HIV

Identity of CAF revealed

Until recently, it was a mystery why some individuals infected with HIV-1 do not become immunodeficient (long-term non-progressors, LTNPs). $CD8^+$ T cells are known to be important, but why are they more effective in some individuals than others? A recent paper in *Nature Immunology* showed that the increased expression of perforin by $CD8^+$ T cells from LTNPs is important for their cytolytic activity (see the Highlight 'Quality control' in our November issue). But, since the first description of CD8 antiviral factor (CAF) — which is secreted by stimulated $CD8^+$ T cells from certain infected individuals — it has been recognized that soluble factors can inhibit virus replication also. Now, Zhang *et al*. report in *Science* the identification of human α-defensins 1, 2 and 3 as one of the main components of CAF.

Previous studies had indicated that β-chemokines (CCL3, CCL4 and CCL5) might account for the antiviral activity of CAF by competing with virus for binding to CCR5, which is used as a co-receptor for virus entry. However, this can only inhibit R5 viruses, and not X4 viruses, which use CXCR4 as a co-receptor. Using protein-chip technology, Zhang *et al.* have shown that the α-defensins carry out much of the anti-HIV activity of supernatants from stimulated $CD8^+$ T cells that is not attributable to β-chemokines.

The authors compared the protein mass spectra of supernatants from stimulated and unstimulated $CD8^+$ T cells of LTNPs, normal progressors and controls. Marked differences between stimulated and unstimulated spectra were observed — specifically, three peaks between 3.3 and 3.5 kD that were present in stimulated cultures from LTNPs and some controls, but not progressors. The three peaks correspond to the molecular masses of human α-defensins 1, 2 and 3, and this result was confirmed by protein sequencing.

INNATE IMMUNITY

Untangling the TLRs

The Toll-like receptor (TLR) family consists of ten germline-encoded microbe sensors that are crucial for host defence. The theory is that each receptor triggers an innate immune response that is appropriate for the class of pathogen that the receptor recognizes. But, differences between TLR signal-transduction pathways that might result in such tailored responses have been hard to find. Now, two studies published in *Nature* show that the adaptor molecule TIRAP (also known as MAL) has a restricted role in a shared TLR2 and TLR4 signal-transduction pathway.

TIRAP is structurally similar to the adaptor protein MYD88, which links the TLRs and interleukin-1 receptors (IL-1Rs) to downstream signalling pathways. MYD88 is essential for the induction of cytokine secretion by all TLR ligands, but the lipopolysaccharide (LPS) receptor TLR4 can stimulate the upregulation of expression of co-stimulatory receptors on dendritic cells (DCs) in the absence of MYD88. Initial *in vitro* studies indicated that TIRAP might function in this MYD88-independent pathway. But, the *Tirap*-knockout mice described by Yamamoto *et al.* and Horng *et al.* show that this is not the case.

Horng and co-workers found that in response to triggering of TLR2 or TLR4, $Tirap^{-/-}$ B cells had impaired proliferative responses and $Tirap^{-/-}$ DCs produced markedly reduced levels of pro-inflammatory cytokines. But, responses to a TLR9 ligand (CpG DNA) were normal in these cells, and injection of the TLR5 ligand flagellin into $Tirap^{-/-}$ mice induced the expression of normal levels of cytokines. Yamamoto *et al.* showed that the production of pro-inflammatory cytokines in response to LPS and various ligands for TLR2 is impaired markedly in $Tirap^{-/-}$ macrophages. Furthermore, $Tirap^{-/-}$ mice were completely resistant to LPS-induced shock. But, the responses of $Tirap^{-/-}$ macrophages to synthetic ligands for TLR7 and TLR3, and CpG DNA, were intact.

In contrast to $Myd88^{-/-}$ mice, both groups showed that IL-1 signalling is not compromised in $Tirap^{-/-}$ mice. So, together, these papers show that TIRAP is dispensable for TLR3, TLR5, TLR7, TLR9 and IL-1R function, but has a specific role in TLR2 and TLR4 signal-transduction pathways.

Similar to MYD88, TIRAP has a crucial role in the activation of nuclear factor-κB and mitogen-activated protein kinases by TLR2 and TLR4. And $Tirap^{-/-}$ mice and $Myd88^{-/-}$ mice have similarly defective responses to LPS, which indicates that TIRAP might be involved in a MYD88-dependent pathway. To test this, Yamamoto and co-workers generated $Myd88^{-/-}Tirap^{-/-}$ mice. The LPS-induced upregulation of expression of co-stimulatory molecules on DCs (a MYD88-independent event) occurred normally in these double-knockout mice, so TIRAP is clearly not part of the MYD88-independent pathway.

Jennifer Bell

References and links

ORIGINAL RESEARCH PAPERS Yamamoto, M. *et al*. Essential role for TIRAP in activation of the signalling cascade shared by TLR2 and TLR4. *Nature* **420**, 324–329 (2002) | Horng, T. *et al*. The adaptor molecule TIRAP provides signalling specificity for Toll-like receptors. *Nature* **420**, 329–333 (2002)

FURTHER READING Medzhitov, R. Toll-like receptors and innate immunity. *Nature Rev. Immunol.* **1**, 135–145 (2001)

WEB SITE

Ruslan Medzhitov's lab:
http://info.med.yale.edu/immuno/fac_medzhitov.html