Neutrophil detox

On page 353, Han and colleagues describe a novel chemical inhibitor that shuts down the production of inflammation-induced oxidants by neutrophils, but does not compromise the ability of the cell to attack invading pathogens. This selective neutrophil disarmament may provide a way to limit the tissue-damaging side effects of neutrophil activation without crippling anti-microbial defenses—a feat presumed by many to be impossible.

Neutrophils are among the immune system’s earliest responders against invading pathogens. If these cells are missing or unable to function properly, life-threatening bacterial and fungal infections ensue. Neutrophil assault on invading pathogens is mediated in part by the release of reactive oxygen intermediates (ROIs) that damage microbes. But the benefits of this protection come at a cost. The same ROIs that help kill microbes contribute to the tissue damage that is often associated with prolonged inflammation.

As a result of this double-edged sword, a major challenge of anti-inflammatory therapy is to block the damaging side effects of neutrophils without crippling their anti-microbial functions. Han and colleagues have now found a chemical inhibitor that meets this tall order. The inhibitor blocked ROI production by neutrophils in response to the inflammatory cytokine tumor necrosis factor (TNF), but not in response to bacterial pathogens or a phorbol ester. Other neutrophil functions, including bacterial killing, migration, and degranulation were also unaffected by the inhibitor. This suggests that it is indeed possible to dissect neutrophil activation, a biological response that, according to senior author Carl Nathan, “was always presumed to be monolithic.”

The inhibitor—dubbed neucalcin-1—worked by blocking the build-up of intracellular calcium that is normally triggered by TNF. The defective calcium flux prevented the activation of soluble adenylyl cyclase, which was required for the activation of a guanosine triphosphatase that associates with the ROI-producing enzyme complex on the plasma membrane. Although many details of this pathway remain to be unraveled, these data identify a completely new branch of TNF signaling and demonstrate the possibility of fine-tuning neutrophil inhibition without blocking TNF, which is required for the activation of other cell types and for protection against many bacterial infections. JEM

Histamine self control

Allergy-provoking histamine keeps itself under control, according to a study on page 387. Schneider and colleagues show that basophil precursor cells pump released histamine back into themselves. Once inside, the histamine shuts off its own production and that of allergy-promoting T helper (Th) 2 cytokines.

Basophils and mast cells are the primary histamine producers of the immune system. In mature cells, histamine is stored in intracellular granules and is rapidly released when the cells are stimulated. Once released, histamine triggers acute allergy symptoms by binding to its receptors on vascular endothelial cells and bronchial smooth muscle cells. Histamine can also be produced by nongranular cells, including macrophages and dendritic cells, which secrete the molecule immediately after synthesis.

This group previously described a population of low-granule basophil precursor cells in the bone marrow that produce histamine and Th2 cytokines. This cell population increases in size during worm infections and may help resolve infection by promoting a protective Th2 response. The authors had noted that these cells could take up histamine from the external environment, but neither the mechanism nor the consequences of this uptake were understood. Schneider et al. now show that the uptake of histamine by these cells triggers a negative feedback loop that inhibits additional histamine synthesis and the production of allergy-promoting cytokines.

Histamine transport was dependent on a cation transporter protein (organic cation transporter 3, or OCT3), which was known to transport histamine in brain cells but had never been identified on basophils. The authors speculate the reverse histamine transport may help limit the severity of allergic responses. They are now testing this idea by assessing allergic responses in OCT3-deficient mice. JEM
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 337). 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.