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CANCER IMMUNOTHERAPY

Engineering smart antibodies

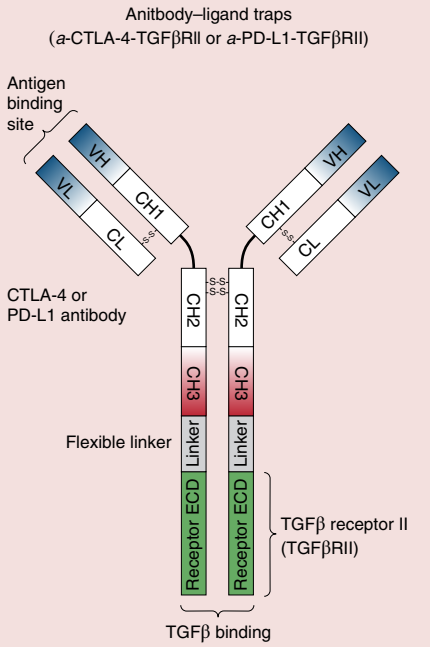
Tumours have the ability to evolve and thwart an immune response by a variety of strategies, including the production of multiple immunomodulatory factors that inhibit cytotoxic T lymphocyte activity. This eventually leads to tumours evading immune-mediated elimination. The therapeutic use of antibodies to counteract tumour-induced immune evasion through prevention of T-cell inhibitory checkpoint activation has led to promising clinical results in many but not all cancer cases. One possibility for poor patient response could be due to the presence of additional inhibitory mechanisms that mediate immune tolerance. Atul Bedi and colleagues[1] now report in *Nature Communications* on the development of a dual-function therapeutic to simultaneously block inhibitory T-cell checkpoint activity while also disabling an immune-suppressive cytokine produced by cancer cells.

The majority of cancer cells express a multifunctional cytokine known as transforming growth factor beta (TGF-β), which is involved in cell invasion and tumour cell metastasis. TGF-β is also involved in regulating the adaptive immune response by suppressing the activity of cytotoxic T lymphocytes, which can destroy cancer cells; limits the differentiation of T helper cells, which secrete cytokines that activate other lymphocytes[2]; and also prevents the immune system from developing immunological memory towards tumour antigens. Therefore, TGF-β is a critical factor in tumour-mediated immune escape.

One strategy to limit tumour-induced immune suppression is to target the receptors or checkpoints of T lymphocytes. These checkpoints maintain self-tolerance and regulate the amplitude and duration of immune responses in order to diminish healthy tissue damage. This strategy is known as immune checkpoint blockade therapy, and a number of antibodies, such as cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) and programmed death-ligand 1 (PD-L1), have been developed and approved — ipilimumab (CTLA-4) and atezolizumab (PD-L1) — for specific indications in cancer immunotherapy[3], although it has been noted that not all patients respond to these antibodies.

Bedi and colleagues utilized an antibody engineering strategy to develop a dual-function therapeutic containing an antibody targeting either CTLA-4 or PD-L1 that is then fused to TGF-β receptor II (TGFβRII) via a flexible linker to form two antibody–ligand traps: *a*-CTLA-4-TGFβRII and *a*-PD-L1-TGFβ RII (pictured). Initially, the researchers screened tissues from patients with a range of cancers and found a strong correlation between TGF-β signalling and expression of transcriptional factors associated with immunosuppression. They carried out in vivo assessment and found that treatment of tumour-bearing mice with the antibody–ligand traps disrupted the TGF-β feedback loop in T lymphocytes and also reduced tumour-infiltrating immunosuppressor regulatory T cells. Moreover, treatment with these antibody–ligand traps significantly inhibited tumour progression, and elevated the percentage of cytotoxic T cells and immunological memory towards the tumour antigens. When they compared treatment with these antibody–ligand traps to treatment with the clinically used antibodies ipilimumab or atezolizumab, there was a superior advantage to using the antibody–ligand traps.

Further investigation of such immunotherapeutics for safety and efficacy is paramount before clinical translation, due to the potential risk of adverse toxicity associated with autoimmunity. However, these bifunctional antibody–ligand traps offer the promise of simultaneously blocking the immune checkpoint and also disrupting TGF-β signalling in the tumour microenvironment, thus further limiting tumour-induced immune suppression. ❐



Credit: adapted from ref. [1], Macmillan Publishers Ltd

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