TUMOUR IMMUNOLOGY

Dealing with tumours

Tumours can prevent the immune system mounting an effective immune response in several ways. Production of the immunosuppressive cytokine transforming growth factor-β (TGF-β) by tumour cells, or by other cells at the tumour site, can contribute to the suppression of anti-tumour immune responses. Reporting in *Nature Medicine*, Leonid Gorelik and Richard Flavell provide evidence to show that blockade of TGF-β signalling in T cells enables the immune system to protect mice against tumours.

TGF-β is a cytokine that mediates immunosuppression in several ways, including inhibition of T-cell activation by antigen-presenting cells, and inhibition of T-cell differentiation into cytotoxic T lymphocytes (CTLs) and T helper 1 cells (T_H1). In this study, Gorelik and Flavell investigated the contribution of TGF-β signalling in anti-tumour responses by T cells. They analysed mice expressing a dominant-negative form of TGF-β receptor type II, whose $CD4^+$ and $CD8^+$ T cells are insensitive to TGF-β signalling. The effect on tumour growth was assessed using the mouse thymoma line EL-4 and the mouse metastatic melanoma line B16-F10, both of which produce TGF-β. Transgenic mice were able to resist challenge by both types of tumour cell, but non-transgenic littermates developed progressive tumours. Although rejection was associated with the development of tumour-specific CTLs, cell-depletion experiments showed that $CD4^+$ T cells were also required for effective tumour eradication.

But does tumour eradication depend on blockade of TGF-β signalling in both $CD4^+$ and $CD8^+$ T cells? To investigate this, the authors used an adoptive-transfer system with *Rag1*$^{-/-}$ mice — which lack endogenous T and B cells — as hosts. Transfer of transgenic $CD8^+$ T cells and non-transgenic $CD4^+$ T cells prevented the development of tumours, but the opposite combination of cells was unable to prevent tumour growth, showing that blockade of TGF-β signalling in $CD8^+$T cells is crucial for tumour eradication.

So, TGF-β-signalling blockade can protect mice against tumour challenge, but can it also combat established tumours? *Rag1*$^{-/-}$ mice were injected with EL-4 tumour cells followed by adoptive transfer of transgenic T cells. T-cell transfer on day 3 after tumour innoculation did prevent tumour growth, but cell transfer on day 7 had no effect.

The results from this study have important implications for cancer therapy. The data support the idea that although tumour cells use several tricks to confound the immune system, one way to enhance anti-tumour responses might be to block TGF-β signalling in T cells.

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References and links

ORIGINAL RESEARCH PAPER Gorelik, L. & Flavell, R. Immune-mediated eradication of tumors through the blockade of transforming growth factor-β signaling in T cells. *Nature Med.* **7**, 1118–1122 (2001)

WEB SITE

Richard Flavell's lab: http://www.biology.yale.edu/FacultyResearch/Flavell.html