IN BRIEF

TRANSPLANTATION

Handling complement for transplant success

Haematopoietic cell transplantation (HCT) is used to treat cancer and blood disorders, but a potentially lethal complication is the development of graft-versus-host disease (GVHD). Total-body irradiation (TBI) is required to facilitate HCT and can promote GVHD by activating host dendritic cells (DCs), although the mechanisms involved are not completely understood. This study shows that, in mice, TBI causes host DCs to upregulate the complement components C3, C5a, factor B and factor D, and to downregulate CD55, a negative regulator of the complement cascade. In HCT using CD55-deficient donor T cells, recipient mice developed exacerbated GVHD, suggesting that upregulation of complement components by host DCs promotes the activation of allogeneic donor T cells. Indeed, less severe GVHD was seen in HCT using donor T cells that were deficient in the C3a and C5a receptors. Treatment of recipients with a C5a receptor antagonist during the post-transplantation period reduced GVHD development, and could be a useful strategy for preventing GVHD in humans after transplantation.

ORIGINAL RESEARCH PAPER Kwan, W.-H. *et al.* Antigen-presenting cell-derived complement modulates graft-versus-host disease. *J. Clin. Invest.* 15 May 2012 (doi:10.1172/JCI61019)

T CELLS

'Leaky' cytokine secretion by immunological synapses

This study used live-cell imaging to investigate whether cytokine secretion by activated T cells is restricted by the immunological synapse to antigen-specific target cells or also affects bystander cells in the local environment. Responses to interferon-γ (IFNγ) were monitored by tracking the intracellular localization of a fluorescent STAT1 protein in ovalbumin-expressing and non-expressing astrocytes cultured with activated ovalbumin-specific $CD8^+$ T cells. Whereas cell lysis was restricted to ovalbumin-expressing target cells, the phosphorylation and nuclear translocation of STAT1 were observed in both ovalbumin-expressing and non-expressing astrocytes. STAT1 translocation generally occurred earlier and to a greater extent in ovalbumin-expressing cells, and this was shown through microtubule disruption to be a result of synaptic signalling rather than proximity to the $CD8^+$ T cell. The authors interpret the results as implying that synaptic IFNγ secretion is 'leaky'.

ORIGINAL RESEARCH PAPER Sanderson, N. S. R. *et al.* Cytotoxic immunological synapses do not restrict the action of interferon-γ to antigenic target cells. *Proc. Natl Acad. Sci. USA* **109**, 7835–7840 (2012)

INNATE IMMUNITY

MHC class I as a negative regulator of TLR signalling

Besides their classical function in antigen presentation, MHC class I molecules have now been shown to negatively regulate Toll-like receptor (TLR)-triggered inflammatory responses. Xu *et al.* first noted that MHC class I-deficient mice produced markedly more pro-inflammatory cytokines in response to TLR ligands and were more sensitive to lethal challenge with lipopolysaccharide (LPS) than control mice. Interaction of MHC class I-expressing macrophages with $CD8^+$ T cells led to the suppression of TLR-triggered cytokine production. Further analyses revealed that the intracellular tyrosine residues in membrane MHC class I molecules are phosphorylated by the kinase SRC after LPS stimulation of macrophages, and this allows the recruitment of the kinase FPS to the MHC class I molecules. FPS mediated the suppressive effect by activating the phosphatase SHP2, which interferes with TLR signalling mediated by TNFR-associated factor 6 (TRAF6).

ORIGINAL RESEARCH PAPER Xu, S. *et al.* Constitutive MHC class I molecules negatively regulate TLR-triggered inflammatory responses via the Fps–SHP-2 pathway. *Nature Immunol.* 22 Apr 2012 (doi:10.1038/ni.2283)