Can DNA repair deficiency predict response to immune checkpoint inhibitors?

Author: Mariane Araujo Branco  
Supervisor: Dra. Sarah Martin  
Barts Cancer Institute – Queen Mary University of London

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 benefit 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

<table>
<thead>
<tr>
<th>HeLa +/- shRNA targeting XRCC1 cells</th>
<th>Treated for 24 hours (n=2) and 48 hours (n=4)</th>
<th>Different concentrations:</th>
<th>PD-L1 upregulation assessed by flow cytometry analysis - FlowJo software</th>
<th>Statistical analysis: GraphPad Prism 6.0 p &lt; 0.05</th>
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<tbody>
<tr>
<td></td>
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<td>Cisplatin (CDDP)</td>
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<td>Fluorouracil (5-FU)</td>
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<td>Irinotecan (CPT-11)</td>
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Results

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 combinatory therapy with anti PDL1/ anti- PD1, once it directly benefits itself with the accumulation of DNA adducts in the absence of a DNA repair molecule.

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 combinatory therapy with anti PDL1/ anti- PD1, once it directly benefits itself with the accumulation of DNA adducts in the absence of a DNA repair molecule.