Restoring appropriate levels of expression of FcγRIIB by the B cells of autoimmune-prone mice might therefore restore tolerance. In the *Science* paper, bone marrow from three autoimmune-prone mouse strains — all of which had a deficiency in FcγRIIB expression — was transduced with a vector expressing FcγRIIB and used to reconstitute irradiated recipients. All of the mice that received *Fcγr2b*-transduced bone marrow had lower levels of DNA-specific antibodies than mice that received bone marrow transduced with the control parental retrovirus or than wild-type mice, indicating that FcγRIIB is a common regulator of autoimmunity on different genetic backgrounds. The *Fcγr2b*-transduced recipients also had a lack of immune-complex deposition in the kidneys and an absence of renal disease compared with wild-type mice. This effect is probably due to FcγRIIB expression by B cells, which was increased by 50% after retroviral transduction. Tolerance was re-established despite only 40% of B cells being effectively transduced, indicating that only small changes in the activating–inhibitory balance are sufficient to re-set the threshold for disease induction.

Kirsty Minton

References and links

ORIGINAL RESEARCH PAPERS Fukuyama, H., Nimmerjahn, F. & Ravetch, J. V. The inhibitory Fcγ receptor modulates autoimmunity by limiting the accumulation of immunoglobulin G+ anti-DNA plasma cells. *Nature Immunol.* **6**, 99–106 (2005) | McGaha, T. L., Sorrentino, B. & Ravetch, J. V. Restoration of tolerance in lupus by targeted inhibitory receptor expression. *Science* **307**, 590–593 (2005).

and WNT signalling, and it was shown that a high proportion of cells in the HSC niche transduced both Notch and WNT signals. Interestingly, although both signalling pathways were active in these cells and WNT3A-induced signalling could promote the survival and growth of HSCs in which the Notch-signalling pathway was inhibited, WNT signalling was unable to maintain these HSCs in an undifferentiated state.

This study shows that Notch signalling is crucial for inhibiting the differentiation of HSCs. What causes a decrease in Notch signalling, thereby allowing differentiation to occur, remains to be determined.

Karen Honey

References and links

ORIGINAL RESEARCH PAPER Duncan, A. W. *et al*. Integration of Notch and Wnt signaling in hematopoietic stem cell maintenance. *Nature Immunol.* **6**, 314–322 (2005).

IN BRIEF

MACROPHAGES

Dynamic changes in Mcl-1 expression regulate macrophage viability or commitment to apoptosis during bacterial clearance.

Marriott, H. M. *et al*. *J. Clin. Invest.* **115**, 359–368 (2005).

On bacterial infection, macrophages must initially maintain viability in the face of toxic bacterial products, thereby contributing to innate immunity, but subsequently, they must undergo apoptosis to facilitate bacterial clearance. So, what mediates this switch from macrophage survival to apoptosis? Marriott *et al.* show that, after pneumococcal infection, macrophages initially upregulate expression of the anti-apoptotic BCL-2-family member MCL1 and survive for up to 14 hours. Then, expression of full-length MCL1 protein is reduced, and expression of a 34-kDa splice variant, $MCL1_{exon\text{-}1}$, is upregulated, which triggers activation of pro-apoptotic pathways. Consistent with a key role for MCL1 in regulating macrophage viability, *Mcl1*-transgenic mice clear pneumococci from the lungs less efficiently than control mice.

HIV

Impaired base excision repair and accumulation of oxidative base lesions in CD4+ T cells of HIV-infected patients.

Aukrust, P. *et al*. *Blood* 10 Feb 2005 (doi:10.1182/blood-2004-11-4272).

Increased oxidative stress contributes to the pathogenesis of HIV infection, by causing endogenous DNA damage. Because the base-excision repair pathway has a crucial role in removing oxidative DNA damage, the authors compared the levels of DNA damage and the activity of the DNA-glycosylase repair enzymes in T cells from HIV-infected patients and controls. They observed that $CD4^+$ T cells from HIV-infected patients had higher levels of 8-oxoguanine (a marker of oxidative DNA damage) and decreased glycosylase activity compared with controls. By contrast, the 8-oxoguanine levels in $CD8^+$ T cells were similar in both HIV-infected patients and controls. Importantly, highly active antiretroviral therapy increased glycosylase activity and normalized 8-oxoguanine levels in $CD4^+$ T cells.

STRUCTURE

Structural basis for the function and regulation of the receptor protein tyrosine phosphatase CD45.

Nam, H.-J. *et al*. *J. Exp. Med.* **201**, 441–452 (2005).

The receptor protein tyrosine phosphatase (PTP) CD45 has two PTP domains D1 and D2, only one of which (D1) is catalytically active. Two crystal structures of the native CD45 D1–D2 domain solved by Nam *et al.* indicate that D1 and D2 have almost identical structures. However, substrate-bound crystal structures of this domain showed that phosphorylated peptides bind the catalytically active D1 but not the catalytically inactive D2. Despite this, the structure of D2 provides support for the hypothesis that it is involved in substrate recruitment. The structures also indicate that the D1–D2 domain does not dimerize, which is incompatible with the idea that CD45 PTP activity is inhibited by dimerization.