Controlling unruly osteoclasts

Monocytes beget macrophages, and fused macrophages beget bone-resorbing osteoclasts. Factors such as monocyte-colony stimulating factor (from stromal cells) and interleukin-1 (IL-1; from macrophages) keep this process ticking along, but now Li and colleagues report (page 1169) that osteoclasts make a protein that forms part of a critical feedback loop. Without the IRAK-M (IL-1 receptor associated kinase M) protein, which was previously thought to be expressed only in macrophages, osteoclasts are hyperactivated and mice get severe osteoporosis.

Bone maintenance depends on the coordination of bone formation by osteoblasts and bone resorption by osteoclasts. Li et al., prompted by the description of IRAK-M as a macrophage-specific inhibitor of signals from the IL-1 and Toll-like receptors, examined the function of this protein in osteoclasts. They found that mice lacking IRAK-M had increased numbers of osteoclasts, which lived longer and were more responsive to growth factor-derived activating signals. IRAK-M–deficient mice developed severe osteoporosis.

The osteoclast growth factor RANKL (receptor activator of the NF-kB ligand) turns on IRAK-M expression; IRAK-M then may inhibit osteoclast differentiation and activation by inhibiting IL-1–dependent signals. IRAK-M also inhibits the fusion process that produces osteoclasts. Genetic mutations that cause aberrant activation of the RANKL signaling pathway have been identified in some cases of severe, inherited osteoporosis—the authors think IRAK-M mutations might be to blame for other unexplained cases. JEM

Overstimulated and ineffective

CD4⁺ T cells become ineffective if repeatedly stimulated through their T cell receptors (TCRs), according to a study by Jelley-Gibbs and colleagues on page 1101. The functional demise of these cells may help explain why persisting pathogens, such as Mycobacterium tuberculosis and HIV, are associated with ineffective CD4⁺ T cell responses during the chronic phase of infection.

Chronic infections have been shown to induce exhaustion or functional unresponsiveness in cytotoxic CD8⁺ T cells, but their effect on CD4⁺ T helper cells has not been well studied. Jelley-Gibbs et al. now show that repeated stimulation of CD4⁺ T cells generated effector cells that were more activated, based on the expression of activation markers CD69 and CD62L, than cells stimulated only once but that secreted lower levels of the cytokines interferon-γ (IFN-γ) and interleukin-4 (IL-4). These repeatedly stimulated cells could not provide help to antibody-producing B cells, nor could they protect against influenza virus infection when transferred into mice.

The decreased function of these repeatedly stimulated cells could not be explained by the down-regulation of their TCRs, whose levels were only marginally affected by the multiple rounds of stimulation. The authors are now studying chromatin remodeling at the IFNγ and IL-4 loci for possible clues to the decreased cytokine production. JEM

The way to the skin

Memory CD4⁺ T cells express characteristic adhesion molecules and chemokine receptors that dictate their recirculation to the tissue in which they first encountered antigen. On page 1045, Baekkevold and colleagues show that T cells may compete for access to the skin and only gain entry if they express the CC-chemokine receptor-4 (CCR4).

Previous studies showed that skin-homing and gut-homing CD4⁺ T cells express distinct chemokine receptors—CCR4 for skin-homing cells and CCR9 for gut-homing cells—and this was mirrored by the expression of the corresponding chemokine ligand in local blood vessels. The authors thus proposed that expression of CCR4 was required for T cells to access the skin (and CCR9 for the gut) but were perplexed by the phenotype of CCR4–deficient mice, which had normal numbers of skin-homing T cells.

Another skin-specific chemokine receptor may have compensated for the absence of CCR4. To test this, Baekkevold et al. staged a competition between wild type and CCR4-deficient bone marrow cells in lymphocyte-deficient mice. They found that CCR4⁺ cells were highly enriched among lymphocytes that trafficked to the skin, particularly during skin inflammation. This suggested that CCR4, although not essential, facilitated the generation of the skin-homing memory T cell population.

Recent studies have shown that tissue-specific dendritic cells (DC) impart CD8⁺ T cells with specific homing instructions and the authors suspect that a DC-derived signal may trigger CCR4 expression and similarly instruct CD4⁺ T cells. JEM