Why less is worse for lupus

Neutrophils need just enough copies of a gene for an antibody-binding receptor, say Willcocks et al. (page 1573). Whereas too few copies can contribute to lupus, too many can predispose to vasculitis.

Cells can have as many as four copies of this gene, \( \text{FCGR3B} \), which encodes the Fc\( \gamma \)RIIIb receptor, but some lupus patients have fewer than two. Willcocks et al. now find that this scarcity leads to fewer receptors on neutrophils, which thus fail to bind and destroy inflammation-causing antibody clusters. The paucity of receptors did not impair other neutrophil functions such as the production of oxygen radicals.

Some healthy individuals also had fewer copies of the gene and thus similarly defective neutrophils. But these individuals do not develop lupus, most likely because they lack other genetic defects required to cause disease. The compensatory influence of other genes might also explain why low copy number of \( \text{FCGR3B} \) is not a risk factor for lupus among all populations.

Having more Fc\( \gamma \)RIIIb receptors, however, doesn’t guarantee good health. The group found that a high copy number of \( \text{FCGR3B} \) was associated with vasculitis—a disease in which neutrophils release damaging oxygen radicals in response to cross-linking of Fc\( \gamma \)RIIIb receptors on blood vessel walls.

Tumor suppressor fends off lung fibrosis

On page 1659, Xia et al. find that a protein that counters cancer also stops wound-healing fibroblasts from overdoing it.

Fibroblasts help repair damaged tissue by proliferating and producing collagen. But too much collagen can create scars and impair tissue function, as seen in patients with a chronic lung disease called idiopathic pulmonary fibrosis (IPF). Collagen normally controls its own levels by binding to integrins on the fibroblast surface, which triggers a negative feedback loop that stops the cell from proliferating further. In patients with IPF, according to Xia et al., this feedback loop falls apart.

The defective cog in this inhibitory loop was a tumor suppressor phosphatase called PTEN, which normally halts the cell cycle by inactivating PI3K/Akt signaling. In fibroblasts from IPF patients, however, collagen-induced stop signals failed to activate PTEN and inhibit proliferation. In response to a chemical irritant, mice with reduced levels of PTEN developed unusually severe lung injury with excess collagen deposition.

Unlike certain tumors, which have low PTEN protein levels, fibroblasts had normal PTEN levels, but the protein failed to relocate to the cell membrane, where it gets activated. The defect that leads to this faulty localization is not yet known.

Other studies have suggested that collagen-producing cells in the lungs of patients with IPF are not good fibroblasts gone bad, but rather epithelial cells that differentiate into fibroblast-like cells in response to chronic exposure to TGF-\( \beta \)—an inflammatory cytokine that is prevalent in the lungs of IPF patients.

Two paths lead to MS

Two T helper (Th) cell subsets trigger the same multiple sclerosis (MS)-like symptoms but varying disease pathologies, say Kroenke et al. (page 1535).

Inflammatory Th1 cells and Th17 cells can both drive experimental autoimmune encephalitis (EAE)—the mouse equivalent of MS. The authors found that mice injected with either cell type developed paralysis with the same speed and severity, which might suggest that both cell types trigger the same pathology.

A closer look at the damage, however, told a different tale. Mice injected with Th1 cells developed macrophage-filled lesions in the central nervous system (CNS)—a sign of conventional MS. But mice injected with Th17 cells developed lesions filled with neutrophils, most likely in response to neutrophil-attracting chemokines that were produced in the CNS.

As neutrophils are highly adept at breaking down the blood–brain barrier, their presence might explain why Th17-induced lesions, unlike Th1-induced lesions, reached deep into CNS tissues. Th17 cells caused severe inflammation in the optic nerves and in sections of the spinal cord—typical of rare variants of MS, which do not respond to conventional treatment.

If similar differences are found in the pathology of MS, patients may benefit from therapies tailored to specifically inhibit the type of Th cell that is to blame.