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GENETICS

Evading antitumour immunity

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A recent article published in *Nature* describes a novel genetic mechanism of immune evasion in a number of cancers that is caused by structural variants (SVs) disrupting the 3′ regulatory region of programmed cell death ligand 1 (*PDL1*; also known as *CD274*).

Increased expression of PDL1 is known to aid immune evasion; if the T cell programmed cell death protein 1 (PD1) receptor binds to its tumour cell ligand (PDL1), the T cell is unable to kill the tumour cell. Some individuals have been successfully treated with antibodies against PD1 and PDL1, but the mechanisms behind the ability to evade the immune response have remained elusive.

The team first searched for evidence of SV-associated breakpoints in the whole-genome sequences of 49 individuals with adult T cell leukaemia, a retrovirus-associated malignancy. They identified several breakpoint cluster regions; the most prominent of these — identified in over one-quarter of the samples — was a cluster in the 3′ region of *PDL1* on chromosome 9p24.1. These breakpoints were variable and included deletions, duplications, inversions and translocations. The SVs resulted in markedly elevated expression of aberrant but apparently functional PDL1 proteins, with intact extracellular binding and transmembrane domains, and thus preserved receptor–ligand binding capacity.

To investigate whether a similar mechanism of immune evasion might be involved in the development of other human cancers, the team looked at RNA-sequencing data for 10,210 samples across 33 tumour panels from The Cancer Genome Atlas. In all 32 cases with aberrant PDL1 transcripts, 3′ disruption of *PDL1* was associated with elevated transcript expression levels.

Finally, to investigate the effects of the 3′ *PDL1* disruption in tumour immunity, mice were inoculated with EG7-OVA (mouse T cell lymphoma) cells, either with or without an intact 3′ region of *Pdl1*. Mice inoculated with intact 3′ *Pdl1* displayed tumour regression, as well as increased levels of $CD8^+$ T cells in the tumour environment, in contrast to mice inoculated with 3′ *Pdl1*-disrupted cells. Blockage of this signalling pathway using a PDL1 antibody restored $CD8^+$ cytotoxic T cell induction and tumour regression in mice inoculated with EG7-OVA cells with a disrupted 3′ region of *Pdl1*.

Importantly, identification of a disrupted 3′ sequence in this genomic region might constitute a diagnostic marker to identify patients most likely to benefit from anti-PDL1 therapy.

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ORIGINAL ARTICLE Kataoka, K. *et al.* Aberrant *PD-L1* expression through 3′-UTR disruption in multiple cancers. *Nature* http://dx.doi.org/10.1038/nature18294 (2016)