IMMUNE REGULATION

BTLA finds its true partner

A recent study provided indirect evidence that B7X could be a ligand for B- and T-lymphocyte attenuator (BTLA).

However, new data published in *Nature Immunology* shows that BTLA does not interact with B7X and that herpesvirus-entry mediator (HVEM) binds BTLA, initiating signalling pathways that impair antigen-induced T-cell proliferation.

The observation that binding of a B7X–Fc fusion protein to BTLA-deficient lymphocytes was reduced compared with binding to BTLA-sufficient lymphocytes led to the idea that B7X might be a BTLA ligand. So, Sedy *et al.* set out to find further evidence of this interaction. However, BTLA tetramers did not bind a B7X-expressing fibroblast cell line, and a B7X–Fc fusion protein did not bind BTLA-expressing cell lines. So, further studies in search of a BTLA-binding partner were carried out.

The physiological ligand for BTLA was first characterized using a BTLA–Fc fusion protein and was found to be expressed by resting T cells. A subsequent cDNA-library screen for cDNA encoding a BTLA-tetramer-binding protein indicated that the tumour-necrosis-factor receptor (TNFR)-family member HVEM was the BTLA-binding protein. Further studies then showed that BTLA bound the most membrane-distal cysteine-rich domain of HVEM. Binding of HVEM to BTLA induced tyrosine phosphorylation of BTLA and its association with SHP2 (SRC-homology-2-domain-containing protein tyrosine phosphatase 2). Furthermore, HVEM expression by antigen-presenting cells impaired peptide-mediated T-cell stimulation (in the presence or absence of co-stimulation) in a manner that was dependent on T-cell expression of BTLA.

This study identifies HVEM as the ligand of BTLA, and this interaction between a TNFR and an immunoglobulin-superfamily member is structurally unique. Although further studies are needed to define the *in vivo* significance of this interaction, the authors suggest that it is an important pathway for regulating lymphocyte activation and/or homeostasis.

Karen Honey

References and links

ORIGINAL RESEARCH PAPER

Sedy, J. R. *et al.* B and T lymphocyte attenuator regulates T cell activation with herpesvirus entry mediator. *Nature Immunol.* **6**, 90–98 (2005).

IMMUNE REGULATION

IL-12 helps keep apoptosis quiet

The removal of apoptotic cells by phagocytes usually results in an anti-inflammatory state that involves the inhibition of pro-inflammatory cytokines, such as interleukin-12 (IL-12). In a recent issue of *Immunity*, Kim *et al.* describe a new mechanism that regulates IL-12 expression in response to apoptotic cells, involving a novel zinc-finger nuclear factor, GC-BP.

Previous studies have focused on the production of anti-inflammatory cytokines, such as IL-10 and transforming growth factor-β (TGF-β), in regulating responses after phagocytosis of apoptotic cells. However, here, Kim *et al.* show that the inhibition of IL-12 production by macrophages in the presence of apoptotic cells is direct and independent of increased IL-10 or TGF-β production. Inhibition of IL-12 production was dependent on macrophage contact with apoptotic cells, because liposomes containing phosphatidylserine (which is exposed on the surface of apoptotic cells) similarly inhibited IL-12 production by macrophages.

IL-12 is a heterodimeric cytokine composed of two chains, p40 and p35; analysis of the levels of mRNA encoding each IL-12 chain indicated that the presence of apoptotic cells mainly reduced the levels of *IL-12p35* mRNA in responding macrophages. This prompted the authors to focus on the transcriptional mechanisms that are involved in inhibition of *IL-12p35* gene expression. In the *IL-12p35* promoter, they identified a GC dinucleotide at position +17–+18 that is crucial for mediating the response to apoptotic cells, and they showed that this region is specifically bound by a novel zinc-finger nuclear factor, which they named GC-binding protein (GC-BP). Over-expression of GC-BP in a mouse macrophage cell line selectively inhibited IL-12p35 expression in response to interferon-γ and lipopolysaccharide. And specific knockdown of GC-BP expression by small interfering RNAs confirmed its inhibitory role.

Because GC-BP was found to be constitutively expressed by macrophages, the authors assessed whether post-translational modifications might regulate its activity. They detected a decrease in tyrosine phosphorylation levels of GC-BP in macrophages that were exposed to apoptotic but not necrotic cells. Mutation of a tyrosine residue at position 15 (Tyr15) abolished the inhibitory effect of GC-BP on IL-12 production, indicating that the activity of GC-BP is likely to be regulated by phosphorylation of Tyr15.

These results uncover a new signalling pathway and further our understanding of cytokine regulation, which is a crucial mechanism for avoiding autoreactivity to apoptotic cells.

Lucy Bird

References and links

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