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

C. Smith, D. Cucchi A. Gibson, K. Brooksbank, T. Elliott, V. Valge-Archer, S. A. Martin

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.

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.

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

DNA Damage

DNA Damage Response

pSTAT1

IRF1

PD–L1 Promoter

PD–L1 Expression

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

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

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

Levels of STAT3 phosphorylation are negatively correlated with 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.