ALLERGY

Mast cells make the most of p110δ

A recent report in *Nature* indicates that the p110δ subunit of phosphatidylinositol 3-kinase (PI3K) is responsible for mediating intracellular signals that lead to mast-cell differentiation and activation, and it describes how targeting this subunit has a beneficial impact on allergic responses.

Stimulation through mast-cell receptors for stem-cell factor (SCF) and allergen-specific IgE triggers the activation of PI3Ks, which generate lipid second-messenger signals, resulting in mast-cell differentiation and activation. PI3K is composed of the catalytic subunits p110α, p110β and p110δ, and a regulatory subunit. Unlike the other catalytic subunits, which are ubiquitously expressed, p110δ is mainly found in leukocytes and is highly expressed by mast cells. So, Vanhaesebroeck and colleagues investigated the role of the p110δ subunit in mast cells. Mice expressing a loss-of-function allele of *p110δ* have a tissue-specific reduction in mast-cell numbers. And although mature mast cells arise from bone-marrow precursors isolated from either wild-type or p110δ-mutant mice and cultured in the presence of mast-cell growth factors, cultures of mutant cells contained fewer mast cells. Moreover, after stimulation with SCF, the p110δ-mutant cells had markedly reduced lipid-kinase activity and showed no increase in intracellular lipid second messengers. Further analysis of the intracellular signalling triggered by SCF showed that p110δ inactivation almost completely abrogated the phosphorylation of protein kinase B but did not affect the activation of extracellular signal-regulated kinase (ERK). The same results were observed using the p110δ-specific inhibitor IC87114. Mast-cell functional responses were also impaired by p110δ inactivation, with SCF-mediated proliferation, adhesion and migration being severely affected. Moreover, after crosslinking of the high-affinity IgE receptor with antigen–IgE complexes, p110δ-mutant mast cells showed reduced degranulation and cytokine release compared with wild-type cells.

Next, the authors examined whether p110δ inactivation affects allergic responses in mice. They used an *in vivo* anaphylaxis model, in which mice primed with an intradermal injection of hapten-specific IgE were challenged with the hapten coupled to a carrier protein, together

MACROPHAGES

Common clearance pathway

According to a study published in *Cell*, a common transcriptional pathway might be used by macrophages to facilitate the clearance of both oxidatively modified lipoproteins and intracellular bacteria that have been phagocytosed. The nuclear liver X receptors LXR-α and LXR-β are known to facilitate the transcription of genes that promote cholesterol efflux from macrophages after scavenger-receptor-mediated uptake of oxidized lipids. Now, they are also shown to mediate innate immune responses to intracellular bacteria, and these responses promote macrophage survival and pathogen clearance.

Mice that are deficient in both LXR-α and LXR-β (LXR-αβ-deficient mice) were highly susceptible to infection with the Gram-positive intracellular bacterium *Listeria monocytogenes*, succumbing to infection earlier than wild-type controls and having higher bacterial burdens in the liver. Susceptibility was shown to be associated mainly with loss of LXR-α. Transplantation of wild-type bone marrow to LXR-αβ-deficient recipients completely reversed the susceptibility phenotype, showing that the defect occurs in bone-marrow-derived cells and not in hepatocytes, in which LXR proteins are also highly expressed.

The early susceptibility of LXR-αβ-deficient mice to *L. monocytogenes* indicated that the innate immune response might be affected. So, to identify LXR-regulated genes that are involved in innate immunity, the authors used transcriptional profiling to identify genes that were induced by both *L. monocytogenes* and LXR agonists, and were preferentially induced by LXR-α compared with LXR-β. The only gene that met these criteria was the gene encoding the anti-apoptotic protein SP-α, which is known to be selectively expressed by macrophages. Furthermore, they identified a putative site in the SP-α promoter for the binding of LXR proteins and their heterodimeric partner retinoid X receptor (RXR). LXR-α–RXR heterodimers bound this site with high affinity compared with LXR-β–RXR heterodimers.

So, SP-α can be directly induced by LXR-α, and the authors showed that, in turn, expression of mRNA encoding LXR-α (but not LXR-β) is strongly induced by bone-marrow-derived macrophages after exposure to *L. monocytogenes*. A similar response was observed for the Gram-negative intracellular bacterium *Shigella flexneri*, but not for Gram-positive and Gram-negative extracellular bacteria, indicating that induction of expression of LXR-α is a preferential response to intracellular bacteria. Induction of LXR-α was shown to be independent of the Toll-like receptor pathway but to involve intracellular NOD (nucleotide-binding oligomerization domain) proteins.

In keeping with the known anti-apoptotic effects of SP-α, macrophages from LXR-αβ-deficient mice infected with *L. monocytogenes* had an increased rate of apoptosis compared with wild-type macrophages. Forced expression of LXR-α by RAW264.7 macrophages, which express LXR-β but not LXR-α, led to the expression of SP-α and inhibited apoptosis when the cells were challenged with *L. monocytogenes*. Expression of LXR-α also decreased the number of viable intracellular bacteria. Because the induction of apoptosis by pathogens is a common strategy to evade the host immune response, the upregulation of SP-α by infected macrophages might be an important counter-defence to facilitate pathogen clearance.

Kirsty Minton

References and links

ORIGINAL RESEARCH PAPER Joseph, S. B. *et al.* LXR-dependent gene expression is important for macrophage survival and the innate immune response. *Cell* **119**, 299–309 (2004).

WEB SITE

Peter Tontonoz's homepage:
http://www.uclaaccess.ucla.edu/UCLAACCESS/Web/Faculty.aspx?ri=789

©2004 Nature Publishing Group