T CELL ACTIVATION

A silent toll for T cells

Toll-like receptors (TLRs) have well-described roles in activating innate immune cell populations, but although T cells have also been shown to express TLRs, their function in these adaptive immune cells remains unclear. Now, a study by Raz and colleagues shows that TLR4 signalling in T cells can negatively regulate activation signals delivered by the T cell receptor (TCR).

In initial experiments, in which colitis-prone interleukin-10 (IL-10)-deficient mice were crossed with TLR-deficient animals, deficiency of TLR4, but not TLR9, accelerated the onset of colitis. In a separate model of colitis, in which naive T cells transferred in the absence of regulatory T cells drive intestinal inflammation, recipients of *Tlr4*$^{-/-}$*Il10*$^{-/-}$ T cells developed earlier and more severe disease than mice that received *Il10*$^{-/-}$ T cells. Increased colitis in the recipients of *Tlr4*$^{-/-}$*Il10*$^{-/-}$ T cells was associated with enhanced production of IL-6, interferon-γ (IFNγ) and IL-17A by intestinal CD4^{+} T cells, suggesting that TLR4 may have inhibitory effects in activated T cells. In support of this, T cells isolated from *Il10*$^{-/-}$ mice that had been treated with a TLR4-specific blocking antibody produced increased levels of pro-inflammatory cytokines following activation with CD3- and CD28-specific antibodies.

To dissect the mechanisms behind this regulatory effect of TLR4, the authors examined the signalling pathways induced in T cells following exposure to lipopolysaccharide (LPS). As in other immune cells, stimulation of TLR4 by LPS led to T cell activation of nuclear factor-κB (NF-κB) and phosphorylation of mitogen-activated protein kinase (MAPK) family members. Reasoning that mucosal T cells may be exposed to soluble LPS draining from the intestine prior to activation by specific antigen, the authors examined the effects of LPS pre-treatment on subsequent TCR activation. Accordingly, T cells from TCR-transgenic mice pre-treated with LPS had lower levels of phosphorylated extracellular signal-regulated kinase (pERK) and produced less IFNγ following TCR activation. This decrease in pERK was not a result of reduced phosphorylation but was due to increased dephosphorylation of pERK by MAPK phosphatases (MKPs). LPS-treated T cells had increased levels of MKPs, and gene silencing of *Mkp3* (also known as *Dusp6*) prevented the LPS-mediated downregulation of pERK and restored T cell IFNγ expression. TLR4-mediated activation of MKP3 was independent of the TLR4 adaptor molecule myeloid differentiation primary-response protein 88 (MYD88) but required TIR-domain-containing adaptor protein inducing IFNβ (TRIF). Finally, treatment of *Il10*$^{-/-}$ mice with MKP inhibitors promoted intestinal inflammation, with T cells from these animals showing higher levels of pERK and producing more pro-inflammatory cytokines.

So, in contrast to its function in promoting pro-inflammatory activities of innate immune cells, TLR4 seems to have a regulatory role in T cell activation by inducing the upregulation of MKPs that can negatively regulate TCR signalling.

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