ANTICANCER DRUGS

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> CAR–T cells can effectively target EGFRvIII-expressing tumours, while avoiding potential toxic effects from interactions with EGFRwt

Enhancing the immune response against cancer cells by transducing T cells from patients with chimeric antigen receptors (CARs) that are specific for antigens expressed by tumours has recently resulted in dramatic clinical responses for some blood cancers. However, a major issue in extending the approach to solid tumours is that if the antigen is not specific enough to the tumour, there is a risk of CAR–T cell toxicity to non-tumour tissues. Johnson *et al.* now describe a CAR–T cell therapy that targets epidermal growth factor receptor variant III (EGFRvIII), an oncogenic mutant of EGFR that is specifically expressed in ~30% of glioblastomas.

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First, the authors created CARs based on EGFRvIII-specific single-chain variable fragments (scFvs). When mice were co-injected daily with temozolomide (a drug used to treat glioma), EGFRvIII-specific CAR–T cells induced rapid regression of EGFRvIII-positive glioblastoma; in particular, a CAR containing the murine 3C10 scFv substantially reduced tumour burden after just 7 days and so was investigated further.

The authors created eight humanized versions of the 3C10 scFv and picked one, 2173, for its favourable selectivity for EGFRvIII over the wild-type EGFR (EGFRwt) — a quality that suggested it might elicit fewer off-tumour effects.

To investigate this possibility, the authors tested the 2173-CAR–T cells versus T cells expressing CARs based on the EGFR-specific antibody, cetuximab (cetux), which binds to EGFRwt and EGFRvIII with equal affinity. Cetux-CAR–T cells proliferated, produced type I cytokines and caused lysis in equal amounts in response to EGFRwt- or EGFRvIII-expressing cells. By contrast, 2173-CAR–T cells exhibited these responses (to a similar extent as did cetux-CAR–T cells) only in response to EGFRvIII-expressing cells.

Next, immunodeficient mice were grafted with human skin, which expresses low levels of EGFR, and injected intravenously 4 weeks later with CAR–T cells. Cetux-CAR–T cell injection led to a high degree of lymphocyte infiltration and lymphocyte-induced apoptosis in the human skin, whereas there was minimal infiltration or cell death in the human skin on animals injected with 2173-CAR–T cells. Together, these results imply that 2173-CAR–T cells do not target the immune response to EGFRwt-expressing tissues.

Finally, the authors tested the 2173-CAR–T cells in an immunodeficient mouse model of intracranial EGFRvIII-expressing glioma; 7 days after tumour cell implantation, 2173-CAR–T cells, untransduced T cells or vehicle solution were injected intravenously. Three days later (11 days after tumour implantation), tumours in the 2173-CAR–T cell-treated group were ~65% smaller than in either of the two control groups.

Overall, this study indicates that CAR–T cells can effectively target EGFRvIII-expressing tumours, while avoiding potential toxic effects from interactions with EGFRwt. Given the current lack of safe and effective drugs for glioblastoma, it may be more feasible to test therapies in this indication, even if they potentially carry relatively high risks of toxicity. A Phase I study of 2173-CAR–T cells in EGFRvIII-positive glioblastoma is currently enrolling.

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ORIGINAL RESEARCH PAPER Johnson, L. A. *et al.* Rational development and characterization of humanized anti-EGFR variant III chimeric antigen receptor T cells for glioblastoma. *Sci. Transl. Med.* **7**, 275ra22 (2015)