NKT cells depend on SAP

An intracellular adaptor protein is indispensable for the development of natural killer T (NKT) cells, according to Pasquier et al. (page 695). The loss of these cells might contribute to the genesis of a lethal immunodeficiency syndrome.

The adaptor protein in question—SAP (SLAM-associated protein)—is expressed in T, NK, and NKT cells and responds to SLAM family receptors by recruiting and activating the downstream tyrosine kinase Fyn. Fyn was known to be required for NKT cell development in the thymus, but the upstream cell surface signals remained unknown.

Pasquier and colleagues now implicate the SLAM family of receptors in NKT cell development by showing that the loss of SAP results in a complete absence of NKT cells in both mice and humans. SAP-transmitted signaling events were uniquely required for the development of NKT cells, as conventional T cells and NK cells developed normally in the absence of SAP.

The need for SAP-mediated signals may reflect the unique requirements for positive selection of NKT cells in the thymus. Whereas conventional T cells interact with thymic epithelial cells for selection, NKT cells must interact with CD1d-expressing thymocytes via their invariant T cell receptors. This unique interaction might also provide the required SLAM-mediated signals.

In an intriguing twist, mutations in SAP cause a fatal disease called X-linked lymphoproliferative syndrome (XLP), which is characterized by uncontrolled Epstein-Barr virus (EBV) infections and B cell lymphomas. The loss of SAP impacts the function of multiple cell types including NK cells and T cells, but based on the current study, NKT cells may also contribute to XLP. Studying NKT cell activation during human EBV infection may give clues about why the lack of SAP, which results in so many immune cell defects, would preferentially increase susceptibility to only one type of virus.

omega-3 fatty acids combined with aspirin reduced the risk of heart attack prompted the authors to look for resolvin E1 in humans. They have now identified this lipid in plasma taken from volunteers given omega-3 fatty acids and aspirin, deciphered its complete stereochemical structure, and identified its receptor.

Human resolvin E1, the authors show, binds to a G protein-coupled receptor called ChemR23 that is expressed on leukocytes, and inhibits the migration of these cells to sites of inflammation. Resolvin E1 might also affect adaptive immunity in response to pathogens, as it reduced the production of interleukin-12 by dendritic cells and inhibited their migration to T cell areas of the spleen in mice.

In previous studies, aspirin promoted the cyclooxygenase-2 (COX-2)-dependent conversion of omega-3 fatty acids to a precursor of resolvin E1. COX-2 also converts arachidonic acid, another essential fatty acid, into proinflammatory prostaglandins. COX-2 inhibitors, designed to block this proinflammatory pathway, have had negative cardiovascular side effects. The authors thus suggest that inhibition of vascular COX-2 might also block the synthesis of resolvin E1, which would eliminate an important antiinflammatory pathway.

The structure of resolvin E1, a potent antiinflammatory lipid derived from omega-3 fatty acids.
Out with the old, in with the new

Muraro et al., reporting on page 805, use stem cell transplants to suppress active multiple sclerosis (MS), and then show that the treatment increased the number of naïve T cells at the expense of the memory T cells that are associated with disease.

Intense immunosuppression followed by stem cell transplantation has been shown to slow or stop the formation of new brain lesions in up to 95% of patients with aggressive MS. Yet it has been controversial and rarely used, mainly because immunosuppression is risky and because nothing was known about how transplantation induced remission. One proposed theory was that transplantation might change the composition of the T cell pool and bias it away from autoreactivity.

Muraro and colleagues now provide the first evidence that stem cell transplantation allows patients to regenerate a new repertoire of T cells that are less activated and more diverse than their pretransplant repertoires. This suggests that many of the disease-causing T cells—most of which have a memory phenotype—were eliminated by the treatment.

However, concrete proof that autoreactive T cells are reduced or eliminated is difficult to obtain, partly because the specificities of the autoreactive T cells that invade the central nervous system are not well defined.

The difficulty in assessing the basis for treatment success is one problem. Another is the possibility that autoreactive cells will reemerge from the pool of transferred stem cells. The authors agree that these cells could eventually come back, but hope that resetting the immune system may improve the quality of life for patients with an otherwise poor prognosis.

They emphasize, however, that this intense therapy is probably only suited to a subset of MS patients who have active and aggressive disease and that its implementation will require careful patient selection. JEM

Refusing to be suppressed

On page 737, Fahlén et al. show that colitis-inducing effector T cells that cannot respond to the suppressive cytokine TGF-β refuse to be controlled by regulatory T (T reg) cells.

Naturally occurring T reg cells suppress the activity of effector CD4+ T cells and are essential for the prevention of autoimmune disease and chronic inflammation. TGF-β appears to be required for T reg cell activity, but determining which cells produce TGF-β and which cells respond to it has proven difficult.

Fahlén and colleagues now attempt to define the role of TGF-β in a mouse model of T cell–induced colitis. In this model, colitis can be reversed when CD4+CD25+ T reg cells are provided along with the disease-inducing effector cells. The authors showed that wild-type T reg cells inhibited the development of colitis induced by wild-type effector T cells but failed to prevent disease caused by effector T cells bearing a signaling-defective TGF-β receptor. This demonstrated that effector cells had to be responsive to TGF-β to be controlled by T reg cells. The T reg cells were not required as a source of TGF-β, as T reg cells from TGF-β–deficient mice were also able to suppress. Thus, T reg cells must be prompting another cell type to produce TGF-β, or may be producing a regulatory signal that operates cooperatively with TGF-β.

But did the T reg cells also require TGF-β signals to induce suppression, as several previous studies had shown? The authors found no differences between the T reg populations in mice with normal or signaling-defective TGF-β receptors, and lymph node–derived T reg cells from both mice suppressed colitis.

Transfer of splenic T reg cells with mutant TGF-β receptors, however, triggered rather than inhibited colitis. The authors suggest that this can be explained by contaminating effector cells that are also mutant for the TGF-β receptor and, therefore, cannot be controlled by the inhibitory signal. Thus, the requirement for TGF-β in T reg cell suppression appears to be dictated primarily by the effector cells. JEM