size of the long-lived pool was reduced by a factor of more than four. This indicates that patients with HIV-1 have a reduced ability to generate long-lived progenitor cells for maintaining the T-cell pool. Effective treatment with antiretroviral therapy was able to restore the capacity to generate these progenitor cells, by reducing the levels of T-cell proliferation and T-cell death in infected individuals.

These data provide evidence against a model in which the characteristic depletion of CD4⁺ T cells that occurs in HIV-1 infection results from direct HIV-mediated cell killing, as long-lived progenitors of both CD4⁺ and CD8⁺ T-cell subpopulations were reduced in patients infected with HIV-1. Moreover, they favour a model in which increased levels of proliferation of effector/memory T cells in HIV infection reflect chronic activation.

Understanding how infection with HIV-1 affects T-cell homeostasis has implications for vaccine design as well as potential new therapeutic strategies.

Lucy Bird

References and links

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TOLERANCE

AIRE control in the thymus

The autoimmune regulator (AIRE) has been shown to regulate the ectopic expression of peripheral tissue-restricted antigens in thymic medullary epithelial cells — a process that is thought to be important for establishing central tolerance. However, the signals that control the expression of this transcription factor in the thymus are unknown. Work by Chin *et al.* now published in *Nature Immunology* shows an essential role for lymphotoxin (LT)-signalling pathways in controlling AIRE expression.

Mutations in *AIRE* result in autoimmune polyendocrinopathy candidiasis ectodermal dystrophy — a disorder characterized by the presence of organ-specific autoantibodies and multiorgan autoimmune destruction. Similarities between the phenotypes of *Aire*^{−/−} mice and animals deficient for LTα or LTβ receptor (LTβR) in terms of peripheral organ lymphocyte infiltration led the authors to investigate the possible link between these pathways.

Real-time polymerase chain reaction showed that the levels of Aire messenger RNA were markedly reduced in thymi from *LTα*^{−/−} or *LTβR*^{−/−} mice, as were the levels of the peripheral tissue-specific protein insulin. The thymic levels of Aire and insulin mRNA specifically and rapidly increased after injections with an agonist LTβR-specific antibody (3C8), showing that LTβR signalling can induce the expression of Aire and ectopic peripheral antigens.

To establish that it is thymic medullary epithelial cells that are responding to the LTβR signalling, Chin *et al.* stimulated a thymic stromal cell line with 3C8. The levels of Aire and insulin mRNA specifically increased following this treatment, indicating that LT signals mediated by medullary epithelial cells regulate Aire expression in the thymus.

Do the reduced levels of expression of Aire and insulin in the *LTα*^{−/−} or *LTβR*^{−/−} mice lead to a breakdown in tolerance? At ~5–7 months of age, increased levels of insulin-specific antibodies were detected in these mice and generalized autoimmune disease developed. To confirm that this autoimmunity developed due to a defect in the lymphoid compartment, the authors transferred splenocytes from *LTβR*^{−/−} or wild-type mice into irradiated recombination activation gene 1-deficient mice. Symptoms of autoimmunity developed in the recipients of *LTβR*^{−/−} cells, but not in mice that received wild-type cells.

So, disruption of LT signalling in the thymus, which prevents Aire-mediated upregulation of ectopic peripheral genes, can lead to the disruption of central tolerance and the development of autoimmunity.

Jenny Buckland

References and links

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FURTHER READING Gommerman, J. L. & Browning, J. L. Lymphotoxin/LIGHT, lymphoid microenvironments and autoimmune disease. *Nature Rev. Immunol.* **3**, 642–655 (2003)