IMMUNE EVASION

Signal disruption enables escape

One way in which viruses escape the host immune response and establish a persistent infection is by impairing T-cell activation. New research now shows that T-cell lymphotropic herpesvirus saimiri (HVS) — which induces T-cell lymphomas in infected primates — is able to achieve this goal by preventing activation of the protein tyrosine kinase ZAP70 (ζ-chain-associated protein kinase of 70 kDa).

The HVS tyrosine-kinase-interacting protein (Tip) has been shown to interact with LCK and disrupt signalling through the T-cell receptor (TCR). So, to investigate the molecular mechanism of this effect, Cho *et al.* overexpressed wild-type Tip and various Tip mutants in purified human peripheral-blood T cells and the Jurkat T-cell line. Overexpression of Tip markedly diminished the production of interleukin-2 and inhibited the rise in intracellular calcium concentration induced by TCR triggering, and this effect was dependent on its interaction with LCK.

LCK is known to phosphorylate tyrosine residues in the CD3 subunits of the TCR, leading to the recruitment and activation of ZAP70 through its phosphorylation. In the presence of Tip, tyrosine phosphorylation of CD3ζ and recruitment of ZAP70 occurred normally, but phosphorylation of ZAP70 was not observed. Further evidence that Tip inhibits ZAP70 activation was provided by the observation that phosphorylation of ZAP70 substrates (linker for activation of T cells (LAT) and phospholipase C-γ1) was not detected in the presence of Tip. In addition, Tip expression inhibited immunological-synapse formation, an event downstream of TCR signalling that is crucial for T-cell activation.

This study shows that HVS uses Tip to inhibit the activation of ZAP70, thereby disrupting the subsequent T-cell signalling cascades required for T-cell activation. The authors suggest that this enables HVS to escape the host immune response and establish a persistent infection.

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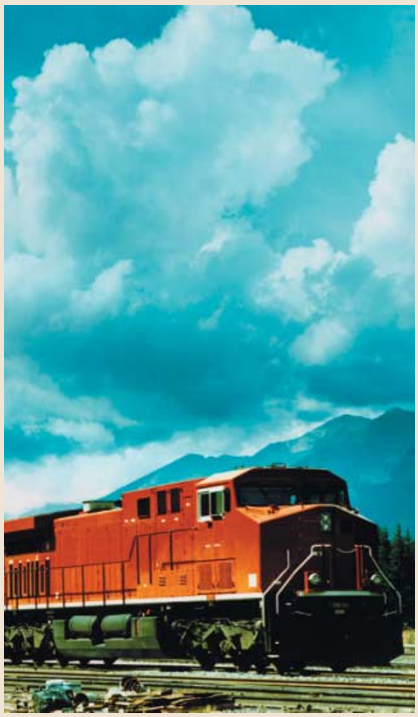

References and links

ORIGINAL RESEARCH PAPER Cho, N. H. *et al.* Inhibition of T cell receptor signal transduction by tyrosine kinase-interacting protein of herpesvirus saimiri. *J. Exp. Med.* **200**, 681–687 (2004).

DENDRITIC CELLS

Remodelling by TLRs

After recognition of microbial products through Toll-like receptors (TLRs), immature dendritic cells (DCs) undergo a programme of maturation that eventually results in reduced endocytic capacity. However, Colin Watts and colleagues, reporting in *Science*, now observe that TLR ligation first acutely upregulates antigen uptake and that this is mediated by remodelling of the actin cytoskeleton.

It is well known that the DC response to microbial products triggers changes at the transcriptional level, leading ultimately to an enhanced ability to activate T cells through the upregulation of expression of MHC and co-stimulatory molecules, and a reduction in endocytic capacity. However, it has recently become clear that more-rapid responses are also induced by TLR ligation. So, the authors assessed the ability of mouse bone-marrow-derived DCs or spleen-derived DCs to take up the endocytosis marker FITC–dextran at early time points following activation with the TLR ligand lipopolysaccharide (LPS). Surprisingly, they saw that TLR ligation transiently enhanced the uptake of FITC–dextran by both cell populations, peaking after 30 to 45 minutes of treatment with LPS. To determine whether this acute stimulation of macropinocytosis also enhanced antigen presentation, they pulsed DCs with antigen, either before or at the same time as exposure to LPS, and assayed their ability to stimulate T-cell clones. Co-administration of antigen with LPS markedly enhanced the presentation of both MHC-class-I- and MHC-class-II-restricted antigen to T cells compared with administration of antigen before exposure to LPS.

Further studies using fluorescence microscopy showed that the accumulation of FITC–dextran after TLR ligation was associated with increased membrane-ruffling activity and could be inhibited by cytochalasin D, indicating that it is actin dependent. In addition, the authors observed TLR-dependent changes in the F-actin-rich structures known as podosomes, which are involved in cell migration and tissue invasion. In particular, TLR activation induced a transient destabilization of podosomes in most DCs after 30 minutes, although these structures were fully restored after 2 hours. This effect was blocked in the presence of inhibitors of two mitogen-activated protein kinases (MAPKs): MEK1 (MAPK/ERK kinase 1) and SAPK2 (stress-activated protein kinase 2). Furthermore, LPS-stimulated endocytosis was also blocked by inhibitors of these MAPKs.

These findings indicate that, in response to innate immune stimuli, the actin cytoskeleton of DCs can be rapidly remodelled to mediate transient increases in actin-dependent endocytosis and enhance antigen presentation.

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References and links

ORIGINAL RESEARCH PAPER West, M. A. *et al.* Enhanced dendritic cell antigen capture via Toll-like receptor-induced actin remodeling. *Science* **305**, 1153–1157 (2004).