IMMUNOTHERAPY

New directions for tumour therapy

Dendritic cell (DC)-based anti-tumour vaccines have been developed that depend on the ability of DCs to present tumour antigens to T cells and enhance T-cell-mediated anti-tumour responses. Vaccines that are being tested at present in clinical trials use DCs that are loaded with tumour antigens *ex vivo* before being re-infused into the recipient. Despite the success of this approach in generating antitumour immune responses, the long-term results have been less promising. Whartenby and colleagues now describe a new bone-marrow transplantation (BMT)-based strategy for treating established tumours, in which haematopoietic stem cells (HSCs) are transduced with genes that encode tumour antigens: these then differentiate *in vivo*.

HSCs were first transduced with lentiviral vectors expressing green-fluorescent protein (GFP) and were then transplanted into lethally irradiated mice. A large proportion of DCs that developed in the lymphoid organs of these recipients expressed GFP, indicating that transduced HSCs develop into DCs that express the GFP transgene and successfully traffic to the peripheral lymphoid organs.

To see if the transduced DCs could activate antigen-specific responses, the authors carried out BMTs with HSCs that had been transduced with control or tumour-antigen (haemagglutinin; HA)-encoding lentiviruses in irradiated mice, which also received transgenic T cells with HA-specific T-cell receptors. Ten days before BMT, the recipients were injected with HA-expressing lymphoma (A20-HA) cells. In addition, three weeks after BMT, Flt3 ligand and antibodies specific for CD40 were administered (to activate DCs), as well as mature T cells from HA-transgenic mice, to help overcome the induction of central tolerance, which could occur following repopulation of the thymus with antigen-expressing DCs.

What was the outcome of this approach, and did it result in therapeutic benefit for established tumours? HA-specific T cells were activated and proliferated in recipients of HA-transduced HSCs, when given in combination with Flt3 ligand, CD40-specific antibodies and mature T cells. The expanded T-cell population had effector function and could be expanded in mice even one year after transplantation. This strategy was shown to be more successful than administration of *ex vivo* generated transduced DCs in mice with established tumours, resulting in the long-term survival of ~50% of treated mice, even when administered T cells were from tumour bearing, non-transgenic mice.

As the authors conclude, although this method would need to be adapted for use in the clinic — and even then it could only be applied to tumours with known antigens — this work highlights a potential new approach for inducing antigen-specific tumour immunity using antigen-gene-transduced HSCs.

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References and links

ORIGINAL RESEARCH PAPER Cui, Y. *et al.* Immunotherapy of established tumors using bone marrow transplantation with antigen gene-modified hematopoietic stem cells. *Nature Med.* 1 June 2003 (DOI: 10.1038/nm882)