The mark of T reg cells

Regulatory T (T reg) cells found in the synovial fluid of inflamed joints can be identified by the coexpression of CD4, CD25, and CD27, according to Ruprecht and colleagues on page 1793.

Suppression of damaging T cell responses by CD4+ T reg cells is critical for the prevention of autoimmun disease. But studying these cells in the context of disease has been problematic, largely because CD4+ T reg cells and activated CD4+ T cells express many of the same surface molecules and are thus difficult to distinguish. Although coexpression of CD4 and the high affinity interleukin (IL)-2 receptor (CD25) identifies T reg cells in the circulation, CD25 cannot distinguish between T reg cells and local effector T cells, which up-regulate this molecule upon activation.

Ruprecht et al. now show that CD4+ CD25+ T reg cells found in the inflamed joints of children with autoimmune arthritis can be distinguished from their CD4+ CD25+ effector T cell counterparts by the expression of the TNF receptor family member CD27—a molecule that is down-regulated on activated T cells. CD27 expression identified T reg cells in these patients, as the ability to suppress T cell proliferation in vitro resided solely in the CD4+CD25+CD27+ T cell subset.

But why does an autoimmune response develop in these patients despite an abundance of T reg cells at the site of disease? The authors suggest that the cytokines IL-7 and IL-15, which were detected in the patients’ synovial fluid, might be to blame, as the combination of these cytokines reversed the in vitro ability of the T reg cells to inhibit T cell proliferation. JEM

Brain–tethered T cells

On page 1805, Kawakami et al. show that antigen–specific CD4+ T cells that attack the brain become stationary within brain tissue, whereas nonspecific T cells cruise through without stopping. These intravital images—the first to capture T cells launching an autoimmune attack on the brain—suggest that antigen–specific T cells behave similarly in dense brain tissue as they do in lymph nodes.

Activated CD4+ T cells specific for the endogenous brain protein myelin basic protein (MBP) trigger fatal encephalomyelitis in a rat model of multiple sclerosis. These cells migrate into the central nervous system (CNS) where they become reactivated.

Previous studies by this group showed that both antigen–specific and nonspecific T cells gain access to the CNS, but only specific cells become reactivated once there. Kawakami et al. now show that a subset of MBP-specific T cells—likely those that have encountered antigen—stopped moving inside the brain, appearing tethered to a fixed point. T cells specific for a control antigen kept moving, suggesting that the presence of antigen was required for T cells to stop moving and to trigger disease.

The authors were surprised to find that T cells move as rapidly through the dense brain tissue as in the more aqueous environment of the lymph nodes. How they do this is not known but the authors suggest that the T cells may produce proteases that help clear a path through the compact tissue. JEM

Signaling commitment

A histone modification thought by many to be a crude bulldozer can contribute to the fine molding of cell behavior, according to a study on page 1825. Rossig et al. show that histone deacetylase (HDAC) activity is required for adult progenitor cells to commit to the endothelial cell lineage. In these cells, HDAC activity was specifically required for the induction of the transcription factor HoxA9, which may be a master regulator of endothelial cell commitment.

HoxA9 was able to drive cell differentiation due to its ability to activate the expression of endothelial cell–specific genes, including endothelial cell nitric oxide synthase (eNOS). In addition, HoxA9–deficient mice were unable to recover from ischemic injury, a process that requires formation of new endothelial cells from circulating progenitors.

But the involvement of HDACs in this process may seem counter–intuitive, as histone deacetylation of gene promoter elements is normally associated with transcriptional silencing. Indeed, recent reports showed that eNOS expression itself is suppressed by HDAC activity in nonendothelial cells.

The protein complex responsible for activating HoxA9 expression was, however, recently shown to contain HDAC proteins. HDACs can modify nonhistone proteins, including transcription factors, and the acetylation or deacetylation state of these factors can influence target gene activation. The authors suspect that modification of nonhistone proteins may govern the induction of HoxA9. JEM