INNATE IMMUNITY

It's what's inside that counts

Chris Karp and colleagues describe a role for the Toll-like receptor (TLR) homologue RP105 (also known as Ly64) in the negative regulation of TLR4 signalling. RP105 might look like a 'regular' TLR from the outside, but the lack of a typical intracellular domain has profound effects on its function on dendritic cells (DCs).

RP105 was originally identified as a B-cell-specific molecule that could induce B-cell proliferation. Similar to TLRs, it has a conserved extracellular leucine-rich-repeat domain and juxtamembrane cysteine residues, but it does not have the intracytoplasmic Toll/interleukin-1 (IL-1)-receptor domain that is required for TLR signalling. Further analysis showed that RP105 is most similar to TLR4 in terms of amino-acid sequence; in addition, similar to the MD2 co-factor-dependent expression and signalling of TLR4, RP105 expression depends on the MD2 homologue MD1.

In this study, the authors showed that RP105 expression is not limited to B cells, being found at the cell surface of human monocytes and myeloid DCs, and mouse peritoneal macrophages, splenic DCs and bone-marrow-derived DCs, with an expression pattern that mirrors that of TLR4. In a $CD14^+$ cell line, transfection with *Tlr4* and *Md2* induced the production of IL-8 (also known as CXCL8) in response to lipopolysaccharide (LPS), whereas expression of the RP105–MD1 complex did not, confirming that, despite its extracellular homology to TLR4, RP105 is not a signalling receptor for LPS. Instead, co-transfected *Rp105* and *Md1* inhibited the TLR4–MD2-mediated response to LPS in a dose-dependent manner. This inhibition was specific in that responses to IL-1 receptor or TLR2 signalling were not affected.

A soluble mutant of RP105 that lacks the transmembrane and intracellular domains could still inhibit TLR4 signalling, indicating that inhibition does not involve RP105 signalling and is probably a consequence of a direct interaction between RP105 and TLR4. Co-immunoprecipitation experiments confirmed a physical association between TLR4–MD2 complexes and RP105–MD1 complexes, which is mediated through MD1–MD2 interaction. Furthermore, the interaction of RP105–MD1 with TLR4–MD2 inhibited the ability of the latter signalling complex to bind LPS.

This TLR4-specific inhibitory role for RP105 was confirmed *in vivo*. DCs from RP105-deficient mice produced significantly higher levels of pro-inflammatory cytokines after stimulation with LPS, but not with other TLR ligands, than did wild-type DCs; in addition, RP105-deficient mice had more severe endotoxicity after high-dose LPS challenge. RP105 therefore joins the list of direct negative regulators of TLR signalling, such as IL-1-receptor-associated kinase M (IRAKM), but it is unique in its specificity for TLR4.

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References and links

ORIGINAL RESEARCH PAPER Divanovic, S. *et al*. Negative regulation of Toll-like receptor 4 signaling by the Toll-like receptor homolog RP105. *Nature Immunol.* **6**, 571–578 (2005)

FURTHER READING Liew, F. Y., Xu, D., Brint, E. K. & O'Neill, L. A. J. Negative regulation of Toll-like receptor-mediated immune responses. *Nature Rev. Immunol.* **5**, 446–458 (2005)