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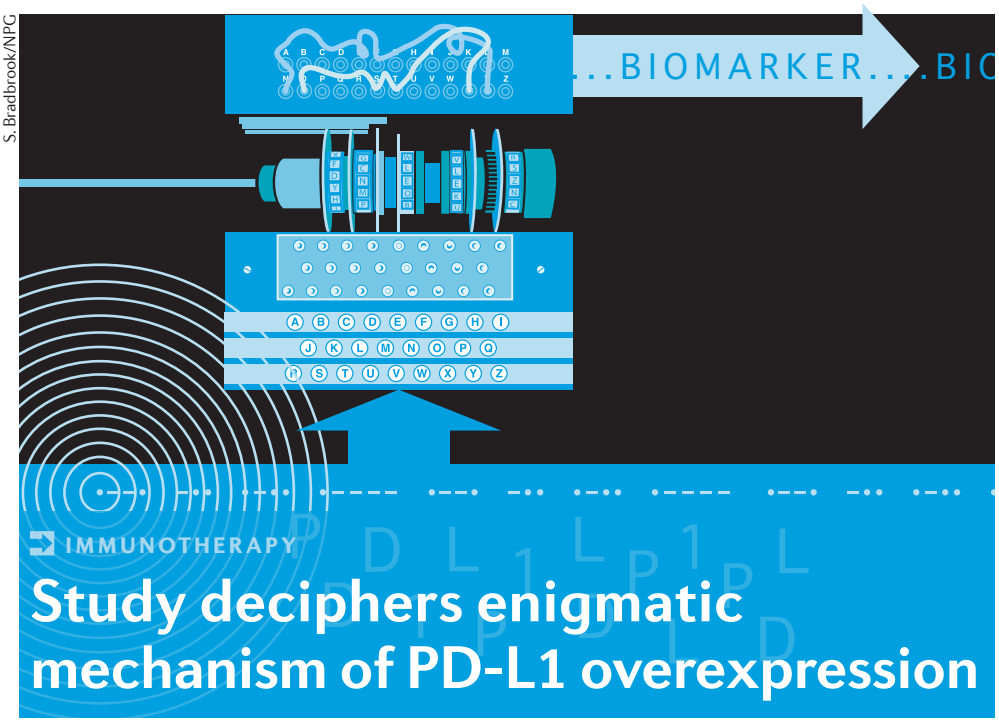
S. Bradbrook/NPG



Study deciphers enigmatic mechanism of PD-L1 overexpression

Anticancer immunotherapy targeting the PD-1–PD-L1 axis results in dramatic tumour responses, but in only a small proportion of patients; thus, biomarkers that reliably identify these patients are needed. Now, a novel genetic mechanism that drives overexpression of PD-L1 has been discovered, with implications for patient stratification.

Overexpression of PD-L1 in tumours increases the likelihood of response to PD-1–PD-L1 blockade; however, with the exception of gene amplifications or translocations that are common in certain tumour types, such as Hodgkin lymphoma, the genetic basis of PD-L1 overexpression in cancers remains largely unknown. Translocations, inversions, tandem duplications, and deletions in noncoding regions of genes can drive oncogene expression, and thus, Seishi Ogawa and colleagues have now investigated whether these 'structural variants' (SVs) affect the gene encoding PD-L1 in adult T-cell leukaemia/lymphoma (ATL) and other cancers.

> Patients with PD-L1 SVs should be prioritized for clinical trials of anti-PD-1/PD-L1 therapy

"To detect PD-L1 SVs, we performed genome-wide mapping of SV-associated breakpoints using whole-genome sequencing data, because this methodology has recently been reported to successfully identify novel activating SVs, such as those involving *GFI1* or *TERT*," Ogawa explains. PD-L1 SVs were identified in 13 of 49 (26.5%) ATL samples. In each of the 13 samples, a PD-L1 transcript with an aberrant 3′ untranslated region (UTR) was generated and overexpression of PD-L1 was observed, with evidence indicating that the 3′-UTR alterations delayed clearance of the transcripts. Importantly, all of the aberrant forms of PD-L1 retained the extracellular domains and could bind to PD-1, suggesting that the mutant forms have the capacity to activate immunosuppressive signals in T cells.

The Cancer Genome Atlas data for 10,210 samples from 33 tumour panels were also analysed. The team discovered only 32 samples with 3′-UTR-truncated PD-L1 transcripts, although these alterations were slightly enriched in diffuse large-B-cell lymphoma (in 4 of 48 samples) and stomach adenocarcinoma (9 of 415 samples).

Thus, SVs that result in overexpression of PD-L1 are present in a variety of cancers, but in only a small proportion of these tumours. Nevertheless, the high efficacy of anti-PD-1/PD-L1 antibodies in patients with Hodgkin lymphoma, in which abnormalities in the gene encoding PD-L1 are often associated with overexpression of this protein, suggests that patients with PD-L1 SVs might also respond well to these agents. In support of this hypothesis, expression of 3′-UTR-truncated PD-L1 transcripts in tumour cells resulted in tumour immune evasion in a mouse model, which was effectively inhibited by PD-1/PD-L1 blockade.

Ogawa summarizes these findings: "a potential implication is that PD-L1 SVs might constitute a genetic marker to identify patients most likely to benefit from anti-PD-1/PD-L1 antibodies. Thus, genetic testing of PD-L1 SVs should be performed in clinical trials evaluating predictive biomarkers of a response to these agents, in addition to PD-L1 immunohistochemistry: some of the PD-L1 SVs are not recognized by anti-PD-L1 *C*-terminal antibodies that are often used in immunohistochemical analyses, one of which is approved by the FDA as a diagnostic test in patients with metastatic urothelial cancer." He concludes, "in addition, patients with PD-L1 SVs should be prioritized for clinical trials of anti-PD-1/PD-L1 therapy."

Owaga and co-workers plan to conduct clinical studies to examine whether PD-L1 SVs are indeed useful genetic markers that predict the effectiveness of anti-PD-1/PD-L1 antibodies.

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