INNATE IMMUNITY

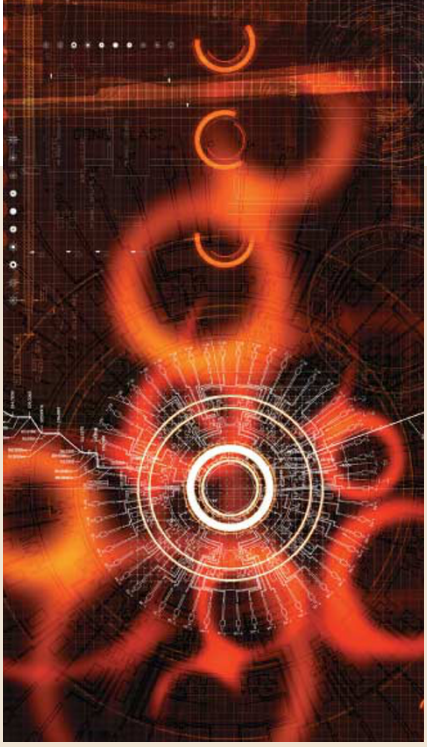
Selective activation

Toll-like receptor (TLR) recognition of microbial compounds initiates signalling cascades that activate inflammatory and immune-response genes. A recent report in *Nature* shows that the nuclear protein IκBζ (inhibitor of nuclear factor-κB (NF-κB), ζ; also known as MAIL and INAP) is required for the initiation of transcription of a subset of these genes.

In this study, IκBζ — previously known to be induced in response to interleukin-1 (IL-1) and the TLR4 ligand lipopolysaccharide (LPS) — was shown to be upregulated in cells stimulated through TLR2, TLR5, TLR7 and TLR9. The importance of this was shown by the observation that macrophages from IκBζ-deficient mice were impaired in their ability to produce IL-6 in response to LPS, as well as ligands for other TLRs and IL-1, whereas tumour-necrosis factor (TNF)-mediated IL-6 production was normal. By contrast, these macrophages produced wild-type levels of other inflammatory mediators (TNF and nitric oxide), indicating that IκBζ is specifically required for IL-6 production in response to TLR and IL-1 signals.

Promoter analysis showed that IκBζ overexpression enhanced LPS-induced *Il6* promoter activity, and this effect was dependent on the NF-κB-binding site in the *Il6* promoter. This site is bound by the p50 subunit of NF-κB, and after LPS stimulation, IκBζ was also detected at this site, interacting directly with p50. Consistent with the idea that IκBζ exerts its effects through p50, the production of IL-6 in response to TLR and IL-1 signals was impaired in p50-deficient macrophages, and IκBζ overexpression in these cells failed to induce high levels of IL-6 production.

This paper identifies inducible IκBζ as an essential first component of a two-step signalling pathway that elicits IL-6 production in response to TLR and IL-1 signals. The authors initial analysis indicates that other LPS-inducible genes, such as *Il12b* and *Csf2*, require IκBζ function, and further studies will provide new insight into the specific pathways that regulate the expression of individual immune-response genes.



Karen Honey

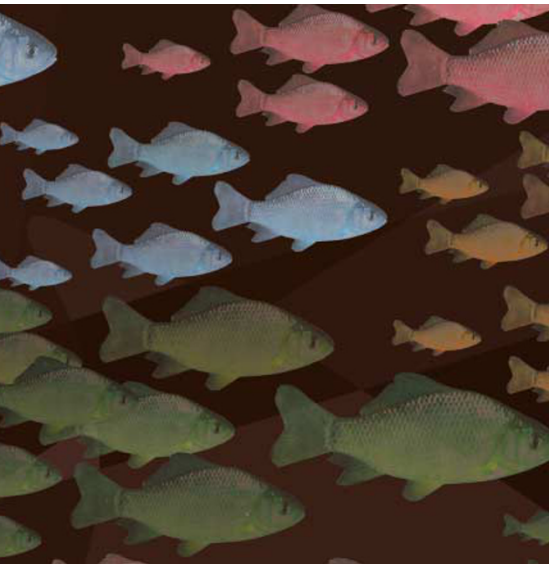
References and links

ORIGINAL RESEARCH PAPER Yamamoto, M. *et al*. Regulation of Toll/IL-1-receptor-mediated gene expression by the inducible nuclear protein IκBζ. *Nature* **430**, 218–222 (2004).

EVOLUTION

Lampreys diversify differently

The ability to generate clonally diverse lymphocytes is a hallmark of the adaptive immune response in jawed vertebrates. This diversity is achieved by combining variable, diverse and joining gene segments in the immunoglobulin and T-cell receptor (TCR) loci. Various aspects of adaptive immune responses — for example, accelerated rejection of second skin grafts and antigen-specific agglutinins — have been identified in jawless vertebrates, but orthologues of the immunoglobulin, TCR and MHC genes have not been found. Now, a team from Max Cooper's laboratory has identified a novel type of variable lymphocyte receptor (VLR), the diversity of which is based on the number and variable sequence of leucine-rich repeats (LRRs).



To search for elements of the vertebrate immune system, the authors generated a subtracted cDNA library based on activated versus non-activated lymphocytes from sea lamprey larvae. The most common sequences contained variable numbers of diverse LRR motifs. Each VLR was shown to have eight different features: a signal peptide, an amino-terminal LRR, a variable number of diverse LRRs, a connecting peptide, a carboxy-terminal LRR, a conserved carboxyl terminus, a glycosylphosphatidylinositol anchor and a hydrophobic tail. Individual lymphocytes were found to express VLRs in a monoallellic manner. Genomic analysis revealed a single germline gene that comprised only four exons and that could not encode the diverse full-length VLRs. The authors identified a series of variable diverse LRR sequences adjacent to the partial *VLR* gene; these are inserted into the partial *VLR* gene to generate mature *VLR* genes.

This study reveals that jawed and jawless vertebrates have evolved similar, but different, systems for generating variable lymphocyte receptors — one is a multigene recombinatorial strategy that uses gene segments encoding immunoglobulin domains, and the other is a somatic diversification strategy that is based on a single germline gene and the insertion of LRR sequences. The precise mechanism for the generation of the mature VLR in lampreys will be elucidated in future studies.

Elaine Bell

References and links

ORIGINAL RESEARCH PAPER Pancer, Z. *et al*. Somatic diversification of variable lymphocyte receptors in the agnathan sea lamprey. *Nature* **430**, 174–180 (2004).

FURTHER READING Flajnik, M. Comparative analysis of immunoglobulin genes: surprises and portents. *Nature Rev. Immunol.* **2**, 688–698 (2002).

WEB SITE

Max Cooper's lab:
http://www.microbio.uab.edu/faculty/cooper/index1.html