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IMMUNOTHERAPY

Checkpoint parley

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Immune checkpoint blockade has emerged as one of the most promising strategies for tackling solid tumours. Although there have been encouraging clinical results, such as in patients with metastatic melanoma, the factors that determine responsiveness to this type of therapy remain unclear. Five recent studies published in *Nature* and two studies from the *New England Journal of Medicine* now advance our understanding of therapies that target the programmed cell death protein 1 (PD1) and cytotoxic T lymphocyte antigen 4 (CTLA4) immune checkpoints.

There is growing evidence that tumour cells exploit the PD1 and CLTA4 pathways to prevent T cell-mediated tumour eradication. Checkpoint blockade therapies attempt to disrupt these pathways to promote an effective antitumour immune response. Collectively, the seven new studies provide important insight into several aspects of PD1- and CTLA4-targeted immunotherapy. First, the reports expand the list of potential cancer types that respond to these therapies. Herbst *et al.* found that treatment with the PD1 ligand 1 (PDL1)-specific monoclonal antibody MPDL3280A reduced metastatic lesions in patients with advanced incurable cancers, including non-small-cell lung cancer, melanoma and renal cell carcinoma; MPDL3280A was also shown by Powles *et al.* to be beneficial in treating patients with metastatic urothelial bladder cancer. In addition, Robert *et al.* found that patients who had metastatic melanoma without a *BRAF* mutation responded significantly better to treatment with the PD1-specific antibody nivolumab than to a standard chemotherapy.

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The studies also identified biomarkers that can predict the success of immune checkpoint blockade. Tumeh *et al.* characterized samples that had been taken from patients with metastatic melanoma before and during therapy with the PD1-specific antibody pembrolizumab; they showed that patients who responded to pembrolizumab had higher pre-existing numbers of $CD8^+$, $PD1^+$ and $PDL1^+$ cells in the tumour microenvironment. The reports by Powles *et al.*, Herbst *et al.* and Robert *et al.* also found that high levels of PDL1 expression in the tumour microenvironment were predictive of a better clinical response to therapies targeting the PD1–PDL1 pathway. High levels of PDL1 expression by tumour-infiltrating immune cells were reported to be the best predictor of treatment efficacy, but increased expression of CTLA4 and greater levels of $CD8^+$ T cell proliferation in the tumour were also associated with a better response to therapies targeting PD1 or PDL1.

Several reports have suggested that cancers with a high rate of somatic mutation respond best to immune checkpoint blockade. An explanation for this is that such mutations may give rise to neoantigens that can be targeted by T cells following their release from PDL1- or CTLA4-mediated inhibition. Snyder *et al.* carried out whole-exome sequencing on tumours from patients with malignant melanoma who were being treated with ipilimumab or tremelimumab, which both target CTLA4. They observed that a high mutational load in the tumour correlated with an improved response to CTLA4 blockade. However, some tumours with a high mutational load did not respond to therapy. Using computational analysis, Synder *et al.* identified a set of neoepitopes that were shared by the tumours of the patients who responded best to CTLA4 blockade. Interestingly, some of these neoepitopes have homology to viral and bacterial antigens. These findings indicate that it may not be the overall number, but rather the nature of the mutations in a tumour that is important for their recognition by T cells.

The studies by Yadav *et al.* and Gubin *et al.* also used whole-exome sequencing and computational analysis to characterize immunogenic tumour mutations in mouse models of cancer. Using these techniques in combination with mass spectrometry, Yadav *et al.* identified candidate neoepitopes in two distinct mouse tumour types and showed that vaccines incorporating these mutated peptides could promote the eradication of established tumours in mice. Similarly, Gubin *et al.* identified tumour-cell-specific mutant peptides that drive T cell-mediated tumour rejection in mice with sarcomas. T cells recognizing these neoepitopes were present in the tumours of untreated mice, and targeting PD1 or CTLA4 activated these T cell populations to promote tumour rejection. Gubin *et al.* also generated therapeutic vaccines based on these neoepitopes and found that the vaccines promoted the rejection of the sarcomas from which the neoepitopes were identified, but not of non-related tumour types. Finally, by analysing gene sets associated with PD1- or CTLA4-targeted therapy, they showed that these therapies promote antitumour responses by regulating predominantly distinct immune and metabolic pathways.

All of these reports will be welcome news to clinicians and patients alike; they aid our understanding of the mechanisms through which immune checkpoint blockade operates and detail an approach that could be used to develop personalized cancer vaccines.

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ORIGINAL RESEARCH PAPERS Herbst, R. S. *et al.* Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. *Nature* **515**, 563–567 (2014) | Powles, T. *et al.* MPDL3280A (anti-PD-L1) treatment leads to clinical activity in metastatic bladder cancer. *Nature* **515**, 558–562 (2014) | Robert, C. *et al.* Nivolumab in previously untreated melanoma without *BRAF* mutation. *N. Engl. J. Med.* http://dx.doi.org/10.1056/NEJMoa1412082 (2014) | Tumeh, P. C. *et al.* PD-1 blockade induces responses by inhibiting adaptive immune resistance. *Nature* **515**, 568–571 (2014) | Snyder, A. *et al.* Genetic basis for clinical response to CTLA-4 blockade in melanoma. *N. Engl. J. Med.* http://dx.doi.org/10.1056/NEJMoa1406498 (2014) | Yadav, M. *et al.* Predicting immunogenic tumour mutations by combining mass spectrometry and exome sequencing. *Nature* **515**, 572–576 (2014) | Gubin, M. M. *et al.* Checkpoint blockade cancer immunotherapy targets tumour-specific mutant antigens. *Nature* **515**, 577–581 (2014)