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Título	Can DNA repair deficiency predict response to immune checkpoint inhibitors?
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Can DNA repair deficiency predict response to immune checkpoint inhibitors?

Background: The tumor mutational load is closely related to the integrity of DNA repair pathways. So, in the absence of DNA repair molecules, neoantigens can emerge and signaling pathways can be activated, leading to a more inflammatory tumor microenvironment. However, tumor cells have the ability to modulate their microenvironment by expressing molecules that can help them to evade the immune system, such as PD-L1, which when interacting with its receptor PD-1, induces functional exhaustion of a cytotoxic immune response. As traditional chemotherapy agents, beyond killing tumor cells, can also upregulate immunosuppressive factors, immune checkpoint inhibitors arise as a possible combinatory therapy, counteracting the action of these negative immune regulatory molecules.

Aims and objectives: It was assessed the modulatory effect of different chemotherapy drugs on the expression of PD- L1 in HeLa +/- XRCC1 cell lines, proposing DNA repair deficiency as a predictive factor to combinatorial treatment with conventional therapy and immune checkpoint inhibitor. Methods and materials: HeLa +/- XRCC1 cells were treated with CPT-11 (0.1 μM, 1 μM and 10 μM), fluorouracil (5-FU) (10 μM, 100 μM and 200 μM) and cisplatin (CDDP) (1 μM, 10 μM, 20 μM, 50 μM and 100 μM) for 24 (n=2) and 48 (n=4) hours and PD-L1 surface expression was assessed by flow cytometry analysis. Statistical analysis was carried out using GraphPad Prism, applying non- parametric tests. P value was considered statically significant at less than 0.05.

Results: CPT-11 treatment upregulated PDL-1 expression more in HeLa – XRCC1 cell line, with better result at 10 μM, but none statistical significance was found. 5-FU did not show significant PDL-1 upregulation, with higher expression in HeLa + XRCC1 treated with 100 μM. CDDP showed higher PDL-1 upregulation in the HeLa – XRCC1 cells, with statistical significance in the lower concentration: 1 μM, $p<0.05$.

Discussion: DNA repair deficiency can be a predictive marker of response to immune checkpoint inhibitors after treatment with DNA-damaging drugs, such as CPT-11 and CDDP, as they showed a higher PD- L1 upregulation in XRCC1-deficient HeLa cells. Cisplatin arising as a promising drug to use as a combinatorial therapy with anti PD-L1/anti- PD1, once it directly beneficiates itself with the accumulation of DNA adducts in the absence of a DNA repair molecule.