Nature Reviews Cancer | Published online 9 Dec 2016; doi:10.1038/nrc.2016.144

IMMUNOTHERAPY

Switching off immune suppression

Neil Smith/Macmillan Publishers Limited

Two papers have shown in mouse tumour models that targeting PI3Kγ in myeloid cells can reduce immune suppression and increase the efficacy of immune checkpoint inhibitors.

Kaneda *et al.* first examined data from The Cancer Genome Atlas on head and neck squamous cell carcinoma (HNSCC) and noted that increased survival correlated with increased mRNA levels of pro-inflammatory genes. They hypothesized that PI3Kγ signalling in macrophages might control a switch between immune suppression and stimulation; indeed growth of HNSCC tumours, as well as lung tumours, was suppressed in mice lacking PI3Kγ (*Pik3cg*$^{-/-}$ mice) or treated with pharmacological inhibitors of PI3Kγ (TG100-115, which inhibits both PI3Kγ and PI3Kδ, and IPI-549, a selective PI3Kγ inhibitor). The cancer cells did not express PI3Kγ and were therefore unaffected by PI3Kγ inhibitors. Levels of macrophage infiltration in tumours were unchanged by PI3Kγ inhibition, but the expression of inflammatory cytokines by these cells was increased, and immunosuppressive factor expression was decreased.

Several lines of evidence supported a role for PI3Kγ specifically in macrophages. Adoptive transfer of *Pik3cg*$^{-/-}$ macrophages with tumour cells into wild-type mice inhibited tumour growth. Furthermore, when tumour-bearing mice were treated with PI3Kγ inhibitors in combination with an agent that depletes macrophages, there was no additional effect. Tumours grown in mice with *Pik3cg*$^{-/-}$ macrophages also had increased CD8^{+} T cell recruitment. These T cells had increased antitumour activity, which was independent of PI3Kγ signalling in the T cells themselves.

The authors then investigated the therapeutic utility of PI3Kγ inhibition in combination with immune checkpoint therapy. A programmed cell death protein 1 (PD1) antibody suppressed tumour growth in *Pik3cg*$^{-/-}$ mice bearing HNSCC tumours. Similarly, the combination of PI3Kγ and PD1 inhibitors also suppressed tumour growth. These interventions led to long-term survival of 60% of male and 90–100% of female mice. A PI3Kγ-driven gene expression signature was predictive of poor survival in patients with HNSCC or lung adenocarcinoma, indicating that PI3Kγ inhibition might be beneficial in these patients.

De Henau *et al.* found that a mouse tumour model (4T1 breast cancer) that is resistant to checkpoint blockade with PD1 or cytotoxic T lymphocyte associated antigen 4 (CTLA4) inhibitors has increased infiltration of immunosuppressive myeloid cells compared with a model (B16-F10 melanoma) that responds to checkpoint blockade. Furthermore, immune checkpoint therapy loses its efficacy in mice bearing B16-F10 melanomas that have been engineered to express granulocyte–macrophage colony-stimulating factor (GM-CSF), which promotes myeloid cell recruitment.

Given the previously described role for PI3Kγ in myeloid cells, the authors investigated the antitumour efficacy of PI3Kγ inhibitors. IPI-549 inhibited tumour growth in models that had high levels of myeloid cell infiltration, but not in models with low infiltration, and switched macrophages from an immunosuppressive phenotype to an inflammatory one. Tumours treated with IPI-549 also had increased infiltration of CD8^{+} T cells, and mice lacking T cells did not respond to IPI-549. Together, these data indicate that PI3Kγ inhibition in myeloid cells reduces immune suppression, enabling the recruitment of cytotoxic T cells to tumours.

> “PI3Kγ inhibition in myeloid cells reduces immune suppression”

The T cells present in tumours had increased PD1 and CTLA4 expression, and the authors found that combining inhibitors of either PD1 or CTLA4 with IPI-549 treatment improved antitumour efficacy. Furthermore, treatment of mice bearing 4T1 or GM-CSF-expressing B16-F10 tumours with PD1, CTLA4 and PI3Kγ inhibitors led to complete remission in 30% and 80% of mice, respectively.

This combination might prove efficacious against tumours that are resistant to checkpoint blockade due to high infiltration of immunosuppressive myeloid cells, and it is being tested in a phase I/Ib clinical trial of IPI-549 as monotherapy and in combination with a PD1 inhibitor (NCT02637531).

Sarah Seton-Rogers

ORIGINAL ARTICLES Kaneda, M. M. *et al.* PI3Kγ is a molecular switch that controls immune suppression. *Nature* **539**, 437–442 (2016) | De Henau, O. *et al.* Overcoming resistance to checkpoint blockade therapy by targeting PI3Kγ in myeloid cells. *Nature* **539**, 443–447 (2016)