Barts Cancer Institute
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Can DNA repair deficiency predict response to immune checkpoint inhibitors?

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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

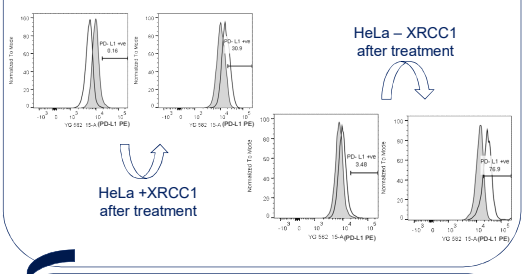
- It is hypothesized that **DNA repair deficient tumors** would beneficiate itself from a **combination of conventional therapy**, which is expected to upregulate PD-L1 and enhance the mutational landscape, and so on, improve the effect of a **subsequent/concomitant immunotherapy with an immune checkpoint inhibitor.**
- To investigate the modulatory effect of different chemotherapy drugs on the expression of PD- L1 in HeLa +/- XRCC1 cell lines.

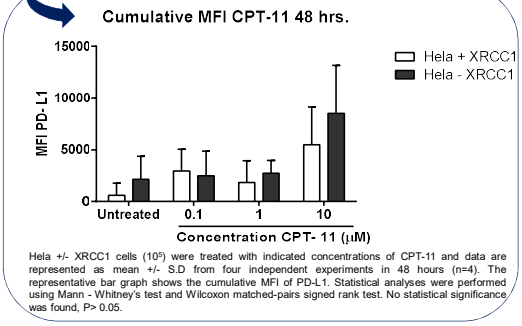
Methods and materials

HeLa +/- shRNA targeting XRCC1 cells → Treated for 24 hours (n=2) and 48 hours (n=4) → Different concentrations: Irinotecan (CPT-11) Fluorouracil (5-FU) Cisplatin (CDDP) → PD- L1 upregulation assessed by flow cytometry analysis- FlowJo software → Statistical analysis: GraphPad Prism 6.0 $p < 0.05$

Results

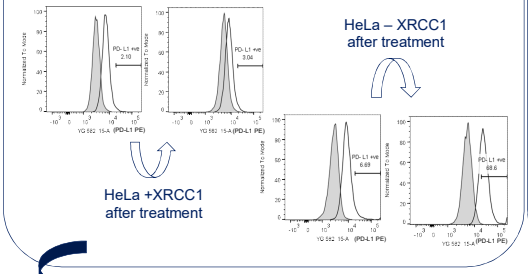
PD- L1 UPREGULATION – HIGHER IN XRCC1 DEFICIENT (CPT-11 10 μM IN 48 HOURS)

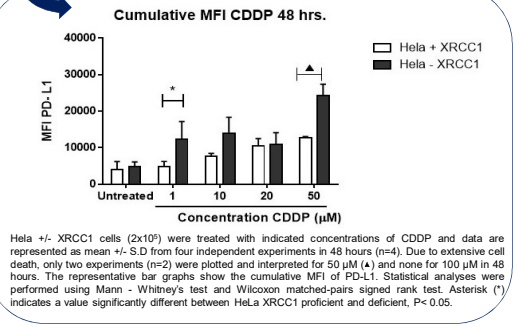




Hela +/- XRCC1 cells (10^5) were treated with indicated concentrations of CPT-11 and data are represented as mean +/- S.D from four independent experiments in 48 hours (n=4). The representative bar graph shows the cumulative MFI of PD-L1. Statistical analyses were performed using Mann - Whitney's test and Wilcoxon matched-pairs signed rank test. No statistical significance was found, P> 0.05.

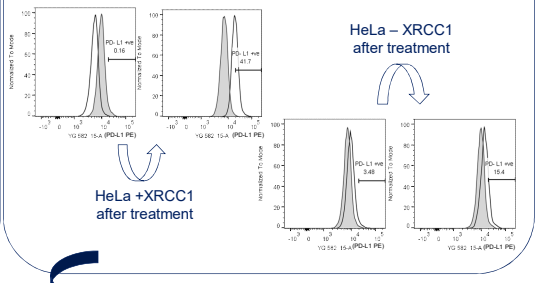
PD- L1 UPREGULATION – HIGHER IN XRCC1 DEFICIENT (CDDP 1 μM IN 48 HOURS)

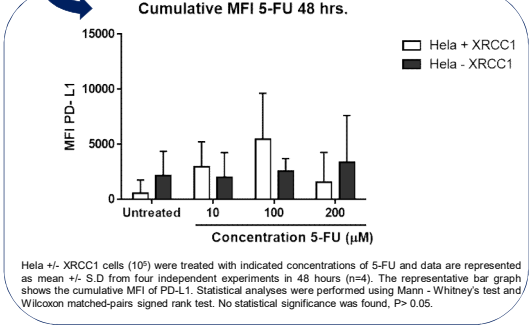




Hela +/- XRCC1 cells ($2x10^5$) were treated with indicated concentrations of CDDP and data are represented as mean +/- S.D from four independent experiments in 48 hours (n=4). Due to extensive cell death, only two experiments (n=2) were plotted and interpreted for 50 μM (▲) and none for 100 μM in 48 hours. The representative bar graphs show the cumulative MFI of PD-L1. Statistical analyses were performed using Mann - Whitney's test and Wilcoxon matched-pairs signed rank test. Asterisk (*) indicates a value significantly different between HeLa XRCC1 proficient and deficient, P< 0.05.

PD- L1 UPREGULATION – HIGHER IN XRCC1 PROFICIENT (5-FU 100 μM IN 48 HOURS)





Hela +/- XRCC1 cells (10^5) were treated with indicated concentrations of 5-FU and data are represented as mean +/- S.D from four independent experiments in 48 hours (n=4). The representative bar graph shows the cumulative MFI of PD-L1. Statistical analyses were performed using Mann - Whitney's test and Wilcoxon matched-pairs signed rank test. No statistical significance was found, 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 PDL1/ anti- PD1, once it directly beneficiates itself with the accumulation of DNA adducts in the absence of a DNA repair molecule.

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