MACROPHAGES

SOCS1 and the innate immune response

The inflammatory response to lipopolysaccharide (LPS) is crucial for protecting the host against pathogenic bacteria, but excessive cytokine production can be harmful and, in some cases, fatal if LPS-induced shock occurs. Therefore, LPS signalling, through the LPS receptor Toll-like receptor 4 (TLR4), needs to be controlled tightly. But, how is this achieved? Two papers in *Immunity* now indicate a central role for suppressor of cytokine signalling 1 (SOCS1) in the negative regulation of LPS signalling.

SOCS1 was identified initially as a negative regulator of signalling downstream of cytokines. However, SOCS1 is expressed by macrophages after stimulation with LPS. This fact, combined with the observation that *Socs1*$^{-/-}$ mice develop inflammatory organ disease, led the authors to ask whether SOCS1 downmodulates LPS signalling.

Both groups looked at the effect of SOCS1 deficiency on the response to LPS. Nakagawa *et al.* showed that *Socs1*$^{-/-}$ mice (pre-disease onset) and *Socs1*$^{+/-}$ mice are hyper-responsive to LPS and are sensitive to LPS-induced lethality. Macrophages from these mice produced increased amounts of the pro-inflammatory cytokines tumour-necrosis factor (TNF) and interleukin-12 (IL-12). Kinjyo *et al.* also investigated the response of *Socs*$^{+/-}$ mice to LPS. First, they crossed these mice onto an interferon-γ (IFN-γ)-deficient background to eliminate any effect of SOCS1 on IFN-γ signalling. IFN-γ-deficient *Socs1*$^{-/-}$ and IFN-γ-deficient *Socs1*$^{+/-}$ mice were more sensitive than IFN-γ-deficient *Socs1*$^{+/+}$ mice to LPS, and macrophages from these mice produced high levels of TNF and nitric oxide in response to LPS.

When wild-type mice are treated with a low dose of LPS, they are protected from the effects of a higher, potentially fatal, dose when administered later on. This phenomenon is known as 'LPS tolerance'. Is SOCS1-mediated downregulation of LPS signal transduction important for this protective mechanism? These studies showed that a similar pre-treatment of *Socs1*$^{-/-}$ mice and *Socs1*$^{-/-}$ macrophages with LPS did not protect them from a subsequent higher dose, indicating that SOCS1 is required for LPS tolerance.

To find out how SOCS1 regulates the response to LPS, both groups overexpressed SOCS1 in a macrophage cell line. SOCS1-overexpressing macrophages produced little nitric oxide and TNF in response to LPS, and the activities of signal transducer and activator of transcription 1 (STAT1) and nuclear factor-κB (which are both required for the generation of nitric oxide) were reduced in these cells.

These studies show that, in addition to a central role in controlling adaptive immune responses downstream of cytokines, SOCS1 can suppress TLR4 signalling directly and modulate the innate immune response.

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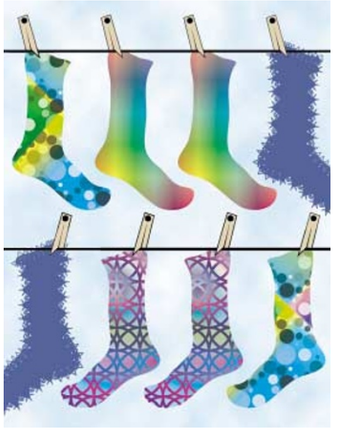

References and links

ORIGINAL RESEARCH PAPERS Kinjyo, I. *et al.* SOCS1/JAB is a negative regulator of LPS-induced macrophage activation. *Immunity* **17**, 583–591 (2002) | Nakagawa, R. *et al*. SOCS-1 participates in negative regulation of LPS responses. *Immunity* **17**, 677–687 (2002)

FURTHER READING Medzhitov, R. Toll-like receptors and innate immunity. *Nature Rev. Immunol.* **1**, 135–146 (2002)

IN BRIEF

T-CELL RESPONSES

IFN-γ represses IL-4 expresssion via IRF-1 and IRF-2.

Elser, B. *et al. Immunity* **17**, 703–712 (2002)

On the basis of patterns of cytokine expression, CD4$^+$ T cells can be divided into T_H1 and T_H2 cells. IFN-γ assists T_H1-cell development, but until now, a direct effect of IFN-γ on the expression of T_H2 cytokines has not been shown. This study shows that IFN-γ represses the expression of IL-4, a crucial T_H2-inducing cytokine, by inducing the expression of interferon regulatory factor 1 (IRF1) and IRF2, which bind to sites in the IL-4 promoter and suppress its activity.

NATURAL KILLER CELLS

A signal peptide derived from hsp60 binds HLA-E and interferes with CD94/NKG2A recognition.

Michaëlsson, J. *et al*. *J. Exp. Med*. **196**, 1403–1414 (2002)

Interaction of HLA-E — a non-classical MHC molecule that presents mainly peptides derived from other MHC class I molecules — with the inhibitory NK-cell receptor CD94–NKG2A prevents the activation of NK cells. This study shows that HLA-E can present a peptide from HSP60 (the expression of which is upregulated in stressed cells), which prevents the complex from being recognized by CD94–NKG2A. A greater number of such complexes are likely to be expressed by stressed cells, which could block inhibitory signalling and allow NK cells to kill stressed cells.

SIGNALLING

Non-T-cell activation linker (NTAL): a transmembrane adaptor protein involved in immunoreceptor signalling.

Brdicka, T. *et al. J. Exp. Med.* **196**, 1617–1626 (2002)

Linker for activation of T cells (LAT) is an important component of TCR signalling pathways. However, B cells and natural killer (NK) cells do not express LAT. Do they express a LAT-like molecule? Here, Brdicka *et al.* identify a new transmembrane adaptor protein that is structurally and evolutionarily related to LAT, known as non-T-cell activation linker (NTAL), which is expressed by B cells, NK cells, monocytes and mast cells, and which seems to function in a LAT-like manner.

INNATE IMMUNITY

Cutting edge: a novel Toll/IL-1 receptor domain-containing adapter that preferentially activates the IFN-β promoter in the Toll-like receptor signaling.

Yamamoto, M. *et al*. *J. Immunol.* **169**, 6668–6672 (2002)

Although the TIR-domain-containing adaptor TIRAP was thought to mediate signalling from TLRs through the MYD88-independent pathway, this was shown recently not to be the case. Now, Yamamoto *et al.* report the identification of a new adaptor, TIR-domain-containing adaptor inducing IFN-β (TRIF). Studies using a dominant-negative form of TRIF show that it is involved in TLR signalling, particularly in the MYD88-independent pathway.