T-CELL RESPONSES

Function and partner found for orphan SIRP-β2

Until now, the expression, specificity and function of the recently identified member of the signal-regulatory protein (SIRP) family, SIRP-β2, was unknown. Reporting in *Blood*, Marco Colonna and colleagues now show that SIRP-β2 has an important role in T-cell adhesion to antigen-presenting cells (APCs), through binding CD47, and that this co-stimulates T-cell proliferation.

So far, three members of the SIRP family of transmembrane glycoproteins have been identified: SIRP-α, SIRP-β1 and SIRP-β2. SIRP-α is an inhibitory receptor that modulates macrophage and dendritic-cell function after it binds CD47 and undergoes phosphorylation of its cytoplasmic immunoreceptor tyrosine-based inhibitory motifs (ITIMs). By contrast, SIRP-β1 lacks ITIMs but associates with the adaptor protein DAP12, through a lysine residue in its transmembrane domain, to mediate activating signals. SIRP-β2, however, lacks both ITIMs and the transmembrane lysine residue, so the authors proposed that it might be involved in cell–cell adhesion rather than in promoting inhibition or activation.

First, the authors showed that, unlike SIRP-α and SIRP-β1 (which are mainly expressed by myeloid cells), SIRP-β2 is expressed by T cells and activated natural killer cells. But similar to SIRP-α, SIRP-β2 binds CD47, although the affinity of this interaction is lower for SIRP-β2 than for SIRP-α. Expression of SIRP-β2 allowed T cells to adhere to cells expressing CD47. Moreover, the SIRP-β2–CD47 interaction between T cells and APCs promoted antigen-specific T-cell proliferation and co-stimulated T-cell activation to a similar extent to ligation of the co-stimulatory molecule CD28.

These results considerably extend our current knowledge of this new SIRP-family

member, and they implicate SIRP-β2 as an important molecule in the regulation of T-cell responses.

Lucy Bird

References and links

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AUTOIMMUNITY

Out of the frying pan into the fire

Whereas the pathogenesis of some autoimmune diseases, such as rheumatoid arthritis and psoriasis, is associated with tumour-necrosis factor (TNF), other diseases such as systemic lupus erythematosus (SLE) and type 1 diabetes are thought to involve interferon-α (IFN-α). Jacques Banchereau and colleagues have studied the reciprocal relationship between these two cytokines in autoimmune disease to explain the finding that treatment of rheumatoid arthritis with TNF antagonists, although an effective therapy for many patients, can induce features of SLE, such as an increased titre of nuclear-specific antibodies.

Peripheral-blood mononuclear cells (PBMCs) isolated from paediatric patients with systemic-onset juvenile arthritis and treated with TNF-specific antibodies were shown to express a set of genes that are known to be upregulated by IFN-α. Because inhibition of TNF is associated with increased transcription of IFN-α-regulated genes, TNF might usually function to downregulate IFN-α responses. Indeed, adding TNF to PBMCs that were isolated from healthy donors and cultured with influenza virus inhibited the production of IFN-α. This was shown to be the result of targeting immature plasmacytoid dendritic cells (pDCs), which are one of the main sources of IFN-α *in vivo*. pDCs were cultured *in vitro* from $CD34^+$ haematopoietic stem cells (HSCs) and then exposed to influenza virus; addition of TNF to the culture inhibited IFN-α production by up to 40%, by stimulating pDC maturation. Conversely, pretreatment of pDCs *in vitro* with TNF-specific antibody resulted in threefold higher levels of IFN-α when the pDCs were re-exposed to influenza virus, by inhibiting virus-induced pDC maturation. Finally, TNF was also shown to block the generation of pDCs, but not myeloid DCs, from HSCs.

These results led the authors to conclude that endogenous TNF controls the production of IFN-α by immature pDCs by inhibiting the generation of these cells and by stimulating their maturation. Therefore, decreased levels of TNF in patients treated with TNF antagonists will result in increased IFN-α levels. This is thought to lead to SLE-like symptoms through stimulating the maturation of myeloid DCs, which can then activate, rather than tolerize, autoreactive T and B cells. This cross-regulation between TNF and IFN-α is supported by the fact that patients with SLE have increased levels of circulating soluble TNF receptors, which correlate with disease activity.

Kirsty Minton

References and links

ORIGINAL RESEARCH PAPER Palucka, A. K., Blanck, J.-P., Bennett, L., Pascual, V. & Banchereau, J. Cross-regulation of TNF and IFN-α in autoimmune diseases. *Proc. Natl Acad. Sci. USA* **102**, 3372–3377 (2005)