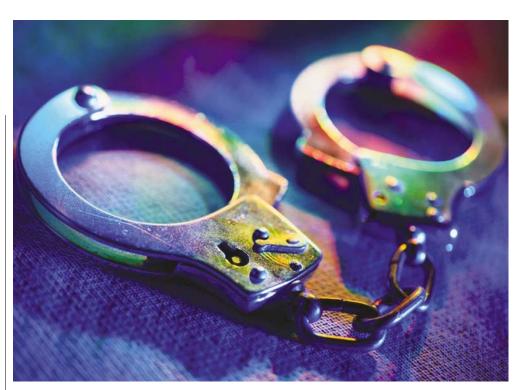
Depletion of these molecules from culture supernatants eliminated activity against X4 viruses and markedly reduced activity against R5 viruses. Residual activity against R5 viruses could be neutralized by the addition of antibodies specific for the β -chemokines. Furthermore, synthetic and purified α -defensins were shown to reduce HIV-1 replication *in vitro*.

So, we are one step closer to understanding the mystery of LTNPs, which can only aid the development of new therapeutics. It remains to be determined how the α -defensins mediate their antiretroviral effects, and whether they are involved directly in non-progression.



Kirsty Minton TOLERANCE

References and links

ORIGINAL RESEARCH PAPER Zhang, L. *et al.* Contribution of human α-defensin 1, 2 and 3 to the anti-HIV-1 activity of CD8 antiviral factor. *Science* **298**, 995–999 (2002)

WEB SITE David Ho's lab

http://www.rockefeller.edu/labheads/ho/ho.html



DCs on the beat

Dendritic cells (DCs) have long been recognized as the body's sentinels, but evidence is emerging that they are responsible also for policing the immune system. It has been proposed that DCs are 'on the beat' constantly, ingesting tissueassociated antigens and presenting them in local lymph nodes. In the absence of inflammation, this should result in the elimination of potentially harmful self-reactive T cells. Three papers in a recent issue of *The Journal of Experimental Medicine* provide further support for this model and indicate that CD8 α ⁺ DCs might be specialized for this task.

A previous study showed that the presentation of tissue-associated self-antigens by bonemarrow-derived cells in draining lymph nodes results in the deletion of self-reactive T cells. DCs have been implicated in this 'cross-tolerance', but the DC subpopulation(s) that is involved has not been pinpointed. Belz and colleagues generated mice that express a fusion protein containing two MHC class-I-restricted epitopes - an ovalbumin peptide and a herpes simplex virus (HSV) peptide - under the control of the rat insulin promoter. Ovalbumin-specific or HSV-specific TCRtransgenic CD8⁺ T cells that were injected into these mice were deleted rapidly. By sorting DC populations in the pancreatic lymph nodes, the authors showed that only $CD8\alpha^+$ DCs could stimulate a highly sensitive HSV-specific T-cell hybridoma, indicating that this DC population, which is implicated in cross-presentation, also mediates cross-tolerance.

The second paper addresses the issue of how tolerogenic DCs might acquire antigen in the steady state. An earlier study showed that CD8 α^+ DCs are highly efficient at taking up and

presenting antigens that are associated with dying cells; but, can this lead to tolerance? Liu et al. injected mice with transporter for antigen presentation (TAP)-deficient splenocytes that had been loaded with small amounts of ovalbumin protein and osmotically shocked to induce cell death. Because they lack TAP proteins, these cells cannot present their own antigens. The ovalbumin was processed and presented by $CD8\alpha^+$ DCs in the spleen. Transferred ovalbumin-specific TCRtransgenic CD8+ T cells proliferated initially, but were deleted subsequently, and the animals were rendered tolerant to ovalbumin. However, the maturation of DCs induced by a CD40-specific antibody resulted in immunity rather than tolerance. Although these data indicate that dying cells target CD8 α^+ DCs, it is not known whether the cells that are targeted normally for presentation of self-antigens are living or dead.

The idea that the same $CD8\alpha^+ DC$ subpopulation induces both cross-tolerance and cross-presentation is attractive. However, there might be dedicated immunogenic and tolerogenic DC subsets in the $CD8\alpha^+ DC$ population. Moreover, studies by other groups have implicated other DC subsets in the induction of tolerance. A paper by Scheinecker and colleagues in the same issue shows that DCs presenting MHC class-II-restricted tissue-specific antigens in the gastric lymph nodes can be CD8⁺ or CD8⁻, and CD11b⁺ or CD11b⁻. Further studies are required to clarify these issues.

Jennifer Bell

References and links

ORIGINAL RESEARCH PAPERS Belz, G. T. *et al.* The CD8α⁺ dendritic cell is responsible for inducing peripheral self-tolerance to tissue-associated antigens. *J. Exp. Med.* **196**, 1099–1104 (2002) | Liu, K. *et al.* Immune tolerance after delivery of dying cells to dendritic cells *in situ. J. Exp. Med.* **196**, 1091–1097 (2002) | Scheinecker, C. *et al.* Constitutive presentation of a natural tissue autoantigen exclusively by dendritic cells in the draining lymph node. *J. Exp. Med.* **196**, 1079–1090 (2002)

FURTHER READING Mougneau, E., Hugues, S. & Glaichenhaus, N. Antigen presentation by dendritic cells *in vivo. J. Exp. Med.* **196**, 1013–1016 (2002)