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Search for new molecular signatures in lung adenocarcinoma: differential expression analysis in current and never tobacco smokers

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Introduction: Each year the trachea, bronchus and lung cancer are responsible for 1.7 million of deaths worldwide. In Brazil, lung cancer is the tenth cause of death. Tobacco smoking leads to almost thirty times more chances of developing lung cancer in comparison to non-smoker. Biomarkers are now being used to choose whether a patient is eligible for specific molecular target drugs and immunotherapy. For example, the Programmed Death-Ligand 1(PD-L1) protein, when highly expressed, enables the use of the immunotherapeutic drug Pembrolizumab. However, it has not been completely effective among patients with a PD-L1 expression lower than 50%. New evidence has shown a good response to immunotherapeutic drugs in tumors with high mutational burden, even in those who have a PD-L1 expression lower than 1%. Although this hypermutated signature emerges as a potential biomarker to immunotherapy, its clinical application is still limited due to the high costs of the test. It was demonstrated that tobacco smoking leads to a different molecular signature in non-small cell lung cancer (NSCLC), with a considerably higher number of general point mutations and mutations involving coding regions when compared to never-smokers. Smoking was significantly associated with an improvement in treatment using Pembrolizumab among NSCLC patients, perhaps due to the higher mutational burden is these tumors. **Objectives:** This exploratory study aims to identify differential expressed genes in tumors from current and never-smokers patients, focusing in potentially new biomarkers related to immune and inflammatory response in tobacco smokers. **Methodology:** We performed bioinformatics analyses using publicly microarray data, downloaded from the Gene Expression Omnibus (GEO) repository. The GSE10072 dataset was selected since it contains gene expression from tumor and adjacent non-tumoral tissues, subdivided into current-smoker and non-smoker groups. Raw data were normalized and the analyses of differential expression and functional enrichment were performed using R. The protein-protein interactions from differentially expressed genes comparing the current and non-smokers groups were predicted using STRING database. **Results:** The analysis showed 85 genes differentially expressed only in smokers and 71 only in non-smokers. 139 were differentially expressed in both groups. Curiously, the regulation of inflammatory response pathway was enriched only in tobacco smokers. Functional protein-protein analysis also revealed that humoral and positive regulation of immune response were enriched only in smokers, when considering genes that were exclusively differentially expressed for each group. Interestingly, the most differentially expressed genes related to these pathways were up-regulated in the adjacent tissue compared to the tumor: *VSIG4, FCER1A* and *C4BPA*. VSIG4 is a B7 family–related protein and as PD-L1 is a negative regulator of T cell activation. Studies also revealed that its expression on macrophages facilitates lung cancer development. The product of *FCER1A*, FcεRI, is a high affinity receptor of IgE, which is responsible for allergic response and appears to play a key role in anti-tumoral defense. Finally, *C4BPA* encodes the C4b-binding protein α-chain, an important element in regulation of complement cascade of many processes, including the induction of B cell proliferation and CD40 activation, which can reverse immune suppression and drive antitumor T cell responses. It was also recently considered as a novel serum biomarker for pancreatic cancer. These results show potentially new biomarkers that can be used to select NSCLC for immunotherapy treatment. This analysis will be expanded using a larger cohort from The Cancer Genome Atlas, which will also allow checking other molecular markers such as the tumor mutational burden.