Bone cells unite

Bone-resorbing osteoclasts can’t pull together in the absence of dendritic cell–specific transmembrane protein (DC-STAMP), according to new data from Yagi and colleagues (page 345). Without this receptor, osteoclast precursor cells cannot fuse with one another. The failure to fuse cripples the bone resorbing function of the cells, causing osteopetrosis (increased bone mass).

DC-STAMP is a seven-transmembrane–spanning receptor that was originally isolated from dendritic cells (DCs). The ligand for DC-STAMP and its function on DCs are unknown, but this receptor was recently found on osteoclasts and shown to be required for these cells to develop from their macrophage precursors.

Yagi and colleagues now refine these data by showing that multinucleated osteoclasts were completely absent in the bones of mice lacking DC-STAMP, although osteoclast development was intact. The DC-STAMP–deficient mice suffered from mild osteopetrosis, as mononucleated osteoclasts can still resorb bone. Whether DC-STAMP triggers fusion directly or triggers the expression of other fusion–inducing receptors remains to be determined.

The absence of DC-STAMP also inhibited the formation of foreign body giant cells—products of macrophage fusion that dispose of foreign bodies in tissues. Although the mechanism is not yet known, DC-STAMP may function as a fusion coreceptor in a fashion analogous to the fusion of HIV with target cells, which depends on seven-transmembrane–spanning chemokine receptors (see commentary from Vignery, on page 337).

Debating DAP12

Mice that lack the adaptor protein DAP12 defy deadly bacterial infections, according to Turnbull and colleagues on page 363. DAP12-deficient mice developed a muted inflammatory response, allowing the immune system to clear the bacteria without triggering septic shock.

DAP12 is a transmembrane adaptor protein that is associated with an array of activating receptors on the surface of immune, brain, and bone cells. DAP12 is required for the development of bone-resorbing osteoclasts, but its role in immune cells is less clear. Some studies have suggested that DAP12-dependent signals amplify cellular activation and inflammatory cytokine production in response to invading microbes, but others argue that DAP12 signaling inhibits these functions.

Turnbull et al. now weigh in on this debate by showing that mice lacking DAP12 can fend off a systemic bacterial infection without producing shock-inducing amounts of inflammatory cytokines such as tumor necrosis factor, suggesting that DAP12 signaling normally amplifies inflammation. These data are consistent with their previous studies in which blocking the DAP12–associated receptor TREM-1, which is expressed on granulocytes and monocytes, protected mice against septic shock.

The resistance of the DAP12-deficient mice to bacterial infections is consistent with the situation in humans. Humans lacking DAP12 develop a lethal bone wasting and neurodegenerative disease, but do not seem to be more susceptible to infections. Thus far, the benefit of expressing DAP12 on immune cells that respond to bacterial infections remains a mystery.

TIM-2 tones down Th2

The TIM (T cell immunoglobulin mucin) proteins are emerging as critical regulators of T helper (Th) cell responses and as potential susceptibility factors for the development of allergic and autoimmune diseases. On page 437, Chakravarti and colleagues add to the developing TIM story by showing that TIM-2 is preferentially expressed on differentiated Th2 cells and inhibits their expansion and function. These molecules, according to senior author Vijay Kuchroo, are not only critical modulators of the CD4+ Th cell response, but are the first reliable markers of differentiated Th cell subsets.

The TIM genes were originally identified as residents of a chromosomal locus that conferred susceptibility to asthma. Since then, this group has shown that TIM3 is expressed exclusively on polarized Th1 cells and dampens their activation. They now show an analogous function for TIM-2 on Th2 cells. Blocking TIM-2 increased the production of Th2 cytokines and protected mice against Th1-driven experimental autoimmune encephalomyelitis, suggesting that TIM-2 normally inhibits excessive activation of Th2 cells.

Although the signals in T cells that drive the expression of TIM2 and TIM3 are not known, their exclusive expression on polarized Th cells (not simply activated T cells) suggests that TIM2 and TIM3 expression may be driven by Th2- and Th1-specific transcription factors, respectively. The structure of the TIM molecules, which most closely resembles the adhesion molecule MAdCAM, suggests that these proteins may also affect lymphocyte trafficking.