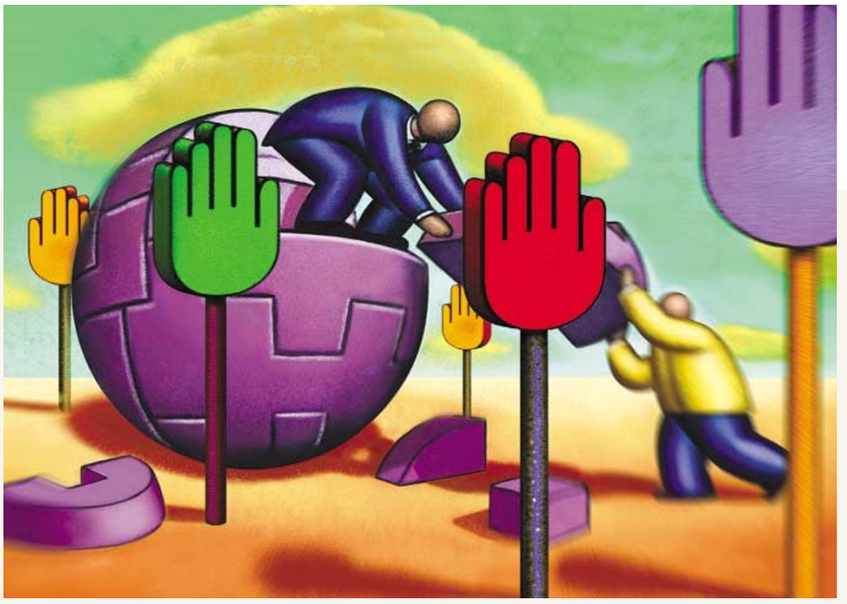
APOPTOSIS

Assembly blocked



The T-cell co-stimulatory molecule CD28 promotes T-cell activation and survival. However, the mechanisms by which CD28 signalling boosts cell survival are poorly understood. Work from Jones and colleagues published in *The Journal of Experimental Medicine* reports a direct role for CD28 in preventing Fas-mediated apoptosis, by activating protein kinase B (PKB)/Akt and preventing the assembly of the death-inducing signalling complex (DISC).

The physiological importance of the Fas (CD95)–Fas ligand (FasL, CD178) apoptotic pathway is clear from studies of *lpr* and *gld* mice — naturally occurring mutants of Fas and FasL, respectively — which develop systemic autoimmunity. To investigate the influence of CD28 signalling on Fas-mediated apoptosis, the authors used various transgenic and gene-deficient mice.

First, they showed that CD4$^+$ T cells from *Cd28*$^{-/-}$ mice are more susceptible to Fas-mediated cell death than those from wild-type mice. Then, they showed that the activation of phosphatidylinositol 3-kinase (PI3K), an important signalling molecule that is recruited by CD28, is required for CD28-mediated protection against Fas-induced apoptosis, because *Cd28*$^{-/-}$ mice that express a mutant *Cd28* transgene that cannot bind to PI3K are as susceptible to Fas-mediated apoptosis as the *Cd28*$^{-/-}$ mice.

Previous studies have shown that the serine/threonine kinase PKB is activated in a PI3K-dependent manner downstream of CD28, so Jones and colleagues analysed Fas–FasL-mediated apoptosis in transgenic mice that express active PKBα in T cells. Fas-mediated apoptosis was impaired in PKBα-expressing T cells *in vitro* and *in vivo*. Further analysis of the Fas–FasL apoptotic cascade showed that the activation of caspase-8, BID and caspase-3 is impaired in these transgenic T cells, because recruitment of procaspase-8 to the DISC is blocked.

These data provide genetic evidence of a survival role for CD28-dependent PKB signalling in preventing Fas-mediated apoptosis by blocking DISC assembly.

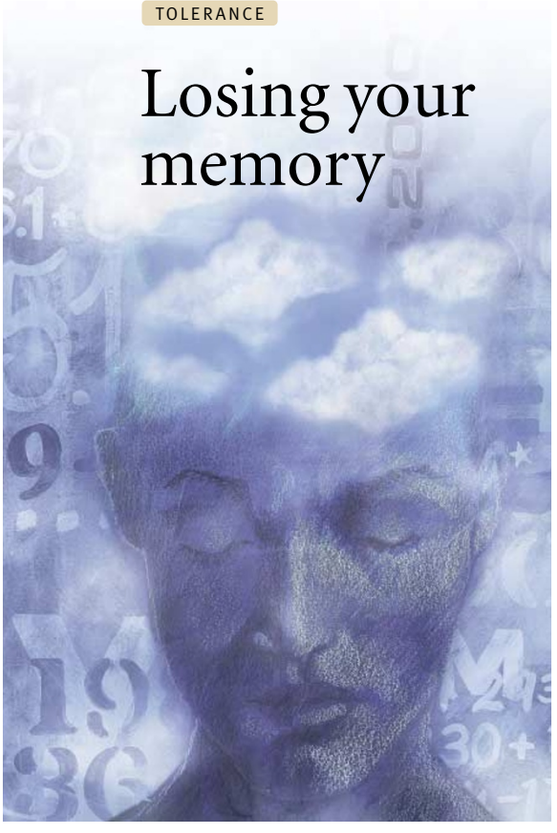
Jenny Buckland

References and links

ORIGINAL RESEARCH PAPER Jones, R. G. *et al.* CD28-dependent activation of protein kinase B/Akt blocks Fas-mediated apoptosis by preventing death-inducing signaling complex assembly. *J. Exp. Med.* **196**, 335–348 (2002)

TOLERANCE

Losing your memory



Many studies have shown that the ectopic expression of a self-antigen in pancreatic β-cells results in cross-presentation on MHC class I molecules to naive CD8$^+$ T cells in the draining lymph nodes. The resulting 'cross-tolerance' is one mechanism by which peripheral tolerance to self-antigens is maintained. However, Kreuwel *et al.* have now found that this phenomenon is not restricted to naive T cells. They suggest that memory CD8$^+$ T cells are as susceptible to tolerance as are naive cells. This 'second chance' at peripheral tolerance might explain how autoimmunity is avoided even if naive autoreactive T cells that have not yet been tolerized become activated.

InsHA mice — which express influenza-virus haemagglutinin (HA) under the control of the rat insulin (Ins) promoter — are tolerant of HA even after immunization with influenza virus. However, cross-presentation does not occur in neonatal mice, which develop diabetes after immunization. But, those neonates that survive gradually recover as cross-presentation of islet antigens develops. The authors show that the responses of HA-specific memory CD8$^+$ T cells that are present three weeks after immunization of neonates are severely diminished by 11 weeks. When naive and memory CD8$^+$ Clone-4 T-cell receptor cells (which are specific for a dominant epitope of HA) were injected into InsHA recipients, both cell types proliferated to a similar extent in an antigen-specific manner. In both cases, the T cells did not increase in number despite division, which indicates that they were tolerized by deletion. The rate of tolerance induction is greater in InsHA$^{+/+}$ mice than in InsHA$^{+/-}$ mice, which indicates that clonal deletion is the result of HA, rather than normal T-cell turnover, and that the rate of deletion is determined by the concentration of antigen that is available for cross-presentation.

This work questions the assumption that naive T cells are fundamentally different to memory T cells with respect to tolerance susceptibility. It also has implications for the development of tumour vaccines. If memory T cells are routinely tolerized to cross-presented antigens, it might not be possible to sustain long-lived T-cell immunity to tumour antigens, which are often also expressed on non-transformed tissues.

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References and links

ORIGINAL RESEARCH PAPER Kreuwel, H. T., Aung, S., Silao, C. & Sherman, L. A. Memory CD8$^+$ T cells undergo peripheral tolerance. *Immunity* **17**, 73–81 (2002)

FURTHER READING Cho, B. K., Wang, C., Sugawa, S., Eisen, H. E. & Chen, J. Functional differences between memory and naive CD8 T cells. *Proc. Natl Acad. Sci. USA* **96**, 2976–2981 (1999)

WEB SITE

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