos afetados, além dos elevados custos requeridos para seu tratamento. Estatísticas mostram que o número de indivíduos com DM está aumentando e providências se fazem necessárias para modificar a trajetória dessa doença. Neste contexto, a descoberta de novos biomarcadores poderá melhorar a identificação de indivíduos em risco para o DM em um período em que medidas preventivas podem ainda ser eficazes.

Além disso, a hiperglicemia crônica nos pacientes com DM está associada ao desenvolvimento de complicações crônico micro- e macrovasculares associadas a elevada morbimortalidade. Uma importante complicação crônica microvascular do DM é a DRD, a qual que afeta 25-40% dos pacientes com DM. A DRD é a maior causa de DRC e de DRCT em todo o mundo, sendo uma grande preditora de mortalidade em pacientes com DM. O comprometimento renal pode ser identificado pela redução da TFGe e/ou pelo aumento da EUA ou outras proteínas relacionadas à função dos túbulos renais. Entretanto, existem pacientes que mesmo com EUA alterada não progridem para DRCT, enquanto outros pacientes progridem rapidamente para os estágios avançados da doença. Além disso, a EUA carece de sensibilidade e especificidade, pois estudos recentes mostram que há pacientes que desenvolvem a DRD antes que um aumento na EUA seja detectado. Ainda, as equações atualmente recomendadas subestimam a TFGe no DM e não permitem avaliar com precisão o curso da função renal. Dessa forma, a descrição de novos

biomarcadores se faz necessária para a identificação de pacientes com alto risco de desenvolver essa complicação do DM e progredir para o estado de DRCT.

MiRNAs e lncRNAs são classes de ncRNAs que regulam a expressão gênica. Mudanças na expressão desses ncRNAs foram observadas em diversas situações patológicas, incluindo no DM e suas complicações crônicas. Os estudos que relacionaram miRNAs/lncRNAs circulantes, urinários ou renais com a DRD em humanos ou em modelos animais sugerem que perfis de miRNAs e de lncRNAs parecem se alterar nas diferentes fases desta complicação. Entretanto, os resultados desses estudos ainda não são conclusivos, isto é, não apontam um perfil único de expressão de miRNAs/lncRNAs circulantes no plasma/soro, urinários ou teciduais que possa ser usado como biomarcador das diferentes fases da DRD. Sendo assim, muitos estudos ainda são necessários para identificar um perfil alterado de expressão de miRNAs/lncRNAs no contexto do DM e suas complicações, incluindo a DRD.

A identificação de perfis de expressão de miRNAs/lncRNAs que possam ser usados como biomarcadores do desenvolvimento de DM ou para o surgimento ou prognóstico da DRD poderá contribuir para a busca da prevenção do DM ou diminuição da progressão da DRD. Além disso, estudos que identifiquem o papel dos miRNAs e lncRNAs na fisiopatogênese do DM e da DRD podem contribuir para a elucidação de importantes mecanismos regulatórios, gerando potenciais alvos terapêuticos e contribuindo para um melhor entendimento da base epigenética dessas doenças.

2 OBJETIVOS

2.1 OBJETIVOS GERAIS

- Investigar um perfil de miRNAs associado ao desenvolvimento ou progressão da DRD, medida pelo declínio rápido na TFGe, através da análise do miRNoma urinário.

- Investigar o papel dos lncRNAs no desenvolvimento de DM, através de uma revisão sistemática e de análises de bioinformática.

- Avaliar os níveis de expressão de lncRNAs em pacientes com DM1 e indivíduos saudáveis.

-Avaliar os níveis de expressão urinária de lncRNAs em pacientes com DM1 com e sem DRD.

- Avaliar a associação de polimorfismos em lncRNAs rs3200401/*MALAT1*, rs1894720/*MIAT*, rs3931283/*PVT1*, rs11993333/*PVT1*, rs5749201/*TUG1*, e rs7158663/*MEG3* e o desenvolvimento de DRD.

2.2 OBJETIVOS ESPECÍFICOS

- Comparar a expressão do miRNoma urinário (todos os miRNAs maduros conhecidos) entre pacientes com DM1 sem DRD e pacientes com DM1 e DRD (divididos em progressores e não-progressores para declínio rápido na TFGe).

- Validar os miRNAs mais diferencialmente expressos entre os grupos da análise do miRNoma em uma amostra independente de pacientes com DM1 sem DRD e DM1 com DRD (divididos em progressores e não-progressores para declínio rápido na TFGe), através de qPCR individual.

- Validar os miRNAs mais diferencialmente expressos entre os grupos da análise do miRNoma, através da comparação dos nossos resultados com um *dataset* público de transcriptômica.

- Investigar as vias metabólicas nas quais os genes regulados pelos miRNAs diferencialmente expressos nos pacientes com DRD participam através de análises de bioinformática.

- Realizar uma revisão sistemática de todos os estudos de expressão de lncRNAs em pacientes com DM, visando identificar um perfil de lncRNAs associados ao desenvolvimento de DM.

- Avaliar a expressão dos lncRNAs *MALAT1*, *MEG3*, *MIAT*, *PVT1* e *TUG1* em células mononucleares de pacientes com DM1 e indivíduos saudáveis, utilizando a técnica de qPCR.

- Correlacionar as expressões dos lncRNAs *MALAT1*, *MEG3*, *MIAT*, *PVT1* e *TUG1* com características laboratoriais relacionadas ao DM.

- Avaliar a expressão dos lncRNAs *MALAT1* e *TUG1* na urina de pacientes com DM1 com e sem DRD, através da técnica de qPCR.

- Correlacionar os níveis de expressões urinárias dos lncRNAs *MALAT1* e *TUG1* com características laboratoriais relacionadas à DRD, tais como EUA e TFGe.

- Comparar as frequências dos polimorfismos rs3200401/*MALAT1*, rs1894720/*MIAT*, rs3931283/*PVT1*, rs11993333/*PVT1*, rs5749201/*TUG1* e rs7158663/*MEG3* em pacientes com DM2 com e sem DRD.

- Avaliar a associação dos polimorfismos rs3200401/*MALAT1*, rs1894720/*MIAT*, rs3931283/*PVT1*, rs11993333/*PVT1*, rs5749201/*TUG1* e rs7158663/*MEG3* com características laboratoriais relacionadas à DRD, tais como EUA e TFGe.

CAPÍTULO 2

LncRNAs e o Diabetes Mellitus

ARTIGO 2

"The impact of lncRNAs in diabetes mellitus: A systematic review and *in silico* analyses"

Artigo publicado na revista Frontiers in Endocrinology 2021 – Fator de impacto 6,055

frontiers in Endocrinology

SYSTEMATIC REVIEW
published: 19 March 2021
doi: 10.3389/fendo.2021.602597

The Impact of lncRNAs in Diabetes Mellitus: A Systematic Review and *In Silico* Analyses

Cristine Dieter[1,2], *Natália Emerim Lemos*[1], *Nathalia Rodrigues de Faria Corrêa*[1], *Taís Silveira Assmann*[1,2] *and Daisy Crispim*[1,2]*

[1] Endocrine Division, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil, [2] Post-Graduate Program in Medical Sciences: Endocrinology, Faculdade de Medicina, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil

Long non-coding RNAs (lncRNAs) are non-coding transcripts that have emerged as one of the largest and diverse RNA families that regulate gene expression. Accumulating evidence has suggested a number of lncRNAs are involved in diabetes mellitus (DM) pathogenesis. However, results about lncRNA expressions in DM patients are still inconclusive. Thus, we performed a systematic review of the literature on the subject followed by bioinformatics analyses to better understand which lncRNAs are dysregulated in DM and in which pathways they act. Pubmed, Embase, and Gene Expression Omnibus (GEO) repositories were searched to identify studies that investigated lncRNA expression in cases with DM and non-diabetic controls. LncRNAs consistently dysregulated in DM patients were submitted to bioinformatics analysis to retrieve their target genes and identify potentially affected signaling pathways under their regulation. Fifty-three eligible articles were included in this review after the application of the inclusion and exclusion criteria. Six hundred and thirty-eight lncRNAs were differentially expressed between cases and controls in at least one study. Among them, six lncRNAs were consistently dysregulated in patients with DM (*Anril*, *Hotair*, *Malat1*, *Miat*, *Kcnq1ot1*, and *Meg3*) compared to controls. Moreover, these six lncRNAs participate in several metabolism-related pathways, evidencing their importance in DM. This systematic review suggests six lncRNAs are dysregulated in DM, constituting potential biomarkers of this disease.

Keywords: lncRNAs (long non-coding RNAs), type 1 diabetes mellitus (DM1), type 2 diabetes mellitus (T2DM), systematic review, target prediction

OPEN ACCESS

Edited by:
Åke Sjöholm,
Gävle Hospital, Sweden

Reviewed by:
Manal Said Fawzy,
Suez Canal University, Egypt
Subrata Chakrabarti,
Western University, Canada

***Correspondence:**
Daisy Crispim
dcmoreira@hcpa.edu.br

Specialty section:
This article was submitted to Diabetes: Molecular Mechanisms, a section of the journal Frontiers in Endocrinology

Received: *03 September 2020*
Accepted: *15 February 2021*
Published: *19 March 2021*

Citation:
Dieter C, Lemos NE, Corrêa NRdF, Assmann TS and Crispim D (2021) The Impact of lncRNAs in Diabetes Mellitus: A Systematic Review and In Silico Analyses. Front. Endocrinol. 12:602597. doi: 10.3389/fendo.2021.602597

INTRODUCTION

Diabetes mellitus (DM) is a group of metabolic disorders that have in common the chronic hyperglycemia, which results from defects in insulin secretion, insulin action, or both (1). Accordingly to the International Diabetes Federation Atlas 2019, an estimated 463 million adults are currently living with DM (9.3% of the world population), and this number is projected to reach 700 million by 2045 (2). Thus, DM has achieved epidemic proportions worldwide, being associated

with increased morbidity and mortality rates due to its specific micro- and macrovascular complications (1, 2).

Type 1 DM (T1DM) accounts for 5–10% of all DM cases and usually appears in people younger than 30 years (1, 2). T1DM is an autoimmune disease caused by the progressive destruction of pancreatic beta-cells by macrophages and T lymphocytes, making patients insulin-dependent for life (1, 3). Type 2 DM (T2DM) comprises 90–95% of worldwide diabetic cases and generally arises in subjects older than 40 years and with obesity. Hyperglycemia in T2DM patients is caused by insulin resistance associated with different degrees of a relative beta-cell failure (1, 2). It is well known that susceptibility for both T1DM and T2DM is triggered by a multifaceted interaction among several environmental, genetic, and epigenetic factors (4–8).

Epigenetic factors regulate the complex crosstalk between genes and environmental factors without altering the DNA sequence and include DNA methylation, histone posttranslational modifications, and non-coding RNAs (ncRNAs) (7, 8). NcRNAs are regulatory RNAs that typically lack protein-coding capacity and play key roles in both physiological and pathological processes (9, 10). According to their length and functions, ncRNAs can be classified into different subtypes, including the long ncRNAs (lncRNAs), which are those ncRNAs with >200 nucleotides in length (10, 11).

LncRNAs can be located in the nucleus or cytoplasm and exhibit more specific expression profiles than mRNAs, being expressed in cell/tissue-, developmental stage-, or disease state-specific manners (10, 12, 13). A number of studies have suggested lncRNAs participate in several molecular processes involved in gene regulation, including epigenetic, transcriptional, and post-transcriptional regulation, through interaction with chromatin-remodeling complexes, binding to transcription factors or regulation of mRNA-binding proteins and microRNAs (another class of ncRNAs) (10, 14–16).

In this context, growing evidence has shown lncRNAs play key roles in regulating beta-cell function, apoptosis, insulin secretion, glucose metabolism, and insulin resistance (10, 17–22). Accordingly, a number of studies have reported changes in lncRNA expressions in patients with DM or in murine models of T1DM or T2DM (10, 23–29). Thus, lncRNAs are likely to be novel potential biomarkers for early diagnosis and prognosis of T1DM or T2DM (10, 29). For example, Carter et al. showed GAS5 might be a prognostic biomarker for T2DM since this lncRNA was decreased in serum of patients with DM from a US military veterans cohort (23). Individuals with lower *GAS5* expression were almost 12× more likely to have T2DM (23). Li et al. reported *ENST00000550337.1* upregulation in blood had high diagnostic value for identifying pre-DM and T2DM in patients from a Chinese cohort (25).

Therefore, to further investigate which lncRNAs may be involved in DM pathogenesis and used as potential biomarkers of this disease, we performed a systematic review of the literature on the subject. Moreover, bioinformatics analyses were performed to investigate the regulatory and functional roles of dysregulated lncRNAs in DM pathogenesis.

MATERIALS AND METHODS

Search Strategy, Eligibility of Studies, and Data Extraction

This systematic review was designed and described in accordance with current guidelines (30, 31), and its protocol was registered at PROSPERO (http://www.crd.york.ac.uk/PROSPERO), under the identification: CRD42019124368. PubMed and EMBASE repositories were searched to retrieve all articles that investigated lncRNA expressions in T1DM or T2DM patients compared to non-diabetic controls. The research question was constructed based on the PICOS strategy (31), as follows: P (Population): patients with T1DM or T2DM; I (Intervention): lncRNA expression; C (Comparators): healthy control groups; O (Outcomes): DM; S (Study designs): case–control study, cross-sectional or cohort. The following medical subject headings (MeSH) were used: ("diabetes mellitus" OR "diabetes mellitus, type 1" OR "diabetes mellitus, type 2") AND ("RNA, long noncoding" OR "untranslated RNA"). The search was restricted to English, Spanish, or Portuguese language papers and was finished on April 2020. Reference lists from all included articles were also manually reviewed in order to identify other relevant citations. Moreover, studies were also searched in the GEO database (https://www.ncbi.nlm.nih.gov/geo/).

We included original articles that analyzed lncRNA expressions in patients with T1DM or T2DM (cases) and subjects without DM (controls). Studies that did not have an appropriate control group were excluded. Two researchers (CD and NL) independently reviewed titles and abstracts of all articles to evaluate if they were eligible for inclusion in this systematic review.

Results were independently collected by two investigators (CD and NL) using a standardized abstraction form (31). Discrepancies between investigators were solved by discussion between them and, when necessary, a third reviewer (DC) was consulted. The following information was collected from each study included in this review: 1) characteristics of studies and samples; 2) information regarding lncRNA expressions, quantification method, analyzed tissue, and number of lncRNAs investigated; and 3) lncRNA expression profile in case and control groups.

Evaluation of lncRNA Putative Target Genes and Functional Enrichment Analysis

Potential target genes for the consistently dysregulated lncRNAs in DM were searched using lncRNA2Target v2.0 (32) and starBase (33). The criteria for selecting the consistently dysregulated lncRNAs were: 1) lncRNAs with concordant results in ≥75% of the studies in which they were analyzed; and 2) lncRNAs analyzed in at least three studies. Statistical significances were reported after Benjamini–Hochberg (q-*value*) corrections for multiple comparisons (34). To better understand the biological relevance of lncRNA target genes, a network analysis was executed using PathDIP (accessed 23th April 2020) (35). The nomenclature of mRNAs and lncRNAs were unified based on HUGO gene nomenclature committee (HGNC) and LNCipedia v5.2, respectively.

RESULTS

Literature Search and Characteristics of Eligible Studies

Figure 1 shows the flowchart illustrating the strategy used to identify and select articles for inclusion in this systematic review. Following the search criteria, a total of 3,314 publications were retrieved from databases; however, after careful full text analysis, only 53 articles fulfilled the eligibility criteria and were included in the present review. The main characteristics of these studies are shown in **Table 1** and the **Supplementary Table 1**.

The number of lncRNAs differentially expressed between case and control groups from the different included studies varied from 1 (23, 39, 41, 43, 46–49, 52, 57, 60, 64, 68, 69, 73–75, 77) to 97,286 (58), and the sample sizes ranged from 4 (66) to 370 (73). Among the 53 studies included in this systematic review, 74% of them analyzed T2DM patients, while 26% did not report which DM type patients had. The tissues most analyzed were serum, plasma, and peripheral blood mononuclear cells (PBMCs).

Differentially Expressed lncRNAs in DM

As shown in the **Supplementary Table 2**, 623 lncRNAs were reported as being dysregulated in patients with DM from one study (17, 21, 24–28, 41, 42, 44, 47, 54, 55, 57–60, 64, 73, 75), while only seven were dysregulated in cases in two studies (*ENST00000550337.1*, *Pluto*, *LncRNAp3134*, *n335556*, *n336109*, *n342533*, and *Pvt1*) (17, 19, 21, 25, 28, 63, 66, 67). Eight lncRNAs were dysregulated in patients from three or more studies, being chosen for further evaluation (**Supplementary Table 2** and **Table 2**). Among these eight lncRNAs, those showing concordant results in more than 75% of the studies were considered consistently dysregulated in DM. Thus, as shown in **Table 2**, six lncRNAs were consistently dysregulated in patients with DM (upregulated: *Anril*, *Hotair*, *Malat1*, *Miat*, and *Kcnq1ot1*; downregulated: *Meg3*) compared to controls. *GAS5* and *H19* were upregulated in patients from some studies and downregulated in others, which could be explained by differences in the tissue types analyzed (serum, pancreatic islets, liver, plasma, and PBMCs) (**Table 2**).

Putative Target Genes and Enrichment Pathway Analysis of the Six Differentially Expressed lncRNAs in Human Samples

Bioinformatics analyses were carried out to find putative targets and biological pathways regulated by the six lncRNAs (*Anril*, *Hotair*, *Malat1*, *Miat*, *Kcnq1ot1*, and *Meg3*) consistently dysregulated in samples of DM patients. These six lncRNAs regulate together the expression of 1,860 unique target genes (**Supplementary Table 3**). *Malat1* has the largest number of target genes (1,671), followed by *Kcnq1ot1* (91), *Miat* (65), and *Hotair* (59), while *Meg3* and *Anril* have the lowest number of targets (32 and 20, respectively) (**Figure 2A** and **Supplementary Table 3**). Among the 1,860 target genes, 1,307 were protein coding genes, 287 were pseudogenes, 100 were small nuclear RNAs (snRNAs), and 225 were other type of ncRNAs, including microRNAs, rRNA, tRNA, and mitochondrial RNA (mtRNA) (**Supplementary Table 3**).

Next, to further explore the functional consequences of the dysregulation of the six lncRNAs of interest, we performed functional enrichment analysis of their protein-encoding target

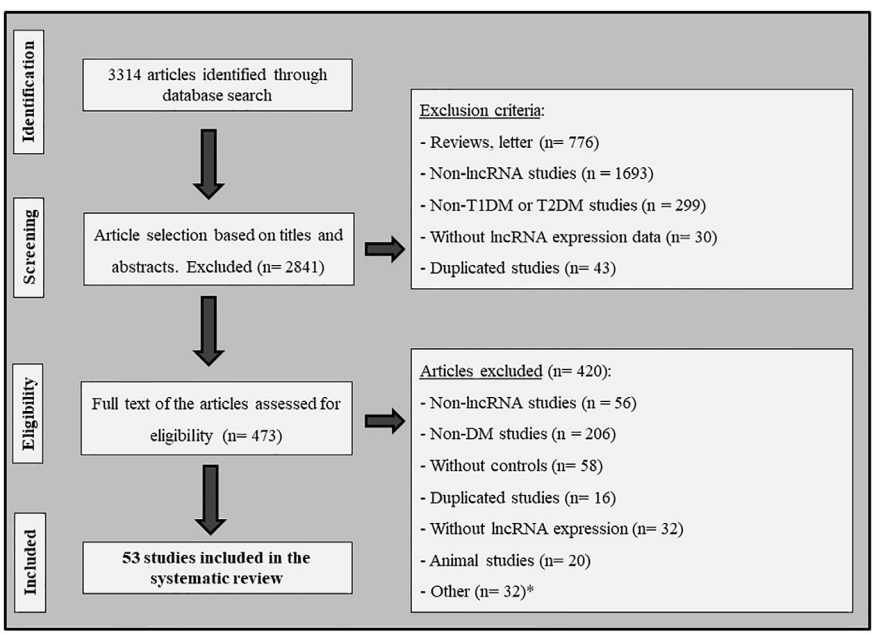

FIGURE 1 | Flowchart illustrating the search strategy used to identify studies that investigated the association between lncRNAs and diabetes mellitus. *Other: articles excluded due to lack of important information; studies with cell lines; and studies written in other idioms (not English, Spanish or Portuguese).

TABLE 1 | Characteristics of studies included in the systematic review.

Author, year [Reference]	Sample size Case/Control	Tissue	Method	Total number of studied lncRNAs	Statistically significant lncRNAs	
					Upregulated	Downregulated
Akerman et al. 2017 (17)	10 T2DM patients/50 controls	Pancreatic islets	RNA-seq and qPCR	2,373	0	16
Alikhah et al. 2018 (36)	18 T2DM patients/18 controls	PBMCs	qPCR	1	0	0
Carter et al. 2015 (23)	5 T2DM patients/5 controls 47 T2DM patients/49 controls (validation)	Serum	Microarray and qPCR	84	0	1
Chen et al. 2019 (37)	25 DM patients/20 controls	Serum	qPCR	1	0	0
Chen et al. 2018 (38)	27 DM patients/17 controls	Serum	qPCR	1	0	0
Cheng et al. 2019 (39)	30 DM patients/30 controls	Peripheral blood	qPCR	1	1	0
Dai et al. 2020 (40)	60 T2DM patients/60 controls	Plasma	qPCR	1	0	0
Das et al. 2018 (41)	5 T2DM patients/5 controls	CD14+ monocytes	qPCR	1	1	0
De Gonzalo-Calvo et al. 2016 (42)	48 T2DM patients/12 controls	Serum	qPCR	12	1	3
Erfanian Omidvar et al. 2019 (24)	100 T2DM patients/100 controls	PBMCs	qPCR	2	0	2
Esguerra et al. 2020 (43)	9 T2DM patients/10 controls	Pancreatic islets	qPCR	1	1	0
Fadista et al. 2014 (44)	12 T2DM patients/51 controls	Pancreatic islets	RNA-seq	493	NA	NA
Fawzy et al. 2020 (45)	53 T2DM patients/110 controls	Plasma	qPCR	2	1	1
Gao et al. 2014 (46)	5 T2DM patients/4 controls	Lateral quadriceps muscle biopsy	qPCR	1	0	1
Jiao et al. 2019 (47)	43 DM patients/48 controls	Serum	qPCR	1	1	0
Kameswaran et al. 2014 (48)	4 T2DM patients/3 controls	Pancreatic islets	qPCR	1	0	1
Li et al. 2018 (49)	10 T2DM patients/10 controls	Liver biopsy	qPCR	1	1	0
Li et al. 2019 (50)	56 T2DM patients/40 controls	Serum	qPCR	1	0	0
Li et al. 2018 (51)	63 DM patients/56 controls	Plasma	qPCR	1	0	0
Li et al. 2018 (25)	6 T2DM patients/6 controls 20 T2DM patients/20 controls (validation)	Peripheral blood	Microarray and qPCR	41,000	14	3
Liu et al. 2019 (52)	90 T2DM patients/30 controls	Serum	qPCR	1	1	0
Luo et al. 2018 (53)	6 T2DM patients/6 controls 26 T2DM patients/26 controls (validation)	PBMCs	Microarray and qPCR	NA	316	126
Ma et al. 2020 (54)	5 T2DM patients/5 controls 122 T2DM patients/125 controls (validation)	PBMCs	Array and qPCR	41,000	44	24
Mansoori et al. 2018 (26)	100 T2DM patients/100 controls	PBMCs	qPCR	2	0	2
Mohamadi et al. 2019 (55)	100 T2DM patients/100 controls	PBMCs	qPCR	2	0	0
Móran et al. 2012 (56)	16 T2DM patients/19 controls	Pancreatic islets	qPCR	13	1	1
Motterle et al. 2017 (57)	10 T2DM patients/10 controls	Pancreatic islets	qPCR	1	0	1
Pengyu et al. 2020 (58)	4 T2DM patients/4 controls	Serum	RNAseq and qPCR	NA	68763	28523
Pradas-Juni et al. 2020 (59)	4 T2DM patients/4 controls	Liver	RNAseq	13,805	126	384
Reddy et al. 2014 (60)	4 T2DM patients/4 controls	Monocytes	qPCR	1	1	0
Ren et al. 2019 (61)	178 T2DM patients/44 controls	Plasma	qPCR	1	0	0
Ruan et al. 2018 (19)	3 T2DM patients/3 controls 30 T2DM patients/30 controls (validation)	Blood	Microarray and qPCR	40,914		2269
	30 T2DM patients/30 controls	Exosome serum/ exosome-free serum	qPCR	1	1	0
Saeidi et al. 2018 (27)	100 T2DM patients/100 controls	PBMCs	qPCR	2	0	2
Sathishkumar et al. 2018 (21)	30 T2DM patients/32 controls	PBMCs	qPCR	17	13	2
Shaker et al. 2019 (62)	30 T2DM patients/81 controls	Blood	qPCR	2	2	0
Toraih et al. 2019 (63)	55 T2DM patients/108 controls	Plasma	qPCR	4	4	0
Wan et al. 2020 (64)	32 T2DM patients/32 controls	Serum	qPCR	1	1	0
Wang et al. 2018 (65)	296 T2DM patients/56 controls	Serum	qPCR	1	0	0
Wang et al. 2018 (66)*	2 T2DM patients/2 controls	Blood	Microarray and qPCR	NA	NA	NA
Wang et al. 2017 (28)	6 T2DM patients/6 controls 60 T2DM patients/60 controls (validation)	Peripheral blood	Microarray and qPCR	NA	39	16

(Continued)

TABLE 1 | Continued

Author, year [Reference]	Sample size Case/Control	Tissue	Method	Total number of studied lncRNAs	Statistically significant lncRNAs	
					Upregulated	Downregulated
Wang et al. 2020 (67)	156 T2DM/100 controls	Peripheral blood	qPCR	3	3	0
Yang et al. 2018 (68)	8 DM patients/8 controls	Serum	qPCR	1	1	0
Yang et al. 2018 (69)	6 DM patients/6 controls	Serum	qPCR	1	1	0
Yang et al. 2018 (70)	36 DM patients/41 controls	Serum	qPCR	1	0	0
Yang et al. 2019 (71)	DM patients/controls	Serum	Array	30,586	245	680
Yin et al. 2019 (72)	62 DM patients/48 controls	Plasma	qPCR	1	0	0
Zha et al. 2019 (73)	244 T2DM patients/126 controls	Plasma	qPCR	1	0	1
Zhang et al. 2018 (74)	28 DM patients/30 controls	Serum	qPCR	1	0	1
Zhang et al. 2020 (75)	99 T2DM patients/50 controls	Serum	qPCR	1	0	1
Zhang et al. 2017 (76)	30 DM patients/28 controls	Plasma	Microarray	NA	NA	NA
Zhang et al. 2019 (77)	24 T2DM patients/26 controls	Serum	qPCR	1	1	0
Zhang et al. 2019 (78)	244 T2DM patients/102 controls	Plasma	qPCR	1	0	0
Zhang et al. 2019 (79)	60 DM patients/60 controls	Plasma	qPCR	1	0	0

**Abstract from congress. DM, diabetes mellitus; NA, information not available; PBMCs, Peripheral blood mononuclear cells; qPCR, quantitative real time PCR; RNA seq, RNA sequencing; T2DM, type 2 diabetes mellitus.*

TABLE 2 | LncRNAs differentially expressed in at least three studies included in the systematic review.

LncRNA	Reference	Samples	Tissue	Change of expression
ANRIL	Sathishkumar et al. (21)	T2DM patients	PBMCs	Up
	Toraih et al. (63)	T2DM patients	Plasma	Up
	Zhang and Wang (77)	T2DM patients	Serum	Up
GAS5	Carter et al. (23)	T2DM patients	Serum	Down
	Esguerra et al. (43)	T2DM patients	Pancreatic islets	Up
	Sathishkumar et al. (21)	T2DM patients	PBMCs	Up
H19	Cheng et al. (39)	T2DM patients	Peripheral blood	Up
	Fawzy et al. (45)	T2DM patients	Plasma	Up
	Gao et al. (46)	T2DM patients	Muscle	Down
HOTAIR	Li et al. (49)	T2DM patients	Liver	Up
	Sathishkumar et al. (21)	T2DM patients	PBMCs	Up
	Shaker et al. (62)	T2DM patients	Blood	Up
Kcnq1ot1	Móran et al. (56)	T2DM patients	Pancreatic islets	Up
	Yang et al. (68)	DM patients	Serum	Up
	Yang et al. (69)	DM patients	Serum	Up
MALAT1	Liu et al. (52)	T2DM patients	Serum	Up
	Luo et al. (53)	T2DM patients	Blood	Up
	Sathishkumar et al. (21)	T2DM patients	PBMCs	Up
	Shaker et al. (62)	T2DM patients	Blood	Up
	Toraih et al. (63)	T2DM patients	Plasma	Up
MEG3	Kameswaran et al. (48)	T2DM patients	Pancreatic islets	Down
	Luo et al. (53)	T2DM patients	Blood	Down
	Sathishkumar et al. (21)	T2DM patients	PBMCs	Up
	Zhang et al. (74)	DM patients	Serum	Down
MIAT	De Gonzalo-Calvo et al. (42)	T2DM patients	Serum	Up
	Sathishkumar et al. (21)	T2DM patients	PBMCs	Up
	Toraih et al. (63)	T2DM patients	Plasma	Up

DM, diabetes mellitus; PBMCs, Peripheral blood mononuclear cells; T2DM, type 2 diabetes mellitus.

genes using pathways maps from the KEGG repository. As a result, a total of 168 unique pathways were enriched for lncRNA target genes (**Supplementary Table 4**). Moreover, as demonstrated in **Figure 2B**, only one pathway is shared among the five lncRNAs (*Anril*, *Hotair*, *Malat1*, *Kcnq1ot1*, and *Meg3*): Kaposi sarcoma-associated herpes virus infection. Many of the 168 pathways are well established to be involved in DM pathogenesis, such as PI3K/Akt, MAPK, apoptosis, AGE/RAGE, and FoxO (**Figure 3** and **Supplementary Table 4**). Of note, we could not find any significant KEGG pathway for *Miat*.

DISCUSSION

Currently, several studies have reported the association between epigenetic mechanisms and DM development [reviewed in

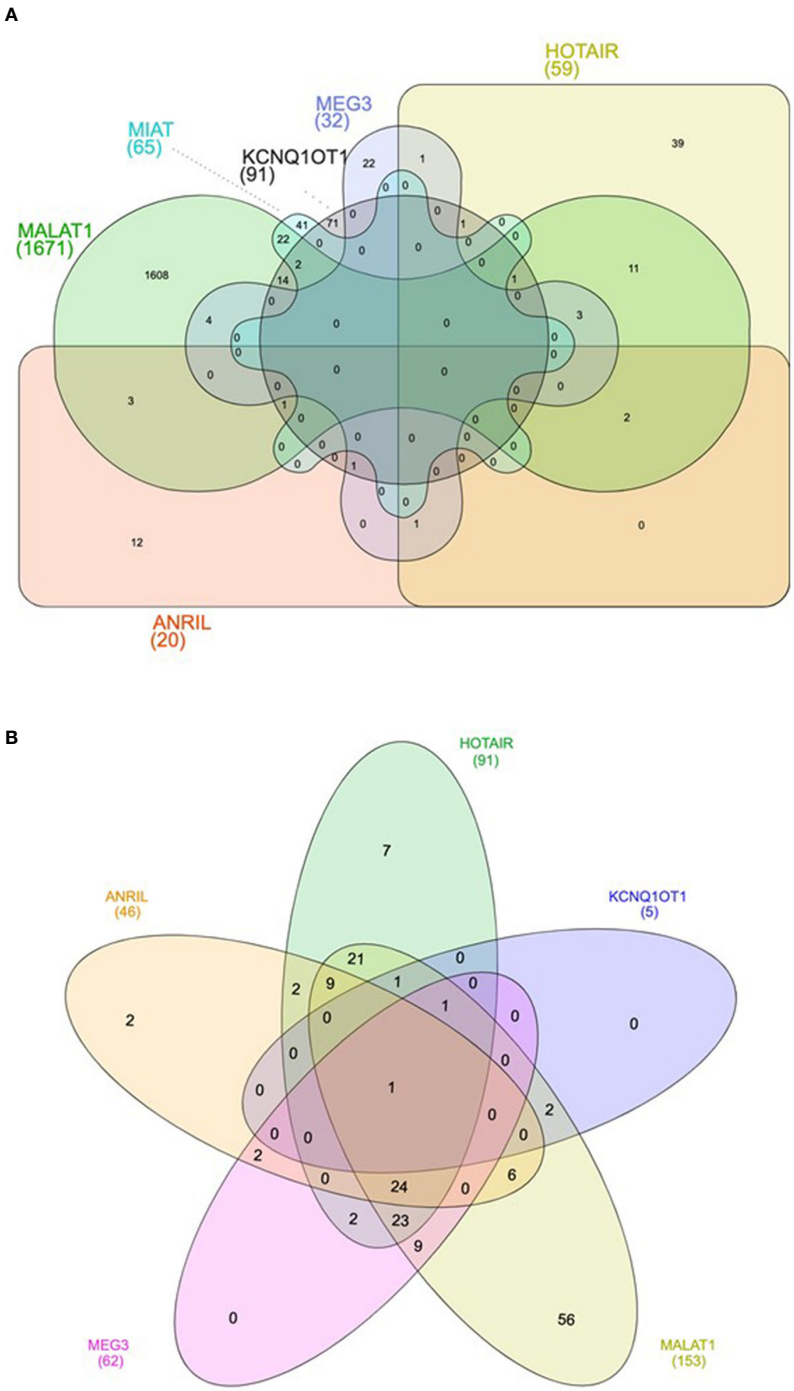

FIGURE 2 | Venn diagram showing the shared target genes **(A)** and pathways **(B)** of the six lncRNAs consistently dysregulated in DM.

(6, 7, 80, 81)]. In this context, lncRNAs are a class of ncRNAs that appear to be involved in DM pathogenesis (10). Thus, here, we performed a systematic review to further investigate which lncRNAs are mainly associated with DM. Our results demonstrated six lncRNAs were consistently dysregulated in patients with DM. *Anril*, *Hotair*, *Kncq1ot1*, *Malat1*, and *Miat* were consistently upregulated, while *Meg3* was downregulated in diabetic cases compared to controls.

Malat1 (metastasis-associated lung adenocarcinoma transcript 1, also known as *Neat2*) is one of the most analyzed lncRNAs in T2DM samples. Here, our qualitative analysis shows this lncRNA is upregulated in serum, plasma, and PBMCs of

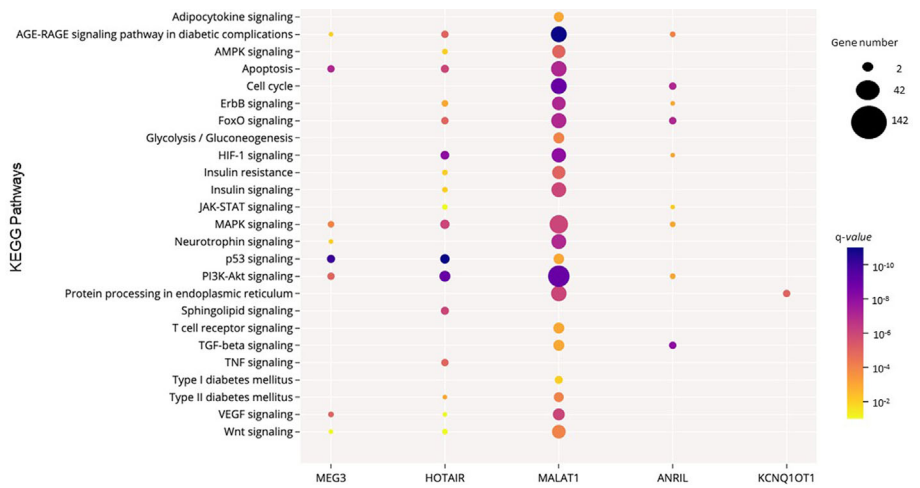

FIGURE 3 | Significant KEGG pathways potentially regulated by the consistently dysregulated lncRNAs in DM. The size and the color of the dots represent the gene number and the range of the pathway's q-value, respectively. The y-axis represents the KEGG pathways, and the x-axis shows the five lncRNAs that participated in each selected pathway. *MIAT* was not significantly enriched in these selected pathways. Q-*values*: P-*values* corrected for multiple tests using the Benjamini–Hochberg method.

T2DM patients (21, 52, 53, 62, 63). Moreover, studies performed in animal models of DM indicate that the expression of *Malat1* is increased in liver, macrophages, and serum of different murine models of T2DM compared to controls (20, 27, 52). *Malat1* is a highly conserved nuclear lncRNA initially identified as a predictor of lung cancer metastasis (82). Several studies have reported the involvement of this lncRNA in signaling pathways related to DM pathogenesis, such as PI3K/Akt (83), NF-κB (84), MAPK/ERK (85, 86), and Wnt/β-catenin (87). Accordingly, our *in silico* analysis shows *Malat1* is involved in a number of pathways involved in DM and its complications that, besides PI3K/Akt, MAPK, and Wnt, include apoptosis, insulin, cell cycle, AMPK, FoxO, ErbB, HIF-1, AGE/RAGE, adipocytokines, and protein processing in endoplasmic reticulum. In agreement with *Malat1* upregulation in T2DM, its expression was also increased in human umbilical vein endothelial cells (HUVECs) cultured with high-glucose (HG) and positively correlated with inflammatory cytokine (IL6 and TNF) levels (88). Additionally, this lncRNA was upregulated in mice with diabetic retinopathy (DR) compared to control animals (89).

Hotair was also consistently upregulated in liver, blood, and PBMCs of patients with T2DM (21, 38, 62). Accordingly, Li et al. reported this lncRNA was upregulated in liver of two T2DM murine models (db/db and C57BL/6J mice) treated with high-fat diet (49). *Hotair* is located within the *HOMEOBOX C* (*HOXC*) gene cluster on chromosome 12q13.13 and is involved in cellular proliferation, inhibition of apoptosis, genomic instability, angiogenesis, and metastasis (90–92). Moreover, *Hotair* upregulation promotes hepatic insulin resistance *via* the Akt/GSK pathway (38), which might partially explain its association with T2DM. Our *in silico* analysis demonstrates the involved of *Hotair* in several DM-related pathways, such apoptosis, PI3K-Akt, MAPK, HIF-1, TNF, and FoxO. This lncRNA seems also to be involved in the pathogenesis of diabetic chronic complications. *Hotair* was upregulated in serum of patients with different degrees of DR compared to healthy controls, and its expression was able to distinguish patients with non-proliferative DR from those with proliferative DR (62). Increased expression of *Hotair* was also found in kidney of patients with diabetic kidney disease (DKD) and in kidneys of *db/db* and STZ-induced diabetic mice (93). Accordingly, mouse podocytes cultured under HG conditions also expressed high levels of *Hotair* (93).

In addition to *Malat1* and *Hotair*, the lncRNA *Anril* was also increased in PBMCs, plasma, or serum of patients with T2DM compared to controls (21, 63, 77). This lncRNA has been associated with several types of cancer, such as gliomas, breast, lung, liver, colon, and thyroid cancers [reviewed in (94)]. *Anril* seems also to be involved in DR pathogenesis, since its expression was upregulated in human retinal endothelial cells (HRECs) cultured under HG conditions and in retinal tissue of STZ-induced diabetic mice (95). Blockade of *Anril* prevented HG-induced *VEGF* upregulation in HRECs, which is a key angiogenic factor in DR pathogenesis (95, 96). In line with these findings, Zhang et al. showed *Anril* overexpression in diabetic rats complicated with cerebral infarction upregulated VEGF and improved angiogenesis through activation of the NF-κB pathway (97). Our *in silico* analysis indicates that *Anril* is also involved in the TGFβ, PI3K-Akt, MAPK, cell cycle, FoxO, and AGE/RAGE pathways, which are known pathways related to DM and its chronic complications.

Kcnq1ot1 is another lncRNA consistently upregulated in islets and serum of patients with T2DM (56, 68, 69). *Kcnq1ot1* is an antisense lncRNA that seems to regulate the expression of both neighboring or distant genes (98), including the *CDKN1C*, a known regulator of beta-cell development (99). Interestingly,

a meta-analysis study, including 51,075 DM cases and 10,6134 controls, demonstrated the association between the rs231362 polymorphism in the *Kcnq1ot1* gene and risk for T2DM [OR 1.10 (95% CI 1.06–1.15), $P < 10^{-4}$] (100). Our *in silico* analysis indicates this lncRNA regulates genes from the protein processing in endoplasmic reticulum stress pathway.

Miat was also consistently upregulated in serum, plasma, or PBMCs of T2DM patients compared to controls (21, 42, 63). This lncRNA seems to act as a regulator of several signaling pathways related to cellular function, such as proliferation and apoptosis and as a competitive endogenous RNA (101). Additionally, *Miat* seems to be involved in diabetic complications (102). *Miat* was upregulated in the myocardium of diabetic rats, while its knockdown inhibited apoptosis in cardiomyocytes exposed to HG (103). In contrast, in renal tubuli of diabetic rats, *Miat* was downregulated compared to control rats and negatively correlated to serum creatinine levels (104). Growing evidence has also shown *Miat* dysregulation in a number of diseases, such as myocardial infarction, age-related cataract, different cancers, and ischemic stroke [reviewed in (101)]. Here, we were not able to find any significant KEGG pathway for *Miat*; therefore, how this lncRNA is involved in DM and other diseases still needs to be clarified.

Our systematic review indicates *Meg3* is downregulated in islets, whole blood, and serum of patients with DM (48, 53, 74). Accordingly, this lncRNA was downregulated in islets of db/db mice (105) and in serum of diabetic patients with DR compared to controls (74). However, it was upregulated in liver or primary hepatocytes of different T2DM murine models (59, 106). In a murine beta-cell line (MIN6), *Meg3* suppression led to increased apoptosis due to *caspase-3* and *Bax* upregulation and *Bcl2* downregulation (105). In addition, *Meg3* seems to regulate insulin synthesis and secretion since its blockade in murine beta-cells decreased the expression of key transcription factors involved in insulin synthesis (Pdx-1 and mafA); thus, decreasing insulin gene transcription (105). Besides apoptosis, our *in silico* analysis suggests this lncRNA is involved in PI3K/Akt, VEGF, and MAPK pathways.

Of note, our bioinformatics analysis also demonstrated that *Anril*, *Hotair*, *Malat1*, *Kcnq1ot1*, and *Meg3* regulate genes from the Kaposi sarcoma-associated herpes virus infection (KSHV) pathway. KSHV, also known as human herpesvirus 8, is a human tumor virus associated with the pathogenesis of Kaposi's sarcoma, primary effusion lymphoma, and Multicentric Castleman's disease. The KSHV pathway contains genes related to IFN antiviral response, inflammatory cytokines, and cell proliferation pathways [https://www.genome.jp/kegg/kegg2.html]. Interestingly, the association between KSHV and DM was previously reported by observational studies (107, 108). Cui et al. described that patients with T2DM had an elevated risk of KSHV (107). Accordingly, Piras et al. showed 58% of T2DM patients were seropositive for KSHV *vs.* 27% of the healthy subjects (108). Even though the mechanisms behind this association are unknown, this virus causes metabolic changes that might lead to altered insulin uptake and accumulation of neutral lipids in cells and also induce an impairment of the immune system [review in (109)], which are mechanisms related to DM pathogenesis.

Even though this systematic review indicates a group of lncRNAs consistently associated with DM and the pathways possible regulated by them, it has few limitations. First, there is no official nomenclature for lncRNAs; thus, we cannot exclude the possibility that we have lost some information. Second, some studies, especially those using RNAseq and microarrays technologies, did not inform which were the differentially expressed lncRNAs or their expression pattern (up- or downregulation) (19, 25, 44, 53, 54, 58, 66, 71, 76). Third, studies used different techniques to quantify lncRNA expressions and usually did not provide the expression values, only the pattern of expression of the dysregulated lncRNAs; therefore, making impossible to perform a reliable quantitative analysis of the data (meta-analysis). Fourth, most of the studies investigated lncRNAs in patients with T2DM or did not inform the type of DM, evidencing the lack of studies in T1DM population. In this context, four of the dysregulated lncRNAs found in this study were analyzed only in T2DM patients (*Anril*, *Hotair*, *Malat1*, and *Miat*). Thus, our results are more representative of this type of DM. Fifth, although six lncRNAs were consistently dysregulated in patients with DM compared to controls, it was not possible to perform a stratified analysis by tissue type since the number of studies that evaluated the same lncRNA in a given tissue is very small. Lastly, as commented above, *Anril*, *Hotair*, *Kcnq1ot1*, *Malat*, *Meg3*, and *Miat* lncRNAs seem to be dysregulated in patients with DR and DKD. However, most of the studies included in this systematic review did not report the percentage of patients with these diabetic chronic complications. Thus, here, it was impossible to evaluate if presence of diabetic chronic complications is impacting our results. Further studies are required to clarify this point.

In conclusion, our systematic review indicates that six lncRNAs are consistently dysregulated in DM, especially in patients with T2DM. This study also contributes to enlighten the pathways regulated by these lncRNAs and involved in the DM pathogenesis, such as PI3K/Akt, MAPK, apoptosis, AGE/RAGE, and FoxO. Although this systematic review included 53 studies which analyzed lncRNA expression in DM-related tissues, further studies are necessary to better understand the involvement of lncRNAs in the pathogenesis of this complex disease and its chronic complications. As much as lncRNAs seem to be good candidates as biomarkers and therapeutic targets for DM, further investigations on organ-specific distribution of these regulatory molecules may be useful to clarify their role in DM.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

CD designed the study, researched data, performed the analysis, and wrote the manuscript. NL researched data, performed the analysis, and reviewed the manuscript. NC researched data and

reviewed the manuscript. TA researched data, performed the bioinformatics analyses, contributed to discussion, and reviewed the manuscript. DC designed the study, contributed to the discussion, and wrote and reviewed the manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

This study was partially supported by grants from the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), Fundo de Incentivo à Pesquisa e Eventos (FIPE, number 2018-0470) at Hospital de Clínicas de Porto Alegre, Fundação de Amparo à Pesquisa do Estado do Rio Grande do Sul (FAPERGS) (Edital FAPERGS/CNPq 12/2014 PRONEX - Processo n° 16/2551 - 0000483-8), and Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES). DC is recipient of scholarships from CNPq, while CD and TSA are recipients from scholarships from CAPES, and NL is recipient of scholarships from FAPERGS.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2021.602597/full#supplementary-material

REFERENCES

1. American Diabetes Association - ADA. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2019. *Diabetes Care* (2019) 42:S13–28. doi: 10.2337/dc19-S002
2. International Diabetes Federation - IDF. *IDF Diabetes Atlas. 9th edn*. Brussels, Belgium: International Diabetes Federation (2019).
3. Katsarou A, Gudbjornsdottir S, Rawshani A, Dabelea D, Bonifacio E, Anderson BJ, et al. Type 1 diabetes mellitus. *Nat Rev Dis Primers* (2017) 3:17016. doi: 10.1038/nrdp.2017.16
4. Ilonen J, Lempainen J, Veijola R. The heterogeneous pathogenesis of type 1 diabetes mellitus. *Nat Rev Endocrinol* (2019) 15:635–50. doi: 10.1038/s41574-019-0254-y
5. Nyaga DM, Vickers MH, Jefferies C, Perry JK, O'Sullivan JM. The genetic architecture of type 1 diabetes mellitus. *Mol Cell Endocrinol* (2018) 477:70–80. doi: 10.1016/j.mce.2018.06.002
6. Zhang H, Pollin TI. Epigenetics Variation and Pathogenesis in Diabetes. *Curr Diabetes Rep* (2018) 18:121. doi: 10.1007/s11892-018-1091-4
7. Dhawan S, Natarajan R. Epigenetics and Type 2 Diabetes Risk. *Curr Diabetes Rep* (2019) 19:47. doi: 10.1007/s11892-019-1168-8
8. Loh M, Zhou L, Ng HK, Chambers JC. Epigenetic disturbances in obesity and diabetes: Epidemiological and functional insights. *Mol Metab* (2019) 27S:S33–41. doi: 10.1016/j.molmet.2019.06.011
9. Mattick JS, Makunin IV. Non-coding RNA. *Hum Mol Genet* (2006) 15(Spec No 1):R17–29. doi: 10.1093/hmg/ddl046
10. Guo J, Liu Z, Gong R. Long noncoding RNA: an emerging player in diabetes and diabetic kidney disease. *Clin Sci (Lond)* (2019) 133:1321–39. doi: 10.1042/CS20190372
11. St Laurent G, Wahlestedt C, Kapranov P. The Landscape of long noncoding RNA classification. *Trends Genet* (2015) 31:239–51. doi: 10.1016/j.tig.2015.03.007
12. Derrien T, Johnson R, Bussotti G, Tanzer A, Djebali S, Tilgner H, et al. The GENCODE v7 catalog of human long noncoding RNAs: analysis of their gene structure, evolution, and expression. *Genome Res* (2012) 22:1775–89. doi: 10.1101/gr.132159.111
13. Quinn JJ, Chang HY. Unique features of long non-coding RNA biogenesis and function. *Nat Rev Genet* (2016) 17:47–62. doi: 10.1038/nrg.2015.10
14. Chen X, Sun Y, Cai R, Wang G, Shu X, Pang W. Long noncoding RNA: multiple players in gene expression. *BMB Rep* (2018) 51:280–9. doi: 10.5483/BMBRep.2018.51.6.025
15. Sun M, Kraus WL. Minireview: Long noncoding RNAs: new "links" between gene expression and cellular outcomes in endocrinology. *Mol Endocrinol* (2013) 27:1390–402. doi: 10.1210/me.2013-1113
16. Paraskevopoulou MD, Hatzigeorgiou AG. Analyzing MiRNA-LncRNA Interactions. *Methods Mol Biol* (2016) 1402:271–86. doi: 10.1007/978-1-4939-3378-5_21
17. Akerman I, Tu Z, Beucher A, Rolando DMY, Sauty-Colace C, Benazra M, et al. Human Pancreatic beta Cell lncRNAs Control Cell-Specific Regulatory Networks. *Cell Metab* (2017) 25:400–11. doi: 10.1016/j.cmet.2016.11.016
18. Jin F, Wang N, Zhu Y, You L, Wang L, De W, et al. Downregulation of Long Noncoding RNA Gas5 Affects Cell Cycle and Insulin Secretion in Mouse Pancreatic β Cells. *Cell Physiol Biochem* (2018) 43:2062–73. doi: 10.1159/000484191
19. Ruan Y, Lin N, Ma Q, Chen R, Zhang Z, Wen W, et al. Circulating LncRNAs Analysis in Patients with Type 2 Diabetes Reveals Novel Genes Influencing Glucose Metabolism and Islet β-Cell Function. *Cell Physiol Biochem* (2018) 46:335–50. doi: 10.1159/000488434
20. Yan C, Chen J, Chen N. Long noncoding RNA MALAT1 promotes hepatic steatosis and insulin resistance by increasing nuclear SREBP-1c protein stability. *Sci Rep* (2016) 6:22640. doi: 10.1038/srep22640
21. Sathishkumar C, Prabu P, Mohan V, Balasubramanyam M. Linking a role of lncRNAs (long non-coding RNAs) with insulin resistance, accelerated senescence, and inflammation in patients with type 2 diabetes. *Hum Genomics* (2018) 12:41. doi: 10.1186/s40246-018-0173-3
22. Feng SD, Yang JH, Yao CH, Yang SS, Zhu ZM, Wu D, et al. Potential regulatory mechanisms of lncRNA in diabetes and its complications. *Biochem Cell Biol* (2017) 95:361–7. doi: 10.1139/bcb-2016-0110
23. Carter G, Miladinovic B, Patel AA, Deland L, Mastorides S, Patel NA. Circulating long noncoding RNA GAS5 levels are correlated to prevalence of type 2 diabetes mellitus. *BBA Clin* (2015) 4:102–7. doi: 10.1016/j.bbacli.2015.09.001
24. Erfanian Omidvar M, Ghaedi H, Kazerouni F, kalbasi S, Shanaki M, Miraalamy G, et al. Clinical significance of long noncoding RNA VIM-AS1 and CTBP1-AS2 expression in type 2 diabetes. *J Cell Biochem* (2019) 120:9315–23. doi: 10.1002/jcb.28206
25. Li X, Zhao Z, Gao C, Rao L, Hao P, Jian D, et al. The Diagnostic Value of Whole Blood lncRNA ENST000005503371 for Pre-Diabetes and Type 2 Diabetes Mellitus. *Exp Clin Endocrinol Diabetes* (2017) 125:377–83. doi: 10.1055/s-0043-100018
26. Mansoori Z, Ghaedi H, Sadatamini M, Vahabpour R, Rahimipour A, Shanaki M, et al. Downregulation of long non-coding RNAs LINC00523 and LINC00994 in type 2 diabetes in an Iranian cohort. *Mol Biol Rep* (2018) 45:1227–33. doi: 10.1007/s11033-018-4276-7
27. Saeidi L, Ghaedi H, Sadatamini M, Vahabpour R, Rahimipour A, Shanaki M, et al. Long non-coding RNA LY86-AS1 and HCG27_201 expression in type 2 diabetes mellitus. *Mol Biol Rep* (2018) 45(6):2601–8. doi: 10.1007/s11033-018-4429-8
28. Wang X, Chang X, Zhang P, Fan L, Zhou T, Sun K. Aberrant Expression of Long Non-Coding RNAs in Newly Diagnosed Type 2 Diabetes Indicates Potential Roles in Chronic Inflammation and Insulin Resistance. *Cell Physiol Biochem* (2017) 43:2367–78. doi: 10.1159/000484388
29. He X, Ou C, Xiao Y, Han Q, Li H, Zhou S. LncRNAs: Key players and novel insights into diabetes mellitus. *Oncotarget* (2017) 8:71325–41. doi: 10.18632/oncotarget.19921
30. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* (2000) 283:2008–12. doi: 10.1001/jama.283.15.2008

31. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* (2009) 339:b2535. doi: 10.1136/bmj.b2535
32. Cheng L, Wang P, Tian R, Wang S, Guo Q, Luo M, et al. LncRNA2Target v2.0: a comprehensive database for target genes of lncRNAs in human and mouse. *Nucleic Acids Res* (2019) 47:D140–4. doi: 10.1093/nar/gky1051
33. Li JH, Liu S, Zhou H, Qu LH, Yang JH. starBase v2.0: decoding miRNA-ceRNA, miRNA-ncRNA and protein-RNA interaction networks from large-scale CLIP-Seq data. *Nucleic Acids Res* (2014) 42:D92–7. doi: 10.1093/nar/gkt1248
34. Benjamini Y, Hochberg Y. Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. *J R Stat Soc.: Ser B (Methodol)* (1995) 57:289–300. doi: 10.1111/j.2517-6161.1995.tb02031.x
35. Rahmati S, Abovsky M, Pastrello C, Jurisica I. pathDIP: an annotated resource for known and predicted human gene-pathway associations and pathway enrichment analysis. *Nucleic Acids Res* (2017) 45:D419–26. doi: 10.1093/nar/gkw1082
36. Alikhah A, Pahlevan Kakhki M, Ahmadi A, Dehghanzad R, Boroumand MA, Behmanesh M. The role of lnc-DC long non-coding RNA and SOCS1 in the regulation of STAT3 in coronary artery disease and type 2 diabetes mellitus. *J Diabetes Its Complications* (2018) 32:342–8. doi: 10.1016/j.jdiacomp.2017.12.001
37. Chen SZ, Zhong HM, Wang Y, Wang ZH, Liang XQ, Li SQ, et al. The clinical significance of long non-coding RNA ANRIL level in diabetic retinopathy. *Acta Diabetol* (2019) 57:409–18. doi: 10.1007/s00592-019-01442-2
38. Chen Y, Tan S, Liu M, Li J. LncRNA TINCR is downregulated in diabetic cardiomyopathy and relates to cardiomyocyte apoptosis. *Scandinavian Cardiovasc J* (2018) 52:335–9. doi: 10.1080/14017431.2018.1546896
39. Cheng XW, Chen ZF, Wan YF, Zhou Q, Wang H, Zhu HQ. Long Non-coding RNA H19 Suppression Protects the Endothelium Against Hyperglycemic-Induced Inflammation via Inhibiting Expression of miR-29b Target Gene Vascular Endothelial Growth Factor a Through Activation of the Protein Kinase B/Endothelial Nitric Oxide Synthase Pathway. *Front Cell Dev Biol* (2019) 7:11. doi: 10.3389/fcell.2019.00263
40. Dai R, Sun Z, Qian Y, Zhang B, Han Y, Deng G. LncRNA LUADT1 inhibits cell apoptosis in diabetic retinopathy by regulating miR-383/peroxiredoxin 3 axis. *Arch Physiol Biochem* (2020) 1–6. doi: 10.1080/13813455.2020.1716016
41. Das S, Reddy MA, Senapati P, Stapleton K, Lanting L, Wang M, et al. Diabetes Mellitus-Induced Long Noncoding RNA Dnm3os Regulates Macrophage Functions and Inflammation via Nuclear Mechanisms. *Arterioscler Thrombosis Vasc Biol* (2018) 38:1806–20. doi: 10.1161/ATVBAHA.117.310663
42. de Gonzalo-Calvo D, Kenneweg F, Bang C, Toro R, van der Meer RW, Rijzewijk LJ, et al. Circulating long-non coding RNAs as biomarkers of left ventricular diastolic function and remodelling in patients with well-controlled type 2 diabetes. *Sci Rep* (2016) 6:37354. doi: 10.1038/srep37354
43. Esguerra JLS, Ofori JK, Nagao M, Shuto Y, Karagiannopoulos A, Fadista J, et al. Glucocorticoid induces human beta cell dysfunction by involving riborepressor GAS5 LincRNA. *Mol Metab* (2020) 32:160–7. doi: 10.1016/j.molmet.2019.12.012
44. Fadista J, Vikman P, Laakso EO, Mollet IG, Esguerra JL, Taneera J, et al. Global genomic and transcriptomic analysis of human pancreatic islets reveals novel genes influencing glucose metabolism. *Proc Natl Acad Sci U S A* (2014) 111:13924–9. doi: 10.1073/pnas.1402665111
45. Fawzy MS, Abdelghany AA, Toraih EA, Mohamed AM. Circulating long noncoding RNAs H19 and GAS5 are associated with type 2 diabetes but not with diabetic retinopathy: A preliminary study. *Bosnian J Basic Med Sci* (2020) 20(3):365–71. doi: 10.17305/bjbms.2019.4533
46. Gao Y, Wu F, Zhou J, Yan L, Jurczak MJ, Lee HY, et al. The H19/let-7 double-negative feedback loop contributes to glucose metabolism in muscle cells. *Nucleic Acids Res* (2014) 42:13799–811. doi: 10.1093/nar/gku1160
47. Jiao H, Xie D, Qiao Y. LncRNA PRINs is involved in the development of nephropathy in patients with diabetes via interaction with smad7. *Exp Ther Med* (2019) 17:3203–8. doi: 10.3892/etm.2019.7307
48. Kameswaran V, Bramswig NC, McKenna LB, Penn M, Schug J, Hand NJ, et al. Epigenetic regulation of the DLK1-MEG3 microRNA cluster in human type 2 diabetic islets. *Cell Metab* (2014) 19:135–45. doi: 10.1016/j.cmet.2013.11.016
49. Li M, Guo Y, Wang XJ, Duan BH, Li L. HOTAIR participates in hepatic insulin resistance via regulating SIRT1. *Eur Rev Med Pharmacol Sci* (2018) 22:7883–90. doi: 10.26355/eurrev_201811_16414
50. Li P, Zhang N, Ping F, Gao Y, Cao L. LncRNA SCAL1 inhibits inducible nitric oxide synthase in lung cells under high-glucose conditions. *Exp Ther Med* (2019) 18:1831–6. doi: 10.3892/etm.2019.7729
51. Wen X, Han XR, Wang YJ, Wang S, Shen M, Zhang ZF, et al. Down-regulated long non-coding RNA ANRIL restores the learning and memory abilities and rescues hippocampal pyramidal neurons from apoptosis in streptozotocin-induced diabetic rats via the NF-κB signaling pathway. *J Cell Biochem* (2018) 119:5821–33. doi: 10.1002/jcb.26769
52. Liu SX, Zheng F, Xie KL, Xie MR, Jiang LJ, Cai Y. Exercise Reduces Insulin Resistance in Type 2 Diabetes Mellitus via Mediating the lncRNA MALAT1/MicroRNA-382-3p/Resistin Axis. *Mol Ther Nucleic Acids* (2019) 18:34–44. doi: 10.1016/j.omtn.2019.08.002
53. Luo L, Ji LD, Cai JJ, Feng M, Zhou M, Hu SP, et al. Microarray Analysis of Long Noncoding RNAs in Female Diabetic Peripheral Neuropathy Patients. *Cell Physiol Biochem* (2018) 46:1209–17. doi: 10.1159/000489071
54. Ma Q, Wang L, Yang Y, Su Y, Wang T, Hou Q, et al. Association between lncRNA and GCKR gene in type 2 diabetes mellitus. *Clin Chim Acta* (2020) 501:66–71. doi: 10.1016/j.cca.2019.10.004
55. Mohamadi M, Ghaedi H, Kazerouni F, Erfanian Omidvar M, Kalbasi S, Shanaki M, et al. Deregulation of long noncoding RNA SNHG17 and TTC28-AS1 is associated with type 2 diabetes mellitus. *Scandinavian J Clin Lab Invest* (2019) 79:519–23. doi: 10.1080/00365513.2019.1664760
56. Morán I, Akerman I, Van De Bunt M, Xie R, Benazra M, Nammo T, et al. Human β cell transcriptome analysis uncovers lncRNAs that are tissue-specific, dynamically regulated, and abnormally expressed in type 2 diabetes. *Cell Metab* (2012) 16:435–48. doi: 10.1016/j.cmet.2012.08.010
57. Motterle A, Gattesco S, Peyot ML, Esguerra JLS, Gomez-Ruiz A, Laybutt DR, et al. Identification of islet-enriched long non-coding RNAs contributing to β-cell failure in type 2 diabetes. *Mol Metab* (2017) 6:1407–18. doi: 10.1016/j.molmet.2017.08.005
58. Pengyu Z, Yan Y, Xiying F, Maoguang Y, Mo L, Yan C, et al. The Differential Expression of Long Noncoding RNAs in Type 2 Diabetes Mellitus and Latent Autoimmune Diabetes in Adults. *Int J Endocrinol* (2020) 2020:12. doi: 10.1155/2020/9235329
59. Pradas-Juni M, Hansmeier NR, Link JC, Schmidt E, Larsen BD, Klemm P, et al. A MAFG-lncRNA axis links systemic nutrient abundance to hepatic glucose metabolism. *Nat Commun* (2020) 11:644. doi: 10.1038/s41467-020-14323-y
60. Reddy MA, Chen Z, Park JT, Wang M, Lanting L, Zhang Q, et al. Regulation of inflammatory phenotype in macrophages by a diabetes-induced long noncoding RNA. *Diabetes* (2014) 63:4249–61. doi: 10.2337/db14-0298
61. Ren S, Zhang Y, Li B, Bu K, Wu L, Lu Y, et al. Downregulation of lncRNA-SRA participates in the development of cardiovascular disease in type II diabetic patients. *Exp Ther Med* (2019) 17:3367–72. doi: 10.3892/etm.2019.7362
62. Shaker OG, Abdelaleem OO, Mahmoud RH, Abdelghaffar NK, Ahmed TI, Said OM, et al. Diagnostic and prognostic role of serum miR-20b, miR-17-3p, HOTAIR, and MALAT1 in diabetic retinopathy. *IUBMB Life* (2019) 71:310–20. doi: 10.1002/iub.1970
63. Toraih EA, Abdelghany AA, Abd El Fadeal NM, Al Ageeli E, Fawzy MS. Deciphering the role of circulating lncRNAs: RNCR2, NEAT2, CDKN2B-AS1, and PVT1 and the possible prediction of anti-VEGF treatment outcomes in diabetic retinopathy patients. *Graefes Arch Clin Exp Ophthalmol* (2019) 257:1897–913. doi: 10.1007/s00417-019-04409-9
64. Wan W, Wan W, Long Y, Li Q, Jin X, Wan G, et al. Physcion 8-O-β-glucopyranoside exerts protective roles in high glucose-induced diabetic retinopathy via regulating lncRNA NORAD/miR-125/STAT3 signalling. *Artif Cells Nanomed Biotechnol* (2020) 48:463–72. doi: 10.1080/21691401.2019.1709861
65. Wang L, Su N, Zhang Y, Wang G. Clinical significance of serum lncRNA cancer susceptibility candidate 2 (CASC2) for chronic renal failure in patients with type 2 diabetes. *Med Sci Monitor* (2018) 24:6079–84. doi: 10.12659/MSM.909510
66. Wang W, Liu H, Zhou S, Yu P. Differential expression of lncRNA MEG3 in patients with different glycometabolism and analysis of related functions. *Diabetes/Metabol Res Rev* (2018) 34:1–2.

67. Wang X, Cheng Y, Zhang P, Chang X, Sun K. Potentials of long non-coding RNAs to differentiate latent autoimmune diabetes in adults from type 2 diabetes. *Int J Clin Exp Med* (2020) 13:742–9.
68. Yang F, Qin Y, Wang Y, Li A, Lv J, Sun X, et al. LncRNA KCNQ1OT1 Mediates Pyroptosis in Diabetic Cardiomyopathy. *Cell Physiol Biochem Int J Exp Cell Physiol Biochem Pharmacol* (2018) 50:1230–44. doi: 10.1159/000494576
69. Yang F, Qin Y, Lv J, Wang Y, Che H, Chen X, et al. Silencing long non-coding RNA Kcnq1ot1 alleviates pyroptosis and fibrosis in diabetic cardiomyopathy. *Cell Death Dis* (2018) 9:13. doi: 10.1038/s41419-018-1029-4
70. Yang H, Kan QE, Su Y, Man H. Long Non-Coding RNA CASC2 Improves Diabetic Nephropathy by Inhibiting JNK Pathway. *Exp Clin Endocrinol Diabetes* (2018) 127(8):533–7. doi: 10.1055/a-0629-9958
71. Yang Y, Lv X, Fan Q, Wang X, Xu L, Lu X, et al. Analysis of circulating lncRNA expression profiles in patients with diabetes mellitus and diabetic nephropathy: Differential expression profile of circulating lncRNA. *Clin Nephrol* (2019) 92:25–35. doi: 10.5414/CN109525
72. Yin L, Sun Z, Ren Q, Su X, Zhang D. Long non-coding RNA BANCR is overexpressed in patients with diabetic retinopathy and promotes apoptosis of retinal pigment epithelial cells. *Med Sci Monitor* (2019) 25:2845–51. doi: 10.12659/MSM.913359
73. Zha T, Su F, Liu X, Yang C, Liu L. Role of Long Non-Coding RNA (LncRNA) LINC-PINT Downregulation in Cardiomyopathy and Retinopathy Progression Among Patients with Type 2 Diabetes. *Med Sci Monit* (2019) 25:8509–14. doi: 10.12659/MSM.918358
74. Zhang D, Qin H, Leng Y, Li X, Zhang L, Bai D, et al. LncRNA MEG3 overexpression inhibits the development of diabetic retinopathy by regulating TGF–β1 and VEGF. *Exp Ther Med* (2018) 16:2337–42. doi: 10.3892/etm.2018.6451
75. Zhang FF, Liu YH, Wang DW, Liu TS, Yang Y, Guo JM, et al. Obesity-induced reduced expression of the lncRNA ROIT impairs insulin transcription by downregulation of Nkx6.1 methylation. *Diabetologia* (2020) 63:811–24. doi: 10.1007/s00125-020-05090-y
76. Zhang L, Li R, He J, Yang Q, Wu Y, Huang J, et al. Co-expression analysis among microRNAs, long non-coding RNAs, and messenger RNAs to understand the pathogenesis and progression of diabetic kidney disease at the genetic level. *Methods* (2017) 124:46–56. doi: 10.1016/j.ymeth.2017.05.023
77. Zhang L, Wang YM. Expression and function of lncRNA ANRIL in a mouse model of acute myocardial infarction combined with type 2 diabetes mellitus. *J Chin Med Assoc* (2019) 82:685–92. doi: 10.1097/JCMA.0000000000000182
78. Zhang X, Zou X, Li Y, Wang Y. Downregulation of lncRNA BANCR participates in the development of retinopathy among diabetic patients. *Exp Ther Med* (2019) 17:4132–8. doi: 10.3892/etm.2019.7444
79. Zhang X, Shi E, Yang L, Fu W, Hu F, Zhou X. LncRNA AK077216 is downregulated in diabetic retinopathy and inhibited the apoptosis of retinal pigment epithelial cells by downregulating miR-383. *Endocrine J* (2019) 66:1011–6. doi: 10.1507/endocrj.EJ19-0080
80. Kato M, Natarajan R. Epigenetics and epigenomics in diabetic kidney disease and metabolic memory. *Nat Rev Nephrol* (2019) 15:327–45. doi: 10.1038/s41581-019-0135-6
81. Rosen ED, Kaestner KH, Natarajan R, Patti ME, Sallari R, Sander M, et al. Epigenetics and Epigenomics: Implications for Diabetes and Obesity. *Diabetes* (2018) 67:1923–31. doi: 10.2337/db18-0537
82. Ji P, Diederichs S, Wang W, Boing S, Metzger R, Schneider PM, et al. MALAT-1, a novel noncoding RNA, and thymosin beta4 predict metastasis and survival in early-stage non-small cell lung cancer. *Oncogene* (2003) 22:8031–41. doi: 10.1038/sj.onc.1206928
83. Dong Y, Liang G, Yuan B, Yang C, Gao R, Zhou X. MALAT1 promotes the proliferation and metastasis of osteosarcoma cells by activating the PI3K/Akt pathway. *Tumour Biol J Int Soc Oncodevelopmental Biol Med* (2015) 36:1477–86. doi: 10.1007/s13277-014-2631-4
84. Zhao G, Su Z, Song D, Mao Y, Mao X. The long noncoding RNA MALAT1 regulates the lipopolysaccharide-induced inflammatory response through its interaction with NF-kappaB. *FEBS Lett* (2016) 590:2884–95. doi: 10.1002/1873-3468.12315
85. Chen L, Feng P, Zhu X, He S, Duan J, Zhou D. Long non-coding RNA Malat1 promotes neurite outgrowth through activation of ERK/MAPK signalling pathway in N2a cells. *J Cell Mol Med* (2016) 20:2102–10. doi: 10.1111/jcmm.12904
86. Liu S, Yan G, Zhang J, Yu L. Knockdown of Long Noncoding RNA(lncRNA) Metastasis-Associated Lung Adenocarcinoma Transcript 1 (MALAT1) Inhibits Proliferation, Migration, and Invasion and Promotes Apoptosis by Targeting miR-124 in Retinoblastoma. *Oncol Res* (2018) 26:581–91. doi: 10.3727/096504017X14953948675403
87. Liang J, Liang L, Ouyang K, Li Z, Yi X. MALAT1 induces tongue cancer cells' EMT and inhibits apoptosis through Wnt/beta-catenin signaling pathway. *J Oral Pathol Med* (2017) 46:98–105. doi: 10.1111/jop.12466
88. Puthanveetil P, Chen S, Feng B, Gautam A, Chakrabarti S. Long non-coding RNA MALAT1 regulates hyperglycaemia induced inflammatory process in the endothelial cells. *J Cell Mol Med* (2015) 19:1418–25. doi: 10.1111/jcmm.12576
89. Liu JY, Yao J, Li XM, Song YC, Wang XQ, Li YJ, et al. Pathogenic role of lncRNA-MALAT1 in endothelial cell dysfunction in diabetes mellitus. *Cell Death Dis* (2014) 5:10. doi: 10.1038/cddis.2014.466
90. Toy HI, Okmen D, Kontou PI, Georgakilas AG, Pavlopoulou A. HOTAIR as a Prognostic Predictor for Diverse Human Cancers: A Meta- and Bioinformatics Analysis. *Cancers* (2019) 11:17. doi: 10.3390/cancers11060778
91. Tang Q, Hann SS. HOTAIR: An Oncogenic Long Non-Coding RNA in Human Cancer. *Cell Physiol Biochem* (2018) 47:893–913. doi: 10.1159/000490131
92. Hajjari M, Salavaty A. HOTAIR: an oncogenic long non-coding RNA in different cancers. *Cancer Biol Med* (2015) 12:1–9. doi: 10.7497/j.issn.2095-3941.2015.0006
93. Majumder S, Hadden MJ, Thieme K, Batchu SN, Niveditha D, Chowdhury S, et al. Dysregulated expression but redundant function of the long non-coding RNA HOTAIR in diabetic kidney disease. *Diabetologia* (2019) 62(11):2129–42. doi: 10.1007/s00125-019-4967-1
94. Kong Y, Hsieh CH, Alonso LC. ANRIL: A lncRNA at the CDKN2A/B Locus With Roles in Cancer and Metabolic Disease. *Front Endocrinol* (2018) 9:405. doi: 10.3389/fendo.2018.00405
95. Thomas AA, Feng B, Chakrabarti S. ANRIL: A Regulator of VEGF in Diabetic Retinopathy. *Invest Ophthalmol Visual Sci* (2017) 58:470–80. doi: 10.1167/iovs.16-20569
96. Ruiz MA, Feng B, Chakrabarti S. Polycomb repressive complex 2 regulates MiR-200b in retinal endothelial cells: potential relevance in diabetic retinopathy. *PLoS One* (2015) 10:e0123987. doi: 10.1371/journal.pone.0123987
97. Zhang B, Wang D, Ji TF, Shi L, Yu JL. Overexpression of lncRNA ANRIL up-regulates VEGF expression and promotes angiogenesis of diabetes mellitus combined with cerebral infarction by activating NF-kappaB signaling pathway in a rat model. *Oncotarget* (2017) 8:17347–59. doi: 10.18632/oncotarget.14468
98. Mitsuya K, Meguro M, Lee MP, Katoh M, Schulz TC, Kugoh H, et al. LIT1, an imprinted antisense RNA in the human KvLQT1 locus identified by screening for differentially expressed transcripts using monochromosomal hybrids. *Hum Mol Genet* (1999) 8:1209–17. doi: 10.1093/hmg/8.7.1209
99. Kassem SA, Ariel I, Thornton PS, Hussain K, Smith V, Lindley KJ, et al. p57 (KIP2) expression in normal islet cells and in hyperinsulinism of infancy. *Diabetes* (2001) 50:2763–9. doi: 10.2337/diabetes.50.12.2763
100. Liu J, Wang F, Wu Y, Huang X, Sheng L, Xu J, et al. Meta-analysis of the effect of KCNQ1 gene polymorphism on the risk of type 2 diabetes. *Mol Biol Rep* (2013) 40:3557–67. doi: 10.1007/s11033-012-2429-7
101. Sun C, Huang L, Li Z, Leng K, Xu Y, Jiang X, et al. Long non-coding RNA MIAT in development and disease: a new player in an old game. *J BioMed Sci* (2018) 25:23. doi: 10.1186/s12929-018-0427-3
102. Yan B, Yao J, Liu JY, Li XM, Wang XQ, Li YJ, et al. lncRNA-MIAT regulates microvascular dysfunction by functioning as a competing endogenous RNA. *Circ Res* (2015) 116:1143–56. doi: 10.1161/CIRCRESAHA.116.305510
103. Zhou X, Zhang W, Jin M, Chen J, Xu W, Kong X. lncRNA MIAT functions as a competing endogenous RNA to upregulate DAPK2 by sponging miR-22-3p in diabetic cardiomyopathy. *Cell Death Dis* (2017) 8:e2929. doi: 10.1038/cddis.2017.321
104. Zhou L, Xu DY, Sha WG, Shen L, Lu GY, Yin X. Long non-coding MIAT mediates high glucose-induced renal tubular epithelial injury. *Biochem Biophys Res Commun* (2015) 468:726–32. doi: 10.1016/j.bbrc.2015.11.023
105. You L, Wang N, Yin D, Wang L, Jin F, Zhu Y, et al. Downregulation of Long Noncoding RNA Meg3 Affects Insulin Synthesis and Secretion in Mouse

Pancreatic Beta Cells. *J Cell Physiol* (2016) 231:852–62. doi: 10.1002/jcp.25175

106. Zhu X, Wu YB, Zhou J, Kang DM. Upregulation of lncRNA MEG3 promotes hepatic insulin resistance via increasing FoxO1 expression. *Biochem Biophys Res Commun* (2016) 469:319–25. doi: 10.1016/j.bbrc.2015.11.048
107. Cui M, Fang Q, Zheng J, Shu Z, Chen Y, Fan Y, et al. Kaposi's sarcoma-associated herpesvirus seropositivity is associated with type 2 diabetes mellitus: A case-control study in Xinjiang, China. *Int J Infect Dis* (2019) 80:73–9. doi: 10.1016/j.ijid.2019.01.003
108. Piras E, Madeddu MA, Palmieri G, Angius F, Contini P, Pompei R, et al. High Prevalence of Human Herpesvirus 8 Infection in Diabetes Type 2 Patients and Detection of a New Virus Subtype. *Adv Exp Med Biol* (2017) 973:41–51. doi: 10.1007/5584_2016_73
109. Pompei R. The Role of Human Herpesvirus 8 in Diabetes Mellitus Type 2: State of the Art and a Medical Hypothesis. *Adv Exp Med Biol* (2016) 901:37–45. doi: 10.1007/5584_2015_5014

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

SUPPLEMENTARY MATERIAL

Supplementary Table 1. Characteristics of patients of the studies included in the systematic review.

Supplementary Table 2. LncRNAs analyzed in human samples.

Supplementary Table 3. Target genes of the consistently dysregulated lncRNAs in DM patients.

Supplementary table 4. Significantly KEGG pathways regulated by the target genes of the lncRNAs dysregulated in DM patients.

Supplementary Table 1. Characteristics of patients of the studies included in the systematic review.

Author, year [Reference]	Sample size Case/Control	Tissue	Gender (% males) Case/control	Age (case/control)	Country
Akerman, 2017 [17]	10 T2DM patients / 50 controls	Pancreatic islets	55.6 / 53.7	57.0 ± 4.0 / 59.0 ± 9.0	Sweden
Alikhah, 2018 [95]	18 T2DM patients / 18 controls	PBMCs	NA	NA	Iran
Carter, 2015 [23]	5 T2DM patients / 5 controls 47 T2DM patients / 49 controls (validation)	Serum	NA	70.3 ± 9.1 / 66.9 ± 9.7	United States
Chen, 2019 [96]	25 DM patients/ 20 controls	Serum	48.0 / 50.0	59.5 ± 9.0 / 55.7 ± 10.1	China
Chen, 2018 [74]	27 DM patients/ 17 controls	Serum	51.8 / 52.9	44.4 ± 5.7 / 41.9 ± 6.2	China
Cheng, 2019 [36]	30 DM patients/ 30 controls	Peripheral blood	NA	NA	China

Dai, 2020 [97]	60 T2DM patients/ 60 controls	Plasma	63.3 / 63.3	44.2 ± 5.0 / 44.3 ± 5.1	China
Das, 2018 [37]	5 T2DM patients / 5 controls	PBMCs	NA	NA	United States
De Gonzalo-Calvo, 2016 [59]	48 T2DM patients / 12 controls	Serum	NA	57.5 ± 5.4 / 57.7 ± 6.7	Netherlands
Erfanian Omidvar, 2019 [24]	100 T2DM patients/ 100	PBMCs	52.0 / 65.0	54.5 ± 8.7 / 52.2 ± 8.5	Iran
Esguerra, 2020 [38]	9 T2DM patients / 10 controls	Pancreatic islets	40.0 /50.0	49.3 / 56.9	Sweden
Fadista, 2014 [56]	12 T2DM patients / 51 controls	Pancreatic islets	50.0 / 64.7	61.0 ± 10.0 / 56.0 ± 12.0	Sweden
Fawzy, 2020 [98]	53 T2DM patients / 110 controls	Plasma	79.2 / 25.5	62.6 ± 7.3 / 60.5 ± 10.7	Egypt
Gao, 2014 [39]	5 T2DM patients / 4 controls	Lateral quadríceps muscle biopsy	40.0 / 25.0	63.0 / 24.7	China
Jiao, 2019 [40]	43 DM patients / 48 controls	Serum	55.8 / 56.2	48.4 ± 7.1 / 48.1 ± 6.2	China
Kameswaran, 2014 [41]	4 T2DM patients / 3 controls	Pancreatic islets	50.0 / 33.3	53.2 / 35.3	United States

Li, 2018 [51]	10 T2DM patients / 10 controls	Liver biopsy	50.0 / 60.0	45.6 ± 7.4 / 48.2 ± 4.2	China
Li, 2019 [99]	56 T2DM patients/ 40 controls	Serum	53.6 / 65.0	44.8 ± 5.2 / 46.0 ± 6.4	China
Li, 2018 [100]	63 DM patients / 56 controls	Plasma	57.1 / 57.1	46.1 ± 6.5 / 45.3 ± 7.2	China
Li, 2017 [25]	6 T2DM patients / 6 controls 20 T2DM patients / 20 controls (validation)	Peripheral blood	NA	NA	China
Liu, 2019 [47]	90 T2DM patients / 30 controls	Serum	62.2 / 53.3	55.5 ± 9.8 / 53.6 ± 9.2	China
Luo, 2018 [64]	6 T2DM patients / 6 controls 26 T2DM patients / 26 controls (validation)	PBMCs	NA	NA	China
Ma, 2020 [57]	5 T2DM patients / 5 controls 122 T2DM patients / 125 controls (validation)	PBMCs	NA	54.3 ± 9.8 / 48.3 ± 10.2	China

Mansoori, 2018 [26]	100 T2DM patients / 100 controls	PBMCs	NA	60.9 ± 0.9 / 58.1 ± 1.2	Iran
Mohamadi, 2019 [58]	100 T2DM patients / 100 controls	PBMCs	52.0 / 65.0	54.5 ± 8.7 / 52.2 ± 8.5	Iran
Móran, 2012 [83]	16 T2DM patients / 19 controls	Pancreatic islets	37.5 / 50.0	55.5 / 49.2	France
Motterle, 2017 [42]	10 T2DM patients / 10 controls	Pancreatic islets	50.0 / 50.0	55.5 ± 3.0 / 56.9 ± 2.5	Switzerland
Pengyu, 2020 [53]	4 T2DM patients / 4 controls	Serum	NA	NA	China
Pradas-Juni, 2020 [55]	4 T2DM patients / 4 controls	Liver	100.0 / 100.0	75.5 ± 0.7 / 60.7 ± 9.0	Germany
Reddy, 2014 [43]	4 T2DM patients / 4 controls	Monocytes	NA	43.2 ± 6.3 / 37.5 ± 3.8	United States
Ren, 2019 [101]	178 T2DM patients / 44 controls	Plasma	53.7 / 61.3	46.2 ± 6.2 / 46.7 ± 5.5	China
Ruan, 2018 [19]	3 T2DM patients / 3 controls 30 T2DM patients / 30 controls (validation)	Blood	66.6 / 46.6	42.2 ± 9.7 / 48.9 ± 10.5	China

	30 T2DM patients / 30 controls	Exosome serum/ exosome-free serum			
Saeidi, 2018 [27]	100 T2DM patients/ 100 controls	PBMCs	36.0 / 35.0	60.90± 0.9 / 58.1 ± 1.2	Iran
Sathishkumar, 2018 [21]	30 T2DM patients /32 controls	PBMCs	56.2 / 60.0	46 ± 8 / 44 ± 8	India
Shaker, 2019 [65]	30 T2DM patients / 81 controls	Blood	63.3 / 66.6	51.0 ± 6.1 / 50.7 ± 7.7	Egypt
Toraih, 2019 [60]	55 T2DM patients/ 108 controls	Plasma	26.9 / 56.5	60.8 ± 8.7 / 59.2 ± 5.6	Egypt
Wan, 2020 [44]	32 T2DM patients / 32 controls	Serum	59.4 / 62.5	45.1 ± 5.6 / 43.5 ± 6.6	China
Wang, 2018 [102]	296 T2DM patients / 56 controls	Serum	56.1 / 53.6	47.4 ± 6.1 / 49.5 ± 7.7	China
Wang, 2018 [54]*	2 T2DM patients / 2 controls	Blood	NA	NA	China
Wang, 2017 [28]	6 T2DM patients / 6 controls 60 T2DM patients / 60 controls (validation)	Peripheral blood	61.7 / 58.3	50.4 ± 13.4 / 51.0 ± 9.0	China

Wang, 2020 [61]	156 T2DM / 100 controls	Peripheral blood	62.2 / 57.0	53.3 ± 11.7 / 51.8 ± 9.6	China
Yang, 2018 [52]	8 DM patients / 8 controls	Serum	NA	NA	China
Yang, 2018 [46]	6 DM patients / 6 controls	Serum	NA	NA	China
Yang, 2018 [103]	36 DM patients / 41 controls	Serum	NA	NA	China
Yang, 2019 [94]	DM patients / controls	Serum	NA	NA	China
Yin, 2019 [104]	62 DM patients / 48 controls	Plasma	54.8 / 47.9	47.9 ± 6.9 / 48.8 ± 6.1	China
Zha, 2019 [45]	244 T2DM patients / 126 controls	Plasma	56.1 / 53.9	48.2±5.6 / 48.9±5.3	China
Zhang, 2018 [48]	28 DM patients / 30 controls	Serum	42.8 / 36.6	53 ± 14.1 / 54 ± 13.7	China
Zhang, 2020 [49]	99 T2DM patients / 50 controls	Serum	50.5 / 54.0	53.1 ± 9.2 /50.9 ± 6.8	China
Zhang, 2017 [93]	30 DM patients / 28 controls	Plasma	60.0 / 60.7	53.2 ± 7.8 / 33.1 ± 10.8	China
Zhang, 2019 [50]	24 T2DM patients / 26 controls	Serum	NA	NA	China

Zhang, 2019 [105]	244 T2DM patients / 102 controls	Plasma	54.5 / 53.6	46.4 ± 5.5 / 48.1 ± 6.2	China
Zhang, 2019 [106]	60 DM patients / 60 controls	Plasma	56.6 / 58.3	49.1 ± 6.3 / 51.9 ± 6.7	China

*Abstract from congress. DM: diabetes mellitus; NA: not available; PBMCs: Peripheral blood mononuclear cells; T2DM: type 2 diabetes mellitus.

Supplementary Table 2. LncRNAs analyzed in human samples.

lncRNA identity	First author, year	Tissue	Change of expression
ADORA2A-AS1 / ENSG00000178803	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ALKBH3-AS1 / ENSG00000244926	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
APOA1-AS / ENSG00000235910	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ASO2208	Li, X. 2017	Peripheral blood from T2DM patients	Up
BAZ2B / ENSG00000226266	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
C1QTNF-AS1 / ENSG00000265096	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
C1RL-AS1 / ENSG00000205885	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
C7orf13 / ENSG00000182648	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
CDKN2BAS1/ANRIL	Zhang, L. 2019	Serum from T2DM patients	Up
CDKN2BAS1/ANRIL	Sathishkumar, C. 2018	PBMCs from T2DM patients	Up
CDKN2BAS1/ANRIL	Toraih, E.A. 2019	Plasma from T2DM patients	Up
CRHR1-IT1	Fadista, J. 2014	Pancreatic islets	NI
CRNDE	Fadista, J. 2014	Pancreatic islets	NI
CTBP1-AS2	Erfanian Omidvar M, 2018	PBMCs from T2DM patients	Down
CTD-2270F17.1 / ENSG00000253647	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
CYP1B1-AS1 / ENSG00000232973	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
DANT2 / ENSG00000235244	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
DKFZp779M0652 / ENSG00000205106	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
DLGAP1-AS1	Fadista, J. 2014	Pancreatic islets	NI
DLX6-AS1	Fadista, J. 2014	Pancreatic islets	NI
DNAJC27-AS1 / ENSG00000224165	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
Dnm3os	Das, S. 2018	CD14+ monocytes from T2DM patients	Up
DPYD-AS1 / ENSG00000232878	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
DSG1-AS1 / ENSG00000266729	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
E330013P06	Reddy, MA. 2014	Bone marrow-derived macrophages from T2DM patients	Up
EIF2B5-AS1 / ENSG00000230215	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000166770	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
ENSG00000167046	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
ENSG00000176659	Pradas-Juni, M. 2020	Liver from T2DM patients	Up

ENSG00000176912	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
ENSG00000176984	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000179141	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000179577	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000187229	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000188525	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
ENSG00000188825	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000196634	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000197099	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000203441	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000203643	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000203709	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000204860	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
ENSG00000204960	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000205181	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
ENSG00000205663	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
ENSG00000205664	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
ENSG00000205790	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000205971	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000213373	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000214039	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000214184	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000214870	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
ENSG00000218537	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000222017	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000223387	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000223511	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
ENSG00000223525	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000223634	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
ENSG00000223754	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000223901	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000224043	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000224220	Pradas-Juni, M. 2020	Liver from T2DM patients	Down

ENSG00000224272	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000224596	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000224794	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000224822	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000224943	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000224959	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
ENSG00000225299	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000225855	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000226163	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000226179	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000226200	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000226263	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
ENSG00000226291	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000226899	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000227258	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000227306	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000227527	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000227531	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000227544	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
ENSG00000227589	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000227681	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000227712	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000227719	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000227733	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
ENSG00000227773	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000227959	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
ENSG00000228013	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000228065	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000228271	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
ENSG00000228323	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
ENSG00000228368	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000228434	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000228862	Pradas-Juni, M. 2020	Liver from T2DM patients	Down

ENSG00000228919	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
ENSG00000228923	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000229017	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000229227	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000229393	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000229719	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000229862	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000229893	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000229996	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000230325	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000230435	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000230550	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000230612	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000230731	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000230815	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000230836	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000231013	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
ENSG00000231064	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000231134	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000231420	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000231731	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000231890	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000232283	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000232300	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000232470	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000232518	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000232533	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
ENSG00000232611	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000232667	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000232721	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000233058	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000233340	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000233376	Pradas-Juni, M. 2020	Liver from T2DM patients	Down

ENSG00000233695	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
ENSG00000233817	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
ENSG00000233985	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000234015	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000234427	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000234449	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
ENSG00000234509	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000234665	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
ENSG00000234675	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000234832	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000234938	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000235099	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000235245	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000235381	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000235532	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000235781	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000236039	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000236209	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000236341	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000236345	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
ENSG00000236514	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000236758	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000236924	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000237076	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000237188	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000237371	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000237390	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000237556	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000237768	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000238156	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
ENSG00000240219	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000240859	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
ENSG00000241169	Pradas-Juni, M. 2020	Liver from T2DM patients	Down

ENSG00000241213	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000241754	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000242086	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000242861	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000243368	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000244128	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000244675	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000245080	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000245694	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
ENSG00000245768	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000246790	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000246851	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000246982	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000247134	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
ENSG00000247373	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000247735	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000248029	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000248092	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000248161	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000248242	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000248359	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000248408	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000248458	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000248884	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000248898	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000248975	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000249173	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000249258	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000249352	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000249359	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000249395	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000249588	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000249614	Pradas-Juni, M. 2020	Liver from T2DM patients	Down

ENSG00000249618	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
ENSG00000249684	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000249790	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000250101	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000250141	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000250413	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
ENSG00000250658	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000250696	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000250893	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000250903	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000251161	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
ENSG00000251487	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
ENSG00000251603	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000251637	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000253196	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000253301	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
ENSG00000253666	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
ENSG00000253821	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000253878	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
ENSG00000254042	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000254162	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000254362	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000254485	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000254687	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000254787	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
ENSG00000254826	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000254859	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000254898	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000255270	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000255462	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
ENSG00000255671	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000256020	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
ENSG00000256139	Pradas-Juni, M. 2020	Liver from T2DM patients	Down

ENSG00000256151	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000256287	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
ENSG00000256403	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000256473	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000256560	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000256637	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000256694	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000256969	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
ENSG00000256995	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
ENSG00000257221	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
ENSG00000257345	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000257443	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000257808	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000257894	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000257925	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
ENSG00000257940	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
ENSG00000258082	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
ENSG00000258096	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
ENSG00000258407	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
ENSG00000258460	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000258498	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000258604	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000258623	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000258667	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
ENSG00000258694	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000258744	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000258768	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000259038	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
ENSG00000259291	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000259334	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000259343	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000259418	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000259498	Pradas-Juni, M. 2020	Liver from T2DM patients	Up

ENSG00000259583	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
ENSG00000259594	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000259967	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000259999	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000260236	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000260340	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000260362	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000260528	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000260855	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000260891	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000260923	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000260975	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000261051	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
ENSG00000261058	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000261096	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000261172	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
ENSG00000261200	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000261211	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000261216	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000261275	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
ENSG00000261404	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000261441	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
ENSG00000261469	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000261734	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000261789	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000261816	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000262115	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
ENSG00000262410	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000262881	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000262995	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000263089	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000263466	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000263590	Pradas-Juni, M. 2020	Liver from T2DM patients	Up

ENSG00000263698	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000263904	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000264546	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000264895	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000265743	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
ENSG00000265799	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000266445	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000266602	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
ENSG00000266664	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
ENSG00000267002	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000267196	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000267284	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000267286	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000267325	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
ENSG00000267610	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000267675	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
ENSG00000267726	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000267749	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000267787	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000267868	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000268683	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000268707	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
ENSG00000269044	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000269102	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000269289	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
ENSG00000269353	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000269524	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000269752	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000269976	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
ENSG00000270403	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
ENSG00000270487	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000270607	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000270933	Pradas-Juni, M. 2020	Liver from T2DM patients	Down

ENSG00000270956	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000271420	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000271715	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000271771	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000271806	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000271828	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000271874	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000271916	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
ENSG00000272189	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
ENSG00000272320	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000272430	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000272505	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000272506	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000272555	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000272663	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
ENSG00000272689	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000272732	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000272789	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
ENSG00000272840	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000272909	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000272927	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
ENSG00000272933	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
ENSG00000272970	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
ENSG00000272989	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
ENSG00000273138	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000273142	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000273151	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000273271	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000273295	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000273350	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000273407	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000273437	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000273448	Pradas-Juni, M. 2020	Liver from T2DM patients	Down

ENSG00000273582	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000273669	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
ENSG00000273824	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000273901	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000274080	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000274173	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
ENSG00000274225	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000274354	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
ENSG00000274685	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000274825	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000274827	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000275216	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000275236	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000275294	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000275392	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
ENSG00000275426	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000275438	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
ENSG00000275894	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
ENSG00000275897	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000275995	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000276107	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
ENSG00000276337	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000276403	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
ENSG00000276434	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000276488	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000276651	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000276854	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000276980	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000277020	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000277697	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000278000	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000278192	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
ENSG00000278464	Pradas-Juni, M. 2020	Liver from T2DM patients	Up

ENSG00000279159	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000279217	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000279440	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
ENSG00000279442	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000279548	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000280007	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000280018	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000280191	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
ENSG00000280207	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000280279	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000280384	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000280434	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000280721	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
ENSG00000281538	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENSG00000282793	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ENST00000364558	Pengyu, Z. 2020	Serum from T2DM patients	Up
ENST00000431705.1	Li, X. 2017	Peripheral blood from T2DM patients	Up
ENST00000451350.1	Li, X. 2017	Peripheral blood from T2DM patients	Down
ENST00000506795.1	Li, X. 2017	Peripheral blood from T2DM patients	Up
ENST00000512246.1	Li, X. 2017	Peripheral blood from T2DM patients	Up
ENST00000539163.1	Li, X. 2017	Peripheral blood from T2DM patients	Up
ENST00000550337.1	Li, X. 2017	Peripheral blood from T2DM patients	Up
ENST00000550337.1	Sathishkumar, C. 2018	PBMCs from T2DM patients	Up
ENST00000565382	Pengyu, Z. 2020	Serum from T2DM patients	Down
ENST00000583854.1	Li, X. 2017	Peripheral blood from T2DM patients	Up
ENST00000588058.1	Li, X. 2017	Peripheral blood from T2DM patients	Up
ENST00000588707.1	Ma, Q. 2019	PBMCs from T2DM patients	Down
ENST00000608916	Pengyu, Z. 2020	Serum from T2DM patients	Up
FLJ22447 / ENSG00000232774	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
FZD10-AS1	Fadista, J. 2014	Pancreatic islets	NI
Gas5	Carter, G. 2015	Serum from T2DM patients	Down
Gas5	Esguerra, JLS. 2020	Islets from T2DM patients	Up
Gas5	Fawzy, MS. 2020	Plasma from T2DM patients	Down

Gas5	Sathishkumar, C. 2018	PBMCs from T2DM patients	Up
GDNF-AS1 / ENSG00000248587	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
H19	Cheng, X. 2019	Peripheral blood from DM patients	Up
H19	Fawzy, MS. 2020	Plasma from T2DM patients	Up
H19	Gao, Y. 2014	Muscle from T2DM patients	Down
HAS2-AS1	Fadista, J. 2014	Pancreatic islets	NI
HCG27_201	Saeidi, L. 2018	PBMCs from T2DM patients	Down
HCP5 / ENSG00000206337	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
HI-LNC1107	Akerman, I. 2017	Islets from T2DM patients	Down
HI-LNC2346	Akerman, I. 2017	Islets from T2DM patients	Down
HI-LNC2579	Akerman, I. 2017	Islets from T2DM patients	Down
HI-LNC2634	Akerman, I. 2017	Islets from T2DM patients	Down
HI-LNC2867	Akerman, I. 2017	Islets from T2DM patients	Down
HI-LNC2972	Akerman, I. 2017	Islets from T2DM patients	Down
HI-LNC3113	Akerman, I. 2017	Islets from T2DM patients	Down
HI-LNC3613	Akerman, I. 2017	Islets from T2DM patients	Down
HI-LNC4105	Akerman, I. 2017	Islets from T2DM patients	Down
HI-LNC45	Morán, I. 2012.	Islets from T2DM patients	Down
HI-LNC4554	Akerman, I. 2017	Islets from T2DM patients	Down
HI-LNC4564	Akerman, I. 2017	Islets from T2DM patients	Down
HI-LNC4567	Akerman, I. 2017	Islets from T2DM patients	Down
HI-LNC683	Akerman, I. 2017	Islets from T2DM patients	Down
HI-LNC71/PLUTO	Akerman, I. 2017	Islets from T2DM patients	Down
HI-LNC71/PLUTO	Sathishkumar, C. 2018	PBMCs from T2DM patients	Up
HI-LNC780	Akerman, I. 2017	Islets from T2DM patients	Down
HI-LNC79	Akerman, I. 2017	Islets from T2DM patients	Down
HIPK1-AS1 / ENSG00000235527	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
Hotair	Li, M. 2018	Liver from T2DM patients	Up
Hotair	Sathishkumar, C. 2018	PBMCs from T2DM patients	Up
Hotair	Shaker, OG. 2018	Blood from T2DM patients	Up
HRAT92 / ENSG00000223855	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
HS1BP3-IT1 / ENSG00000231948	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
HTR2A-AS1 / ENSG00000224517	Pradas-Juni, M. 2020	Liver from T2DM patients	Down

IGF2-AS / ENSG00000099869	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ITGB2-AS1 / ENSG00000227039	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
JAKMIP2-AS1 / ENSG00000280780	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
KCNMA1-AS2 / ENSG00000225497	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
Kcnq1ot1	Morán, I. 2012.	Islets from T2DM patients	Up
Kcnq1ot1	Yang, F. 2018[a]	Serum from DM patients	Up
Kcnq1ot1	Yang, F. 2018[b]	Serum from DM patients	Up
KCTD21-AS1 / ENSG00000246174	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
KRTAP5-AS1 / ENSG00000233930	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
LET	Sathishkumar, C. 2018	PBMCs from T2DM patients	Up
LINC00035	Fadista, J. 2014	Pancreatic islets	NI
LINC00239	Fadista, J. 2014	Pancreatic islets	NI
LINC00240 / ENSG00000224843	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
LINC00313 / ENSG00000185186	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
LINC00399 / ENSG00000229792	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
LINC00479	Fadista, J. 2014	Pancreatic islets	NI
LINC00485 / ENSG00000258169	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
LINC00524 / ENSG00000259023	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
LINC00528 / ENSG00000269220	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
LINC00540 / ENSG00000276476	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
LINC00562 / ENSG00000260388	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
LINC00574 / ENSG00000231690	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
LINC00589 / ENSG00000251191	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
LINC00896 / ENSG00000236499	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
LINC00960 / ENSG00000242516	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
Linc00994	Mansoori, Z. 2018	PBMCs from T2DM patients	Down
LINC01018 / ENSG00000250056	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
LINC01126 / ENSG00000279873	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
LINC01410 / ENSG00000238113	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
LINC01441 / ENSG00000224008	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
LINC01443 / ENSG00000266554	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
LINC01561 / ENSG00000177234	Pradas-Juni, M. 2020	Liver from T2DM patients	Up

LINC01569 / ENSG00000262468	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
LINC01609 / ENSG00000253103	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
Linc0523	Mansoori, Z. 2018	PBMCs from T2DM patients	Down
Lincp21	Sathishkumar, C. 2018	PBMCs from T2DM patients	Up
Lnc PINT	Zha, T. 2019	Plasma from T2DM patients	Down
LncRNA PRINS	Jiao, H. 2019	Serum from DM patients	Up
LncRNAp3134	Ruan, Y. 2018	Blood from T2DM patients	Up
LncRNAp3134	Ruan, Y. 2018	Exosome serum from T2DM patients	Up
LOC100129175 / ENSG00000224090	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
LOC100130111 / ENSG00000256802	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
LOC100130417 / ENSG00000223764	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
LOC100131635 / ENSG00000228804	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
LOC100133286 / ENSG00000230212	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
LOC100133985	Fadista, J. 2014	Pancreatic islets	NI
LOC100288846 / ENSG00000258940	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
LOC100506082 / ENSG00000254480	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
LOC100506085 / ENSG00000248319	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
LOC100506585 / ENSG00000233038	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
LOC100507053 / ENSG00000246090	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
LOC100996286 / ENSG00000245954	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
LOC101927124 / ENSG00000250365	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
LOC101927138 / ENSG00000227599	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
LOC101927587 / ENSG00000233008	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
LOC101927653 / ENSG00000257259	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
LOC101927683 / ENSG00000236497	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
LOC101927746 / ENSG00000232445	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
LOC101927768 / ENSG00000228624	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
LOC101927815 / ENSG00000254319	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
LOC101927843 / ENSG00000233215	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
LOC101927907 / ENSG00000234653	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
LOC101928137 / ENSG00000258123	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
LOC101928651 / ENSG00000248529	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
LOC101928694 / ENSG00000259293	Pradas-Juni, M. 2020	Liver from T2DM patients	Down

LOC101928731 / ENSG00000258274	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
LOC101928737 / ENSG00000260750	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
LOC101928782 / ENSG00000224865	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
LOC101928791 / ENSG00000258826	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
LOC101928880 / ENSG00000260420	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
LOC101928947 / ENSG00000264968	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
LOC101929384 / ENSG00000256577	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
LOC101929415 / ENSG00000254254	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
LOC101929475 / ENSG00000229656	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
LOC101929592 / ENSG00000229444	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
LOC101929710 / ENSG00000251314	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
LOC101930100 / ENSG00000278932	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
LOC101930452 / ENSG00000260423	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
LOC102546228 / ENSG00000248107	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
LOC102723493 / ENSG00000259347	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
LOC102724058 / ENSG00000236107	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
LOC102724190 / ENSG00000258819	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
LOC102724913 / ENSG00000265352	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
LOC102724927 / ENSG00000262185	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
LOC102724933 / ENSG00000258171	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
LOC105370489 / ENSG00000258843	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
LOC105370792 / ENSG00000174171	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
LOC105372751 / ENSG00000237484	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
LOC105374524 / ENSG00000248837	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
LOC105378405 / ENSG00000227896	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
LOC105379695 / ENSG00000272273	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
LOC116437	Fadista, J. 2014	Pancreatic islets	NI
LOC151475 / ENSG00000226125	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
LOC283177	Fadista, J. 2014	Pancreatic islets	NI
LOC283575 / ENSG00000246548	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
LOC643623 / ENSG00000224506	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
LY86_AS1	Saeidi, L. 2018	PBMCs from T2DM patients	Down
MALAT1	Liu, SX. 2019	Serum from T2DM patients	Up

MALAT1	Luo, L. 2018	PBMCs from T2DM patients	Up
MALAT1	Sathishkumar, C. 2018	PBMCs from T2DM patients	Up
MALAT1	Shaker, OG. 2018	Blood from T2DM patients	Up
MALAT1	Toraih, E.A. 2019	Plasma from T2DM patients	Up
MANEA-AS1 / ENSG00000261366	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
MEG3	Kameswaran, V. 2014	Islets from T2DM patients	Down
MEG3	Luo, L. 2018	PBMCs from T2DM patients	Down
MEG3	Sathishkumar, C. 2018	PBMCs from T2DM patients	Up
MEG3	Zhang, D. 2018	Serum from DM patients	Down
Miat	De Gonzalo-Calvo, 2016	Serum from T2DM patients	Up
Miat	Sathishkumar, C. 2018	PBMCs from T2DM patients	Up
Miat	Toraih, E.A. 2019	Plasma from T2DM patients	Up
MIR2052HG / ENSG00000254349	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
MIR4500HG / ENSG00000228824	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
MIR503HG / ENSG00000223749	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
MIR600HG	Fadista, J. 2014	Pancreatic islets	NI
MRPL23-AS1 / ENSG00000226416	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
MTHFS / ENSG00000261229	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
n324738	Wang, X. 2017	Peripheral blood from T2DM patients	Down
n325222	Wang, X. 2017	Peripheral blood from T2DM patients	Down
n325643	Wang, X. 2017	Peripheral blood from T2DM patients	Down
n325833	Wang, X. 2017	Peripheral blood from T2DM patients	Down
n326353	Wang, X. 2017	Peripheral blood from T2DM patients	Up
n333279	Wang, X. 2017	Peripheral blood from T2DM patients	Up
n335556	Wang, X. 2017	Peripheral blood from T2DM patients	Up
n335556	Wang, X. 2020	Peripheral blood from T2DM patients	Up
n336109	Wang, X. 2017	Peripheral blood from T2DM patients	Up
n336109	Wang, X. 2020	Peripheral blood from T2DM patients	Up
n336302	Wang, X. 2017	Peripheral blood from T2DM patients	Up
n336551	Wang, X. 2017	Peripheral blood from T2DM patients	Down
n336823	Wang, X. 2017	Peripheral blood from T2DM patients	Down
n337573	Wang, X. 2017	Peripheral blood from T2DM patients	Down
n338909	Wang, X. 2017	Peripheral blood from T2DM patients	Down

n341012	Wang, X. 2017	Peripheral blood from T2DM patients	Down
n341216	Wang, X. 2017	Peripheral blood from T2DM patients	Up
n341270	Wang, X. 2017	Peripheral blood from T2DM patients	Up
n341520	Wang, X. 2017	Peripheral blood from T2DM patients	Down
n341587	Wang, X. 2017	Peripheral blood from T2DM patients	Up
n341903	Wang, X. 2017	Peripheral blood from T2DM patients	Up
n341954	Wang, X. 2017	Peripheral blood from T2DM patients	Up
n342270	Wang, X. 2017	Peripheral blood from T2DM patients	Down
n342324	Wang, X. 2017	Peripheral blood from T2DM patients	Up
n342443	Wang, X. 2017	Peripheral blood from T2DM patients	Down
n342476	Wang, X. 2017	Peripheral blood from T2DM patients	Down
n342533	Wang, X. 2017	Peripheral blood from T2DM patients	Up
n342533	Wang, X. 2020	Peripheral blood from T2DM patients	Up
n344987	Wang, X. 2017	Peripheral blood from T2DM patients	Down
n346259	Wang, X. 2017	Peripheral blood from T2DM patients	Up
n384014	Wang, X. 2017	Peripheral blood from T2DM patients	Up
n384561	Wang, X. 2017	Peripheral blood from T2DM patients	Up
n385322	Wang, X. 2017	Peripheral blood from T2DM patients	Up
n385775	Wang, X. 2017	Peripheral blood from T2DM patients	Up
n405950	Wang, X. 2017	Peripheral blood from T2DM patients	Up
n406639	Wang, X. 2017	Peripheral blood from T2DM patients	Up
n409152	Wang, X. 2017	Peripheral blood from T2DM patients	Down
n409772	Wang, X. 2017	Peripheral blood from T2DM patients	Up
n410159	Wang, X. 2017	Peripheral blood from T2DM patients	Down
n410510	Wang, X. 2017	Peripheral blood from T2DM patients	Up
NAV2-AS5 / ENSG00000255043	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
NBR2	Sathishkumar, C. 2018	PBMCs from T2DM patients	Up
NCOA7-AS1 / ENSG00000232131	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
NORAD	Wan, W. 2020	Serum from T2DM patients	Up
Panda	Sathishkumar, C. 2018	PBMCs from T2DM patients	Up
PCAT4 / ENSG00000251321	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
PCAT6 / ENSG00000228288	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
PKI55	Fadista, J. 2014	Pancreatic islets	NI

PRKX-AS1 / ENSG00000236188	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
PSORS1C3 / ENSG00000204528	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
PVT1	Wang, W. 2018	Blood from DM patients	Up
PVT1	Toraih, E.A. 2019	Plasma from T2DM patients	Up
RAB30-AS1 / ENSG00000246067	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
RDH10-AS1 / ENSG00000250295	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ROIT	Zhang, FF. 2020	Serum from T2DM patients	Down
RPL34-AS1 / ENSG00000234492	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
RRS1-AS1 / ENSG00000246145	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
SALRNA1	Sathishkumar, C. 2018	PBMCs from T2DM patients	Down
SCGB1B2P / ENSG00000268751	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
SENCR / ENSG00000254703	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
SLC6A1-AS1 / ENSG00000232287	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
SMIM2-IT1 / ENSG00000235285	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
SNAI3-AS1 / ENSG00000260630	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
SNHG17	Mohamadi, M. 2019	PBMCs from T2DM patients	Down
SNHG5	Fadista, J. 2014	Pancreatic islets	NI
SNHG8	Fadista, J. 2014	Pancreatic islets	NI
ST7-AS2 / ENSG00000226367	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
TCONS_00000886	Li, X. 2017	Peripheral blood from T2DM patients	Up
TCONS_00004187	Ma, Q. 2019	PBMCs from T2DM patients	Down
TCONS_00007244	Li, X. 2017	Peripheral blood from T2DM patients	Up
TCONS_00024610	Li, X. 2017	Peripheral blood from T2DM patients	Up
TDRG1	Fadista, J. 2014	Pancreatic islets	NI
THRIL	Sathishkumar, C. 2018	PBMCs from T2DM patients	Down
TMEM92-AS1 / ENSG00000251179	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
TMEM9B-AS1 / ENSG00000254860	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
TPRG1-AS1 / ENSG00000234076	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
TTC28AS1	Mohamadi, M. 2019	PBMCs from T2DM patients	Down
uc.167+	Li, X. 2017	Peripheral blood from T2DM patients	Up
uc011fnr.2	Li, X. 2017	Peripheral blood from T2DM patients	Down
uc011llp.1	Li, X. 2017	Peripheral blood from T2DM patients	Down
uc011mfi.2	De Gonzalo-Calvo, 2016	Serum from T2DM patients	Down

uc022bqu.1	De Gonzalo-Calvo, 2016	Serum from T2DM patients	Down
uc022bqw.1	De Gonzalo-Calvo, 2016	Serum from T2DM patients	Down
VIM-AS1	Erfanian Omidvar M, 2018	PBMCs from T2DM patients	Down
Xist	Sathishkumar, C. 2018	PBMCs from T2DM patients	Up
XR_242704.2	Li, X. 2017	Peripheral blood from T2DM patients	Up
XR_427389.1	Li, X. 2017	Peripheral blood from T2DM patients	Up
ZNF337-AS1 / ENSG00000213742	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ZNF350-AS1 / ENSG00000269235	Pradas-Juni, M. 2020	Liver from T2DM patients	Down
ZNF385D-AS1 / ENSG00000225542	Pradas-Juni, M. 2020	Liver from T2DM patients	Up
β-linc3	Motterle, A. 2017	Islets from T2DM patients	Down

623 lncRNAs analyzed in only one study.
7 lncRNAs analyzed in two studies;
8 lncRNAs analyzed in three or more studies;
6 lncRNAs consistently* dysregulated in DM samples *vs*. control groups.

* Consistently dysregulated = those lncRNAs with concordant results in 3 or more studies.

NI= no information about the change in expression

Yang, F. 2018[a] - LncRNA KCNQ1OT1 Mediates Pyroptosis in Diabetic Cardiomyopathy.

Yang, F. 2018[b] - Silencing long non-coding RNA Kcnq1ot1 alleviates pyroptosis and fibrosis in diabetic cardiomyopathy

Supplementary Table 3. Target genes of the consistently dysregulated lncRNAs in DM patients

lncRNA	*Target*	Gene type
ANRIL	*ABCB1*	protein coding
ANRIL	*ABCC1*	protein coding
ANRIL	*ABCC2*	protein coding
ANRIL	*ADIPOR1*	protein coding
ANRIL	*CARD8*	protein coding
ANRIL	*CDKN1A*	protein coding
ANRIL	*CDKN2B*	protein coding
ANRIL	*KLF2*	protein coding
ANRIL	*MIR122*	protein coding
ANRIL	*MIR125A*	protein coding
ANRIL	*MIR199A1*	miRNA
ANRIL	*MIRLET7A1*	miRNA
ANRIL	*MYC*	miRNA
ANRIL	*SMAD2*	miRNA
ANRIL	*SMAD7*	protein coding
ANRIL	*SOX2*	protein coding
ANRIL	*TGFB1*	protein coding
ANRIL	*TMEM258*	protein coding
ANRIL	*VAMP3*	protein coding
ANRIL	*VEGFA*	protein coding
HOTAIR	*ABCC1*	protein coding
HOTAIR	*ADAMTS5*	protein coding
HOTAIR	*AKT1*	protein coding
HOTAIR	*ANGPT2*	protein coding
HOTAIR	*AR*	protein coding
HOTAIR	*ARID4A*	protein coding
HOTAIR	*BCL2*	protein coding
HOTAIR	*C22ORF28*	protein coding
HOTAIR	*CACNA1C*	protein coding
HOTAIR	*CASP3*	protein coding
HOTAIR	*CAV1*	protein coding
HOTAIR	*CCNE1*	protein coding
HOTAIR	*CD82*	protein coding
HOTAIR	*CDH1*	protein coding
HOTAIR	*CDKN1A*	protein coding
HOTAIR	*DNMT1*	protein coding
HOTAIR	*E7*	protein coding
HOTAIR	*eIF4AIII*	protein coding
HOTAIR	*ERBB2*	protein coding
HOTAIR	*EZH2*	protein coding
HOTAIR	*FASN*	protein coding
HOTAIR	*FMRP*	protein coding
HOTAIR	*FUS*	protein coding
HOTAIR	*HIF1A*	protein coding
HOTAIR	*hnRNPC*	protein coding
HOTAIR	*HOXA5*	protein coding
HOTAIR	*HuR*	protein coding

HOTAIR	*IGF2BP1*	protein coding
HOTAIR	*IGF2BP2*	protein coding
HOTAIR	*IGF2BP3*	protein coding
HOTAIR	*LAMB3*	protein coding
HOTAIR	*LAMC2*	protein coding
HOTAIR	*LIN28A*	protein coding
HOTAIR	*LIN28B*	protein coding
HOTAIR	*MAPK8*	protein coding
HOTAIR	*MMP1*	protein coding
HOTAIR	*MMP3*	protein coding
HOTAIR	*MMP9*	protein coding
HOTAIR	*PTEN*	protein coding
HOTAIR	*PUM2*	protein coding
HOTAIR	*QKI*	protein coding
HOTAIR	*RB1*	protein coding
HOTAIR	*RBM38*	protein coding
HOTAIR	*RN7SKP80*	misc RNA
HOTAIR	*RN7SKP9*	misc RNA
HOTAIR	*RUNX3*	protein coding
HOTAIR	*SETD2*	protein coding
HOTAIR	*SIRT1*	protein coding
HOTAIR	*SNAI1*	protein coding
HOTAIR	*TJP1*	protein coding
HOTAIR	*TNFRSF10B*	protein coding
HOTAIR	*TP53*	protein coding
HOTAIR	*TWIST1*	protein coding
HOTAIR	*U2AF65*	protein coding
HOTAIR	*UPF1*	protein coding
HOTAIR	*VEGFA*	protein coding
HOTAIR	*WIF1*	protein coding
HOTAIR	*ZC3H7B*	protein coding
HOTAIR	*ZEB1*	protein coding
KCNQ1OT1	*ABCB1*	protein coding
KCNQ1OT1	*AC010186.4*	processed transcript
KCNQ1OT1	*AC025627.3*	processed pseudogene
KCNQ1OT1	*AC026471.1*	antisense
KCNQ1OT1	*AC044810.1*	processed pseudogene
KCNQ1OT1	*AC079949.1*	miRNA
KCNQ1OT1	*AD000090.1*	antisense
KCNQ1OT1	*ADAT1*	protein coding
KCNQ1OT1	*ADIPOR1*	protein coding
KCNQ1OT1	*AL355315.1*	protein coding
KCNQ1OT1	*AL359915.2*	antisense
KCNQ1OT1	*ALDOA*	protein coding
KCNQ1OT1	*ANKS6*	protein coding
KCNQ1OT1	*ANXA7*	protein coding
KCNQ1OT1	*ARL17A*	protein coding
KCNQ1OT1	*ARPC4-TTLL3*	protein coding
KCNQ1OT1	*Asp_tRNA*	tRNA
KCNQ1OT1	*ATXN7*	protein coding

KCNQ1OT1	*BCLAF1*	protein coding
KCNQ1OT1	*CHD4*	protein coding
KCNQ1OT1	*DGCR8*	protein coding
KCNQ1OT1	*DPM2*	protein coding
KCNQ1OT1	*DUSP3*	protein coding
KCNQ1OT1	*EEF1A1P29*	processed pseudogene
KCNQ1OT1	*EIF2AK2*	protein coding
KCNQ1OT1	*EIF4H*	protein coding
KCNQ1OT1	*EPC1*	protein coding
KCNQ1OT1	*FAM122A*	protein coding
KCNQ1OT1	*FNTA*	protein coding
KCNQ1OT1	*FUS*	protein coding
KCNQ1OT1	*GGA1*	protein coding
KCNQ1OT1	*GGA2*	protein coding
KCNQ1OT1	*GNB1*	protein coding
KCNQ1OT1	*HACE1*	protein coding
KCNQ1OT1	*HECTD4*	protein coding
KCNQ1OT1	*HMGB2*	protein coding
KCNQ1OT1	*HNRNPL*	protein coding
KCNQ1OT1	*HOXA9*	protein coding
KCNQ1OT1	*HSP90B1*	protein coding
KCNQ1OT1	*KIF1B*	protein coding
KCNQ1OT1	*LIG3*	protein coding
KCNQ1OT1	*LUC7L3*	protein coding
KCNQ1OT1	*MAP2K7*	protein coding
KCNQ1OT1	*MAP3K2*	protein coding
KCNQ1OT1	*MIR424*	miRNA
KCNQ1OT1	*miR504*	miRNA
KCNQ1OT1	*MRRF*	protein coding
KCNQ1OT1	*MT-ND1*	protein coding
KCNQ1OT1	*MTRNR2L8*	protein coding
KCNQ1OT1	*MT-TL1*	Mt_tRNA
KCNQ1OT1	*MT-TV*	Mt_tRNA
KCNQ1OT1	*NCAPG2*	protein coding
KCNQ1OT1	*NR2F1*	protein coding
KCNQ1OT1	*NUMB*	protein coding
KCNQ1OT1	*PAPD5*	protein coding
KCNQ1OT1	*PDCD6IPP2*	transcribed unprocessed pseudogene
KCNQ1OT1	*PGLS*	protein coding
KCNQ1OT1	*PI4K2A*	protein coding
KCNQ1OT1	*PLCG2*	protein coding
KCNQ1OT1	*PPIF*	protein coding
KCNQ1OT1	*PPME1*	protein coding
KCNQ1OT1	*RAC3*	protein coding
KCNQ1OT1	*RF00019*	misc RNA
KCNQ1OT1	*RIC8A*	protein coding
KCNQ1OT1	*RMRP*	lincRNA
KCNQ1OT1	*RN7SKP50*	misc RNA
KCNQ1OT1	*RNA18N5*	rRNA
KCNQ1OT1	*RNA28S5*	rRNA

KCNQ1OT1	*RP13-996F3.3*	pseudogene
KCNQ1OT1	*RPL38*	protein coding
KCNQ1OT1	*RRP1B*	protein coding
KCNQ1OT1	*SARAF*	protein coding
KCNQ1OT1	*SBF1*	protein coding
KCNQ1OT1	*SDR39U1*	protein coding
KCNQ1OT1	*SEC31A*	protein coding
KCNQ1OT1	*SEPT8*	protein coding
KCNQ1OT1	*SSNA1*	protein coding
KCNQ1OT1	*SSR3*	protein coding
KCNQ1OT1	*STRADA*	protein coding
KCNQ1OT1	*TBX1*	protein coding
KCNQ1OT1	*TBX3*	protein coding
KCNQ1OT1	*TMEM115*	protein coding
KCNQ1OT1	*TRABD*	protein coding
KCNQ1OT1	*TRAP1*	protein coding
KCNQ1OT1	*TRMU*	protein coding
KCNQ1OT1	*TTLL3*	protein coding
KCNQ1OT1	*UBXN7*	protein coding
KCNQ1OT1	*UNC119B*	protein coding
KCNQ1OT1	*UPF1*	protein coding
KCNQ1OT1	*XRCC6*	protein coding
KCNQ1OT1	*ZNF592*	protein coding
MALAT1	*AARS*	protein coding
MALAT1	*ABCA1*	protein coding
MALAT1	*ABCC4*	protein coding
MALAT1	*ABCD4*	protein coding
MALAT1	*ABR*	protein coding
MALAT1	*ABT1*	protein coding
MALAT1	*AC005515.1*	transcribed unprocessed pseudogene
MALAT1	*AC005899.4*	processed transcript
MALAT1	*AC005912.1*	processed pseudogene
MALAT1	*AC006511.5*	processed transcript
MALAT1	*AC007192.1*	protein coding
MALAT1	*AC007285.1*	antisense
MALAT1	*AC007906.1*	sense_intronic
MALAT1	*AC007952.4*	lincRNA
MALAT1	*AC007969.1*	processed pseudogene
MALAT1	*AC008038.1*	processed pseudogene
MALAT1	*AC008731.1*	pseudogene
MALAT1	*AC008758.3*	transcribed unprocessed pseudogene
MALAT1	*AC008758.4*	protein coding
MALAT1	*AC009245.1*	processed pseudogene
MALAT1	*AC009336.2*	protein coding
MALAT1	*AC009362.1*	processed pseudogene
MALAT1	*AC010343.1*	processed pseudogene
MALAT1	*AC010542.4*	lincRNA
MALAT1	*AC010547.6*	unprocessed pseudogene
MALAT1	*AC011503.2*	sense_intronic
MALAT1	*AC011825.1*	processed pseudogene

MALAT1	*AC011979.1*	processed pseudogene
MALAT1	*AC016739.1*	processed pseudogene
MALAT1	*AC017035.1*	processed pseudogene
MALAT1	*AC018523.1*	processed pseudogene
MALAT1	*AC019176.2*	unprocessed pseudogene
MALAT1	*AC020765.3*	unprocessed pseudogene
MALAT1	*AC022861.1*	processed pseudogene
MALAT1	*AC023157.1*	processed pseudogene
MALAT1	*AC023813.2*	processed pseudogene
MALAT1	*AC024293.1*	processed pseudogene
MALAT1	*AC024451.1*	unprocessed pseudogene
MALAT1	*AC025458.1*	processed pseudogene
MALAT1	*AC026410.1*	processed pseudogene
MALAT1	*AC026784.1*	transcribed processed pseudogene
MALAT1	*AC026826.1*	processed pseudogene
MALAT1	*AC046176.1*	processed pseudogene
MALAT1	*AC068580.4*	protein coding
MALAT1	*AC068831.7*	protein coding
MALAT1	*AC068946.2*	protein coding
MALAT1	*AC073508.2*	protein coding
MALAT1	*AC073610.1*	processed pseudogene
MALAT1	*AC073610.3*	protein coding
MALAT1	*AC073861.1*	processed pseudogene
MALAT1	*AC078817.1*	processed pseudogene
MALAT1	*AC078991.1*	processed pseudogene
MALAT1	*AC087632.1*	protein coding
MALAT1	*AC090498.1*	processed pseudogene
MALAT1	*AC090543.2*	processed pseudogene
MALAT1	*AC090589.1*	processed pseudogene
MALAT1	*AC091078.2*	processed pseudogene
MALAT1	*AC091167.2*	protein coding
MALAT1	*AC091685.2*	processed pseudogene
MALAT1	*AC092035.1*	processed pseudogene
MALAT1	*AC092597.1*	processed pseudogene
MALAT1	*AC093668.2*	protein coding
MALAT1	*AC093809.1*	processed pseudogene
MALAT1	*AC098614.2*	processed pseudogene
MALAT1	*AC099654.3*	unprocessed pseudogene
MALAT1	*AC100771.1*	processed pseudogene
MALAT1	*AC104390.1*	processed pseudogene
MALAT1	*AC104563.1*	processed pseudogene
MALAT1	*AC104619.3*	processed pseudogene
MALAT1	*AC107890.1*	processed pseudogene
MALAT1	*AC107956.1*	processed pseudogene
MALAT1	*AC108134.2*	lincRNA
MALAT1	*AC108161.1*	processed pseudogene
MALAT1	*AC108725.1*	processed pseudogene
MALAT1	*AC115223.1*	processed pseudogene
MALAT1	*AC116533.1*	processed pseudogene
MALAT1	*AC124312.1*	protein coding

MALAT1	*AC131235.1*	processed pseudogene
MALAT1	*AC132825.1*	unprocessed pseudogene
MALAT1	*AC135068.6*	processed pseudogene
MALAT1	*AC138761.1*	transcribed unprocessed pseudogene
MALAT1	*AC138894.1*	protein coding
MALAT1	*AC140481.3*	pseudogene
MALAT1	*AC211485.1*	processed pseudogene
MALAT1	*AC241584.1*	processed pseudogene
MALAT1	*AC245014.3*	lincRNA
MALAT1	*AC245047.2*	processed pseudogene
MALAT1	*AC246787.1*	processed pseudogene
MALAT1	*ACBD6*	protein coding
MALAT1	*ACOT8*	protein coding
MALAT1	*ACTA2*	protein coding
MALAT1	*ACTB*	protein coding
MALAT1	*ACTBP11*	processed pseudogene
MALAT1	*ACTBP12*	processed pseudogene
MALAT1	*ACTBP9*	processed pseudogene
MALAT1	*ACTG1*	protein coding
MALAT1	*ACTG1P10*	processed pseudogene
MALAT1	*ACTG1P19*	processed pseudogene
MALAT1	*ACTR3*	protein coding
MALAT1	*AD000090.1*	antisense
MALAT1	*ADAMTS12*	protein coding
MALAT1	*ADAT1*	protein coding
MALAT1	*ADD3*	protein coding
MALAT1	*ADGRG5*	protein coding
MALAT1	*ADGRL2*	protein coding
MALAT1	*ADH5P4*	processed pseudogene
MALAT1	*ADIPOR1*	protein coding
MALAT1	*ADIPOR2*	protein coding
MALAT1	*ADNP*	protein coding
MALAT1	*ADO*	protein coding
MALAT1	*ADSS*	protein coding
MALAT1	*AFDN*	protein coding
MALAT1	*AGPAT5*	protein coding
MALAT1	*AHSA2P*	transcribed_unitary_pseudogene
MALAT1	*AK2*	protein coding
MALAT1	*AKAP8L*	protein coding
MALAT1	*AKR1A1*	protein coding
MALAT1	*AKR1B1P7*	processed pseudogene
MALAT1	*AKR7A2*	protein coding
MALAT1	*AKT1*	protein coding
MALAT1	*AL021546.1*	protein coding
MALAT1	*AL021707.2*	pseudogene
MALAT1	*AL022311.1*	sense_overlapping
MALAT1	*AL031727.1*	processed pseudogene
MALAT1	*AL035456.1*	processed pseudogene
MALAT1	*AL080243.2*	processed pseudogene
MALAT1	*AL132838.1*	processed pseudogene

MALAT1	*AL133352.1*	protein coding
MALAT1	*AL135925.1*	lincRNA
MALAT1	*AL136126.1*	processed pseudogene
MALAT1	*AL136295.1*	protein coding
MALAT1	*AL136295.4*	protein coding
MALAT1	*AL138785.1*	processed pseudogene
MALAT1	*AL139819.1*	pseudogene
MALAT1	*AL157392.5*	protein coding
MALAT1	*AL158201.1*	processed pseudogene
MALAT1	*AL354710.1*	processed pseudogene
MALAT1	*AL355075.4*	antisense
MALAT1	*AL356488.2*	lincRNA
MALAT1	*AL358113.1*	protein coding
MALAT1	*AL359918.1*	processed pseudogene
MALAT1	*AL360012.1*	lincRNA
MALAT1	*AL390728.4*	transcribed unprocessed pseudogene
MALAT1	*AL390728.5*	lincRNA
MALAT1	*AL391416.1*	processed pseudogene
MALAT1	*AL450405.1*	processed pseudogene
MALAT1	*AL512488.1*	sense_intronic
MALAT1	*AL513328.1*	processed pseudogene
MALAT1	*AL590762.3*	processed pseudogene
MALAT1	*AL591806.3*	protein coding
MALAT1	*AL592293.2*	processed pseudogene
MALAT1	*AL627402.1*	processed pseudogene
MALAT1	*AL645465.1*	antisense
MALAT1	*AL669983.1*	processed pseudogene
MALAT1	*Ala_tRNA*	tRNA
MALAT1	*ALCAM*	protein coding
MALAT1	*ALDOA*	protein coding
MALAT1	*ALDOAP2*	processed pseudogene
MALAT1	*ALG2*	protein coding
MALAT1	*AMD1P2*	processed pseudogene
MALAT1	*AMMECR1L*	protein coding
MALAT1	*ANAPC16*	protein coding
MALAT1	*ANKRD10*	protein coding
MALAT1	*ANKRD17*	protein coding
MALAT1	*ANKRD46*	protein coding
MALAT1	*ANKRD50*	protein coding
MALAT1	*ANLN*	protein coding
MALAT1	*ANO10*	protein coding
MALAT1	*ANO5*	protein coding
MALAT1	*ANP32E*	protein coding
MALAT1	*ANXA11*	protein coding
MALAT1	*AP000354.1*	processed pseudogene
MALAT1	*AP000763.2*	processed pseudogene
MALAT1	*AP000781.2*	protein coding
MALAT1	*AP000902.1*	processed pseudogene
MALAT1	*AP000936.3*	processed pseudogene
MALAT1	*AP000942.1*	processed pseudogene

MALAT1	*AP001024.1*	processed pseudogene
MALAT1	*AP001453.4*	lincRNA
MALAT1	*AP001646.2*	processed pseudogene
MALAT1	*AP001888.1*	processed pseudogene
MALAT1	*AP002990.1*	protein coding
MALAT1	*AP003108.2*	protein coding
MALAT1	*AP003175.1*	processed transcript
MALAT1	*AP1B1*	protein coding
MALAT1	*AP2A2*	protein coding
MALAT1	*AP5M1*	protein coding
MALAT1	*APLP2*	protein coding
MALAT1	*APPBP2*	protein coding
MALAT1	*APRT*	protein coding
MALAT1	*ARCN1*	protein coding
MALAT1	*ARF1*	protein coding
MALAT1	*ARF3*	protein coding
MALAT1	*ARF6*	protein coding
MALAT1	*Arg_tRNA*	tRNA
MALAT1	*ARHGAP12*	protein coding
MALAT1	*ARHGAP17*	protein coding
MALAT1	*ARHGAP21*	protein coding
MALAT1	*ARHGAP45*	protein coding
MALAT1	*ARHGAP5*	protein coding
MALAT1	*ARHGAP8*	protein coding
MALAT1	*ARHGEF12*	protein coding
MALAT1	*ARHGEF2*	protein coding
MALAT1	*ARL6IP5*	protein coding
MALAT1	*ARMCX3*	protein coding
MALAT1	*ARPP19*	protein coding
MALAT1	*ASH1L*	protein coding
MALAT1	*ASH2L*	protein coding
MALAT1	*Asp_tRNA*	tRNA
MALAT1	*ATF4P3*	processed pseudogene
MALAT1	*ATF4P4*	transcribed processed pseudogene
MALAT1	*ATG3*	protein coding
MALAT1	*ATG9A*	protein coding
MALAT1	*ATIC*	protein coding
MALAT1	*ATP1A1*	protein coding
MALAT1	*ATP5F1C*	protein coding
MALAT1	*ATP5F1D*	protein coding
MALAT1	*ATP5MC2*	protein coding
MALAT1	*ATP5PBP7*	processed pseudogene
MALAT1	*ATP5PO*	protein coding
MALAT1	*ATP6V0E2*	protein coding
MALAT1	*ATRN*	protein coding
MALAT1	*B2M*	protein coding
MALAT1	*B3GAT3*	protein coding
MALAT1	*B4GALT1*	protein coding
MALAT1	*BABAM2*	protein coding
MALAT1	*BACH1*	protein coding

MALAT1	*BAG3*	protein coding
MALAT1	*BAG6*	protein coding
MALAT1	*BBS2*	protein coding
MALAT1	*BBS9*	protein coding
MALAT1	*BCAP29*	protein coding
MALAT1	*BCAT1*	protein coding
MALAT1	*BCL2L2*	protein coding
MALAT1	*BCLAF1P1*	processed pseudogene
MALAT1	*BDH1*	protein coding
MALAT1	*BHLHE40*	protein coding
MALAT1	*BIRC5*	protein coding
MALAT1	*BLACAT1*	lincRNA
MALAT1	*BLOC1S5-TXNDC5*	protein coding
MALAT1	*BMP8B*	protein coding
MALAT1	*BMPER*	protein coding
MALAT1	*BORCS8*	protein coding
MALAT1	*BORCS8-MEF2B*	protein coding
MALAT1	*BPTF*	protein coding
MALAT1	*BRD4*	protein coding
MALAT1	*BRD7P2*	processed pseudogene
MALAT1	*BRK1*	protein coding
MALAT1	*BSG*	protein coding
MALAT1	*BTBD10*	protein coding
MALAT1	*BTG2*	protein coding
MALAT1	*BTG3P1*	processed pseudogene
MALAT1	*BX284668.2*	lincRNA
MALAT1	*BX842559.2*	processed pseudogene
MALAT1	*C11orf98*	protein coding
MALAT1	*C14orf119*	protein coding
MALAT1	*C17orf62*	protein coding
MALAT1	*C19orf48*	protein coding
MALAT1	*C19orf54*	protein coding
MALAT1	*C1orf226*	protein coding
MALAT1	*C1orf43*	protein coding
MALAT1	*C20orf194*	protein coding
MALAT1	*C20orf204*	protein coding
MALAT1	*C21orf59*	protein coding
MALAT1	*C5orf17*	lincRNA
MALAT1	*C5orf24*	protein coding
MALAT1	*C6orf48*	protein coding
MALAT1	*C6orf62*	protein coding
MALAT1	*C8orf37*	protein coding
MALAT1	*CA2*	protein coding
MALAT1	*CACNB4*	protein coding
MALAT1	*CALR*	protein coding
MALAT1	*CALU*	protein coding
MALAT1	*CAPN1*	protein coding
MALAT1	*CAPNS1*	protein coding
MALAT1	*CARHSP1*	protein coding
MALAT1	*CASC3*	protein coding

MALAT1	*CASD1*	protein coding
MALAT1	*CASP3*	protein coding
MALAT1	*CASP9*	protein coding
MALAT1	*CBS*	protein coding
MALAT1	*CBSL*	protein coding
MALAT1	*CBX1*	protein coding
MALAT1	*CC2D1B*	protein coding
MALAT1	*CCAR1*	protein coding
MALAT1	*CCAR2*	protein coding
MALAT1	*CCDC144CP*	transcribed processed pseudogene
MALAT1	*CCDC6*	protein coding
MALAT1	*CCL2*	protein coding
MALAT1	*CCL22*	protein coding
MALAT1	*CCL3L1*	protein coding
MALAT1	*CCL4L1*	protein coding
MALAT1	*CCNB2*	protein coding
MALAT1	*CCND1*	protein coding
MALAT1	*CCND2*	protein coding
MALAT1	*CCNG1*	protein coding
MALAT1	*CCNH*	protein coding
MALAT1	*CCNT1*	protein coding
MALAT1	*CCT3*	protein coding
MALAT1	*CCT4*	protein coding
MALAT1	*CD276*	protein coding
MALAT1	*CD33*	protein coding
MALAT1	*CD36*	protein coding
MALAT1	*CDC25A*	protein coding
MALAT1	*CDC7*	protein coding
MALAT1	*CDCA3*	protein coding
MALAT1	*CDCP1*	protein coding
MALAT1	*CDH1*	protein coding
MALAT1	*CDH2*	protein coding
MALAT1	*CDH5*	protein coding
MALAT1	*CDHR1*	protein coding
MALAT1	*CDK12*	protein coding
MALAT1	*CDK2*	protein coding
MALAT1	*CDK4*	protein coding
MALAT1	*CDKN1A*	protein coding
MALAT1	*CDKN1B*	protein coding
MALAT1	*CENPV*	protein coding
MALAT1	*CFL1*	protein coding
MALAT1	*CHAF1B*	protein coding
MALAT1	*CHCHD2P7*	processed pseudogene
MALAT1	*CHD8*	protein coding
MALAT1	*CHTF18*	protein coding
MALAT1	*CIC*	protein coding
MALAT1	*CKAP2L*	protein coding
MALAT1	*CLASP1*	protein coding
MALAT1	*CLDN4*	protein coding
MALAT1	*CLDN5*	protein coding

MALAT1	*CLIC4*	protein coding
MALAT1	*CLN3*	protein coding
MALAT1	*CLNS1A*	protein coding
MALAT1	*CNIH4*	protein coding
MALAT1	*CNNM2*	protein coding
MALAT1	*CNNM4*	protein coding
MALAT1	*CNOT3*	protein coding
MALAT1	*CNOT9*	protein coding
MALAT1	*CNPPD1*	protein coding
MALAT1	*COA1*	protein coding
MALAT1	*COCH*	protein coding
MALAT1	*COG3*	protein coding
MALAT1	*COG4*	protein coding
MALAT1	*COL6A1*	protein coding
MALAT1	*COPB1*	protein coding
MALAT1	*CORO1B*	protein coding
MALAT1	*CORO1C*	protein coding
MALAT1	*COTL1*	protein coding
MALAT1	*COX5A*	protein coding
MALAT1	*COX6A1*	protein coding
MALAT1	*COX6B1*	protein coding
MALAT1	*CPM*	protein coding
MALAT1	*CPSF1*	protein coding
MALAT1	*CPSF6*	protein coding
MALAT1	*CPT2*	protein coding
MALAT1	*CRCP*	protein coding
MALAT1	*CRKL*	protein coding
MALAT1	*CRTC2*	protein coding
MALAT1	*CS*	protein coding
MALAT1	*CSF1*	protein coding
MALAT1	*CSNK1D*	protein coding
MALAT1	*CSNK2A2*	protein coding
MALAT1	*CSNK2B*	protein coding
MALAT1	*CSTB*	protein coding
MALAT1	*CTHRC1*	protein coding
MALAT1	*CTNNA1*	protein coding
MALAT1	*CTNNB1*	protein coding
MALAT1	*CTNND1*	protein coding
MALAT1	*CTSD*	protein coding
MALAT1	*CXCL14*	protein coding
MALAT1	*CXCL5*	protein coding
MALAT1	*CYB5D2*	protein coding
MALAT1	*Cys_tRNA*	tRNA
MALAT1	*DAD1*	protein coding
MALAT1	*DANCR*	processed transcript
MALAT1	*DAZAP2*	protein coding
MALAT1	*DBN1*	protein coding
MALAT1	*DBT*	protein coding
MALAT1	*DCAF13*	protein coding
MALAT1	*DCAF7*	protein coding

MALAT1	*DCTN1*	protein coding
MALAT1	*DCTN3*	protein coding
MALAT1	*DCTN4*	protein coding
MALAT1	*DDI2*	protein coding
MALAT1	*DDIT4*	protein coding
MALAT1	*DDX17*	protein coding
MALAT1	*DDX23*	protein coding
MALAT1	*DDX41*	protein coding
MALAT1	*DDX5*	protein coding
MALAT1	*DDX56*	protein coding
MALAT1	*DEAF1*	protein coding
MALAT1	*DEF8*	protein coding
MALAT1	*DGAT1*	protein coding
MALAT1	*DGCR2*	protein coding
MALAT1	*DGKH*	protein coding
MALAT1	*DGUOK*	protein coding
MALAT1	*DHX15*	protein coding
MALAT1	*DHX9P1*	processed pseudogene
MALAT1	*DIAPH1*	protein coding
MALAT1	*DIP2A*	protein coding
MALAT1	*DLEU2*	antisense
MALAT1	*DMTF1*	protein coding
MALAT1	*DNAJA3*	protein coding
MALAT1	*DNAJB5*	protein coding
MALAT1	*DNAJC14*	protein coding
MALAT1	*DNASE1*	protein coding
MALAT1	*DNM2*	protein coding
MALAT1	*DOCK3*	protein coding
MALAT1	*DOLPP1*	protein coding
MALAT1	*DPP3*	protein coding
MALAT1	*DPY19L1*	protein coding
MALAT1	*DRD1*	protein coding
MALAT1	*DSC2*	protein coding
MALAT1	*DSC3*	protein coding
MALAT1	*DSP*	protein coding
MALAT1	*DST*	protein coding
MALAT1	*DTX2*	protein coding
MALAT1	*DUSP14*	protein coding
MALAT1	*DUSP23*	protein coding
MALAT1	*DUSP5*	protein coding
MALAT1	*DYNLL1P7*	processed pseudogene
MALAT1	*DYNLT1*	protein coding
MALAT1	*E2F4*	protein coding
MALAT1	*ECHDC3*	protein coding
MALAT1	*EDARADD*	protein coding
MALAT1	*EEF1A1*	protein coding
MALAT1	*EEF1A1P10*	processed pseudogene
MALAT1	*EEF1A1P12*	processed pseudogene
MALAT1	*EEF1A1P13*	processed pseudogene
MALAT1	*EEF1A1P14*	processed pseudogene

MALAT1	*EEF1A1P16*	processed pseudogene
MALAT1	*EEF1A1P19*	processed pseudogene
MALAT1	*EEF1A1P22*	processed pseudogene
MALAT1	*EEF1A1P24*	processed pseudogene
MALAT1	*EEF1A1P29*	processed pseudogene
MALAT1	*EEF1A1P4*	processed pseudogene
MALAT1	*EEF1A1P5*	processed pseudogene
MALAT1	*EEF1A1P6*	processed pseudogene
MALAT1	*EEF1A1P8*	processed pseudogene
MALAT1	*EEF1A1P9*	processed pseudogene
MALAT1	*EEF1G*	protein coding
MALAT1	*EEF1GP5*	processed pseudogene
MALAT1	*EEF2*	protein coding
MALAT1	*EFR3A*	protein coding
MALAT1	*EHMT1*	protein coding
MALAT1	*EIF2S3B*	protein coding
MALAT1	*EIF3E*	protein coding
MALAT1	*EIF3L*	protein coding
MALAT1	*EIF3LP1*	processed pseudogene
MALAT1	*EIF4A2*	protein coding
MALAT1	*EIF4B*	protein coding
MALAT1	*EIF4EBP2*	protein coding
MALAT1	*EIF4G1*	protein coding
MALAT1	*EIF4G2*	protein coding
MALAT1	*EIF5A*	protein coding
MALAT1	*ELK4*	protein coding
MALAT1	*ELOVL6*	protein coding
MALAT1	*EMC1*	protein coding
MALAT1	*EMC10*	protein coding
MALAT1	*EMC6*	protein coding
MALAT1	*EMC8*	protein coding
MALAT1	*ENO1*	protein coding
MALAT1	*ENO1P1*	transcribed processed pseudogene
MALAT1	*EPB41*	protein coding
MALAT1	*EPB41L2*	protein coding
MALAT1	*EPHB4*	protein coding
MALAT1	*EPM2AIP1*	protein coding
MALAT1	*EPS15L1*	protein coding
MALAT1	*ERCC1*	protein coding
MALAT1	*ERG28*	protein coding
MALAT1	*ERK1*	protein coding
MALAT1	*ERMP1*	protein coding
MALAT1	*ESPL1*	protein coding
MALAT1	*ETF1*	protein coding
MALAT1	*ETFA*	protein coding
MALAT1	*EXT2*	protein coding
MALAT1	*EZH2*	protein coding
MALAT1	*EZR*	protein coding
MALAT1	*F11R*	protein coding
MALAT1	*FAM117A*	protein coding

MALAT1	*FAM193B*	protein coding
MALAT1	*FANCD2*	protein coding
MALAT1	*FAR1*	protein coding
MALAT1	*FBLN1*	protein coding
MALAT1	*FBXO22*	protein coding
MALAT1	*FBXO30*	protein coding
MALAT1	*FBXW11*	protein coding
MALAT1	*FCF1*	protein coding
MALAT1	*FDPSP5*	processed pseudogene
MALAT1	*FEN1*	protein coding
MALAT1	*FIG4*	protein coding
MALAT1	*FKBP5*	protein coding
MALAT1	*FLNA*	protein coding
MALAT1	*FLOT2*	protein coding
MALAT1	*FMNL2*	protein coding
MALAT1	*FN1*	protein coding
MALAT1	*FO393411.1*	processed pseudogene
MALAT1	*FP565260.1*	protein coding
MALAT1	*FRAS1*	protein coding
MALAT1	*FRAT2*	protein coding
MALAT1	*FREM2*	protein coding
MALAT1	*FSD1*	protein coding
MALAT1	*FTH1P16*	processed pseudogene
MALAT1	*FTL*	protein coding
MALAT1	*FTLP17*	processed pseudogene
MALAT1	*FTLP2*	processed pseudogene
MALAT1	*FTLP3*	processed pseudogene
MALAT1	*FUS*	protein coding
MALAT1	*FXYD6*	protein coding
MALAT1	*G6PC3*	protein coding
MALAT1	*GAB2*	protein coding
MALAT1	*GABARAPL1*	protein coding
MALAT1	*GABBR1*	protein coding
MALAT1	*GALNT18*	protein coding
MALAT1	*GANAB*	protein coding
MALAT1	*GAPDH*	protein coding
MALAT1	*GAPDHP25*	processed pseudogene
MALAT1	*GAPDHP40*	processed pseudogene
MALAT1	*GAPDHP41*	processed pseudogene
MALAT1	*GAPDHP46*	processed pseudogene
MALAT1	*GAPDHP62*	processed pseudogene
MALAT1	*GAPDHP70*	processed pseudogene
MALAT1	*GAPDHP72*	transcribed processed pseudogene
MALAT1	*GAPDHP73*	processed pseudogene
MALAT1	*GAS5*	processed transcript
MALAT1	*GATA3*	protein coding
MALAT1	*GCDH*	protein coding
MALAT1	*GDE1*	protein coding
MALAT1	*GDI2P1*	processed pseudogene
MALAT1	*GFRA1*	protein coding

MALAT1	*GGT7*	protein coding
MALAT1	*GINM1*	protein coding
MALAT1	*GLG1*	protein coding
MALAT1	*Glu_tRNA*	tRNA
MALAT1	*GLUD2*	protein coding
MALAT1	*GLUL*	protein coding
MALAT1	*Gly_tRNA*	tRNA
MALAT1	*GNAS*	protein coding
MALAT1	*GNB1*	protein coding
MALAT1	*GNL2*	protein coding
MALAT1	*GPC6*	protein coding
MALAT1	*GPI*	protein coding
MALAT1	*GPR137*	protein coding
MALAT1	*GRWD1*	protein coding
MALAT1	*GSPT1*	protein coding
MALAT1	*GSTA4*	protein coding
MALAT1	*GTF2I*	protein coding
MALAT1	*GTF3C5*	protein coding
MALAT1	*GTPBP1*	protein coding
MALAT1	*GTPBP6*	protein coding
MALAT1	*GUCA1A*	protein coding
MALAT1	*HADH*	protein coding
MALAT1	*HBP1*	protein coding
MALAT1	*HCFC1*	protein coding
MALAT1	*HCP5*	sense_overlapping
MALAT1	*HDDC3*	protein coding
MALAT1	*HDGF*	protein coding
MALAT1	*HDGFL3*	protein coding
MALAT1	*HEATR1*	protein coding
MALAT1	*HEMK1*	protein coding
MALAT1	*HEXDC*	protein coding
MALAT1	*HGSNAT*	protein coding
MALAT1	*HIC2*	protein coding
MALAT1	*HIF1A*	protein coding
MALAT1	*HINT1*	protein coding
MALAT1	*HIPK2*	protein coding
MALAT1	*His_tRNA*	tRNA
MALAT1	*HIST1H1C*	protein coding
MALAT1	*HIST1H2AE*	protein coding
MALAT1	*HIST1H2APS2*	transcribed processed pseudogene
MALAT1	*HIST1H3A*	protein coding
MALAT1	*HIST2H3A*	protein coding
MALAT1	*HLA-A*	protein coding
MALAT1	*HLA-B*	protein coding
MALAT1	*HLA-C*	protein coding
MALAT1	*HLA-DMA*	protein coding
MALAT1	*HLA-DRA*	protein coding
MALAT1	*HLA-E*	protein coding
MALAT1	*HLA-J*	transcribed unprocessed pseudogene
MALAT1	*HM13*	protein coding

MALAT1	*HMGA1*	protein coding
MALAT1	*HMGB1*	protein coding
MALAT1	*HMGCR*	protein coding
MALAT1	*HMGCS1*	protein coding
MALAT1	*HMMR*	protein coding
MALAT1	*HNF4G*	protein coding
MALAT1	*HNRNPA0*	protein coding
MALAT1	*HNRNPA2B1*	protein coding
MALAT1	*HNRNPC*	protein coding
MALAT1	*HNRNPDL*	protein coding
MALAT1	*HNRNPK*	protein coding
MALAT1	*HNRNPL*	protein coding
MALAT1	*HNRNPUL1*	protein coding
MALAT1	*HOMER1*	protein coding
MALAT1	*HOTAIRM1*	antisense
MALAT1	*HOXD4*	protein coding
MALAT1	*HS6ST3*	protein coding
MALAT1	*hsa-miR-4485*	miRNA
MALAT1	*hsa-miR-7641*	miRNA
MALAT1	*HSD17B10*	protein coding
MALAT1	*HSF1*	protein coding
MALAT1	*HSP90AA2P*	processed pseudogene
MALAT1	*HSP90AB1*	protein coding
MALAT1	*HSP90AB3P*	processed pseudogene
MALAT1	*HSPA4*	protein coding
MALAT1	*HSPA8*	protein coding
MALAT1	*HSPA8P1*	processed pseudogene
MALAT1	*HSPA8P5*	processed pseudogene
MALAT1	*HSPA9*	protein coding
MALAT1	*HSPG2*	protein coding
MALAT1	*IARS*	protein coding
MALAT1	*IFI30*	protein coding
MALAT1	*IFI6*	protein coding
MALAT1	*IGDCC3*	protein coding
MALAT1	*IGF1R*	protein coding
MALAT1	*IGF2*	protein coding
MALAT1	*IGF2BP1*	protein coding
MALAT1	*IGF2BP2*	protein coding
MALAT1	*IGSF8*	protein coding
MALAT1	*IGSF9*	protein coding
MALAT1	*IKZF2*	protein coding
MALAT1	*ILF2*	protein coding
MALAT1	*ILF3*	protein coding
MALAT1	*IMMT*	protein coding
MALAT1	*IMPACT*	protein coding
MALAT1	*INPP5D*	protein coding
MALAT1	*INTS8*	protein coding
MALAT1	*IPO7*	protein coding
MALAT1	*IRF4*	protein coding
MALAT1	*IRF6*	protein coding

MALAT1	*ISOC1*	protein coding
MALAT1	*ISYNA1*	protein coding
MALAT1	*ITGA3*	protein coding
MALAT1	*ITGB1*	protein coding
MALAT1	*ITPRIPL2*	protein coding
MALAT1	*JADE2*	protein coding
MALAT1	*JPH4*	protein coding
MALAT1	*JPT1*	protein coding
MALAT1	*JRK*	protein coding
MALAT1	*JUND*	protein coding
MALAT1	*JUP*	protein coding
MALAT1	*KAT6A*	protein coding
MALAT1	*KAT7*	protein coding
MALAT1	*KCNK1*	protein coding
MALAT1	*KDELR1*	protein coding
MALAT1	*KDELR2*	protein coding
MALAT1	*KDM5B*	protein coding
MALAT1	*KHDC4*	protein coding
MALAT1	*KHSRP*	protein coding
MALAT1	*KIAA0040*	protein coding
MALAT1	*KIF1C*	protein coding
MALAT1	*KIF3C*	protein coding
MALAT1	*KIFC1*	protein coding
MALAT1	*KLHL8*	protein coding
MALAT1	*KMT2A*	protein coding
MALAT1	*KPNA2*	protein coding
MALAT1	*KRCC1*	protein coding
MALAT1	*KRT13*	protein coding
MALAT1	*KRT5*	protein coding
MALAT1	*KRT7*	protein coding
MALAT1	*LAD1*	protein coding
MALAT1	*LAPTM5*	protein coding
MALAT1	*LARP1*	protein coding
MALAT1	*LAYN*	protein coding
MALAT1	*LBHD1*	protein coding
MALAT1	*LCP1*	protein coding
MALAT1	*LDB1*	protein coding
MALAT1	*LDHA*	protein coding
MALAT1	*LDHAP3*	processed pseudogene
MALAT1	*LDHAP5*	processed pseudogene
MALAT1	*LENG8*	protein coding
MALAT1	*Leu_tRNA*	tRNA
MALAT1	*LGALS9B*	protein coding
MALAT1	*LHFPL2*	protein coding
MALAT1	*LIMA1*	protein coding
MALAT1	*LIMD1*	protein coding
MALAT1	*LINC00426*	lincRNA
MALAT1	*LINC01553*	lincRNA
MALAT1	*LINC01588*	lincRNA
MALAT1	*LINC01933*	lincRNA

MALAT1	*LINGO1*	protein coding
MALAT1	*LITAF*	protein coding
MALAT1	*LNPEP*	protein coding
MALAT1	*LONP1*	protein coding
MALAT1	*LPAR1*	protein coding
MALAT1	*LPXN*	protein coding
MALAT1	*LRCH1*	protein coding
MALAT1	*LRIF1*	protein coding
MALAT1	*LRIG3*	protein coding
MALAT1	*LRPPRC*	protein coding
MALAT1	*LRRC58*	protein coding
MALAT1	*LRRC61*	protein coding
MALAT1	*LRRN1*	protein coding
MALAT1	*LSM12*	protein coding
MALAT1	*LSM2*	protein coding
MALAT1	*LSM3*	protein coding
MALAT1	*LSM4*	protein coding
MALAT1	*LTBP3*	protein coding
MALAT1	*LY6K*	protein coding
MALAT1	*Lys_tRNA*	tRNA
MALAT1	*MAGT1*	protein coding
MALAT1	*MAN1B1*	protein coding
MALAT1	*MAN2B1*	protein coding
MALAT1	*MAP2K1*	protein coding
MALAT1	*MAP2K2*	protein coding
MALAT1	*MAP3K4*	protein coding
MALAT1	*MAPK1*	protein coding
MALAT1	*MAPK10*	protein coding
MALAT1	*MAPK14*	protein coding
MALAT1	*MAPK3*	protein coding
MALAT1	*MAPK8*	protein coding
MALAT1	*MAPK9*	protein coding
MALAT1	*MARCH6*	protein coding
MALAT1	*MARCKS*	protein coding
MALAT1	*MARCKSL1*	protein coding
MALAT1	*MARK3*	protein coding
MALAT1	*MARS*	protein coding
MALAT1	*MAT2A*	protein coding
MALAT1	*MATN2*	protein coding
MALAT1	*MATR3*	protein coding
MALAT1	*MBD2*	protein coding
MALAT1	*MBNL1*	protein coding
MALAT1	*MCAM*	protein coding
MALAT1	*MCL1*	protein coding
MALAT1	*MCM3*	protein coding
MALAT1	*MCM7*	protein coding
MALAT1	*MCTS2P*	processed pseudogene
MALAT1	*MDFIC*	protein coding
MALAT1	*MDH1*	protein coding
MALAT1	*MDK*	protein coding

MALAT1	*MEK1*	protein coding
MALAT1	*Met_tRNA*	tRNA
MALAT1	*METTL2B*	protein coding
MALAT1	*METTL4*	protein coding
MALAT1	*METTL9*	protein coding
MALAT1	*MGAT3*	protein coding
MALAT1	*MGEA5*	protein coding
MALAT1	*MGLL*	protein coding
MALAT1	*MGST1*	protein coding
MALAT1	*MIA2*	protein coding
MALAT1	*MICAL3*	protein coding
MALAT1	*MIER1*	protein coding
MALAT1	*MIOS*	protein coding
MALAT1	*miR-101*	miRNA
MALAT1	*miR-124*	miRNA
MALAT1	*MIR124-1*	miRNA
MALAT1	*MIR129-1*	miRNA
MALAT1	*MIR140*	miRNA
MALAT1	*MIR142*	miRNA
MALAT1	*MIR143*	miRNA
MALAT1	*MIR144*	miRNA
MALAT1	*MIR145*	miRNA
MALAT1	*MIR195*	miRNA
MALAT1	*MIR200A*	miRNA
MALAT1	*MIR200C*	miRNA
MALAT1	*MIR203A*	miRNA
MALAT1	*MIR205*	miRNA
MALAT1	*MIR205HG*	miRNA
MALAT1	*MIR206*	miRNA
MALAT1	*MIR217*	miRNA
MALAT1	*MIR218-1*	miRNA
MALAT1	*MIR23B*	miRNA
MALAT1	*MIR26B*	miRNA
MALAT1	*miR-30b*	miRNA
MALAT1	*MIR320A*	miRNA
MALAT1	*MIR363*	miRNA
MALAT1	*MIR375*	miRNA
MALAT1	*MIR376A1*	miRNA
MALAT1	*MIR506*	miRNA
MALAT1	*MKNK2*	protein coding
MALAT1	*MKRN1*	protein coding
MALAT1	*MLEC*	protein coding
MALAT1	*MLF2*	protein coding
MALAT1	*MLLT11*	protein coding
MALAT1	*MMGT1*	protein coding
MALAT1	*MMP14*	protein coding
MALAT1	*MMP2*	protein coding
MALAT1	*MMP9*	protein coding
MALAT1	*MOB1A*	protein coding
MALAT1	*MON1B*	protein coding

MALAT1	*MPZ*	protein coding
MALAT1	*MPZL1*	protein coding
MALAT1	*MRI1*	protein coding
MALAT1	*MROH1*	protein coding
MALAT1	*MRPL2*	protein coding
MALAT1	*MRPL33*	protein coding
MALAT1	*MRPL40*	protein coding
MALAT1	*MRPL42*	protein coding
MALAT1	*MRPL43*	protein coding
MALAT1	*MRPL44*	protein coding
MALAT1	*MRPS16*	protein coding
MALAT1	*MRPS25*	protein coding
MALAT1	*MRPS6*	protein coding
MALAT1	*MT-ATP6*	protein coding
MALAT1	*MTATP6P1*	unprocessed pseudogene
MALAT1	*MT-ATP8*	protein coding
MALAT1	*MTATP8P1*	unprocessed pseudogene
MALAT1	*MTATP8P2*	processed pseudogene
MALAT1	*MTCH2*	protein coding
MALAT1	*MT-CO1*	protein coding
MALAT1	*MTCO1P12*	unprocessed pseudogene
MALAT1	*MTCO1P15*	processed pseudogene
MALAT1	*MTCO1P18*	unprocessed pseudogene
MALAT1	*MTCO1P2*	unprocessed pseudogene
MALAT1	*MTCO1P22*	processed pseudogene
MALAT1	*MTCO1P3*	processed pseudogene
MALAT1	*MTCO1P40*	processed pseudogene
MALAT1	*MTCO1P53*	processed pseudogene
MALAT1	*MTCO1P55*	processed pseudogene
MALAT1	*MT-CO2*	protein coding
MALAT1	*MTCO2P12*	unprocessed pseudogene
MALAT1	*MTCO2P2*	processed pseudogene
MALAT1	*MT-CO3*	protein coding
MALAT1	*MTCO3P12*	unprocessed pseudogene
MALAT1	*MTCO3P13*	unprocessed pseudogene
MALAT1	*MTCO3P22*	processed pseudogene
MALAT1	*MTCO3P24*	unprocessed pseudogene
MALAT1	*MTCYBP13*	unprocessed pseudogene
MALAT1	*MTCYBP18*	processed pseudogene
MALAT1	*MTCYBP22*	processed pseudogene
MALAT1	*MTCYBP35*	processed pseudogene
MALAT1	*MTCYBP41*	processed pseudogene
MALAT1	*MT-ND1*	protein coding
MALAT1	*MTND1P23*	unprocessed pseudogene
MALAT1	*MTND1P32*	processed pseudogene
MALAT1	*MTND2P20*	processed pseudogene
MALAT1	*MTND2P28*	unprocessed pseudogene
MALAT1	*MT-ND4*	protein coding
MALAT1	*MT-ND4L*	protein coding
MALAT1	*MTND4LP1*	processed pseudogene

MALAT1	*MTND4LP30*	processed pseudogene
MALAT1	*MTND4LP5*	processed pseudogene
MALAT1	*MTND4P12*	processed pseudogene
MALAT1	*MTND4P24*	processed pseudogene
MALAT1	*MTND4P35*	processed pseudogene
MALAT1	*MT-ND5*	protein coding
MALAT1	*MTND5P10*	processed pseudogene
MALAT1	*MTND5P11*	processed pseudogene
MALAT1	*MTND5P12*	processed pseudogene
MALAT1	*MTND5P32*	processed pseudogene
MALAT1	*MTPN*	protein coding
MALAT1	*MT-RNR1*	Mt_rRNA
MALAT1	*MT-RNR2*	Mt_rRNA
MALAT1	*MTRNR2L1*	protein coding
MALAT1	*MTRNR2L11*	protein coding
MALAT1	*MTRNR2L12*	protein coding
MALAT1	*MTRNR2L3*	protein coding
MALAT1	*MTRNR2L8*	protein coding
MALAT1	*MUC16*	protein coding
MALAT1	*MUC19*	protein coding
MALAT1	*MUC4*	protein coding
MALAT1	*MVB12B*	protein coding
MALAT1	*MXD3*	protein coding
MALAT1	*MYBL2*	protein coding
MALAT1	*MYC*	protein coding
MALAT1	*MYDGF*	protein coding
MALAT1	*MYH9*	protein coding
MALAT1	*MYL8P*	processed pseudogene
MALAT1	*MYO1E*	protein coding
MALAT1	*NACA*	protein coding
MALAT1	*NAGPA*	protein coding
MALAT1	*NAPRT*	protein coding
MALAT1	*NARS*	protein coding
MALAT1	*NCAM1*	protein coding
MALAT1	*NCAPH2*	protein coding
MALAT1	*NDFIP1*	protein coding
MALAT1	*NDOR1*	protein coding
MALAT1	*NDUFB11*	protein coding
MALAT1	*NDUFB8*	protein coding
MALAT1	*NDUFV1*	protein coding
MALAT1	*NEAT1*	lincRNA
MALAT1	*NECAP1*	protein coding
MALAT1	*NEDD8*	protein coding
MALAT1	*NEK4*	protein coding
MALAT1	*NEK7*	protein coding
MALAT1	*NEK9*	protein coding
MALAT1	*NFATC2IP*	protein coding
MALAT1	*NFE2L1*	protein coding
MALAT1	*NFE2L2*	protein coding
MALAT1	*NFXL1*	protein coding

MALAT1	*NGRN*	protein coding
MALAT1	*NIF3L1*	protein coding
MALAT1	*NIN*	protein coding
MALAT1	*NIPSNAP1*	protein coding
MALAT1	*NNMT*	protein coding
MALAT1	*NOA1*	protein coding
MALAT1	*NOC3L*	protein coding
MALAT1	*NOP9*	protein coding
MALAT1	*NOTCH2*	protein coding
MALAT1	*NOTCH2P1*	processed pseudogene
MALAT1	*NPDC1*	protein coding
MALAT1	*NPM1P35*	processed pseudogene
MALAT1	*NPM1P50*	transcribed processed pseudogene
MALAT1	*NR2F2*	protein coding
MALAT1	*NRBP1*	protein coding
MALAT1	*NRDE2*	protein coding
MALAT1	*NREP*	protein coding
MALAT1	*NRXN1*	protein coding
MALAT1	*NT5C*	protein coding
MALAT1	*NUBP1*	protein coding
MALAT1	*NUCKS1*	protein coding
MALAT1	*NUDT21*	protein coding
MALAT1	*NUFIP2*	protein coding
MALAT1	*NUMA1*	protein coding
MALAT1	*NUP153*	protein coding
MALAT1	*NUP62*	protein coding
MALAT1	*NUTM2A-AS1*	antisense
MALAT1	*NUTM2B-AS1*	antisense
MALAT1	*OAS2*	protein coding
MALAT1	*OAS3*	protein coding
MALAT1	*OBSL1*	protein coding
MALAT1	*OCLN*	protein coding
MALAT1	*OGT*	protein coding
MALAT1	*OR2A25*	protein coding
MALAT1	*OST4*	protein coding
MALAT1	*P2RX5-TAX1BP3*	protein coding
MALAT1	*P2RY11*	protein coding
MALAT1	*P4HB*	protein coding
MALAT1	*PABPC1*	protein coding
MALAT1	*PAFAH1B1*	protein coding
MALAT1	*PAK1*	protein coding
MALAT1	*PAPD7*	protein coding
MALAT1	*PARP10*	protein coding
MALAT1	*PAXIP1-AS2*	antisense
MALAT1	*PBRM1*	protein coding
MALAT1	*PCBD1*	protein coding
MALAT1	*PCBP2*	protein coding
MALAT1	*PCBP4*	protein coding
MALAT1	*PCDH11Y*	protein coding
MALAT1	*PCLAF*	protein coding

MALAT1	*PCNA*	protein coding
MALAT1	*PCSK9*	protein coding
MALAT1	*PCTP*	protein coding
MALAT1	*PCYOX1L*	protein coding
MALAT1	*PDCD2*	protein coding
MALAT1	*PDCD4*	protein coding
MALAT1	*PDCD6IP*	protein coding
MALAT1	*PDIA3*	protein coding
MALAT1	*PDIA6*	protein coding
MALAT1	*PDZD8*	protein coding
MALAT1	*PFN1*	protein coding
MALAT1	*PGAM1P8*	transcribed processed pseudogene
MALAT1	*PGK1*	protein coding
MALAT1	*PGM1*	protein coding
MALAT1	*PGS1*	protein coding
MALAT1	*PHF2*	protein coding
MALAT1	*PHIP*	protein coding
MALAT1	*PHTF2*	protein coding
MALAT1	*PIK3CB*	protein coding
MALAT1	*PIP5K1A*	protein coding
MALAT1	*PJA2*	protein coding
MALAT1	*PKIG*	protein coding
MALAT1	*PKM*	protein coding
MALAT1	*PKMP1*	processed pseudogene
MALAT1	*PLAGL1*	protein coding
MALAT1	*PLCG2*	protein coding
MALAT1	*PLEKHA1*	protein coding
MALAT1	*PLEKHF2*	protein coding
MALAT1	*PLEKHG3*	protein coding
MALAT1	*PLEKHM1*	protein coding
MALAT1	*PLIN3*	protein coding
MALAT1	*PLXNA1*	protein coding
MALAT1	*PLXNA4*	protein coding
MALAT1	*PLXND1*	protein coding
MALAT1	*PMPCB*	protein coding
MALAT1	*PNISR*	protein coding
MALAT1	*PNMA8A*	protein coding
MALAT1	*PNPT1P1*	processed pseudogene
MALAT1	*POFUT1*	protein coding
MALAT1	*POLM*	protein coding
MALAT1	*POLR3E*	protein coding
MALAT1	*POLRMT*	protein coding
MALAT1	*POM121C*	protein coding
MALAT1	*POTEJ*	protein coding
MALAT1	*POU2F1*	protein coding
MALAT1	*PPA2*	protein coding
MALAT1	*PPARGC1B*	protein coding
MALAT1	*PPIA*	protein coding
MALAT1	*PPIAP19*	processed pseudogene
MALAT1	*PPIAP4*	processed pseudogene

MALAT1	*PPIF*	protein coding
MALAT1	*PPIG*	protein coding
MALAT1	*PPIL2*	protein coding
MALAT1	*PPIL3*	protein coding
MALAT1	*PPOX*	protein coding
MALAT1	*PPP1CB*	protein coding
MALAT1	*PPP1R12A*	protein coding
MALAT1	*PPP1R12C*	protein coding
MALAT1	*PPP1R8*	protein coding
MALAT1	*PPP2CA*	protein coding
MALAT1	*PPP2R1A*	protein coding
MALAT1	*PPP2R5D*	protein coding
MALAT1	*PPP4R1*	protein coding
MALAT1	*PPT1*	protein coding
MALAT1	*PRC1*	protein coding
MALAT1	*PRKCD*	protein coding
MALAT1	*PRKCE*	protein coding
MALAT1	*PRKDC*	protein coding
MALAT1	*PRKRIP1*	protein coding
MALAT1	*PRMT2*	protein coding
MALAT1	*PRPF18*	protein coding
MALAT1	*PRPF19*	protein coding
MALAT1	*PRPF8*	protein coding
MALAT1	*PRR13P2*	processed pseudogene
MALAT1	*PRR14*	protein coding
MALAT1	*PRR5-ARHGAP8*	protein coding
MALAT1	*PRRC2B*	protein coding
MALAT1	*PRTG*	protein coding
MALAT1	*PSAP*	protein coding
MALAT1	*PSAT1*	protein coding
MALAT1	*PSMA4*	protein coding
MALAT1	*PSMB5*	protein coding
MALAT1	*PSMC1P1*	processed pseudogene
MALAT1	*PSMC5*	protein coding
MALAT1	*PSMC6*	protein coding
MALAT1	*PSMD3*	protein coding
MALAT1	*PSMD5*	protein coding
MALAT1	*PSMD7*	protein coding
MALAT1	*PSMF1*	protein coding
MALAT1	*PTBP1*	protein coding
MALAT1	*PTBP3*	protein coding
MALAT1	*PTDSS2*	protein coding
MALAT1	*PTK2*	protein coding
MALAT1	*PTMA*	protein coding
MALAT1	*PTPN1*	protein coding
MALAT1	*PTPN11*	protein coding
MALAT1	*PTPRCAP*	protein coding
MALAT1	*PTPRD*	protein coding
MALAT1	*PTPRF*	protein coding
MALAT1	*PWP2*	protein coding

MALAT1	*PWWP2A*	protein coding
MALAT1	*PXDN*	protein coding
MALAT1	*PXN*	protein coding
MALAT1	*PYCR1*	protein coding
MALAT1	*PYM1*	protein coding
MALAT1	*QRICH1*	protein coding
MALAT1	*QSOX1*	protein coding
MALAT1	*R3HDM2*	protein coding
MALAT1	*RAB11B*	protein coding
MALAT1	*RAB12*	protein coding
MALAT1	*RAB6A*	protein coding
MALAT1	*RAB7A*	protein coding
MALAT1	*RABAC1*	protein coding
MALAT1	*RABGGTB*	protein coding
MALAT1	*RAC2*	protein coding
MALAT1	*RACK1*	protein coding
MALAT1	*RAD51AP1*	protein coding
MALAT1	*RALGAPA1*	protein coding
MALAT1	*RALGPS2*	protein coding
MALAT1	*RAP1B*	protein coding
MALAT1	*RAPGEF1*	protein coding
MALAT1	*RAPH1*	protein coding
MALAT1	*RASA4B*	protein coding
MALAT1	*RASSF5*	protein coding
MALAT1	*RASSF6*	protein coding
MALAT1	*RBM19*	protein coding
MALAT1	*RBM25*	protein coding
MALAT1	*RBM33*	protein coding
MALAT1	*RBM5*	protein coding
MALAT1	*RCAN3*	protein coding
MALAT1	*RCC2*	protein coding
MALAT1	*RCOR2*	protein coding
MALAT1	*REEP3*	protein coding
MALAT1	*RER1*	protein coding
MALAT1	*RF00019*	misc RNA
MALAT1	*RF00409*	snoRNA
MALAT1	*RF00568*	snoRNA
MALAT1	*RGPD2*	protein coding
MALAT1	*RGS10*	protein coding
MALAT1	*RHBDF2*	protein coding
MALAT1	*RHOA*	protein coding
MALAT1	*RIC8A*	protein coding
MALAT1	*RIMBP3*	protein coding
MALAT1	*RIPOR1*	protein coding
MALAT1	*RMC1*	protein coding
MALAT1	*RN7SKP104*	misc RNA
MALAT1	*RN7SKP111*	misc RNA
MALAT1	*RN7SKP131*	misc RNA
MALAT1	*RN7SKP160*	misc RNA
MALAT1	*RN7SKP180*	misc RNA

MALAT1	*RN7SKP187*	misc RNA
MALAT1	*RN7SKP281*	misc RNA
MALAT1	*RN7SKP80*	misc RNA
MALAT1	*RN7SKP87*	misc RNA
MALAT1	*RN7SKP95*	misc RNA
MALAT1	*RN7SL128P*	misc RNA
MALAT1	*RN7SL151P*	misc RNA
MALAT1	*RN7SL166P*	misc RNA
MALAT1	*RN7SL230P*	misc RNA
MALAT1	*RN7SL444P*	misc RNA
MALAT1	*RN7SL566P*	misc RNA
MALAT1	*RN7SL573P*	misc RNA
MALAT1	*RN7SL575P*	misc RNA
MALAT1	*RN7SL610P*	misc RNA
MALAT1	*RN7SL617P*	misc RNA
MALAT1	*RN7SL674P*	misc RNA
MALAT1	*RN7SL685P*	misc RNA
MALAT1	*RN7SL70P*	misc RNA
MALAT1	*RN7SL828P*	misc RNA
MALAT1	*RN7SL861P*	misc RNA
MALAT1	*RN7SL87P*	misc RNA
MALAT1	*RNA18N5*	rRNA
MALAT1	*RNA18S5*	rRNA
MALAT1	*RNA28S5*	rRNA
MALAT1	*RNA5-8S5*	rRNA
MALAT1	*RNA5-8SP2*	rRNA
MALAT1	*RNA5-8SP6*	rRNA
MALAT1	*RNA5S1*	rRNA
MALAT1	*RNA5S10*	rRNA
MALAT1	*RNA5S11*	rRNA
MALAT1	*RNA5S12*	rRNA
MALAT1	*RNA5S13*	rRNA
MALAT1	*RNA5S14*	rRNA
MALAT1	*RNA5S16*	rRNA
MALAT1	*RNA5S17*	rRNA
MALAT1	*RNA5S2*	rRNA
MALAT1	*RNA5S4*	rRNA
MALAT1	*RNA5S6*	rRNA
MALAT1	*RNA5S7*	rRNA
MALAT1	*RNA5SP122*	rRNA
MALAT1	*RNA5SP141*	rRNA
MALAT1	*RNA5SP19*	rRNA
MALAT1	*RNA5SP225*	rRNA
MALAT1	*RNA5SP267*	rRNA
MALAT1	*RNA5SP283*	rRNA
MALAT1	*RNA5SP329*	rRNA
MALAT1	*RNA5SP336*	rRNA
MALAT1	*RNA5SP348*	rRNA
MALAT1	*RNA5SP350*	rRNA
MALAT1	*RNA5SP352*	rRNA

MALAT1	*RNA5SP358*	rRNA
MALAT1	*RNA5SP370*	rRNA
MALAT1	*RNA5SP382*	rRNA
MALAT1	*RNA5SP426*	rRNA
MALAT1	*RNA5SP429*	rRNA
MALAT1	*RNA5SP442*	rRNA
MALAT1	*RNA5SP48*	rRNA
MALAT1	*RNA5SP506*	rRNA
MALAT1	*RNA5SP74*	rRNA
MALAT1	*RNA5SP77*	rRNA
MALAT1	*RNA5SP86*	rRNA
MALAT1	*RNASE6*	protein coding
MALAT1	*RNF111*	protein coding
MALAT1	*RNF150*	protein coding
MALAT1	*RNF167*	protein coding
MALAT1	*RNF170*	protein coding
MALAT1	*RNF213*	protein coding
MALAT1	*RNF26*	protein coding
MALAT1	*RNF41*	protein coding
MALAT1	*RNU1-1*	snRNA
MALAT1	*RNU1-100P*	snRNA
MALAT1	*RNU1-106P*	snRNA
MALAT1	*RNU1-117P*	snRNA
MALAT1	*RNU1-11P*	snRNA
MALAT1	*RNU1-124P*	snRNA
MALAT1	*RNU1-131P*	snRNA
MALAT1	*RNU1-133P*	snRNA
MALAT1	*RNU1-135P*	snRNA
MALAT1	*RNU1-136P*	snRNA
MALAT1	*RNU1-138P*	snRNA
MALAT1	*RNU1-141P*	snRNA
MALAT1	*RNU1-148P*	snRNA
MALAT1	*RNU1-14P*	snRNA
MALAT1	*RNU1-150P*	snRNA
MALAT1	*RNU1-18P*	snRNA
MALAT1	*RNU1-19P*	snRNA
MALAT1	*RNU1-2*	snRNA
MALAT1	*RNU1-21P*	snRNA
MALAT1	*RNU1-27P*	snRNA
MALAT1	*RNU1-28P*	snRNA
MALAT1	*RNU1-3*	snRNA
MALAT1	*RNU1-32P*	snRNA
MALAT1	*RNU1-35P*	snRNA
MALAT1	*RNU1-39P*	snRNA
MALAT1	*RNU1-4*	snRNA
MALAT1	*RNU1-42P*	snRNA
MALAT1	*RNU1-43P*	snRNA
MALAT1	*RNU1-44P*	snRNA
MALAT1	*RNU1-49P*	snRNA
MALAT1	*RNU1-51P*	snRNA

MALAT1	*RNU1-56P*	snRNA
MALAT1	*RNU1-61P*	snRNA
MALAT1	*RNU1-67P*	snRNA
MALAT1	*RNU1-69P*	snRNA
MALAT1	*RNU1-72P*	snRNA
MALAT1	*RNU1-74P*	snRNA
MALAT1	*RNU1-75P*	snRNA
MALAT1	*RNU1-77P*	snRNA
MALAT1	*RNU1-7P*	snRNA
MALAT1	*RNU1-80P*	snRNA
MALAT1	*RNU1-82P*	snRNA
MALAT1	*RNU1-84P*	snRNA
MALAT1	*RNU1-87P*	snRNA
MALAT1	*RNU1-88P*	snRNA
MALAT1	*RNU1-89P*	snRNA
MALAT1	*RNU1-94P*	snRNA
MALAT1	*RNU2-23P*	snRNA
MALAT1	*RNU2-2P*	snRNA
MALAT1	*RNU2-32P*	snRNA
MALAT1	*RNU2-35P*	snRNA
MALAT1	*RNU2-38P*	snRNA
MALAT1	*RNU2-42P*	snRNA
MALAT1	*RNU2-46P*	snRNA
MALAT1	*RNU2-48P*	snRNA
MALAT1	*RNU2-5P*	snRNA
MALAT1	*RNU4-1*	snRNA
MALAT1	*RNU4-2*	snRNA
MALAT1	*RNU4-76P*	snRNA
MALAT1	*RNU5A-1*	snRNA
MALAT1	*RNU5A-8P*	snRNA
MALAT1	*RNU5B-1*	snRNA
MALAT1	*RNU5B-2P*	snRNA
MALAT1	*RNU5E-1*	snRNA
MALAT1	*RNU6-116P*	snRNA
MALAT1	*RNU6-1175P*	snRNA
MALAT1	*RNU6-1332P*	snRNA
MALAT1	*RNU6-140P*	snRNA
MALAT1	*RNU6-16P*	snRNA
MALAT1	*RNU6-18P*	snRNA
MALAT1	*RNU6-208P*	snRNA
MALAT1	*RNU6-25P*	snRNA
MALAT1	*RNU6-31P*	snRNA
MALAT1	*RNU6-346P*	snRNA
MALAT1	*RNU6-393P*	snRNA
MALAT1	*RNU6-42P*	snRNA
MALAT1	*RNU6-48P*	snRNA
MALAT1	*RNU6-4P*	snRNA
MALAT1	*RNU6-585P*	snRNA
MALAT1	*RNU6-5P*	snRNA
MALAT1	*RNU6-61P*	snRNA

MALAT1	*RNU6-628P*	snRNA
MALAT1	*RNU6-671P*	snRNA
MALAT1	*RNU6-672P*	snRNA
MALAT1	*RNU6-7*	snRNA
MALAT1	*RNU6-776P*	snRNA
MALAT1	*RNU6-893P*	snRNA
MALAT1	*RNU6-905P*	snRNA
MALAT1	*RNU6-908P*	snRNA
MALAT1	*RNU6-984P*	snRNA
MALAT1	*RNU6ATAC*	snRNA
MALAT1	*RNU6ATAC4P*	snRNA
MALAT1	*RNVU1-1*	snRNA
MALAT1	*RNVU1-11*	snRNA
MALAT1	*RNVU1-14*	snRNA
MALAT1	*RNVU1-15*	snRNA
MALAT1	*RNVU1-17*	snRNA
MALAT1	*RNVU1-18*	snRNA
MALAT1	*RNVU1-6*	snRNA
MALAT1	*RNVU1-7*	snRNA
MALAT1	*RNY1*	misc RNA
MALAT1	*RNY3*	misc RNA
MALAT1	*RNY3P15*	misc RNA
MALAT1	*RNY5*	misc RNA
MALAT1	*ROBO1*	protein coding
MALAT1	*ROMO1*	protein coding
MALAT1	*RPL10AP2*	processed pseudogene
MALAT1	*RPL10AP5*	processed pseudogene
MALAT1	*RPL10P16*	processed pseudogene
MALAT1	*RPL11*	protein coding
MALAT1	*RPL11P5*	processed pseudogene
MALAT1	*RPL12*	protein coding
MALAT1	*RPL12P32*	processed pseudogene
MALAT1	*RPL12P38*	transcribed processed pseudogene
MALAT1	*RPL13*	protein coding
MALAT1	*RPL13A*	protein coding
MALAT1	*RPL13AP20*	processed pseudogene
MALAT1	*RPL13AP25*	processed pseudogene
MALAT1	*RPL13AP3*	transcribed processed pseudogene
MALAT1	*RPL13AP5*	processed pseudogene
MALAT1	*RPL13AP7*	processed pseudogene
MALAT1	*RPL13P12*	processed pseudogene
MALAT1	*RPL13P2*	processed pseudogene
MALAT1	*RPL15*	protein coding
MALAT1	*RPL17*	protein coding
MALAT1	*RPL18A*	protein coding
MALAT1	*RPL18AP3*	processed pseudogene
MALAT1	*RPL18AP8*	processed pseudogene
MALAT1	*RPL21P119*	processed pseudogene
MALAT1	*RPL22*	protein coding
MALAT1	*RPL22L1*	protein coding

MALAT1	*RPL23*	protein coding
MALAT1	*RPL24*	protein coding
MALAT1	*RPL28*	protein coding
MALAT1	*RPL29P23*	processed pseudogene
MALAT1	*RPL3*	protein coding
MALAT1	*RPL30*	protein coding
MALAT1	*RPL30P14*	processed pseudogene
MALAT1	*RPL30P4*	processed pseudogene
MALAT1	*RPL32*	protein coding
MALAT1	*RPL32P26*	processed pseudogene
MALAT1	*RPL32P28*	processed pseudogene
MALAT1	*RPL32P34*	processed pseudogene
MALAT1	*RPL35*	protein coding
MALAT1	*RPL36P16*	processed pseudogene
MALAT1	*RPL37A*	protein coding
MALAT1	*RPL37AP8*	processed pseudogene
MALAT1	*RPL37P2*	processed pseudogene
MALAT1	*RPL39*	protein coding
MALAT1	*RPL3P2*	processed pseudogene
MALAT1	*RPL3P4*	processed pseudogene
MALAT1	*RPL4*	protein coding
MALAT1	*RPL41P5*	processed pseudogene
MALAT1	*RPL4P2*	processed pseudogene
MALAT1	*RPL4P4*	processed pseudogene
MALAT1	*RPL4P5*	processed pseudogene
MALAT1	*RPL5P14*	processed pseudogene
MALAT1	*RPL5P30*	processed pseudogene
MALAT1	*RPL5P9*	processed pseudogene
MALAT1	*RPL7AP6*	processed pseudogene
MALAT1	*RPL7AP66*	processed pseudogene
MALAT1	*RPL7L1*	protein coding
MALAT1	*RPL8*	protein coding
MALAT1	*RPL8P2*	processed pseudogene
MALAT1	*RPL9*	protein coding
MALAT1	*RPL9P8*	pseudogene
MALAT1	*RPLP0*	protein coding
MALAT1	*RPLP0P2*	transcribed processed pseudogene
MALAT1	*RPLP0P6*	processed pseudogene
MALAT1	*RPLP1*	protein coding
MALAT1	*RPLP2*	protein coding
MALAT1	*RPS11*	protein coding
MALAT1	*RPS11P5*	processed pseudogene
MALAT1	*RPS12P26*	transcribed processed pseudogene
MALAT1	*RPS12P28*	processed pseudogene
MALAT1	*RPS13*	protein coding
MALAT1	*RPS14P4*	processed pseudogene
MALAT1	*RPS15AP1*	processed pseudogene
MALAT1	*RPS15AP11*	processed pseudogene
MALAT1	*RPS16*	protein coding
MALAT1	*RPS18*	protein coding

MALAT1	*RPS18P9*	processed pseudogene
MALAT1	*RPS2*	protein coding
MALAT1	*RPS20*	protein coding
MALAT1	*RPS23*	protein coding
MALAT1	*RPS23P2*	processed pseudogene
MALAT1	*RPS23P8*	processed pseudogene
MALAT1	*RPS26*	protein coding
MALAT1	*RPS26P43*	processed pseudogene
MALAT1	*RPS2P7*	processed pseudogene
MALAT1	*RPS3*	protein coding
MALAT1	*RPS3AP37*	processed pseudogene
MALAT1	*RPS3AP6*	processed pseudogene
MALAT1	*RPS3P6*	processed pseudogene
MALAT1	*RPS4XP13*	processed pseudogene
MALAT1	*RPS4XP14*	processed pseudogene
MALAT1	*RPS4XP2*	processed pseudogene
MALAT1	*RPS4XP22*	processed pseudogene
MALAT1	*RPS6*	protein coding
MALAT1	*RPS6P22*	processed pseudogene
MALAT1	*RPS8P10*	unprocessed pseudogene
MALAT1	*RPS9*	protein coding
MALAT1	*RPSA*	protein coding
MALAT1	*RPSAP12*	processed pseudogene
MALAT1	*RPSAP54*	processed pseudogene
MALAT1	*RPUSD3*	protein coding
MALAT1	*RRP36*	protein coding
MALAT1	*RSC1A1*	protein coding
MALAT1	*RSPRY1*	protein coding
MALAT1	*RTF1*	protein coding
MALAT1	*RTN3*	protein coding
MALAT1	*RUFY3*	protein coding
MALAT1	*S1PR2*	protein coding
MALAT1	*SAP130*	protein coding
MALAT1	*SARS2*	protein coding
MALAT1	*SBF2*	protein coding
MALAT1	*SCAMP1*	protein coding
MALAT1	*SCARNA7*	snoRNA
MALAT1	*SCD*	protein coding
MALAT1	*SCDP1*	processed pseudogene
MALAT1	*SCNM1*	protein coding
MALAT1	*SCPEP1*	protein coding
MALAT1	*SDHAF2*	protein coding
MALAT1	*SDHB*	protein coding
MALAT1	*SDHC*	protein coding
MALAT1	*SEC11A*	protein coding
MALAT1	*SEC23A*	protein coding
MALAT1	*SEC61A1*	protein coding
MALAT1	*SELL*	protein coding
MALAT1	*SEMA3F*	protein coding
MALAT1	*SEMA6C*	protein coding

MALAT1	*SENP1*	protein coding
MALAT1	*SEPT10*	protein coding
MALAT1	*SEPT11*	protein coding
MALAT1	*SEPT2*	protein coding
MALAT1	*SEPT6*	protein coding
MALAT1	*SERF2*	protein coding
MALAT1	*SERINC2*	protein coding
MALAT1	*SERPINB6*	protein coding
MALAT1	*SETD2*	protein coding
MALAT1	*SETD5*	protein coding
MALAT1	*SF3A3*	protein coding
MALAT1	*SF3B4*	protein coding
MALAT1	*SFRP1*	protein coding
MALAT1	*SGCB*	protein coding
MALAT1	*SH3KBP1*	protein coding
MALAT1	*SHC1*	protein coding
MALAT1	*SHMT1*	protein coding
MALAT1	*SIGMAR1*	protein coding
MALAT1	*SIM2*	protein coding
MALAT1	*SIPA1L1*	protein coding
MALAT1	*SKIV2L*	protein coding
MALAT1	*SLAMF6*	protein coding
MALAT1	*SLC12A6*	protein coding
MALAT1	*SLC12A7*	protein coding
MALAT1	*SLC12A8*	protein coding
MALAT1	*SLC16A1*	protein coding
MALAT1	*SLC17A3*	protein coding
MALAT1	*SLC18B1*	protein coding
MALAT1	*SLC25A11*	protein coding
MALAT1	*SLC25A15*	protein coding
MALAT1	*SLC25A3*	protein coding
MALAT1	*SLC25A44*	protein coding
MALAT1	*SLC25A5P3*	processed pseudogene
MALAT1	*SLC25A6*	protein coding
MALAT1	*SLC29A1*	protein coding
MALAT1	*SLC29A3*	protein coding
MALAT1	*SLC38A1*	protein coding
MALAT1	*SLC41A1*	protein coding
MALAT1	*SLC43A3*	protein coding
MALAT1	*SLC44A2*	protein coding
MALAT1	*SLC6A9*	protein coding
MALAT1	*SLCO4A1*	protein coding
MALAT1	*SLK*	protein coding
MALAT1	*SLMAP*	protein coding
MALAT1	*SMAD2*	protein coding
MALAT1	*SMARCA1*	protein coding
MALAT1	*SMARCA2*	protein coding
MALAT1	*SMARCD2*	protein coding
MALAT1	*SMARCE1*	protein coding
MALAT1	*SMDT1*	protein coding

MALAT1	*SMG1*	protein coding
MALAT1	*SMG1P1*	transcribed unprocessed pseudogene
MALAT1	*SMYD4*	protein coding
MALAT1	*SMYD5*	protein coding
MALAT1	*SNAI2*	protein coding
MALAT1	*SNCA*	protein coding
MALAT1	*SNHG14*	processed transcript
MALAT1	*SNHG8*	lincRNA
MALAT1	*SNORA40*	snoRNA
MALAT1	*SNORA63*	snoRNA
MALAT1	*SNORA66*	snoRNA
MALAT1	*SNORA73B*	snoRNA
MALAT1	*SNORA74A*	snoRNA
MALAT1	*SNORD118*	snoRNA
MALAT1	*SNORD13*	snoRNA
MALAT1	*SNORD14A*	snoRNA
MALAT1	*SNORD14C*	snoRNA
MALAT1	*SNORD14D*	snoRNA
MALAT1	*SNORD3A*	snoRNA
MALAT1	*SNORD3B-1*	snoRNA
MALAT1	*SNORD3B-2*	snoRNA
MALAT1	*SNORD3C*	snoRNA
MALAT1	*SNRNP25*	protein coding
MALAT1	*SNRPD2P1*	processed pseudogene
MALAT1	*SNRPN*	protein coding
MALAT1	*SNU13*	protein coding
MALAT1	*SNURF*	protein coding
MALAT1	*SNX13*	protein coding
MALAT1	*SORD*	protein coding
MALAT1	*SOX4*	protein coding
MALAT1	*SOX8*	protein coding
MALAT1	*SP1*	protein coding
MALAT1	*SP100*	protein coding
MALAT1	*SPCS2*	protein coding
MALAT1	*SPEN*	protein coding
MALAT1	*SRCIN1*	protein coding
MALAT1	*SRGN*	protein coding
MALAT1	*SRP68*	protein coding
MALAT1	*SRP72*	protein coding
MALAT1	*SRRT*	protein coding
MALAT1	*SRSF2*	protein coding
MALAT1	*SRSF6*	protein coding
MALAT1	*SRSF9*	protein coding
MALAT1	*SRSF9P1*	processed pseudogene
MALAT1	*SSR4*	protein coding
MALAT1	*STAT1*	protein coding
MALAT1	*STC1*	protein coding
MALAT1	*STK38L*	protein coding
MALAT1	*STMN1*	protein coding
MALAT1	*STMP1*	protein coding

MALAT1	*STRAP*	protein coding
MALAT1	*STT3B*	protein coding
MALAT1	*STXBP3*	protein coding
MALAT1	*SUCLG1*	protein coding
MALAT1	*SULF2*	protein coding
MALAT1	*SUMO2*	protein coding
MALAT1	*SUPT16HP1*	processed pseudogene
MALAT1	*suz12*	protein coding
MALAT1	*SYMPK*	protein coding
MALAT1	*SYNRG*	protein coding
MALAT1	*SYT7*	protein coding
MALAT1	*SZRD1*	protein coding
MALAT1	*TAB3*	protein coding
MALAT1	*TACC3*	protein coding
MALAT1	*TAF1D*	protein coding
MALAT1	*TAGLN2*	protein coding
MALAT1	*TALDO1*	protein coding
MALAT1	*TAOK3*	protein coding
MALAT1	*TARS*	protein coding
MALAT1	*TAX1BP1*	protein coding
MALAT1	*TAX1BP3*	protein coding
MALAT1	*TBL1XR1*	protein coding
MALAT1	*TCEA1P2*	processed pseudogene
MALAT1	*TCL1A*	protein coding
MALAT1	*TCOF1*	protein coding
MALAT1	*TCP1*	protein coding
MALAT1	*TCTA*	protein coding
MALAT1	*TEAD3*	protein coding
MALAT1	*TEX261*	protein coding
MALAT1	*TFAP4*	protein coding
MALAT1	*TGIF1*	protein coding
MALAT1	*THOC6*	protein coding
MALAT1	*Thr_tRNA*	tRNA
MALAT1	*TICAM1*	protein coding
MALAT1	*TIGD5*	protein coding
MALAT1	*TIMM10B*	protein coding
MALAT1	*TIMM23*	protein coding
MALAT1	*TJAP1*	protein coding
MALAT1	*TJP1*	protein coding
MALAT1	*TJP2*	protein coding
MALAT1	*TKT*	protein coding
MALAT1	*TLN1*	protein coding
MALAT1	*TM9SF1*	protein coding
MALAT1	*TMBIM6*	protein coding
MALAT1	*TMED10P1*	processed pseudogene
MALAT1	*TMEM107*	protein coding
MALAT1	*TMEM123*	protein coding
MALAT1	*TMEM132A*	protein coding
MALAT1	*TMEM184C*	protein coding
MALAT1	*TMEM199*	protein coding

MALAT1	*TMEM206*	protein coding
MALAT1	*TMEM245*	protein coding
MALAT1	*TMEM248*	protein coding
MALAT1	*TMEM259*	protein coding
MALAT1	*TMEM50A*	protein coding
MALAT1	*TMPO*	protein coding
MALAT1	*TMSB4X*	protein coding
MALAT1	*TNFAIP3*	protein coding
MALAT1	*TNPO2*	protein coding
MALAT1	*TNS4*	protein coding
MALAT1	*TOB1*	protein coding
MALAT1	*TOB2*	protein coding
MALAT1	*TOGARAM1*	protein coding
MALAT1	*TOLLIP*	protein coding
MALAT1	*TOMM40*	protein coding
MALAT1	*TOMM7*	protein coding
MALAT1	*TOMM70*	protein coding
MALAT1	*TOP2B*	protein coding
MALAT1	*TP53*	protein coding
MALAT1	*TP73-AS1*	transcribed_unitary_pseudogene
MALAT1	*TPI1*	protein coding
MALAT1	*TPPP*	protein coding
MALAT1	*TPR*	protein coding
MALAT1	*TPT1*	protein coding
MALAT1	*TPT1P13*	processed pseudogene
MALAT1	*TPT1P2*	processed pseudogene
MALAT1	*TRAPPC1*	protein coding
MALAT1	*TRIP10*	protein coding
MALAT1	*TRIP13*	protein coding
MALAT1	*TRNP1*	protein coding
MALAT1	*TROVE2*	protein coding
MALAT1	*TRRAP*	protein coding
MALAT1	*TSC22D3*	protein coding
MALAT1	*TSSC4*	protein coding
MALAT1	*TSTA3*	protein coding
MALAT1	*TTC17*	protein coding
MALAT1	*TTC3*	protein coding
MALAT1	*TTC38*	protein coding
MALAT1	*TTL*	protein coding
MALAT1	*TUBA1A*	protein coding
MALAT1	*TUBA1B*	protein coding
MALAT1	*TUBA1C*	protein coding
MALAT1	*TUBA4A*	protein coding
MALAT1	*TUBAP2*	processed pseudogene
MALAT1	*TUBAP4*	transcribed processed pseudogene
MALAT1	*TUBB*	protein coding
MALAT1	*TUBB4B*	protein coding
MALAT1	*TUBBP1*	transcribed processed pseudogene
MALAT1	*TUFM*	protein coding
MALAT1	*TXNDC5*	protein coding

MALAT1	*TXNP5*	processed pseudogene
MALAT1	*TYSND1*	protein coding
MALAT1	*U2SURP*	protein coding
MALAT1	*UBA1*	protein coding
MALAT1	*UBA52*	protein coding
MALAT1	*UBAP2L*	protein coding
MALAT1	*UBB*	protein coding
MALAT1	*UBC*	protein coding
MALAT1	*UBD*	protein coding
MALAT1	*UBE2G1*	protein coding
MALAT1	*UBE2H*	protein coding
MALAT1	*UBE2J1*	protein coding
MALAT1	*UBE2L6*	protein coding
MALAT1	*UBE2M*	protein coding
MALAT1	*UBE2R2*	protein coding
MALAT1	*UBE2V1*	protein coding
MALAT1	*UBE3C*	protein coding
MALAT1	*UBE4A*	protein coding
MALAT1	*UBL3*	protein coding
MALAT1	*UBL5*	protein coding
MALAT1	*UBL7*	protein coding
MALAT1	*UCHL1*	protein coding
MALAT1	*UHRF1*	protein coding
MALAT1	*UNC5B*	protein coding
MALAT1	*UPRT*	protein coding
MALAT1	*UQCRFS1P1*	processed pseudogene
MALAT1	*UQCRH*	protein coding
MALAT1	*URB2*	protein coding
MALAT1	*UTP14A*	protein coding
MALAT1	*UTP4*	protein coding
MALAT1	*UTP6*	protein coding
MALAT1	*UTRN*	protein coding
MALAT1	*VAMP3*	protein coding
MALAT1	*VAPA*	protein coding
MALAT1	*VDAC1P1*	processed pseudogene
MALAT1	*VEGFA*	protein coding
MALAT1	*VEGFB*	protein coding
MALAT1	*VOPP1*	protein coding
MALAT1	*VPS13C*	protein coding
MALAT1	*VPS25*	protein coding
MALAT1	*VPS39*	protein coding
MALAT1	*VTI1B*	protein coding
MALAT1	*VTRNA1-1*	misc RNA
MALAT1	*WAC*	protein coding
MALAT1	*WARS*	protein coding
MALAT1	*WASF2*	protein coding
MALAT1	*WASHC2A*	protein coding
MALAT1	*WASHC5*	protein coding
MALAT1	*WBP11*	protein coding
MALAT1	*WDR26*	protein coding

MALAT1	*WDR27*	protein coding
MALAT1	*WDR73*	protein coding
MALAT1	*WDR74*	protein coding
MALAT1	*WDTC1*	protein coding
MALAT1	*WIZ*	protein coding
MALAT1	*WLS*	protein coding
MALAT1	*XIST*	lincRNA
MALAT1	*XRCC6*	protein coding
MALAT1	*XRCC6P2*	processed pseudogene
MALAT1	*YBX2*	protein coding
MALAT1	*YJEFN3*	protein coding
MALAT1	*YWHAB*	protein coding
MALAT1	*YWHAE*	protein coding
MALAT1	*YWHAEP5*	processed pseudogene
MALAT1	*YWHAQ*	protein coding
MALAT1	*YWHAZ*	protein coding
MALAT1	*ZBED1*	protein coding
MALAT1	*ZBTB41*	protein coding
MALAT1	*ZEB1*	protein coding
MALAT1	*ZEB2*	protein coding
MALAT1	*ZER1*	protein coding
MALAT1	*ZFAS1*	antisense
MALAT1	*ZFP36L1*	protein coding
MALAT1	*ZFP91*	protein coding
MALAT1	*ZFYVE27*	protein coding
MALAT1	*ZIK1*	protein coding
MALAT1	*ZKSCAN1*	protein coding
MALAT1	*ZMIZ1*	protein coding
MALAT1	*ZNF142*	protein coding
MALAT1	*ZNF160*	protein coding
MALAT1	*ZNF174*	protein coding
MALAT1	*ZNF175*	protein coding
MALAT1	*ZNF202*	protein coding
MALAT1	*ZNF207*	protein coding
MALAT1	*ZNF224*	protein coding
MALAT1	*ZNF232*	protein coding
MALAT1	*ZNF277*	protein coding
MALAT1	*ZNF282*	protein coding
MALAT1	*ZNF354B*	protein coding
MALAT1	*ZNF500*	protein coding
MALAT1	*ZNF518A*	protein coding
MALAT1	*ZNF646*	protein coding
MALAT1	*ZNF678*	protein coding
MALAT1	*ZZEF1*	protein coding
MEG3	*ABCB1*	protein coding
MEG3	*ABCC1*	protein coding
MEG3	*ABCG2*	protein coding
MEG3	*AKAP11*	protein coding
MEG3	*ATG3*	protein coding
MEG3	*BCL2*	protein coding

MEG3	*BMP4*	protein coding
MEG3	*CASP3*	protein coding
MEG3	*CASP8*	protein coding
MEG3	*CASP9*	protein coding
MEG3	*EZH2*	protein coding
MEG3	*IDH1*	protein coding
MEG3	*KDR*	protein coding
MEG3	*LC3-II*	protein coding
MEG3	*MDM2*	protein coding
MEG3	*MIR127*	miRNA
MEG3	*MIR140*	miRNA
MEG3	*MIR181A1*	miRNA
MEG3	*MIR181B1*	miRNA
MEG3	*MIR183*	miRNA
MEG3	*MIR21*	miRNA
MEG3	*MIR214*	miRNA
MEG3	*MIR421*	miRNA
MEG3	*MIR664A*	miRNA
MEG3	*miRNA-9*	miRNA
MEG3	*Notch1*	protein coding
MEG3	*osteocalcin*	protein coding
MEG3	*RAC2*	protein coding
MEG3	*RUNX2*	protein coding
MEG3	*SP7*	protein coding
MEG3	*TP53*	protein coding
MEG3	*UBE2B*	protein coding
MIAT	*ATP5F1BP1*	lincRNA
MIAT	*ATP5MC2P1*	lincRNA
MIAT	*BEX3*	lincRNA
MIAT	*CAPRIN1*	lincRNA
MIAT	*CDC16*	protein coding
MIAT	*CEP170*	lincRNA
MIAT	*CFL1*	lincRNA
MIAT	*COPS5*	lincRNA
MIAT	*CORO1C*	lincRNA
MIAT	*CREB3*	protein coding
MIAT	*CSRP2*	protein coding
MIAT	*DLG3*	protein coding
MIAT	*EEF1A1P5*	processed pseudogene
MIAT	*ERP29*	protein coding
MIAT	*EZR*	lincRNA
MIAT	*FASTKD5*	lincRNA
MIAT	*FTL*	protein coding
MIAT	*GDI2*	protein coding
MIAT	*Glu_tRNA*	tRNA
MIAT	*HADHB*	lincRNA
MIAT	*HSP90AB3P*	lincRNA
MIAT	*HUWE1*	protein coding
MIAT	*INO80B*	protein coding
MIAT	*IST1*	protein coding

MIAT	*KIF4A*	lincRNA
MIAT	*LINGO1*	protein coding
MIAT	*LSM12*	lincRNA
MIAT	*LSM14B*	protein coding
MIAT	*MAZ*	lincRNA
MIAT	*MEGF8*	lincRNA
MIAT	*MIATNB*	lincRNA
MIAT	*MLF2*	lincRNA
MIAT	*MTCH1*	protein coding
MIAT	*MTCO1P53*	lincRNA
MIAT	*MTCO3P12*	lincRNA
MIAT	*NONO*	lincRNA
MIAT	*PFN1*	lincRNA
MIAT	*PGAM1P5*	transcribed processed pseudogene
MIAT	*PLAGL2*	protein coding
MIAT	*POU5F1P3*	processed pseudogene
MIAT	*PPP1R42*	lincRNA
MIAT	*PRODH*	lincRNA
MIAT	*PRR5*	lincRNA
MIAT	*PRRC2A*	lincRNA
MIAT	*PTMS*	protein coding
MIAT	*PYCR2*	protein coding
MIAT	*RF00019*	misc RNA
MIAT	*RHEB*	protein coding
MIAT	*RNA18N5*	lincRNA
MIAT	*RNA18S5*	lincRNA
MIAT	*RPL13P2*	processed pseudogene
MIAT	*RPL3*	protein coding
MIAT	*RPS3*	lincRNA
MIAT	*RPS4XP11*	processed pseudogene
MIAT	*RPSA*	lincRNA
MIAT	*SAP18*	protein coding
MIAT	*SART3*	protein coding
MIAT	*SIGMAR1*	lincRNA
MIAT	*STAU1*	protein coding
MIAT	*TINF2*	lincRNA
MIAT	*TPI1P2*	lincRNA
MIAT	*TUBA1B*	lincRNA
MIAT	*UBE2V1*	protein coding
MIAT	*YBX1*	lincRNA
MIAT	*YWHAE*	lincRNA

Supplementary table 4. Significant KEGG pathways regulated by the target genes of the 5 lncRNAs.

Pathway Source	Pathway Name	p-*value*	q-value (FDR: BH-method)
KEGG	Ribosome	6,37E-25	1,87E-22
KEGG	MicroRNAs in cancer	9,92E-22	1,45E-19
KEGG	Proteoglycans in cancer	1,45E-20	1,41E-18
KEGG	Focal adhesion	2,14E-17	1,57E-15
KEGG	Cellular senescence	3,33E-16	1,95E-14
KEGG	Epstein-Barr virus infection	1,01E-15	4,91E-14
KEGG	Pathways in cancer	2,57E-15	1,07E-13
KEGG	Parkinson disease	9,61E-15	3,52E-13
KEGG	Hepatitis B	1,50E-14	4,89E-13
KEGG	Prostate cancer	1,10E-13	2,93E-12
KEGG	PI3K-Akt signaling	1,01E-13	2,97E-12
KEGG	Fluid shear stress and atherosclerosis	1,55E-13	3,79E-12
KEGG	Adherens junction	2,94E-13	6,63E-12
KEGG	Human cytomegalovirus infection	3,49E-13	7,31E-12
KEGG	Tight junction	4,83E-13	9,43E-12
KEGG	Kaposi sarcoma-associated herpesvirus infection	1,56E-12	2,86E-11
KEGG	Cell cycle	1,73E-12	2,97E-11
KEGG	Bladder cancer	2,91E-12	4,49E-11
KEGG	Human T-cell leukemia virus 1 infection	2,83E-12	4,60E-11
KEGG	Hepatitis C	4,54E-12	6,65E-11
KEGG	AGE-RAGE signaling pathway in diabetic complications	9,75E-12	1,36E-10
KEGG	Colorectal cancer	1,84E-11	2,45E-10
KEGG	Leukocyte transendothelial migration	2,95E-11	3,76E-10
KEGG	Human papillomavirus infection	4,73E-11	5,77E-10
KEGG	Pancreatic cancer	5,40E-11	6,33E-10
KEGG	Hippo signaling	8,28E-11	9,33E-10
KEGG	FoxO signaling	1,88E-10	2,04E-09
KEGG	Viral myocarditis	1,98E-10	2,07E-09
KEGG	Pathogenic Escherichia coli infection	6,80E-10	6,64E-09

KEGG	Small cell lung cancer	6,72E-10	6,79E-09
KEGG	Thermogenesis	7,49E-10	7,08E-09
KEGG	Hepatocellular carcinoma	7,76E-10	7,10E-09
KEGG	Human immunodeficiency virus 1 infection	1,01E-09	9,00E-09
KEGG	Viral carcinogenesis	1,24E-09	1,07E-08
KEGG	Herpes simplex infection	2,38E-09	1,99E-08
KEGG	Protein processing in endoplasmic reticulum	2,52E-09	2,05E-08
KEGG	HIF-1 signaling	2,93E-09	2,32E-08
KEGG	Sphingolipid signaling	3,01E-09	2,32E-08
KEGG	Chronic myeloid leukemia	3,66E-09	2,75E-08
KEGG	Alzheimer disease	5,90E-09	4,32E-08
KEGG	MAPK signaling	6,59E-09	4,71E-08
KEGG	Rap1 signaling	8,99E-09	6,27E-08
KEGG	Fc gamma R-mediated phagocytosis	1,28E-08	8,51E-08
KEGG	Apoptosis	1,25E-08	8,51E-08
KEGG	Endometrial cancer	1,36E-08	8,88E-08
KEGG	Gastric cancer	1,71E-08	1,09E-07
KEGG	Neurotrophin signaling	1,79E-08	1,11E-07
KEGG	ErbB signaling	2,17E-08	1,33E-07
KEGG	Oxidative phosphorylation	3,55E-08	2,12E-07
KEGG	Thyroid hormone signaling	5,22E-08	3,06E-07
KEGG	p53 signaling	6,10E-08	3,50E-07
KEGG	Regulation of actin cytoskeleton	6,47E-08	3,65E-07
KEGG	Autophagy - animal	7,42E-08	4,10E-07
KEGG	Huntington disease	9,45E-08	4,94E-07
KEGG	TNF signaling	9,31E-08	4,96E-07
KEGG	Fc epsilon RI signaling	1,00E-07	4,99E-07
KEGG	Influenza A	9,26E-08	5,03E-07
KEGG	VEGF signaling	9,99E-08	5,05E-07
KEGG	Relaxin signaling	9,99E-08	5,13E-07
KEGG	Thyroid cancer	1,25E-07	6,10E-07
KEGG	Glioma	2,98E-07	1,43E-06
KEGG	AMPK signaling	4,34E-07	2,05E-06

KEGG	Bacterial invasion of epithelial cells	5,44E-07	2,53E-06
KEGG	Cell adhesion molecules (CAMs)	5,92E-07	2,71E-06
KEGG	Non-small cell lung cancer	6,22E-07	2,76E-06
KEGG	IL-17 signaling	6,21E-07	2,80E-06
KEGG	Toxoplasmosis	6,75E-07	2,95E-06
KEGG	Renal cell carcinoma	9,36E-07	4,04E-06
KEGG	Insulin signaling	1,07E-06	4,53E-06
KEGG	Ras signaling	1,29E-06	5,42E-06
KEGG	Choline metabolism in cancer	1,39E-06	5,73E-06
KEGG	Melanoma	2,03E-06	8,24E-06
KEGG	Spliceosome	2,18E-06	8,77E-06
KEGG	Oocyte meiosis	2,36E-06	9,33E-06
KEGG	Chagas disease (American trypanosomiasis)	2,54E-06	9,91E-06
KEGG	Central carbon metabolism in cancer	2,92E-06	1,13E-05
KEGG	Mitophagy - animal	2,92E-06	1,13E-05
KEGG	Shigellosis	2,92E-06	1,13E-05
KEGG	C-type lectin receptor signaling	3,39E-06	1,26E-05
KEGG	Estrogen signaling	3,57E-06	1,31E-05
KEGG	Non-alcoholic fatty liver disease (NAFLD)	4,48E-06	1,60E-05
KEGG	Salmonella infection	4,48E-06	1,62E-05
KEGG	Insulin resistance	5,15E-06	1,82E-05
KEGG	Gap junction	6,11E-06	2,13E-05
KEGG	Prolactin signaling	7,34E-06	2,53E-05
KEGG	mRNA surveillance	9,56E-06	3,26E-05
KEGG	GnRH signaling	1,10E-05	3,72E-05
KEGG	Endocytosis	1,14E-05	3,80E-05
KEGG	Breast cancer	1,24E-05	4,08E-05
KEGG	Toll-like receptor signaling	1,39E-05	4,52E-05
KEGG	TGF-beta signaling	1,49E-05	4,80E-05
KEGG	Phagosome	1,89E-05	6,00E-05
KEGG	RNA transport	2,59E-05	8,07E-05
KEGG	Measles	2,57E-05	8,09E-05
KEGG	Vibrio cholerae infection	2,73E-05	8,43E-05

KEGG	Phospholipase D signaling	3,02E-05	9,22E-05
KEGG	Transcriptional misregulation in cancer	4,39E-05	1,33E-04
KEGG	Arrhythmogenic right ventricular cardiomyopathy (ARVC)	4,86E-05	1,45E-04
KEGG	cAMP signaling	5,41E-05	1,60E-04
KEGG	Type II diabetes mellitus	7,05E-05	2,07E-04
KEGG	Progesterone-mediated oocyte maturation	7,55E-05	2,19E-04
KEGG	Cushing syndrome	7,97E-05	2,29E-04
KEGG	NOD-like receptor signaling	9,33E-05	2,65E-04
KEGG	Antigen processing and presentation	1,00E-04	2,82E-04
KEGG	Ribosome biogenesis in eukaryotes	1,31E-04	3,66E-04
KEGG	Wnt signaling	1,39E-04	3,85E-04
KEGG	Apoptosis - multiple species	1,67E-04	4,57E-04
KEGG	Chemokine signaling	1,84E-04	5,00E-04
KEGG	Natural killer cell mediated cytotoxicity	2,25E-04	6,04E-04
KEGG	Th17 cell differentiation	2,62E-04	6,99E-04
KEGG	Pertussis	3,51E-04	9,28E-04
KEGG	Platelet activation	3,60E-04	9,41E-04
KEGG	Necroptosis	3,85E-04	9,99E-04
KEGG	Axon guidance	4,21E-04	1,08E-03
KEGG	Epithelial cell signaling in Helicobacter pylori infection	4,96E-04	1,26E-03
KEGG	Glycolysis / Gluconeogenesis	4,96E-04	1,26E-03
KEGG	RNA degradation	5,06E-04	1,27E-03
KEGG	Osteoclast differentiation	5,67E-04	1,40E-03
KEGG	Tuberculosis	5,65E-04	1,40E-03
KEGG	N-Glycan biosynthesis	6,15E-04	1,49E-03
KEGG	Th1 and Th2 cell differentiation	6,13E-04	1,50E-03
KEGG	Parathyroid hormone synthesis, secretion and action	7,68E-04	1,84E-03
KEGG	Ubiquitin mediated proteolysis	1,30E-03	3,09E-03
KEGG	Cysteine and methionine metabolism	2,04E-03	4,83E-03
KEGG	B cell receptor signaling	2,34E-03	5,49E-03
KEGG	Vascular smooth muscle contraction	2,57E-03	5,97E-03
KEGG	Retrograde endocannabinoid signaling	2,89E-03	6,66E-03
KEGG	Non-homologous end-joining	3,05E-03	6,98E-03

KEGG	Citrate cycle (TCA cycle)	3,19E-03	7,24E-03
KEGG	Pentose phosphate	3,19E-03	7,24E-03
KEGG	mTOR signaling	3,31E-03	7,39E-03
KEGG	Oxytocin signaling	3,53E-03	7,84E-03
KEGG	Signaling pathways regulating pluripotency of stem cells	3,66E-03	8,06E-03
KEGG	T cell receptor signaling	4,02E-03	8,79E-03
KEGG	Rheumatoid arthritis	4,60E-03	9,99E-03
KEGG	Protein export	4,82E-03	1,04E-02
KEGG	Acute myeloid leukemia	5,23E-03	1,11E-02
KEGG	Cardiac muscle contraction	5,20E-03	1,11E-02
KEGG	Dopaminergic synapse	5,69E-03	1,17E-02
KEGG	Legionellosis	5,59E-03	1,18E-02
KEGG	ABC transporters	5,67E-03	1,19E-02
KEGG	Aminoacyl-tRNA biosynthesis	5,67E-03	1,19E-02
KEGG	Proteasome	6,44E-03	1,32E-02
KEGG	Prion diseases	7,06E-03	1,43E-02
KEGG	Adipocytokine signaling	7,01E-03	1,43E-02
KEGG	Apelin signaling	7,88E-03	1,58E-02
KEGG	Long-term depression	8,55E-03	1,70E-02
KEGG	Allograft rejection	9,30E-03	1,84E-02
KEGG	Leishmaniasis	1,01E-02	1,98E-02
KEGG	Inositol phosphate metabolism	1,10E-02	2,15E-02
KEGG	Hippo signaling pathway - multiple species	1,15E-02	2,23E-02
KEGG	Adrenergic signaling in cardiomyocytes	1,27E-02	2,45E-02
KEGG	Longevity regulating	1,29E-02	2,48E-02
KEGG	Graft-versus-host disease	1,52E-02	2,89E-02
KEGG	cGMP-PKG signaling	1,54E-02	2,90E-02
KEGG	Type I diabetes mellitus	1,90E-02	3,56E-02
KEGG	Amoebiasis	1,97E-02	3,66E-02
KEGG	Lysosome	1,97E-02	3,67E-02
KEGG	ECM-receptor interaction	2,06E-02	3,79E-02
KEGG	Inflammatory mediator regulation of TRP channels	2,40E-02	4,39E-02
KEGG	Bile secretion	2,45E-02	4,45E-02

KEGG	Proximal tubule bicarbonate reclamation	2,54E-02	4,60E-02
KEGG	Lysine degradation	2,67E-02	4,79E-02
KEGG	Vibrio cholerae infection	2,73E-02	4,26E-02
KEGG	Phospholipase D signaling	3,02E-02	4,22E-02
KEGG	Transcriptional misregulation in cancer	4,39E-02	4,33E-02
KEGG	Arrhythmogenic right ventricular cardiomyopathy (ARVC)	4,86E-02	4,93E-02
KEGG	cAMP signaling	4,41E-02	4,92E-02

CONCLUSÕES GERAIS

O envolvimento dos fatores epigenéticos no desenvolvimento de patologias vem sendo muito investigado nos últimos anos. Dentre esses fatores epigenéticos, temos os miRNAs e lncRNAs, que são RNAs não-codificantes de proteínas que exercem funções relacionadas à regulação da expressão gênica e vêm sendo sugeridos como potenciais biomarcadores para diagnósticos de diversas patologias, incluindo o DM e a DRD. Neste contexto, buscando entender o envolvimento dos miRNAs e lncRNAs no DM e DRD, bem como seu possível uso como potenciais biomarcadores dessas patologias, realizamos cinco estudos sobre este tema.

O primeiro artigo identificou 79 miRNAs desregulados entre pacientes com DRD e pacientes sem esta complicação. Visto que classificamos os pacientes com DRD de acordo com o declínio da TFGe (progressores e não-progressores), destacamos que identificamos um grupo específico de 15 miRNAs que difere entre indivíduos progressores e não-progressores para declínio rápido na TFGe, possibilitando assim, um melhor entendimento dos fatores associados à progressão da DRD em pacientes com DM1. Dentre esses miRNAs, validamos o hsa-miR-30a-5p, confirmando que sua expressão está aumentada nos pacientes com DM1 e DRD progressores em comparação aos demais grupos. Ainda, por meio da comparação dos nossos dados com um estudo público de transcriptômica, validamos mais 3 miRNAs diferencialmente expressos entre progressores e não-progressores em comparação ao grupo sem DRD (TFGe normal). Análises de bioinformática demonstraram que esses miRNAs regulam genes envolvidos na patogênese da DRD, tais como apoptose, insulina, TGF-β e estresse oxidativo.

Num estudo de revisão sistemática sobre lncRNAs envolvidos no DM, identificamos 6 lncRNAs diferencialmente expressos em pacientes com DM em comparação ao grupo

controle (*ANRIL*, *HOTAIR*, *MALAT1*, *MIAT*, *KCNQ1OT1* e *MEG3*). Nossas análises de bioinformática demonstraram que esses lncRNAs estão envolvidos em vias relacionadas à patogênese do DM, tais como PI3K/Akt, MAPK, apoptose, AGE/RAGE e FoxO. Através deste estudo também destacamos a falta de dados sobre o papel e expressão de lncRNAs em pacientes com DM1 visto que a maioria dos estudos incluídos na presente revisão foram feitos em pacientes com DM2.

Assim, para investigar o papel dos lncRNAs em pacientes com DM1, realizamos um estudo de caso-controle (artigo 3) e identificamos que as expressões dos lncRNAs *MALAT1*, *MEG3* e *TUG1* estão desreguladas em pacientes com <5 anos de DM1. Também demonstramos que os níveis de expressão de *MALAT1* e *TUG1* foram negativamente correlacionados com o tempo de duração do DM1 e os níveis de *MEG3* e *TUG1* foram positivamente correlacionados com os valores de HbA1c, indicando assim o envolvimento dos lncRNAs *MALAT1*, *MEG3* e *TUG1* no desenvolvimento do DM1.

No que se refere à expressão de lncRNAs em pacientes com DRD, nosso quarto estudo identificou um aumento nos níveis de expressão do lncRNA *MALAT1* na urina de pacientes com DRD em comparação ao grupo com DM1 sem DRD. Análises de bioinformática demonstraram que esse lncRNA está envolvido em vias relacionadas ao DM e a DRD, incluindo: glicólise/gliconeogênese, PI3K-Akt, MAPK e a via do DM1.

Por fim, realizamos mais um estudo de caso-controle onde avaliamos a associação dos polimorfismos rs3200401/*MALAT1*, rs1894720/*MIAT*, rs3931283/*PVT1*, rs11993333/*PVT1*, rs5749201/*TUG1* e rs7158663/*MEG3* com a DRD. Neste estudo, demonstramos que o genótipo G/G do polimorfismo rs3931283/*PVT1* estava associado com risco para DRD e com maiores níveis de EUA nos pacientes com DM2. Além disso, o polimorfismo rs7158663/*MEG3* também parece estar envolvido com a DRD, uma vez que

pacientes com o genótipo G/G tinham níveis diminuídos de creatinina e aumentados de TFGe em comparação aos portadores do alelo A.

Assim, a presente tese identificou miRNAs associados com a DRD e gerou uma lista de novos miRNAs que são potenciais alvos de estudos futuros que visem identificar o papel específico de cada um deles no desenvolvimento e progressão da DRD. Além disso, lncRNAs foram identificados no contexto do DM e da DRD, demonstrando o envolvimento dessa classe de RNAs não-codificantes de proteínas na patogênese dessas doenças.

Como perspectivas futuras, pretendemos validar mais miRNAs identificados no estudo do miRNoma urinário e posteriormente avaliar a expressão dos miRNAs validados em amostras de exossomos urinários de pacientes com DM1 e em amostras de pacientes com DM2, buscando assim identificar um perfil de expressão de miRNAs que possa ser usado como biomarcador das fases iniciais da DRD ou da sua progressão para a DRCT.

Além disso, pretendemos realizar uma análise de dados transcriptômicos de pacientes com DM com e sem DRD para melhor compreender mecanismos moleculares associados com esta importante complicação do DM. Nesta análise, pretendemos investigar as expressões de mRNAs, miRNAs e lncRNAs e assim, integrar conjuntos de dados distintos, revelando mudanças globais nos padrões de expressão gênica associados à DRD. Por meio de uma abordagem de bioinformática, também investigaremos as potenciais interações e processos biológicos associados aos mRNAs, miRNAs e lncRNAs encontrados diferencialmente expressos na nossa análise dos dados de *microarray* disponíveis em bancos de dados públicos.

OUTRAS PRODUÇÕES NO PERÍODO

Artigos produzidos durante o período do doutorado como primeira autora, ou dividindo a primeira autoria.

Archives of Endocrinology and Metabolism

Decision Letter (AEM-2022-0100.R1)

From: bschaan@hcpa.edu.br

To: dcmoreira@hcpa.edu.br

CC:

Subject: Archives of Endocrinology and Metabolism - Decision on Manuscript ID AEM-2022-0100.R1

Body: 06-Dec-2022

Dear Dr. Crispim:

It is a pleasure to accept your manuscript entitled "Polymorphisms in TIE2 and ANGPT-1 genes are associated with protection to diabetic retinopathy in a Brazilian population" in its current form for publication in the Archives of Endocrinology and Metabolism. The comments of the reviewer(s) who reviewed your manuscript are included at the foot of this letter.

Thank you for your fine contribution. On behalf of the Editors of the Archives of Endocrinology and Metabolism, we look forward to your continued contributions to the Journal.

Please provide an editorial certificate of English language as required in the "Instructions for Authors", which is mandatory for publication in the AE&M.

Sincerely,
Prof. Beatriz Schaan
Editor-in-Chief, Archives of Endocrinology and Metabolism
bschaan@hcpa.edu.br

Associate Editor
Comments to the Author:
(There are no comments.)

Entire Scoresheet:

Date Sent: 06-Dec-2022

Close Window

Polymorphisms in *TIE2* and *ANGPT*-1 genes are associated with protection to diabetic retinopathy in a Brazilian population

Cristine Dieter[a,b], Natália Emerim Lemos[a,b], Nathalia Rodrigues de Faria Corrêa[a], Taís Silveira Assmann[a,b], Felipe Mateus Pellenz[a,b], Luís Henrique Canani[a,b], Letícia de Almeida Brondani[a], Andrea Carla Bauer[a,b,c], Daisy Crispim[1a,b*].

a – Endocrine Division, Hospital de Clínicas de Porto Alegre. Porto Alegre, Rio Grande do Sul, Brazil.

b – Universidade Federal do Rio Grande do Sul, Faculty of Medicine, Department of Internal Medicine, Postgraduate Program in Medical Sciences: Endocrinology.

c - Nephrology Division, Hospital de Clínicas de Porto Alegre. Porto Alegre, Rio Grande do Sul, Brazil.

* Correspondence to: Dr. Daisy Crispim. Rua Ramiro Barcelos 2350; prédio 12; 4° andar. Zip Code 90035-003. Porto Alegre, Rio Grande do Sul, Brazil. E-mail: dcmoreira@hcpa.edu.br

Abbreviated title: *TIE2* and *ANGPT-1* genes and DR

Keywords: *ANGPT-1* gene; *TIE2* gene; polymorphism, type 2 diabetes mellitus; diabetic retinopathy.

Word count: 3126

Original Article

genes

MDPI

Article

Polymorphisms in *ACE1*, *TMPRSS2*, *IFIH1*, *IFNAR2*, and *TYK2* Genes Are Associated with Worse Clinical Outcomes in COVID-19

Cristine Dieter [1,2], Leticia de Almeida Brondani [1,3], Natália Emerim Lemos [1], Ariell Freires Schaeffer [2], Caroline Zanotto [1], Denise Taurino Ramos [1], Eliandra Girardi [1], Felipe Mateus Pellenz [1,2], Joiza Lins Camargo [2,3,4], Karla Suzana Moresco [5], Lucas Lima da Silva [1], Mariana Rauback Aubin [1], Mayara Souza de Oliveira [1,2], Tatiana Helena Rech [2,4], Luís Henrique Canani [1,2,4], Fernando Gerchman [1,2,4], Cristiane Bauermann Leitão [1,2,4] and Daisy Crispim [1,2,4,*]

1 Endocrine Division, Hospital de Clínicas de Porto Alegre, Porto Alegre 90035-903, RS, Brazil
2 Post-Graduate Program in Medical Sciences, Endocrinology, Department of Internal Medicine, Faculty of Medicine, Universidade Federal do Rio Grande do Sul, Porto Alegre 91501-970, RS, Brazil
3 Experimental Research Center, Hospital de Clínicas de Porto Alegre, Porto Alegre 90035-903, RS, Brazil
4 Diabetes and Metabolism Group, Centro de Pesquisa Clínica, Hospital de Clínicas de Porto Alegre, Porto Alegre 90035-903, RS, Brazil
5 Campus Realeza, Universidade Federal da Fronteira Sul, Realeza 85770-000, PR, Brazil
* Correspondence: dcmoreira@hcpa.edu.br

Abstract: Although advanced age, male sex, and some comorbidities impact the clinical course of COVID-19, these factors only partially explain the inter-individual variability in disease severity. Some studies have shown that genetic polymorphisms contribute to COVID-19 severity; however, the results are inconclusive. Thus, we investigated the association between polymorphisms in *ACE1*, *ACE2*, *DPP9*, *IFIH1*, *IFNAR2*, *IFNL4*, *TLR3*, *TMPRSS2*, and *TYK2* and the clinical course of COVID-19. A total of 694 patients with COVID-19 were categorized as: (1) ward inpatients (moderate symptoms) or patients admitted at the intensive care unit (ICU; severe symptoms); and (2) survivors or non-survivors. In females, the rs1990760/*IFIH1* T/T genotype was associated with risk of ICU admission and death. Moreover, the rs1799752/*ACE1* Ins and rs12329760/*TMPRSS2* T alleles were associated with risk of ICU admission. In non-white patients, the rs2236757/*IFNAR2* A/A genotype was associated with risk of ICU admission, while the rs1799752/*ACE1* Ins/Ins genotype, rs2236757/*IFNAR2* A/A genotype, and rs12329760/*TMPRSS2* T allele were associated with risk of death. Moreover, some of the analyzed polymorphisms interact in the risk of worse COVID-19 outcomes. In conclusion, this study shows an association of rs1799752/*ACE1*, rs1990760/*IFIH1*, rs2236757/*IFNAR2*, rs12329760/*TMPRSS2*, and rs2304256/*TYK2* polymorphisms with worse COVID-19 outcomes, especially among female and non-white patients.

Keywords: polymorphisms; SARS-CoV-2; COVID-19; *ACE1*; *IFIH1*; *IFNAR2*; *TMPRSS2*; *TYK2*

check for updates

Citation: Dieter, C.; de Almeida Brondani, L.; Lemos, N.E.; Schaeffer, A.F.; Zanotto, C.; Ramos, D.T.; Girardi, E.; Pellenz, F.M.; Camargo, J.L.; Moresco, K.S.; et al. Polymorphisms in *ACE1*, *TMPRSS2*, *IFIH1*, *IFNAR2*, and *TYK2* Genes Are Associated with Worse Clinical Outcomes in COVID-19. *Genes* **2023**, *14*, 29. https://doi.org/10.3390/genes14010029

Received: 28 October 2022
Revised: 29 November 2022
Accepted: 10 December 2022
Published: 22 December 2022

1. Introduction

Coronavirus Disease 2019 (COVID-19) is a respiratory and systemic disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. According to the World Health Organization, 626 million people around the world have been infected by this virus, and 6,564,556 have died due to COVID-19 (https://covid19.who.int/ accessed on 25 October 2022). This disease is characterized by a variety of clinical manifestations ranging from asymptomatic to severe symptoms, which can progress to pneumonia, respiratory failure, multiple organ dysfunction, and death [2].

Although advanced age, male sex, obesity, diabetes mellitus (DM), and other comorbidities are associated with risk for the severe forms of the disease, these factors alone do not completely explain inter-individual variability in COVID-19 severity [2,3]. Therefore,

PLOS ONE

RESEARCH ARTICLE

Genetic polymorphisms associated with susceptibility to COVID-19 disease and severity: A systematic review and meta-analysis

Cristine Dieter[1,2☯], Letícia de Almeida Brondani[1,2☯], Cristiane Bauermann Leitão[1,2], Fernando Gerchman[1,2], Natália Emerim Lemos[1,2], Daisy Crispim[1,2]*

1 Endocrine and Metabolism Division, Hospital de Clínicas de Porto Alegre, Porto Alegre, Rio Grande do Sul, Brazil, **2** Postgraduate Program in Medical Sciences: Endocrinology, Faculdade de Medicina, Universidade Federal do Rio Grande do Sul, Porto Alegre, Rio Grande do Sul, Brazil

☯ These authors contributed equally to this work.
* dcmoreira@hcpa.edu.br

OPEN ACCESS

Citation: Dieter C, Brondani LdA, Leitão CB, Gerchman F, Lemos NE, Crispim D (2022) Genetic polymorphisms associated with susceptibility to COVID-19 disease and severity: A systematic review and meta-analysis. PLoS ONE 17(7): e0270627. https://doi.org/10.1371/journal.pone.0270627

Editor: Giuseppe Novelli, Universita degli Studi di Roma Tor Vergata, ITALY

Received: March 8, 2022

Accepted: June 15, 2022

Published: July 6, 2022

Peer Review History: PLOS recognizes the benefits of transparency in the peer review process; therefore, we enable the publication of all of the content of peer review and author responses alongside final, published articles. The editorial history of this article is available here: https://doi.org/10.1371/journal.pone.0270627

Data Availability Statement: All relevant data are within the manuscript and its Supporting Information files.

Abstract

Although advanced age and presence of comorbidities significantly impact the variation observed in the clinical symptoms of COVID-19, it has been suggested that genetic variants may also be involved in the disease. Thus, the aim of this study was to perform a systematic review with meta-analysis of the literature to identify genetic polymorphisms that are likely to contribute to COVID-19 pathogenesis. Pubmed, Embase and GWAS Catalog repositories were systematically searched to retrieve articles that investigated associations between polymorphisms and COVID-19. For polymorphisms analyzed in 3 or more studies, pooled OR with 95% CI were calculated using random or fixed effect models in the Stata Software. Sixty-four eligible articles were included in this review. In total, 8 polymorphisms in 7 candidate genes and 74 alleles of the *HLA* loci were analyzed in 3 or more studies. The *HLA-A*30* and *CCR5* rs333Del alleles were associated with protection against COVID-19 infection, while the *APOE* rs429358C allele was associated with risk for this disease. Regarding COVID-19 severity, the *HLA-A*33*, *ACE1* Ins, and *TMPRSS2* rs12329760T alleles were associated with protection against severe forms, while the *HLA-B*38*, *HLA-C*6*, and *ApoE* rs429358C alleles were associated with risk for severe forms of COVID-19. In conclusion, polymorphisms in the *ApoE*, *ACE1*, *TMPRSS2*, *CCR5*, and *HLA* loci appear to be involved in the susceptibility to and/or severity of COVID-19.

Introduction

Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was identified in China near the end of 2019, and progressed to a pandemic condition in March 2020, resulting in a major public health problem worldwide due to its social and economic burdens [1]. As of February 1, 2022, COVID-19 affected more than

Microvascular Research 143 (2022) 104378

Contents lists available at ScienceDirect

Microvascular Research

journal homepage: www.elsevier.com/locate/ymvre

The rs705708 A allele of the *ERBB3* gene is associated with lower prevalence of diabetic retinopathy and arterial hypertension and with improved renal function in type 1 diabetic patients

Eloísa Toscan Massignam [a,b,1], Cristine Dieter [a,b,1], Taís Silveira Assmann [a,b], Guilherme Coutinho Kullmann Duarte [a,b], Andrea Carla Bauer [c], Luis Henrique Canani [a,b], Daisy Crispim [a,b,*]

[a] Endocrine Division, Hospital de Clínicas de Porto Alegre, Porto Alegre, Rio Grande do Sul, Brazil
[b] Universidade Federal do Rio Grande do Sul, Faculty of Medicine, Department of Internal Medicine, Graduate Program in Medical Sciences: Endocrinology, Porto Alegre, Rio Grande do Sul, Brazil
[c] Nephrology Division, Hospital de Clínicas de Porto Alegre, Porto Alegre, Rio Grande do Sul, Brazil

ARTICLE INFO

Keywords:
Type 1 diabetes mellitus
Polymorphism
ERBB3
PA2G4
Microvascular complications
Hypertension

ABSTRACT

Introduction: The Erb-b2 receptor tyrosine kinase 3 (ERBB3) is involved in autoimmune processes related to type 1 diabetes mellitus (T1DM) pathogenesis. Accordingly, some studies have suggested that single nucleotide polymorphisms (SNPs) in the ERBB3 gene confer risk for T1DM. Proliferation-associated protein 2G4 (PA2G4) is another candidate gene for this disease because it regulates cell proliferation and adaptive immunity. Moreover, PA2G4 regulates ERBB3. To date, no study has evaluated the association of PA2G4 SNPs and T1DM. ***Aim:*** To evaluate the association of *ERBB3* rs705708 (G/A) and *PA2G4* rs773120 (C/T) SNPs with T1DM and its clinical and laboratory characteristics.
Methods: This case-control study included 976 white subjects from Southern Brazil, categorized into 501 cases with T1DM and 475 non-diabetic controls. The *ERBB3* and *PA2G4* SNPs were genotyped by allelic discrimination-real-time PCR.
Results: ERBB3 rs705708 and *PA2G4* rs773120 SNPs were not associated with T1DM considering different inheritance models and also when controlling for covariables. However, T1DM patients carrying the *ERBB3* rs705708 A allele developed T1DM at an earlier age vs. G/G patients. Interestingly, in the T1DM group, the rs705708 A allele was associated with lower prevalence of diabetic retinopathy and arterial hypertension as well as with improved renal function (higher estimated glomerular filtration rate and lower urinary albumin excretion levels) compared to G/G patients.
Conclusions: Although no association was observed between the *ERBB3* rs705708 and *PA2G4* rs773120 SNPs and T1DM, the rs705708 A allele was associated, for the first time in literature, with lower prevalence of diabetic retinopathy and arterial hypertension. Additionally, this SNP was associated with improved renal function.

1. Introduction

Type 1 diabetes mellitus (T1DM) accounts for 5–10% of all cases of diabetes, and is characterized by the cellular-mediated autoimmune destruction of pancreatic beta cells, causing absolute insulin deficiency (American Diabetes Association, 2021). The resulting chronic

Abbreviations: ASP, Affected sibling pair; BP, Blood pressure; BMI, Body mass index; CKD, Chronic kidney disease; CI, Confidence intervals; DKD, Diabetic kidney disease; DR, Diabetic retinopathy; DBP, Diastolic BP; EGF, Epidermal growth factor; EGFR, Epidermal growth factor receptor; ERBB3, Erb-b2 receptor tyrosine kinase 3; eGFR, Estimated glomerular filtration rate; HWE, Hardy–Weinberg Equilibrium; HBDI, human Biological Data Interchange; OD, Odd ratios; PA2G4, Proliferation-associated protein 2G4; SNPs, Single nucleotide polymorphisms; SHRs, Spontaneously hypertensive rats; SBP, Systolic BP; TGF-β, Transforming growth-factor beta; T1DGC, Type 1 Diabetes Genetics Consortium; T1DM, Type 1 diabetes mellitus; T2DM, Type 2 diabetes mellitus; UAE, Urinary albumin excretion.

* Corresponding author at: 2350 Ramiro Barcelos St., building 12, 4th floor, 90035-003 Porto Alegre, Rio Grande do Sul, Brazil.
E-mail address: dcmoreira@hcpa.edu.br (D. Crispim).

[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.mvr.2022.104378
Received 7 March 2022; Received in revised form 21 April 2022; Accepted 11 May 2022
Available online 17 May 2022

Acta Ophthalmologica

Involvement of *miR-126* rs4636297 and *miR-146a* rs2910164 polymorphisms in the susceptibility for diabetic retinopathy: a case–control study in a type 1 diabetes population

Eloísa Toscan Massignam,[1,2] Cristine Dieter,[1,2] Felipe Mateus Pellenz,[1,2] Taís Silveira Assmann[1,2] and Daisy Crispim[1,2]

[1]Endocrine Division, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil
[2]Graduate Program in Medical Sciences: Endocrinology, Faculty of Medicine, Department of Internal Medicine, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil

ABSTRACT.

Background and purpose: **MicroRNAs (miRNAs) are small non-coding RNAs that regulate gene expression. *MiRNA-126* and *miRNA-146a* have been described as having abnormal expressions in diabetic retinopathy (DR) patients. Polymorphisms in genes codifying miRNAs (miRSNPs) may alter the expression of the corresponding miRNA and, thus, interfere with susceptibility to DR. Therefore, miRSNPs in *miR-126* and *miR-146a* genes could be associated with DR susceptibility. The purpose of this study was to investigate the association between *miR-126* rs4636297 (G/A) and *miR-146a* rs2910164 (G/C) miRSNPs and DR.**

Methods: **This case–control study included 195 type 1 diabetes mellitus (T1DM) patients with DR (cases) and 215 patients without DR and with ≥10 years of T1DM (controls). MiRSNPs were genotyped by real-time PCR.**

Results: **Genotype distributions of two analysed miRSNPs were in Hardy–Weinberg equilibrium in controls ($p > 0.050$). Frequencies of the *miR-126* rs4636297 miRSNP were not significantly different between case and control groups ($p = 0.169$). However, after adjustment for age, glycated haemoglobin, triglycerides, estimated glomerular filtration rate and ethnicity, the A allele of this miRSNP was associated with protection for DR under additive [OR: 0.444 (95% CI: 0.211–0.936), $p = 0.033$] and dominant [OR: 0.512 (95% CI: 0.303–0.865), $p = 0.012$] inheritance models. Genotype and allele frequencies of *miR-146a* rs2910164 miRSNP did not differ between groups ($p = 0.368$ and $p = 0.957$), and this polymorphism was not associated with DR when assuming different inheritance models.**

Conclusion: **Our results suggest an association between the A allele of *miR-126* rs4636297 miRSNP and protection for DR in a Southern Brazilian population.**

Key words: diabetic retinopathy – microRNA – polymorphism – rs2910164 – rs4636297 – type 1 diabetes mellitus

†These authors contributed equally to the study.

Acta Ophthalmol. 2021: 99: e461–e469

doi: 10.1111/aos.14638

Introduction

Diabetic retinopathy (DR) is a common microvascular complication of diabetes mellitus (DM) and is the leading cause of vision loss in working middle-aged adults worldwide (Solomon et al. 2017; Kusuhara et al. 2018). DR has a higher incidence in patients with type 1 DM (T1DM) than type 2 DM (T2DM) (Yau et al. 2012), and in Brazil, it affects 35.7% of the T1DM patients (Melo et al. 2018). Known risk factors for DR, such as poor glycaemic control, long-term duration of DM, arterial hypertension and dyslipidaemia, explain some of the disease heterogeneity. However, there are patients who develop this complication despite excellent glycaemic control and others who do not develop DR even with long-term DM and chronic hyperglycaemia. Thus, genetic and epigenetic factors may explain some of the remaining heterogeneity in DR development (Cho & Sobrin 2014; Kowluru & Mishra 2015).

Epigenetic modifications regulate the complex interplay between genes and environmental factors without altering the DNA sequence (Kowluru & Mishra 2015; Kumari et al. 2019). The three major classes of epigenetic factors are DNA methylation, histone modification and non-coding RNAs (ncRNAs) (Kowluru & Mishra 2015; Kumari et al. 2019). NcRNAs are regulatory RNAs that lack protein-coding

The rs2442598 polymorphism in the *ANGPT-2* gene is associated with risk for diabetic retinopathy in patients with type 1 diabetes mellitus in a Brazilian population

[1] Divisão de Endocrinologia, Hospital de Clínicas de Porto Alegre, Porto Alegre, RS, Brasil
[2] Programa de Pós-graduação em Ciências Médicas – Endocrinologia, Faculdade de Medicina, Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brasil
[3] Divisão de Nefrologia, Hospital de Clínicas de Porto Alegre, Porto Alegre, RS, Brasil

Cristine Dieter[1,2]
https://orcid.org/0000-0003-2765-930X

Natália Emerim Lemos[1,2]
https://orcid.org/0000-0002-0096-5801

Nathalia Rodrigues de Faria Corrêa[1]
https://orcid.org/0000-0001-9654-9433

Aline Rodrigues Costa[1,2]
https://orcid.org/0000-0003-4736-2319

Luís Henrique Canani[1,2]
https://orcid.org/0000-0002-1813-4491

Daisy Crispim[1,2]
https://orcid.org/0000-0001-5095-9269

Andrea Carla Bauer[1,2,3]
https://orcid.org/0000-0002-5041-4792

ABSTRACT

Objective: As studies have reported the involvement of angiopoietin-2 (ANGPT-2) in the pathogenesis of diabetic retinopathy (DR), the aim of this study was to investigate the association between the *ANGPT-2* rs2442598 polymorphism and DR. **Materials and methods:** This case-control study comprised 107 patients with type 1 diabetes mellitus (T1DM) and DR (cases) and 129 patients with T1DM without DR (controls) and with ≥ 10 years of DM. The *ANGPT-2* rs2442598 (G/A) polymorphism was genotyped by real-time PCR using TaqMan MGB probes. **Results:** Genotype distributions of this polymorphism were consistent with the Hardy-Weinberg equilibrium. The frequency of the rs2442598 A allele was higher in cases compared to controls (p = 0.011). Moreover, the A/A genotype was more frequent in cases than in controls (p = 0.017) and was associated with risk for DR after adjustments for duration of DM, HbA1c, triglycerides, estimated glomerular filtration rate, and hypertension (odds ratio [OR] = 5.19, 95% confidence interval [CI] 1.21-22.27). This association was maintained under recessive (OR = 4.78, 95% CI 1.14-19.99) and additive (OR = 6.861, 95% CI 1.45-32.38) inheritance models. **Conclusion:** Our data demonstrated, for the first time, an association between the *ANGPT-2* rs2442598 A allele and risk for DR in T1DM patients from southern Brazil. Additional studies are necessary to replicate this association in other populations. Arch Endocrinol Metab. 2021;65(6):794-800

Keywords
ANGPT-2 gene; polymorphism; type 1 diabetes mellitus; diabetic retinopathy

Correspondence to:
Andrea Carla Bauer
Rua Ramiro Barcelos, 2.350, prédio 12, 4º andar
90035-003 – Porto Alegre, RS, Brasil
abauer@hcpa.edu.br

Received on Feb/01/2021
Accepted on July/12/2021

DOI: 10.20945/2359-3997000000417

INTRODUCTION

Diabetic retinopathy (DR) is one of the most disabling microvascular complications of diabetes mellitus (DM) (1). According to the International Diabetes Federation, DR is the leading cause of blindness in working-age adults (2). Clinically, DR is characterized by the presence of typical retinal microvascular signs, such as microaneurysms, hemorrhages, cotton-wool spots, hard exudates, and neovascularization (1). The development and progression of DR depend on the complex interaction of clinical risk factors, environmental factors, and genetic factors (1,3). In this context, the identification of new genetic polymorphisms associated with DR can contribute to a better understanding of the risk factors and predisposition to this diabetic complication.

The A allele of the rs759853 single nucleotide polymorphism in the *AKR1B1* gene confers risk for diabetic kidney disease in patients with type 2 diabetes from a Brazilian population

[1] Divisão Endócrina do Hospital de Clínicas de Porto Alegre, Porto Alegre, RS, Brasil
[2] Universidade Federal do Rio Grande do Sul, Faculdade de Medicina, Departamento de Clínica Médica, Programa de Pós-graduação em Ciências Médicas: Endocrinologia, Porto Alegre, RS, Brasil
[3] Serviço de Nefrologia do Hospital de Clínicas de Porto Alegre, Porto Alegre, RS, Brasil

Cristine Dieter[1,2]
https://orcid.org/0000-0003-2765-930X

Natália Emerim Lemos[1,2]
https://orcid.org/0000-0002-0096-5801

Nathalia Rodrigues de Faria Corrêa[1]
https://orcid.org/0000-0001-9654-9433

Felipe Mateus Pellenz[1,2]
https://orcid.org/0000-0002-7829-9407

Luís Henrique Canani[1,2]
https://orcid.org/0000-0002-1813-4491

Daisy Crispim[1,2]
https://orcid.org/0000-0001-5095-9269

Andrea Carla Bauer[1,2,3]
https://orcid.org/0000-0002-5041-4792

ABSTRACT

Objective: The *AKR1B1* gene encodes an enzyme that catalyzes the reduction of glucose into sorbitol. Chronic hyperglycemia in patients with diabetes mellitus (DM) leads to increased AKR1B1 affinity for glucose and, consequently, sorbitol accumulation. Elevated sorbitol increases oxidative stress, which is one of the main pathways related to chronic complications of diabetes, including diabetic kidney disease (DKD). Accordingly, some studies have suggested the rs759853 polymorphism in the *AKR1B1* gene is associated with DKD; however, findings are still contradictory. The aim was to investigate the association of the rs759853 polymorphism in the *AKR1B1* gene and DKD. **Materials and methods:** The sample comprised 695 patients with type 2 DM (T2DM) and DKD (cases) and 310 patients with T2DM of more than 10 years' duration, but no DKD (controls). The polymorphism was genotyped by real-time PCR. **Results:** Allelic and genotype frequencies of this polymorphism did not differ significantly between groups. However, the A/A genotype was associated with risk for DKD after adjustment for gender, triglycerides, BMI, presence of hypertension and diabetic retinopathy, and duration of DM, under both recessive (P = 0.048) and additive (P = 0.037) inheritance models. **Conclusion:** Our data suggest an association between the *AKR1B1* rs759853A/A genotype and risk for DKD in Brazilians T2DM patients. Arch Endocrinol Metab. 2022;66(1):12-8

Keywords
AKR1B1 gene, DNA polymorphism, diabetic kidney disease

Correspondence to:
Andrea Carla Bauer
Rua Ramiro Barcelos, 2.350, prédio 12, 4º andar
90035-003 – Porto Alegre, RS, Brasil
andreacarlabauer@gmail.com

Received on March/30/2021
Accepted on Sept/22/2021

DOI: 10.20945/2359-3997000000432

INTRODUCTION

Diabetic kidney disease (DKD) is an important microvascular complication that affects around 40% of all patients with diabetes mellitus (DM), and is the leading cause of end-stage renal disease in individuals on renal replacement therapy. Moreover, patients with DKD have increased cardiovascular mortality compared to patients with DM without this complication (1,2). DKD is defined clinically by presence of albuminuria and/or a gradual decline in the glomerular filtration rate (GFR) (3). Known risk factors for DKD are long-lasting hyperglycemia, arterial hypertension, dyslipidemia, and genetic polymorphisms (1,4).

Aldo-keto reductase family 1 member B (AKR1B1), also known as aldose reductase, belongs to the aldo/keto reductase superfamily and is the first enzyme of the polyol pathway, catalyzing the reduction of glucose into sorbitol using NADPH as a cofactor [reviewed in (5,6)]. This reaction is the rate-limiting step of the polyol pathway. Under chronic hyperglycemia in patients with

The rs11755527 polymorphism in the *BACH2* gene and type 1 diabetes mellitus: case control study in a Brazilian population

[1] Divisão de Endocrinologia, Hospital de Clínicas de Porto Alegre, Porto Alegre, RS, Brasil
[2] Faculdade de Medicina, Universidade Federal do Rio Grande do Sul (UFRGS), Porto Alegre, RS, Brasil
[3] Universidade do Vale do Rio dos Sinos (Unisinos), São Leopoldo, RS, Brasil
[4] Departamento de Nutrición, Ciencia de los Alimentos y Fisiología, Universidad de Navarra, Navarra, Espanha

* The authors participated similarly in the study

Cristine Dieter[1,2*]
http://orcid.org/0000-0003-2765-930X

Natália Emerim Lemos[1,2*]
http://orcid.org/0000-0002-0096-5801

Luiza Emy Dorfman[3]
http://orcid.org/0000-0001-5903-5185

Guilherme Coutinho Kullmann Duarte[1,2]
http://orcid.org/0000-0003-3678-4639

Taís Silveira Assmann[1,4]
http://orcid.org/0000-0001-9114-8243

Daisy Crispim[1,2]
http://orcid.org/0000-0001-5095-9269

Correspondence to:
Natália Emerim Lemos
Rua Ramiro Barcelos, 2350, prédio 12; 4° andar
90035-003 – Porto Alegre, RS, Brasil
natiemerim@hotmail.com

Received on May/2/2019
Accepted on Sept/2/2019

DOI: 10.20945/2359-3997000000214

ABSTRACT

Objective: Type 1 diabetes mellitus (T1DM) is an autoimmune disorder caused by a complex interaction between environmental and genetic risk factors. BTB domain and CNC homolog 2 (*BACH2*) gene encodes a transcription factor that acts on the differentiation and formation of B and T lymphocytes. BACH2 is also involved in the suppression of apoptosis and inflammation in pancreatic beta-cells, indicating a role for it in the development of T1DM. Therefore, the aim of this study was to evaluate the association of the *BACH2* rs11755527 single nucleotide polymorphism (SNP) with T1DM. **Subjects and methods:** This case-control study comprised 475 patients with T1DM and 598 nondiabetic individuals. The *BACH2* rs11755527 (C/G) SNP was genotyped using real-time PCR with TaqMan MGB probes. **Results:** Genotype distributions of rs11755527 SNP were in accordance with frequencies predicted by the Hardy–Weinberg equilibrium in case and control groups and were similar between groups (P = 0.729). The minor allele frequency was 43.6% in cases and 42.5% in controls (P = 0.604). Moreover, the G allele frequency did not differ between groups when considering different inheritance models and adjusting for age, gender, body mass index, and *HLA DR/DQ* genotypes of high-risk for T1DM. Although, well-known high-risk T1DM *HLA DR/DQ* genotypes were associated with T1DM in our population [OR= 7.42 (95% CI 3.34 – 17.0)], this association was not influenced by the rs11755527 SNP. **Conclusion:** The *BACH2* rs11755527 SNP seems not to be associated with T1DM in a Brazilian population. Arch Endocrinol Metab. 2020;64(2):138-43

Keywords
Type 1 diabetes mellitus; DNA polymorphisms; *BACH2* gene

INTRODUCTION

Type 1 diabetes mellitus (T1DM) affects 10-15% of patients with diabetes mellitus (DM) and is caused by autoimmune destruction of pancreatic beta-cells, making patients dependent of insulin for life (1,2). This disease most likely arises from a multifaceted interaction between multiple environmental and genetic risk factors (2). The *HLA DR/DQ* locus has the greatest impact on susceptibility, accounting for up to 30-50% of the genetic variance of T1DM (3). Although more than 50 genes have been described as having smaller effects on T1DM susceptibility in comparison to *HLA* loci, it has been suggested that the interaction between *HLA* haplotypes and non-*HLA* single nucleotide polymorphisms (SNPs) could be useful to help improve prediction of the disease (4,5). Consequently, identification of non-*HLA* SNPs associated with T1DM may help disease prediction (6).

Many genome-wide association studies (GWAS) have found a number of *loci* associated with T1DM [reviewed in (4,7)], including polymorphisms in the BTB domain and CNC homolog 2 (*BACH2*) gene. *BACH2* encodes a transcription factor that acts in the immune system, which is involved in the development

Gene 735 (2020) 144405

Contents lists available at ScienceDirect

Gene

journal homepage: www.elsevier.com/locate/gene

Review

Association of long non-coding RNA and leukemia: A systematic review

Cristine Dieter*, Eloir Dutra Lourenco, Natália Emerim Lemos

Universidade Feevale, Novo Hamburgo, Rio Grande do Sul, Brazil

ARTICLE INFO

Keywords:
Leukemia
lncRNAs
Systematic review
Epigenetics

ABSTRACT

Introduction: Long non-coding RNAs (lncRNAs) are RNA molecules that structurally resemble mRNA but do not encode proteins. Studies have been associated this class of non-coding RNA with the development of several disease, among them the different types of leukemia. However, the results are contradictory. Thus, we performed a systematic review of the literature available in order to better understand the involvement of lncRNAs in the development of leukemia.

Materials and methods: Pubmed and Embase databases were used to identify all studies that evaluated the expression of one or more lncRNA between human samples (peripheral blood, bone marrow) with leukemia (cases) and without leukemia (controls).

Results: A total of 3675 articles were found in the databases, and after exclusion of articles that did not meet the eligibility criteria, 86 articles were included in this systematic review. In the 86 included studies, 3927 lncRNAs were differentially expressed between cases and controls. Among these, 110 lncRNAs were reported as being altered in samples from at least 2 studies and only 16 of them in ≥3 studies, which were selected for further evaluation. Of these, 12 lncRNAs were consistently dysregulated between cases and controls (CCAT1, CCDC26, CRNDE, HOTAIR, KCNQ5IT1, LINC00265, MALAT1, PVT1, SNHG5, TUG1: increased in cases, MEG3 and NEAT1: decreased in cases) in human samples of patients with some type of leukemia.

Conclusion: Our data demonstrate that 12 lncRNAs are dysregulated in leukemia.

1. Introduction

Leukemia is a type of cancer that affects the blood and bone marrow and is characterized by the uncontrolled production and accumulation of blood cells (Juliusson and Hough, 2016). According to American Cancer Society (Society, 2019), cancer the second leading cause of deaths among children, adolescents and young adults younger than 20 years, and leukemia is the main type of cancer that affect children. In addition, 381,774 people are living with or in remission from leukemia in the US (Society, 2019). Radiation exposure, viral infections, ethnicity, gender and genetic mutations are some of the risk factors of leukemia (Juliusson and Hough, 2016). However, more studies are necessary to better understand the development and the pathogenesis of the different types of leukemia.

In this context, epigenetic factors, such as non-coding RNAs (ncRNA), have been associated with leukemia development. NcRNAs are a group of regulatory RNAs that are not translated into protein (Mattick and Makunin, 2006). NcRNAs longer than 200 nucleotides are classified as long non-coding RNAs (lncRNAs). LncRNAs are located in nucleus, where they can act as molecular scaffolds, help in alternative splicing or modify chromatin structures. In addition, there are some lncRNAs that have functions in cytoplasm, such as modulating translation, promoting or inhibiting mRNA degradation, and acting as miRNAs sponges (Knoll et al., 2015).

Dysregulated expression of this lncRNAs is highly associated with human diseases, including the different types of leukemia [review in (Alvarez-Dominguez et al., 2014; Alvarez-Dominguez and Lodish, 2017; Lammens et al., 2017)]. Take into account that a large number of studies have demonstrated the association of lncRNA expression with leukemia and that many findings are contradictory, the aim of this study is clarify the involvement of lncRNAs in the pathogenesis of leukemia, performing a systemic review of the literature on the subject.

Abbreviations: ALL, acute lymphoid leukemia; AML, acute myeloid leukemia; BBMC, bone marrow mononuclear cell; CLL, chronic lymphoid leukemia; CML, chronic myeloid leukemia; FAB, French American Bristish; JMML, juvenile myelomonocytic leukemia; LncRNA, long non-coding RNA; MESH, medical subject heading; NcRNA, non-coding RNA; NOS, New Castle-Ottawa Scale; PBMC, peripheral blood mononuclear cell; WHO, World Health Organization

* Corresponding author at: Universidade Feevale, ERS-239, 2755, 93525-075 Novo Hamburgo, Rio Grande do Sul, Brazil.
E-mail address: tinedieter@hotmail.com (C. Dieter).

https://doi.org/10.1016/j.gene.2020.144405
Received 6 November 2019; Accepted 27 January 2020
Available online 31 January 2020
0378-1119/

Genetics and Molecular Biology, 43, 2, e20180374 (2020)

DOI: https://doi.org/10.1590/1678-4685-GMB-2018-0374

Research Article
Human and Medical Genetics

-866G/A and Ins/Del polymorphisms in the *UCP2* gene and diabetic kidney disease: case-control study and meta-analysis

Cristine Dieter[1,2], Taís Silveira Assmann[3], Natália Emerim Lemos[1,2], Eloísa Toscan Massignam[1], Bianca Marmontel de Souza[1,2], Andrea Carla Bauer[1,2,4] and Daisy Crispim[1,2]

[1]*Hospital de Clínicas de Porto Alegre, Endocrine Division, Porto Alegre, RS, Brazil.*
[2]*Universidade Federal do Rio Grande do Sul, Faculdade de Medicina, Programa de Pós-Graduação em Ciências Médicas: Endocrinologia, Porto Alegre, RS, Brazil.*
[3]*Universidad de Navarra, Department of Nutrition, Food Science and Physiology, Pamplona, Spain.*
[4]*Hospital de Clínicas de Porto Alegre, Nephrology Division, Porto Alegre, RS, Brazil.*

Abstract

Uncoupling protein 2 (UCP2) decreases reactive oxygen species (ROS). ROS overproduction is a key contributor to the pathogenesis of diabetic kidney disease (DKD). Thus, *UCP2* polymorphisms are candidate risk factors for DKD; however, their associations with this complication are still inconclusive. Here, we describe a case-control study and a meta-analysis conducted to investigate the association between *UCP2* -866G/A and Ins/Del polymorphisms and DKD. The case-control study comprised 385 patients with type 1 diabetes mellitus (T1DM): 223 patients without DKD and 162 with DKD. *UCP2* -866G/A (rs659366) and Ins/Del polymorphisms were genotyped by real-time PCR and conventional PCR, respectively. For the meta-analysis, a literature search was conducted to identify all studies that investigated associations between *UCP2* polymorphisms and DKD in patients with T1DM or type 2 diabetes mellitus. Pooled odds ratios were calculated for different inheritance models. Allele and genotype frequencies of -866G/A and Ins/Del polymorphisms did not differ between T1DM case and control groups. Haplotype frequencies were also similar between groups. Four studies plus the present one were eligible for inclusion in the meta-analysis. In agreement with case-control data, the meta-analysis results showed that the -866G/A and Ins/Del polymorphisms were not associated with DKD. In conclusion, our case-control and meta-analysis studies did not indicate an association between the analyzed *UCP2* polymorphisms and DKD.

Keywords: UCP2, polymorphisms, diabetic kidney disease.

Received: Dezembro 11, 2018; Accepted: April 11, 2019.

Introduction

Diabetic kidney disease (DKD) is a common microvascular complication that affects 40% of patients with diabetes mellitus (DM) (Gross *et al.*, 2005, Macisaac *et al.*, 2014). DKD is the leading cause of end-stage renal disease in subjects starting renal replacement therapy and is associated with increased cardiovascular mortality (Gross *et al.*, 2005, Assmann *et al.*, 2018). This complication is a progressive disease, characterized by pathophysiological changes resulting from the diabetic milieu, which begin with glomerular hypertrophy and hyperfiltration, and might progress to albuminuria and a gradual decline in the glomerular filtration rate (GFR) (Kanwar *et al.*, 2011, Ritz *et al.*, 2011). The progressive decline in renal function during DKD is a result of pathophysiological alterations in the kidneys, such as mesangial expansion and tubulointerstitial fibrosis due to the accumulation of extracellular matrix proteins, basement membrane thickening, and podocyte dysfunction (Assmann *et al.*, 2018) (Figure 1). The main risk factors for DKD are the duration of chronic hyperglycemia, arterial hypertension, dyslipidemia, and genetic susceptibility (Carpena *et al.*, 2010, Ahlqvist *et al.*, 2015).

At the cellular level, chronic hyperglycemia causes renal damage through five main mechanisms: increased formation of advanced glycation end-products; increased expression of the receptor for advanced glycation end-products; activation of protein kinase C isoforms; increased flux of glucose through the polyol pathway; and upregulation of the hexosamine pathway (Du *et al.*, 2000, Giacco and Brownlee, 2010). Several lines of evidence have shown that the mitochondrial overproduction of reactive oxygen species (ROS) is the unifying upstream mechanism by which hyperglycemia activates all these five pathways (Brownlee, 2005; Rich, 2006; Giacco and Brownlee, 2010).

Uncoupling protein 2 (UCP2) is a mitochondrial anion carrier protein expressed in a number of tissues, including adipose tissue, liver, kidney, and retina (Souza *et al.*, 2011; Donadelli *et al.*, 2014). This protein mildly uncouples the

Send correspondence to Daisy Crispim. Hospital de Clínicas de Porto Alegre, Endocrine Division, Porto Alegre, RS, Brazil. E-mail: dcmoreira@hcpa.edu.br.

frontiers in Genetics

ORIGINAL RESEARCH
published: 12 June 2019
doi: 10.3389/fgene.2019.00563

MiR-30e-5p and MiR-15a-5p Expressions in Plasma and Urine of Type 1 Diabetic Patients With Diabetic Kidney Disease

*Cristine Dieter[1,2], Taís Silveira Assmann[3], Aline Rodrigues Costa[1], Luís Henrique Canani[1,2], Bianca Marmontel de Souza[1,2], Andrea Carla Bauer[1,2,4] and Daisy Crispim[1,2]**

[1] Endocrine Division, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil, [2] Post-Graduate Program in Medical Sciences: Endocrinology, Faculdade de Medicina, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil, [3] Department of Food Science and Physiology, School of Pharmacy and Nutrition, University of Navarra, Pamplona, Spain, [4] Nephrology Division, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil

OPEN ACCESS

Edited by:
Rui Henrique,
Portuguese Oncology Institute, Portugal

Reviewed by:
Ling-Qing Yuan,
Central South University, China
Charles Affourtit,
University of Plymouth, United Kingdom

***Correspondence:**
Daisy Crispim
dcmoreira@hcpa.edu.br

Specialty section:
This article was submitted to Epigenomics and Epigenetics, a section of the journal Frontiers in Genetics

Received: 31 January 2019
Accepted: 29 May 2019
Published: 12 June 2019

Citation:
Dieter C, Assmann TS, Costa AR, Canani LH, de Souza BM, Bauer AC and Crispim D (2019) MiR-30e-5p and MiR-15a-5p Expressions in Plasma and Urine of Type 1 Diabetic Patients With Diabetic Kidney Disease. Front. Genet. 10:563. doi: 10.3389/fgene.2019.00563

Introduction: Diabetic kidney disease (DKD) is a common microvascular complication that affects 40% of patients with diabetes mellitus (DM). Emerging evidence suggests a role for several microRNAs (miRNAs) in the development of DKD. In this context, miR-15a-5p and miR-30e-5p have been shown to regulate the expression of the uncoupling protein 2 (UCP2), a mitochondrial protein that decreases reactive oxygen species (ROS) formation by the mitochondria. Since ROS overproduction is a key contributor to the pathogenesis of DKD, dysregulation of these two miRNAs could be involved in DKD pathogenesis. Thus, the aim of this study was to compare the expressions of miR-15a-5p and miR-30e-5p in type 1 DM (T1DM) patients with DKD (cases) and without this complication (controls), and to perform bioinformatics analyses to investigate their putative targets and biological pathways under their regulation.

Methods: MiR-15a-5p and miR-30e-5p expressions were analyzed in plasma and urine of 17 T1DM controls and 23 DKD cases (12 with moderate DKD and 11 with severe DKD) using qPCR. Bioinformatics analyses were performed in Cytoscape software.

Results: MiR-30e-5p expression was downregulated in plasma of patients with moderate and severe DKD compared to T1DM controls. Moreover, this miRNA was also downregulated in urine of patients with severe DKD compared to the other groups. No difference was found in miR-15a-5p expression between groups. Bioinformatics analyses indicated that miR-30e-5p and miR-15a-5p regulate various genes that participate in pathways related to angiogenesis, apoptosis, cell differentiation, oxidative stress, and hypoxia.

Conclusion: MiR-30e-5p seems to be downregulated in plasma and urine of patients with DKD.

Keywords: microRNA expression, miR-15a-5p, miR-30e-5p, diabetic kidney disease, bioinformatics analysis, type 1 diabetes mellitus

Demais produções no período do doutorado.

Original Article
Genetics

Diabetes Metab J 2021;45:899-908
https://doi.org/10.4093/dmj.2020.0194
pISSN 2233-6079 · eISSN 2233-6087

dmj
DIABETES & METABOLISM JOURNAL

The rs2304256 Polymorphism in *TYK2* Gene Is Associated with Protection for Type 1 Diabetes Mellitus

Felipe Mateus Pellenz[1,2], Cristine Dieter[1,2], Guilherme Coutinho Kullmann Duarte[1,2], Luís Henrique Canani[1,2], Bianca Marmontel de Souza[1,2], Daisy Crispim[1,2]

[1]Endocrinology Division, Hospital de Clínicas de Porto Alegre, Porto Alegre,
[2]Department of Internal Medicine, Graduate Program in Medical Sciences: Endocrinology, Federal University of Rio Grande do Sul, Faculty of Medicine, Porto Alegre, Brazil

Background: Tyrosine kinase 2 (*TYK2*) is a candidate gene for type 1 diabetes mellitus (T1DM) since it plays an important role in regulating apoptotic and pro-inflammatory pathways in pancreatic β-cells through modulation of the type I interferon signaling pathway. The rs2304256 single nucleotide polymorphism (SNP) in *TYK2* gene has been associated with protection for different autoimmune diseases. However, to date, only two studies have evaluated the association between this SNP and T1DM, with discordant results. This study thus aimed to investigate the association between the *TYK2* rs2304256 SNP and T1DM in a Southern Brazilian population.
Methods: This case-control study comprised 478 patients with T1DM and 518 non-diabetic subjects. The rs2304256 (C/A) SNP was genotyped by real-time polymerase chain reaction technique using TaqMan minor groove binder (MGB) probes.
Results: Genotype and allele frequencies of the rs2304256 SNP differed between T1DM patients and non-diabetic subjects ($P<0.0001$ and $P=0.001$, respectively). Furthermore, the A allele was associated with protection against T1DM under recessive (odds ratio [OR], 0.482; 95% confidence interval [CI], 0.288 to 0.806) and additive (OR, 0.470; 95% CI, 0.278 to 0.794) inheritance models, adjusting for human leukocyte antigen (*HLA*) *DR/DQ* genotypes, gender, and ethnicity.
Conclusion: The A/A genotype of *TYK2* rs2304256 SNP is associated with protection against T1DM in a Southern Brazilian population.

Keywords: Autoimmune diseases; Diabetes mellitus, type 1; Polymorphism, genetic; Polymorphism, single nucleotide; TYK2 kinase

INTRODUCTION

Chronic hyperglycemia in type 1 diabetes mellitus (T1DM) is caused by the severe autoimmune destruction of pancreatic β-cells by macrophages and T lymphocytes, which renders subjects insulin-dependent for life [1]. Autoimmunity against β-cells occurs in the context of crosstalk between invading immune cells and the target β-cells, and is triggered by a multifaceted interaction between several genetic and environmental risk factors [1-3]. To date, genome-wide association studies have identified more than 60 loci associated with T1DM. Among these loci, the human leukocyte antigen (HLA) class II (DR/DQ) region has shown the greatest impact on T1DM susceptibility, with an odds ratio (OR) >7 [2,4,5]. Although single nucleotide polymorphisms (SNPs) in other loci confer modest risks (OR <2) for T1DM, studies have suggested the combination of *HLA* genotypes with non-*HLA* SNPs may be useful for disease prediction [5-7].

β-Cells express 80% of T1DM candidate genes [8-10], which may contribute to T1DM pathogenesis by regulating important pathways in these cells, such as activation of apoptosis, antiviral activity, and innate immunity, involving retinoic acid-

Corresponding author: Daisy Crispim https://orcid.org/0000-0001-5095-9269
Endocrinology Division, Hospital de Clínicas de Porto Alegre, Rua Ramiro Barcelos 2350, prédio 12, 4º Andar, Porto Alegre 90035-003, Brazil
E-mail: dcmoreira@hcpa.edu.br

Received: Aug. 6, 2020; Accepted: Dec. 4, 2020

Genetics and Molecular Biology, 44, 2, e20200425 (2021)

DOI: https://doi.org/10.1590/1678-4685-GMB-2020-0425

Research Article
Human and Medical Genetics

Association of *TYK2* polymorphisms with autoimmune diseases: A comprehensive and updated systematic review with meta-analysis

Felipe Mateus Pellenz[1,2], Cristine Dieter[1,2], Natália Emerim Lemos[1,2], Andrea Carla Bauer[1,2,3], Bianca Marmontel de Souza[1,2] and Daisy Crispim[1,2]

[1]*Hospital de Clínicas de Porto Alegre, Serviço de Endocrinologia, Porto Alegre, RS, Brazil.*
[2]*Universidade Federal do Rio Grande do Sul, Faculdade de Medicina, Programa de Pós-Graduação em Ciências Médicas, Porto Alegre, RS, Brazil.*
[3]*Hospital de Clínicas de Porto Alegre, Serviço de Nefrologia, Porto Alegre, RS, Brazil.*

Abstract

Autoimmune diseases are characterized by the loss of self-tolerance, leading to immune-mediated tissue destruction and chronic inflammation. Tyrosine kinase 2 (TYK2) protein plays a key role in immunity and apoptosis pathways. Studies have reported associations between single nucleotide polymorphisms (SNPs) in the *TYK2* gene and autoimmune diseases; however, results are still inconclusive. Thus, we conducted a systematic review followed by meta-analysis. A literature search was performed to find studies that investigated associations between *TYK2* SNPs and autoimmune diseases (multiple sclerosis, systemic lupus erythematosus, Crohn's disease, ulcerative colitis, psoriasis, rheumatoid arthritis, type 1 diabetes, and inflammatory bowel disease). Pooled odds ratios (OR) with 95 % CI were calculated using random (REM) or fixed (FEM) effects models in the Stata 11.0 Software. Thirty-four articles were eligible for inclusion in the meta-analyses, comprising 9 different SNPs: rs280496, rs280500, rs280523, rs280519, rs2304256, rs12720270, rs12720356, rs34536443, and rs35018800. Meta-analysis results showed the minor alleles of rs2304256, rs12720270, rs12720356, rs34536443, and rs35018800 SNPs were associated with protection against autoimmune diseases. Moreover, the A allele of the rs280519 SNP was associated with risk for systemic lupus erythematosus. Our meta-analyses demonstrated that the rs2304256, rs12720270, rs12720356, rs34536443, rs35018800, and rs280519 SNPs in the *TYK2* gene are associated with different autoimmune diseases.

Keywords: *Tyrosine kinase 2*, autoimmunity, autoimmune disease, single nucleotide polymorphism, meta-analysis.

Received: November 19, 2020; Accepted: March 09, 2021.

Introduction

Autoimmune diseases are complex diseases triggered by multifaceted interactions between several genetic and environmental factors (Gutierrez-Roelens and Lauwerys, 2008; Rose, 2016), and are characterized by the loss of self-tolerance leading to immune-mediated tissue destruction and chronic inflammation (Marrack *et al.*, 2001; Lee and Bae, 2016; Odhams *et al.*, 2017). These diseases share common etiological pathways, with genetic factors being considered as strong determinants of their development (Gutierrez-Roelens and Lauwerys, 2008; Lee and Bae, 2016). Regarding genetic factors, *tyrosine kinase 2* (*TYK2*) is a candidate gene for autoimmune diseases since it encodes a member of Janus Kinase (JAK) family of tyrosine kinases, which have a central role in immune response since they mediate signaling pathways for several cytokines and type I interferon (IFN-I) (Ghoreschi *et al.*, 2009; Strobl *et al.*, 2011).

TYK2 is a non-receptor protein that bounds to the IFN-I receptor (IFNAR1) on the cell surface in its inactive form. After IFN-α binding to IFNAR1, TYK2 and JAK1 proteins are activated, leading to the recruitment and phosphorylation of the signal of transducers and activators of transcription (STAT) 1 and 2. STAT1/2 heterodimers then translocate to the nucleus, where they are major regulators of the expression of a number of IFN-stimulated genes (Yamaoka *et al.*, 2004; Strobl *et al.*, 2011). TYK2 is also associated with IL-6, IL-10, IL-12, and IL-23 receptors, playing a key role in the activation of these cytokine pathways (Ghoreschi *et al.*, 2009; O'Shea and Plenge, 2012). Abnormal expression of IFN-I and other cytokines or JAK kinase members in immune cells are well known players in the pathogenesis of autoimmune diseases (Strobl *et al.*, 2011; O'Shea and Plenge, 2012; Deng *et al.*, 2019). Besides its role in the IFN-I and other type I and II cytokine receptor pathways, TYK2 plays a key role in other immune processes, including the activity of natural killer cells, maturation of B and Treg cells, and differentiation of Th1 and Th17 cells. Accordingly, dysregulated *TYK2* expression has been associated with autoimmune diseases, specially systemic lupus erythematosus (SLE) [reviewed in (Deng *et al.*, 2019)].

Consistent with the role of TYK2 in immune processes, several studies have suggested common single nucleotide polymorphisms (SNPs) in this gene are associated with different autoimmune diseases, including multiple sclerosis (MS) (Tao *et al.*, 2011), SLE (Tao *et al.*, 2011; Lee *et al.*, 2012; Lee and Bae, 2016; Yin *et al.*, 2018), Crohn's Disease (CD) (Lees *et al.*, 2011; Tao *et al.*, 2011; Ellinghaus *et al.*, 2016), ulcerative colitis (UC) (Lees *et al.*, 2011; Tao *et al.*, 2011; Ellinghaus *et al.*, 2016), rheumatoid arthritis (RA) (Tao *et al.*, 2011; Lee and Bae, 2016; Westra *et al.*, 2018), type 1

Send correspondence to Daisy Crispim. Hospital de Clínicas de Porto Alegre, Serviço de Endocrinologia, Rua Ramiro Barcelos 2350, prédio 12, 4° andar, 90035-003, Porto Alegre, RS, Brazil. E-mail: dcmoreira@hcpa.edu.br.

Human Immunology 81 (2020) 18–25

Contents lists available at ScienceDirect

Human Immunology

journal homepage: www.elsevier.com/locate/humimm

The effects of gene polymorphisms on susceptibility to acute GVHD and survival of allogeneic HSCT recipients: IL-10 gene polymorphisms as a more accessible target to predict prognosis

Mariela Granero Farias[a,b,*], Camila Andrade dos Santos[b], Bruna de Mello Vicente[c], Muriel Habigzang[c], Priscila de Oliveira da Silva[b], Natália Emerim Lemos[b], Cristine Dieter[b], Alessandra Paz[b], Liane Esteves Daudt[a,b,c]

[a] Graduate Program in Child and Adolescent Health, Federal University of Rio Grande, do Sul/UFRGS, Brazil
[b] Hospital de Clínicas de Porto Alegre/HCPA, Brazil
[c] Federal University of Rio Grande do Sul/UFRGS, Brazil

ARTICLE INFO

Keywords:
Cytokine gene polymorphism
Allogeneic stem cell transplantation
Interleukin
Graft-versus-host disease

ABSTRACT

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a therapeutic modality commonly used to treat hematological and immunological disorders. Among the main complications of allo-HSCT is the acute graft-versus-host disease (a-GVHD), a condition which accounts for a high incidence of mortality. Several genes encoding inflammatory mediators may present polymorphisms, which have been implicated in the risk of developing a-GVHD. In our study, we investigated the association between genotypes of cytokine-encoding genes and the incidence and severity of a-GVHD and survival of HSCT recipients. No statistically significant association was found between IL and 6-174 G/C, INF-γ + 874 T/A, TNF-α -238 A/G, -308 A/G and IL-10-819C/T, -592 A/C polymorphisms and the presence or severity of a-GVHD. A higher risk of a-GVHD was associated with the IL-10-1082 GG genotype compared to the AA + AG genotypes of recipients and donors. The IL-10-1082 genotype can be used as a prognostic determinant to predict which HSCT recipient will be more responsive to the transplant. Thus, cytokine gene assays may be useful in the individualization of prophylactic regimens and for an appropriate selection of immunosuppressants based on the HSCT recipient's responsiveness.

1. Introduction

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) has been used to treat various hematological, metabolic, and immunodeficiency diseases [1]. Despite the extensive progress of allo-HSCT protocols achieved so far, the recipient's post-transplant survival rate is as low as 50–68% according to the literature [2,3]. The transplant prognosis depends on many factors such as the underlying disease, the type of conditioning regimen and the characteristics of recipients and donors. Acute graft-versus-host disease (a-GVHD) and infections are the leading causes of morbidity and mortality in HSCT patients [4].

GVHD is a major complication following allo-HSCT whose acute form occurs in 40–60% of recipients, even in cases where the recipient and donor are HLA-compatible [5,6]. The pathophysiology of a-GVHD involves a "cytokine storm" induced by the pre-transplant conditioning regimen, with a massive release of inflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α) and interleukin-2 (IL-2). Other cytokines, such as interleukin 10 (IL-10), are responsible for modulating the effect of inflammatory mediators. This process is amplified by the activation of transplanted donor T cells and host tissue damage caused by a direct effect of cytokines and toxic effects of the conditioning regimen, ultimately leading to apoptotic cell death [7].

Cytokines are gene-encoded products involved in an extensive network of synergistic and antagonistic interactions that may exhibit either a positive or negative regulatory effect on several cell types [8]. Nucleotide variations in the regulatory region of the genes encoding these proteins have a strong influence on the susceptibility to, and severity of, several diseases. Recent evidence has demonstrated the role of polymorphisms in inflammatory genes, both in recipients and donors, in the occurrence of GVHD [8]. Mounting evidence has proven the role of cytokine gene polymorphisms, such as *TNF-α, IL-10, IL-6* and *INF-γ,* in the prognosis of HSCT, specifically in the risk for a-GVHD, transplant-

* Corresponding author at: Specialized Diagnostic Unit, Flow Cytometry, Hospital de Clínicas de Porto Alegre, Rua Ramiro Barcellos, 2350 Porto Alegre, Brazil.
E-mail address: mgfarias@hcpa.edu.br (M. Granero Farias).

https://doi.org/10.1016/j.humimm.2019.12.002
Received 19 August 2019; Received in revised form 28 November 2019; Accepted 5 December 2019
Available online 27 December 2019

Molecular Biology Reports (2019) 46:2197–2207
https://doi.org/10.1007/s11033-019-04674-1

ORIGINAL ARTICLE

Renal effects of exendin-4 in an animal model of brain death

Natália Emerim Lemos[1,2] · Cristine Dieter[1,2] · Rodrigo Carlessi[3] · Jakeline Rheinheimer[1,2] · Letícia de Almeida Brondani[1,2] · Cristiane Bauermann Leitão[1,2] · Andrea Carla Bauer[1,2,4] · Daisy Crispim[1,2]

Received: 12 November 2018 / Accepted: 5 February 2019 / Published online: 13 February 2019

Abstract
Organ transplantation is the gold standard therapy for the majority of patients with terminal organ failure. However, it is still a limited treatment especially due to the low number of brain death (BD) donors in relation to the number of waiting list recipients. Strategies to increase the quantity and quality of donor organs have been studied, and the administration of exendin-4 (Ex-4) to the donor may be a promising approach. Male Wistar rats were randomized into 3 groups: (1) control, without central nervous system injury; (2) BD induced experimentally, and (3) BD induced experimentally + Ex-4 administered immediately after BD induction. After BD induction, animals were monitored for 6 h before blood collection and kidney biopsy. Kidney function was assessed by biochemical quantification of plasma kidney markers. Gene and protein expressions of inflammation- and stress-related genes were evaluated by RT-qPCR and immunoblot analysis. Animals treated with Ex-4 had lower creatinine and urea levels compared with controls. BD induced oxidative stress in kidney tissue through increased expression of *Ucp2, Sod2* and *Inos*, and Ex-4 administration reduced the expression of these genes. Ex-4 also induced increased expression of the anti-apoptotic *Bcl2* gene. *Nlrp3* and *Tnf* expressions were up-regulated in the BD group compared with controls, but Ex-4 treatment had no effect on these genes. Our findings suggest that Ex-4 administration in BD rats reduces BD-induced kidney damage by decreasing the expression of oxidative stress genes and increasing the expression of *Bcl2*.

Keywords Brain death · Kidney transplantation · Renal tissue · Exendin-4

Introduction

Organ transplantation is currently the gold standard therapy for the majority of patients with terminal organ failure. However, it is still a limited treatment especially due to the low number of brain death (BD) donors in relation to the number of waiting list recipients. Because of this, a rising number of "marginal" brain-dead donors have been accepted for transplantation, even though this approach is related to increased risk for primary graft non-function and/or delayed primary function, besides worse long-term graft survival [1]. There are currently over 120,000 patients waiting for lifesaving organ transplants in the United States. The majority of those patients (n = 100,791) are waiting for a kidney transplant [2].

BD is an irreversible cessation of all brain functions associated with a systemic inflammation that causes a massive catecholamine release, leading to worse graft outcomes [3–5]. Therefore, strategies to increase the quantity and quality of donor organs have been studied and are of great interest [6–8]. One of the target points is the management of donor candidates with interventions to reduce damage caused by BD itself. It is known that BD is associated with a cascade of inflammatory reactions that can lead to donor organ dysfunction and has been associated with risk of rejection [9–12]. Despite the progressive improvement in kidney transplant graft survival rates in the last years, delayed graft

✉ Daisy Crispim
dcmoreira@hcpa.edu.br

1 Laboratory of Human Pancreatic Islet Biology, Endocrine Division, Hospital de Clínicas de Porto Alegre, Rua Ramiro Barcelos 2350, prédio 12, 4° andar, Porto Alegre, Rio Grande Do Sul 90035-003, Brazil

2 Postgraduation Program in Medical Sciences: Endocrinology, Faculdade de Medicina, Universidade Federal do Rio Grande do Sul, Porto Alegre, Rio Grande Do Sul, Brazil

3 School of Biomedical Sciences, Curtin Health Innovation Research Institute, Curtin University, Kent St., Bentley, Perth, WA 6102, Australia

4 Nephrology Division, Hospital de Clínicas de Porto Alegre, Porto Alegre, Rio Grande Do Sul, Brazil

Artigos em fase de submissão/finalização.

- **The rs1800469 T/T and rs1800470 C/C genotypes of the *TGFB1* gene confer protection against diabetic retinopathy in a Southern Brazilian population.**

  Autores: Aline Rodrigues Costa, **Cristine Dieter**, Luís Henrique Canani, Taís Silveira Assmann, Daisy Crispim.

  Artigo em fase de R1 na revista *Genetics and Molecular Biology*.

- **Exenatide improves function of rat pancreatic islets exposed to inflammatory stress: an in vitro study**

  Autores: Natália Emerim Lemos, **Cristine Dieter**, Rodrigo Carlessi, Jakeline Rheinheimer, Bianca Marmontel de Souza, Cristiane Bauermann Leitão, Andrea Carla Bauer, Daisy Crispim.

  Artigo em fase de R1 na revista *Arquives of Endocrinology and Metabolism.*

- **Development of a polygenic risk score to predict the risk of type 1 diabetes mellitus in a Southern Brazilian population.**

  Autores: Felipe Mateus Pellenz, Taís Silveira Assmann, Mayara Souza de Oliveira, Guilherme Coutinho Kullmann Duarte, **Cristine Dieter**, Daisy Crispim.

PREMIAÇÕES NO PERÍODO DO DOUTORADO

- **DESTAQUE** no **Seminário de Pós-Graduação** do **INOVAMUNDI 2022 / UNIVERSIDADE FEEVALE** na Grande Área **CIÊNCIAS DA SAÚDE** com o trabalho "**MicroRNAs na urina são potenciais biomarcadores para identificação de progressão de doença renal em pacientes com diabetes mellitus tipo 1**". – Este trabalho está relacionado ao artigo 1 da presente tese.

- **PRIMEIRO LUGAR GERAL** no **Seminário de Pós-Graduação** do **INOVAMUNDI 2022 / UNIVERSIDADE FEEVALE** com o trabalho "M**icroRNAs na urina são potenciais biomarcadores para identificação de progressão de doença renal em pacientes com diabetes mellitus tipo 1**". – Este trabalho está relacionado ao artigo 1 da presente tese.

- **Destaque de Melhor Apresentação Oral** da **42ª Semana Científica do HCPA** com o trabalho **"The rs1799752/ACE1, rs12329760/TMRPSS2 and rs1990760/IFIH1 polymorphisms are associated with risk to COVID-19 severity in women".** – Este trabalho está relacionado ao artigo intitulado "**Polymorphisms in ACE1, TMPRSS2, IFIH1, IFNAR2, and TYK2 Genes Are Associated with Worse Clinical Outcomes in COVID-19**", publicado na revista Genes (fator de impacto 4.141) em dezembro de 2022, com primeira autoria de Cristine Dieter.