bacteria) could stimulate the Nod1–NF-κB pathway. Using the same method, intracellular presentation of Gram-negative bacterial supernatants to isolated intestinal epithelial cells from Nod1-deficient mice did not activate the NF-κB pathway, which indicates that Nod1 has a crucial role in the response of epithelial cells to this subset of bacteria. Similarly, Chamaillard *et al.* showed that Nod1 is required for the macrophage response to intracellular bacteria, by looking at the ability of DAP-containing peptides to stimulate cytokine secretion by macrophages. Macrophages from Nod1-deficient mice failed to produce interleukin-6 and tumour-necrosis factor in response to these peptides.

So, it seems that there is no such thing as a safe hiding place for these bacteria. They can hide from TLR-mediated detection by invading the cell cytoplasm, but are still spotted by the innate immune system through Nod1. Both groups speculate that in contrast to Nod2, which can recognize a broad range of bacteria, Nod1 is a subset-specific bacterial sensor (recognizing mainly Gram-negative bacteria). The functional relevance of this has yet to be determined.

Kirsty Minton

References and links

ORIGINAL RESEARCH PAPERS Girardin, S. E. *et al*. Nod1 detects a unique muropeptide from Gram-negative bacterial peptidoglycan. *Science* **300**, 1584–1587 (2003) | Chamaillard, M. *et al*. An essential role for NOD1 in host recognition of bacterial peptidoglycan containing diaminopimelic acid. *Nature Immunol*. 8 June 2003 (DOI: 10.1038/ni945)

FURTHER READING Inohara, N. & Nuñez, G. NODs: intracellular proteins involved in inflammation and apoptosis. *Nature Rev. Immunol.* **3**, 371–382 (2003)

previously shown that co-stimulation of macrophages with lipopolysaccharide (LPS) — a virulence factor of Gram-negative bacteria — and the pan-caspase inhibitor zVAD resulted in caspase-independent death of macrophages *in vitro*. Here, they confirmed these observations *in vivo* in a mouse sepsis model. Apoptosis of activated peritoneal macrophages was increased following treatment with zVAD. Signalling through Toll-like receptors TLR2 and TLR4 was shown to be required for macrophage death in this system.

Next, as zVAD-promoted macrophage death was not mediated by the classic caspase pathway for cell death, Kim *et al.* asked whether any death genes were induced during this process. Treatment of a mouse macrophage cell line with LPS and zVAD resulted in increased expression of Nur77 before cell death, indicating that this death receptor could trigger cell death in this setting. This was confirmed by experiments with a putative dominant-active Nur77 mutant protein (which caused increased macrophage death) and with Nur77-deficient macrophages (which were less susceptible to cell death).

Detailed signalling analysis led the authors to propose that a dual signalling pathway leads to the induction of Nur77 expression by macrophages that are destined to undergo AICD. Activation of the extracellular signal-regulated kinase (ERK) pathway, which is downstream of TLR signalling, and activity of the myocyte-specific enhancer binding factor 2 (Mef2), which is upregulated by zVAD, were both required for the induction of *Nur77* transcription and for Nur77-mediated caspase-independent macrophage cell death.

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References and links

ORIGINAL RESEARCH PAPER Kim, S. O. *et al.* Orphan nuclear receptor Nur77 is involved in caspase-independent macrophage cell death. *J. Exp. Med.* **197**, 1441–1452 (2003)

IN BRIEF

LYMPHOCYTE ACTIVATION

Caspase activity is required for stimulated B lymphocytes to enter the cell cycle.

Olson, N. R. *et al. J. Immunol.* **170**, 6065–6072 (2003)

Caspases are best known for their role in apoptosis, but they have also been implicated in the regulation of cell proliferation. In particular, caspase-8 — the factor that is at the top of the proteolytic caspase cascade — has a role in T-cell proliferation, but the specific caspases that are involved downstream are unknown. This new study shows that caspase-8 and caspase-6 are essential for human B-cell proliferation. Inhibition of caspase-6 blocked the upregulation of expression of the cell-cycle regulators D-type cyclins and cyclin-dependent kinase 4 by activated B cells, indicating a possible mechanism by which caspase-6 could regulate cell-cycle entry. Notably, other aspects of B-cell activation, such as cytokine secretion, were unaffected, indicating a specific role for caspase-6 in proliferation.

LYMPHOCYTE ACTIVATION

The B cell-specific major raft protein, Raftlin, is necessary for the integrity of lipid raft and BCR signal transduction.

Saeki, K. *et al. EMBO J.* **22**, 3015–3026 (2003)

Membrane lipid microdomains known as rafts, which are rich in signalling molecules, have been proposed to have a crucial role in lymphocyte signalling. This study describes a new component of rafts in B cells, which has no homology to any other known protein and has been named Raftlin (for raft-linking protein). This molecule seems to localize in rafts by means of an acylated motif and is constitutively associated with the B-cell receptor (BCR), although it does not bind the BCR directly. In the absence of Raftlin, BCR signalling was impaired and levels of other key raft components, such as the tyrosine kinase LYN and ganglioside GM1, were markedly reduced, indicating that Raftlin is important for raft integrity .

MUCOSAL IMMUNOLOGY

Mast cells disrupt epithelial barrier function during enteric nematode infection.

McDermott, J. R. *et al. Proc. Natl Acad. Sci. USA* **100**, 7761–7766 (2003)

Expulsion of nematode parasites is associated with elevated epithelial permeability. Mast cells are also important for parasite expulsion, but the mechanism is not well understood. In this study, McDermott and colleagues show that mast cells are responsible for inducing the increased intestinal permeability, which seems to depend on degradation of the tight-junction protein occludin. The authors used c-Kit-specific antibodies to block mast-cell accumulation, which prevented parasite expulsion and correlated with less permeability than in control animals. Mice overexpressing interleukin-9, which have higher numbers of mast cells than normal mice, showed enhanced intestinal permeability and could get rid of the parasites faster.