NPY’s mixed messages

A stress hormone sends mixed signals to immune cells, according to a study on page 1527. Wheway and colleagues show that neuropeptide Y (NPY) activates antigen-presenting cells (APCs) but shuts off T cells. If correctly sequenced, these activities would both turn on and then limit certain immune responses.

NPY is an abundant neuropeptide that is released from sympathetic nerve endings. In the brain, NPY regulates physiological and emotional processes, including metabolism, heart rate, and depression. NPY is also produced by activated immune cells and has been shown to dampen cytokine production by macrophages and inhibit the killer activity of natural killer cells.

The effects of NPY on T cells, however, have been controversial. Treatment with NPY ameliorates autoimmune disease in a mouse model of multiple sclerosis, suggesting a suppressive effect on the disease-inducing T helper (Th)-1 cells. But mice lacking the major lymphoid receptor for NPY (Y1) were protected from colitis, another Th1-driven autoimmune disease, suggesting that NPY signaling normally activates Th1 cells.

The study by Wheway and colleagues helps clear up these conflicting reports. They show that NPY indeed inhibits Th1 responses, as T cells from Y1-deficient mice produced more interferon (IFN)-γ than wild-type cells when stimulated in vitro. When transferred, Y1-deficient T cells were hyperactive and triggered more severe colitis in recipient mice than did wild-type T cells.

However, the receptor-deficient mice themselves were resistant to T cell-mediated colitis when treated with an intestinal irritant. The defect was traced to APCs, which could not be activated in the absence of NPY signaling. APCs from the Y1-deficient mice failed to produce the Th1-promoting cytokines interleukin-12 and TNF and could not activate naive T cells. These mice were thus protected because the T cell response never got started.

How is a T cell response ever mounted if the same signal that turns on the APC turns off the T cell? The authors suspect that it comes down to timing. The expression of the Y1 receptor on T cells might be induced only after activation, thus providing a negative feedback loop that keeps activated T cells from running amok. The authors now plan to study NPY-induced signaling in different cell types to determine how the same molecule tells some cells to go and others to stop. JEM

Dangerous debris

According to a study on page 1575, cellular debris might help trigger the autoimmune disease systemic lupus erythematosus (SLE). Vollmer and colleagues show that endogenous complexes of RNA and protein, often released from dying cells, engage activating receptors in dendritic cells (DCs). The activated DCs then launch an inappropriate immune response against these self-complexes, thus triggering autoimmune disease.

In patients with SLE, the clearance of apoptotic cells is often delayed, in part because of unexplained defects in macrophage phagocytosis. As a result, cellular debris accumulates and is thought to be a source of autoantigens. But a simple piling up of undisposed waste does not explain the specificity of the autoantibody response in patients with SLE—a response selectively targeted against nucleic acid–containing molecules, including chromatin and small nuclear ribonucleoproteins (snRNPs).

Vollmer and colleagues now show that snRNPs, such as U1, can be taken up by human DCs when complexed with antibodies from SLE serum. Once inside, the RNA component of the snRNPs engages the intracellular receptors Toll-like receptor (TLR)-7 and TLR8—which are normally triggered by microbial RNAs—thus activating the immune response. The ability to engage TLR7 depended on uridine-rich sequences in the U1 RNA. These sequences were also found in other autoantigens targeted in SLE, suggesting that the ability to engage intracellular TLRs might be a key to autoantibody specificity in SLE.

How the process of autoantibody formation is initiated is still unclear. Recent studies have shown evidence for tolerance defects in patients with SLE that allow autoreactive antibody-producing B cells to escape deletion. Others have shown that RNA-associated autoantigens can trigger TLR7 signaling in B cells, suggesting the possibility that autoreactive B cell escapes and immune-stimulating DCs conspire to trigger an immune response against RNA-associated antigens. JEM