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INNATE IMMUNITY

Living without Toll-like receptors

Signals from the Toll-like receptor (TLR) family of microbial sensors are essential for generating innate immune responses to a broad range of pathogens. At least in mice. A recent report in *Science* shows, surprisingly, that in humans, the main TLR signal-transduction pathway is not essential for survival and has a much narrower role than expected.

The TLRs recognize molecular patterns that are characteristic of particular classes of microorganism, such as lipopolysaccharide (LPS; Gram-negative bacteria), double-stranded RNA (viruses) and mannan (fungi). The cytoplasmic domains of the TLRs and members of the interleukin-1 receptor (IL-1R) family contain a conserved signal-transduction module — the TIR domain — which, through TIR-containing adaptor molecules, recruits the IL-1R-associated kinase (IRAK) complex, consisting of IRAK1, IRAK2, IRAKM and IRAK4. Subsequently, tumour-necrosis factor receptor (TNFR)-associated factor 6 (TRAF6) is activated, triggering the nuclear factor- κ B (NF- κ B) and mitogen-activated protein kinase (MAPK) pathways, which leads to secretion of pro-inflammatory cytokines.

The group, led by Jean-Laurent Casanova, were investigating three unrelated children with poor inflammatory responses, who suffered from non-life-threatening recurrent infections that were always caused by extracellular pyogenic (pus-forming) bacteria — most frequently, the Gram-positive bacteria *Streptococcus*

pneumoniae and *Staphylococcus aureus*. It was known that one individual did not respond to LPS, a TLR4 ligand, which raised the possibility that the TLR signalling pathway was faulty in these patients. Indeed, various white blood cells of all three patients failed to respond to IL-1 β and IL-18 (an IL-1-family cytokine), as well as ligands for TLR2, TLR3, TLR4, TLR5 and TLR9, although responses to TNF were intact. This indicates that these patients have a defect in the TIR-IRAK pathway upstream of TRAF6 (which is common to TLR/IL-1R and TNFR signalling).

No mutations were found in the genes encoding the TIR-containing adaptor molecules MYD88 or TIRAP, or in *IRAK1*, *IRAK2* or *IRAKM*. But, all patients were homozygous for loss-of-function mutations in *IRAK4*. Biochemical analysis of the patients' fibroblasts showed that, in response to IL-1 β , activation of both NF- κ B and MAPK pathways was defective. And

transfection of these fibroblasts with wild-type *IRAK4* restored normal responses, confirming that the *IRAK4* deficiency is responsible for the phenotype.

This new type of immunodeficiency caused by *IRAK4* mutations is an important 'natural experiment', which clearly shows an essential and specific role for the TIR-IRAK pathway in protection against pyogenic bacteria. However, an alternative TLR-signalling pathway that leads to the production of the antiviral cytokine interferon- β has been reported in mice. If this pathway exists in humans, and is intact in these children, it could potentially explain why they do not suffer from recurrent virus infections.

Jennifer Bell

References and links

ORIGINAL RESEARCH PAPER Picard, C. *et al.* Pyogenic bacterial infection in humans with *IRAK4* deficiency. *Science* 13 March 2003 (DOI: 10.1126/science.1081902)

FURTHER READING Beutler, B. & Rietschel, E. T. Innate immune sensing and its roots: the story of endotoxin. *Nature Rev. Immunol.* **3**, 169–175 (2003)