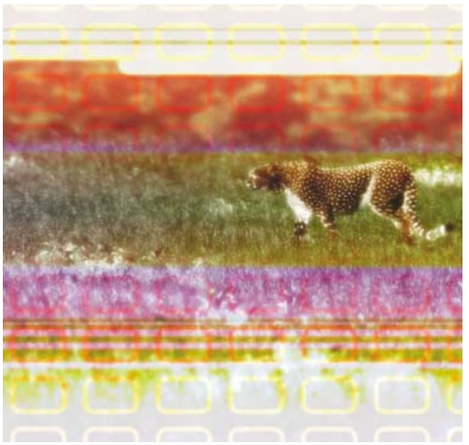


pancreatic tissue indicated that β cells were the main source of CXCL10 during insulitis.

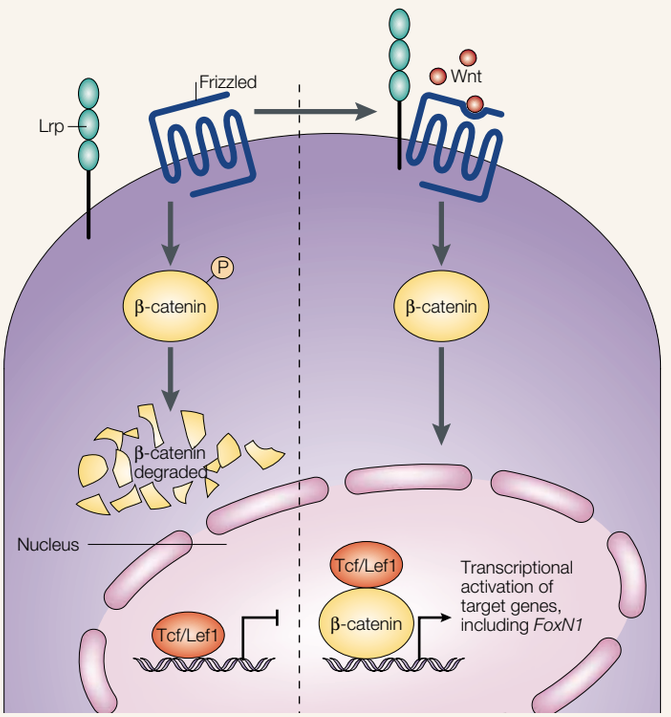
So, chemokines are expressed in islets during insulitis, but are T cells attracted to these chemokines? *In vitro* and *in vivo* studies showed that LCMV-activated T cells are attracted to the chemokines that are present in inflamed islets. To investigate which chemokine receptors are involved, Frigerio *et al.* exposed T cells from LCMV-infected mice to CXCL10 (to desensitize CXCR3 on these cells) before they were cultured with the supernatant from a β-cell line. CXCL10 treatment led to a reduced migratory capacity of T cells towards the supernatants of stimulated β cells, indicating that β-cell chemokines preferentially attract T cells through CXCR3. These observations were confirmed *in vivo* by studies of RIP-GP mice deficient for CXCR3. In the absence of CXCR3, insulitis, diabetes and hyperglycaemia were delayed.

Therefore, in type 1 diabetes, β cells contribute to their own destruction by secreting CXCL9 and CXCL10, which specifically attract $CXCR3^+$ effector T cells to the islets. The authors conclude that CXCR3 might be a new target for therapeutic intervention early in disease.

Jenny Buckland

References and links

ORIGINAL RESEARCH PAPER Frigerio, S. *et al.* β cells are responsible for CXCR3-mediated T-cell infiltration in insulitis. *Nature Med.* 4 November 2002 (DOI: 10.1038/nm792)



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FURTHER READING Anderson, G. & Jenkinson, E. J. Lymphostromal interactions in thymic development and function. *Nature Rev. Immunol.* **1**, 31–40 (2002)

TRIAL WATCH

Attack of the clones

Although many studies have shown that tumour-specific T cells can slow tumour growth in mice, there has been little evidence that T-cell-based immunotherapy is effective in human cancer patients. A Phase I clinical trial involving the adoptive transfer of melanoma-specific T-cell clones into patients with therapy-resistant metastatic melanoma has provided new evidence that T cells can be induced to target tumours.

Yee *et al.* isolated cytotoxic T lymphocytes (CTLs) that were specific for two well-defined melanoma/melanocyte antigens, MART1 and gp100, from ten stage-IV melanoma patients. They primed these T cells *in vitro* using peptide-loaded dendritic cells, and then selected those that specifically lysed MART1- or gp100-expressing cells. These CTL clones were expanded in culture, and transferred back into patients in four separate infusions. After the first infusion, the cells were initially observed to have a short survival time (6.7 days), but when interleukin-2 was co-administered with subsequent infusions, the average CTL survival time increased to almost 17 days.

Biopsies taken 3 days post-infusion revealed that the tumour-specific CTLs preferentially localized to the tumour. In one patient, the tumour-antigen-specific CTLs were found to make up 37% of the total tumour-infiltrating CTL population, whereas these cells made up less than 1% of the total CTLs in the peripheral blood. Melanoma-antigen-specific T cells were found to make up 0.5–2.2% of all CTLs, compared with the 0.0–0.3% of tumour-specific CTLs detected in previous studies of patients who received vaccine-based therapies.

The adoptive T-cell therapy resulted in disease stabilization in five of ten patients, and minor or mixed responses in an additional three patients for up to 21 months. The average survival time of patients was 11 months, and some patients survived for as long as 21 months. Although the number of patients in this study is small, this is a large improvement over the median survival time of 4 months for patients with refractory metastatic disease. No serious toxicity was observed in any patients after adoptive therapy.

In an accompanying editorial, Drew Pardoll points out that none of the patients experienced significant tumour regression. This doesn't mean, however, that the transferred CTLs were incapable of antitumour activity. Based on analysis of tumour biopsies, tumour-cell expression of the targeted antigens was lost in three of the five patients examined. This indicates that antigen-expressing tumour cells were eliminated by the CTLs.

These findings support the emerging view that tumour-reactive T cells are present in the peripheral blood of individuals with cancer, and that these can be activated and traffic to metastatic tumour deposits, where they eliminate tumour cells that express target antigen. Further studies to determine the specific signals that regulate T-cell proliferation, as well as ways to increase T-cell activation, localization to tumours and affinity for their antigenic target are necessary to improve this immunotherapeutic approach.

Kristine Novak, Senior Editor, Nature Reviews Cancer

ORIGINAL RESEARCH PAPER Yee, C. *et al.* Adoptive T cell therapy using antigen-specific $CD8^+$ T cell clones for the treatment of patients with metastatic melanoma: *in vivo* persistence, migration, and anti-tumor effect of transferred T cells. *Proc. Natl Acad. Sci. USA* 11 November 2002 (DOI:10.1073/pnas.242600099)