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Identification of genetic determinants of DNA mismatch repair loss that predict response to immune checkpoint blockade

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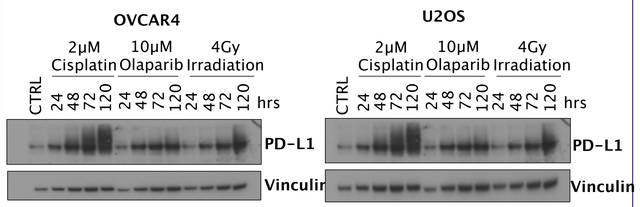
1. Response to immune checkpoint blockade (ICB) is observed in mismatch repair (MMR) deficient tumours

Despite showing great clinical promise, response rates to (ICB) in MMR-deficient tumours vary greatly.
We hypothesised that the loss of different MMR genes can lead to differential regulation of PD-L1 expression, therefore stratifying specific MMR deficiencies can better predict ICB response.

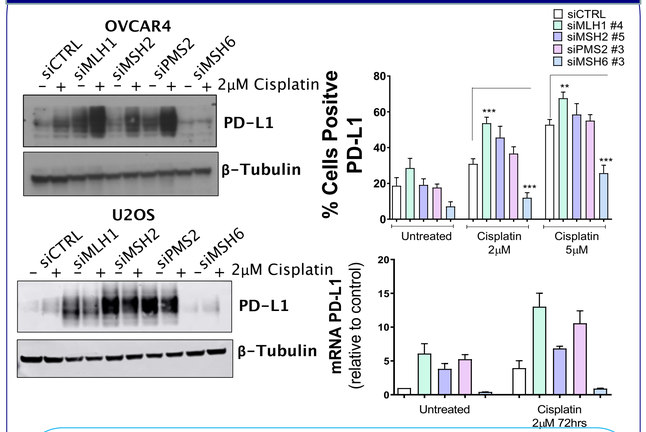
2. DNA damage induces PD-L1 expression

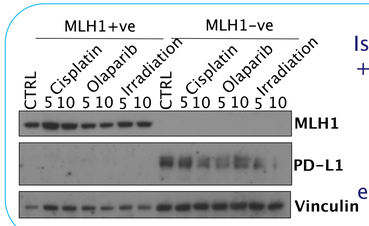
DNA damage was induced in the MMR-proficient OVCAR4 and U2OS cancer cell lines. We observe an upregulation of PD-L1 expression in both cancer cells after induced DNA damage.



We next aimed to investigate the involvement of the four key MMR genes in the regulation of PD-L1 after DNA damage, by silencing the MMR genes in our cell models.

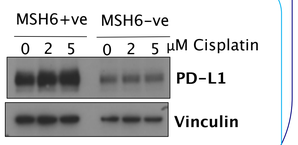
3. MMR-deficiency induces differential PD-L1 regulation





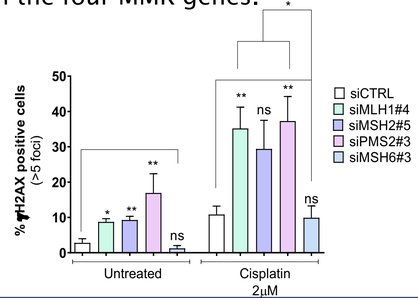
Isogenically paired MLH1 +/- HCT116 CRC cancer cells support our findings. MLH1-deficiency leads to increased PD-L1 expression compared to MLH1-proficient cells

Isogenically paired MSH6 +/- U251 GBM cancer cells support our findings MSH6-deficiency leads to reduced PD-L1 expression compared to MSH6-proficient cells

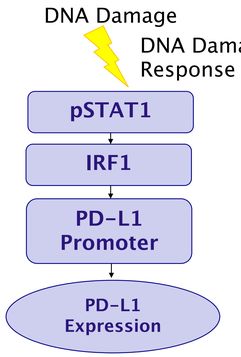


4. PD-L1 expression is positively correlated with DNA damage accumulation

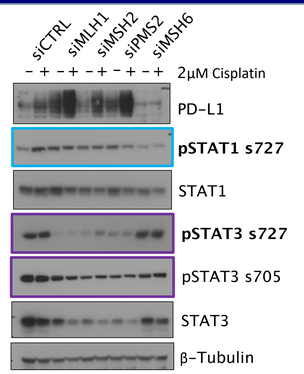
We investigated the relationship between PD-L1 expression and DNA damage, by measuring γH2AX foci formation in OVCAR4 cells proficient and deficient in the four MMR genes.



5. DNA damage upregulates PD-L1 via STAT1-IRF1



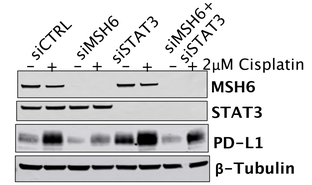
6. STAT1-phosphorylation is positively correlated with PD-L1 upregulation



Levels of STAT1 phosphorylation are positively correlated with PD-L1 expression

Levels of STAT3 phosphorylation are negatively correlated with PD-L1 expression

7. Inhibition of STAT3 in MSH6-deficient cancer can increase PD-L1 expression



8. Clinically, varied response to ICB in MMR-deficient patients could be attributed to loss of MSH6, where cells accumulate lower levels of DNA damage, lower levels of pSTAT1 and lower levels of PD-L1 expression. Pharmacological inhibition of STAT3 could reverse this phenotype and should be considered in combination with ICB treatment.

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