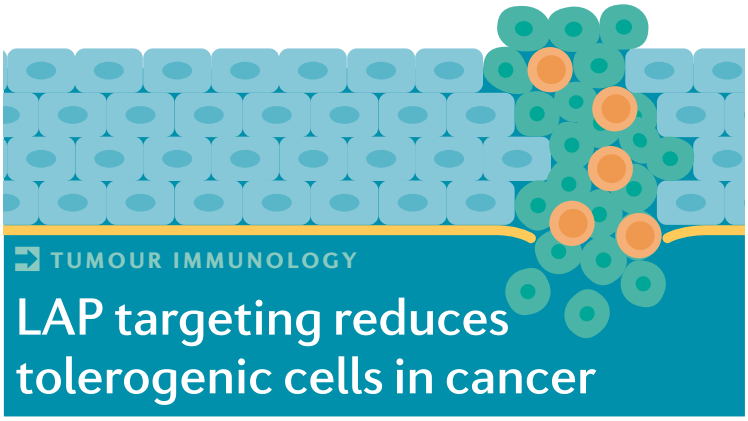

TUMOUR IMMUNOLOGY

LAP targeting reduces tolerogenic cells in cancer

Regulatory T (T_{reg}) cells can promote cancer development by suppressing immune responses and have therefore become attractive targets for anti-cancer immunotherapy. However, finding druggable targets that are specific for immunosuppressive cells has been challenging. Now, reporting in *Science Immunology*, Howard Weiner and colleagues demonstrate that antibodies directed against latency-associated peptide (LAP) reduce the frequency of tolerogenic cells in the tumour microenvironment and show promising results in several mouse models of cancer.

The authors were particularly interested in targeting LAP^+ transforming growth factor-β $(TGFβ)^+$ $FOXP3^+$ T cells, a highly immunosuppressive subset of T_{reg} cells that are upregulated in human malignancies. These cells express LAP and TGFβ, which are encoded by the same gene (*TGFB1*), as a small latent complex on their cell surface, in which LAP keeps TGFβ in its inactive form. TGFβ has multiple roles in cancer: it can increase tumour cell proliferation and invasion, induce angiogenesis, affect the maturation of antigen-presenting cells and promote immunosuppression.

Treatment with an anti-LAP antibody reduced tumour growth in several mouse models of melanoma, glioblastoma and colorectal cancer. It lowered the frequency of LAP^+ $TGFβ^+$ T_{reg} cells and also increased the frequency and tumour infiltration of cytotoxic T lymphocytes (CTLs) and natural killer (NK) cells. Moreover, it promoted the development of dendritic cells (DCs) with a pro-inflammatory phenotype. *In vitro* experiments showed that the antibody directly inhibited the release of TGFβ from the cell surface, which may explain some of its systemic effects. Interestingly, the antibody also reduced the frequency of $CD103^+$ $CD8^+$ T cells. Adoptive transfer experiments showed that these cells have a tolerogenic phenotype and suppress the proliferation of CTLs via the programmed cell death 1 (PD1)–PD1 ligand 1 (PDL1) axis. In the B16 model of melanoma, anti-LAP and anti-PD1 treatment had similar efficacy.

> “the antibody directly inhibited the release of TGFβ from the cell surface, which may explain some of its systemic effects”

Since anti-LAP antibodies affect the maturation of DCs, the authors also tested possible synergistic effects when they are used in combination with DC-based vaccination. Mice were first vaccinated with DCs loaded with ovalbumin (OVA), then challenged with OVA-expressing melanoma or glioblastoma cells and treated with anti-LAP antibody. In all cases, animals receiving both vaccination and anti-LAP treatment remained tumour free, whereas 100% of control mice and 60% of mice that were vaccinated but treated with a control antibody developed tumours. Moreover, the authors found that anti-LAP treatment increased the number of OVA-specific $CD8^+$ memory T cells.

These results indicate that targeting LAP may be an effective way to enhance anticancer immune responses and boost immune memory. The authors point out that LAP is also expressed by some $CD8^+$ T cells, γδ T cells, NK cells, B cells and DCs, so the antitumour effect could be related to multiple targets. In patients with cancer, LAP expression is associated with a poor prognosis, making anti-LAP an attractive candidate for cancer immunotherapy.

Alexandra Flemming, Chief Editor
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