Lymphocytes that can't let go

On page 1987, Semmrich and colleagues show that immune cells expressing a perpetually activated form of the integrin LFA-1 get traction at the front of the cell, but get stuck from behind. Their lagging ends prevent them from crawling through the endothelium and initiating a normal immune response.

Integrins, such as LFA-1, are adhesive molecules that switch between active and inactive conformations and control migration of circulating immune cells to sites of infection and inflammation. LFA-1 is also required for the formation of stable interactions between T cells and antigen presenting cells (APCs). Previous studies had shown that both tumor-specific T cell responses and neutrophil migration are compromised in the absence of this integrin.

The importance of LFA-1 deactivation, however, has been less clear. In vitro studies have shown that locking LFA-1 in its activated conformation impairs both neutrophil chemotaxis and T cell activation. Semmrich et al. now confirm these findings in vivo, and show that lymphocytes from mice expressing a constitutively active LFA-1 moved more slowly than wild-type cells and failed to migrate across endothelial cell monolayers. Video microscopy revealed that these defective movements were due to an inability of the cells to release their trailing edges.

CD4+ T cell proliferation and antibody production were also impaired in these mice. The development of antigen-specific CD8+ cytotoxic T cells, by contrast, was not altered by the mutated LFA-1, but the ability of these cells to lyse target cells was decreased. The authors suggest that defects in T cell activation and function may reflect the need for serial engagement of T cell receptors with peptide–MHC complexes on APCs, a process that may be compromised by the inability to inactivate LFA-1 and thus to terminate cell–cell contacts.

Mice expressing the mutant LFA-1 closely resembled mice lacking the protein completely, suggesting that, for immune cells, letting go is just as important as grabbing on. JEM

Indecisive interleukin–4?

A study on page 1899 may explain the seemingly fickle ways of the cytokine interleukin (IL)-4. Yao and colleagues show how this quintessential T helper (Th) 2 cytokine can sometimes promote the opposite Th1 response.

IL-4 is known as the key cytokine for polarizing naive T cells toward a Th2 phenotype, which is important for antibody production and protection against parasitic infections. Under some conditions, however, IL-4 has been shown to instead induce a Th1 response. Indeed, a recent study showed that mice treated with IL-4 during initial infection with Leishmania major had increased Th1 responses and were protected. If given later, IL-4 increased Th2 responses and exacerbated disease.

Yao et al. now suggest that the regulation of another cytokine—IL-10—may explain these perplexing observations. They show that dendritic cells (DCs) stimulated in the presence of IL-4 made less IL-10 than those stimulated without IL-4. As a result, the IL-4–treated DCs produced more of the Th1-polarizing cytokine IL-12—known to be inhibited by IL-10—and polarized naive T cells toward a Th1 phenotype more effectively. IL-10 was critical for the increased Th1 response, as IL-4 did not increase IL-12 production or T cell polarization by IL-10–deficient DCs.

IL-4 had the opposite effect on B cells, provoking increased IL-10 production. The authors suggest that the differential effect of IL-4 at different times during infection may reflect a switch from DCs to B cells as the predominant cell type that is presenting antigen. JEM