IN BRIEF

SIGNALLING

The kinases MSK1 and MSK2 act as negative regulators of Toll-like receptor signaling.

Ananieva, O. *et al. Nature Immunol.* 10 August 2008 (doi:10.1038/ni.1644)

In addition to their role in pro-inflammatory signalling pathways, p38, extracellular-signal-regulated kinase 1 (ERK1) and ERK2 also function to control excessive inflammation. This study shows that mitogen- and stress-activated kinase 1 (MSK1) and MSK2, which are downstream of p38, ERK1 and ERK2, mediate negative feedback pathways that control Toll-like receptor (TLR)-induced inflammation. MSK1 and MSK2 are activated by TLR ligands in bone-marrow-derived macrophages, and loss of MSK1 and MSK2 expression in these cells resulted in higher pro-inflammatory cytokine production in response to lipopolysaccharide (LPS). Further analyses showed that MSKs induce the expression of the phosphatase DUSP1 (which inactivates p38) and the anti-inflammatory cytokine interleukin-10, through the activation of the transcription factors ATF1 and CREB. Mice deficient for both MSKs were hypersensitive to LPS-induced endotoxic shock, confirming their role as negative regulators of TLR-induced pro-inflammatory signals.

NATURAL KILLER T CELLS

Rapid NKT cell responses are self-terminating during the course of microbial infection.

Chiba, A. *et al. J. Immunol.* **181**, 2292–2302 (2008)

Natural killer T (NKT) cells have been implicated in various immune responses, but when they are activated and when their responses are terminated during the natural course of infection was not known. Chiba ***et al.*** infected mice with *Mycobacterium bovis* bacillus Calmette–Guérin and showed that NKT cells expand, proliferate and produce interferon-γ (IFNγ) early after infection. However, by day 14, NKT-cell numbers were markedly reduced owing to the induction of apoptosis, although MHC-restricted T cells were still expanding and actively producing IFNγ. The remaining NKT cells were unresponsive to T-cell receptor stimuli, even though the bacterial burden persisted. So, the authors propose that NKT cells participate during the early phase of the immune response, but the NKT-cell response is then terminated (by apoptotic contraction and unresponsiveness) once the adaptive immune response has been established.

IMMUNE TOLERANCE

Induction of immunological tolerance by apoptotic cells requires caspase-dependent oxidation of high-mobility group box-1 protein.

Kazama, H. *et al. Immunity* **29**, 21–32 (2008)

Necrotic cells are known to induce an immune response, whereas apoptotic cells are generally thought to promote immune tolerance *in vivo* through effects on dendritic cells. Now, a recent study has uncovered a mechanism that explains this differential immune response. The authors show that, in addition to the known requirement for caspase activation, the induction of tolerance to an antigen by apoptotic cells *in vivo* depends on high-mobility group box 1 protein (HMGB1) and the caspase-dependent generation of reactive oxygen species. Whereas HMGB1 release from necrotic cells can act as a danger signal for surrounding immune cells, this study shows that apoptotic cells release an oxidized form of HMGB1 that prevents an immune response *in vivo* and instead promotes tolerance to the antigen.