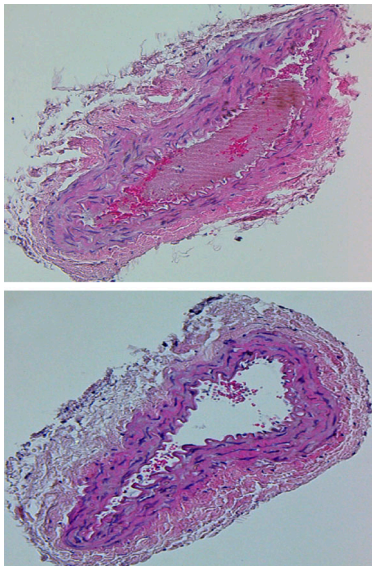


Vessel-blocking clots (top) are avoided when platelets lack STIM1 (bottom).

STIM1 strengthens clotting

On page 1583, Varga-Szabo et al. show that platelets missing a calcium channel opener build puny, feeble clots that may actually save lives.

Platelets require calcium to initiate clotting in response to extracellular cues. When calcium is needed, most cells first deplete their ER stores. This depletion is sensed by an ER protein called STIM1, which sits near enough to the plasma membrane to open up calcium channels on the cell surface. But since platelets have only stunted ER-like tubules, they were thought to rely instead on an activation-induced lipid, which opens surface calcium channels independently of internal stores.

Platelets also have plenty of STIM1, however, which Varga-Szabo et al. now show is needed for slow-but-steady clot formation. Activated STIM1-deficient platelets, the authors found, did not accumulate calcium from external sources.

Internal calcium stores in the mutant platelets were sufficient for rapid clot formation in response to short-lived ligands such as thrombin. But platelets needed STIM1-induced calcium influx to clot in response to collagen on injured vessels, which triggers a slower signaling pathway. In the absence of STIM1, clots were small and disintegrated easily, particularly under conditions that mimicked blood flow. The defective platelets continually broke away from the clots, suggesting that STIM1 helps make platelets stickier.

The results suggest that a quick calcium burst from ER-like tubules might be sufficient to build small clots to patch up a minor tear. The STIM1-driven calcium spike, on the other hand, might be necessary to form larger clots under high shear, as occurs in small or fat-clogged vessels.

Mice lacking STIM1 were protected from injury-induced vessel blockage and strokes, as their feeble clots allowed some blood to flow into injured brain tissues. As the clotting problem didn't prolong bleeding, a small, transient clot might be all that's needed to prevent hemorrhage, with the added bonus of avoiding a complete halt in blood flow. JEM

Timing tolerance to cancer

Cancer cells outwit the immune system long before they debut as visible tumors, say Willimsky et al. (page 1687).

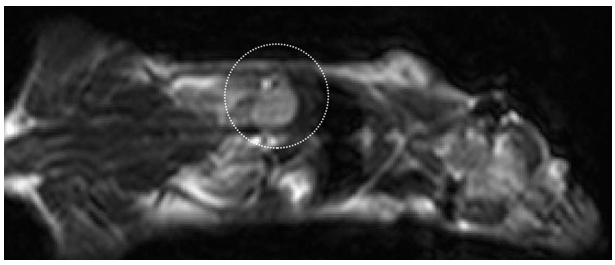
Despite a wealth of studies, researchers still don't know when the immune system is alerted to the presence of cancer cells or when its response is subverted. Part of the problem stems from the fact that T cell responses in most animal models are tracked only after tumors form.

To get an earlier start, Willimsky et al. designed a mouse model in which a gene silencer was inserted near an oncogene. When a random mutation disabled the silencer, the mice expressed the oncogene and eventually developed cancer. These mice could be identified by the presence of antioncogene antibodies, which appeared before tumors formed. The presence of antibodies indicated an activated immune system, allowing the authors to study T cell responses as the earliest possible time during cancer development.

The researchers now find that the T cells fail months before tumors appear. Antitumor antibodies often appeared by six months of age, at which point the T cells were already disabled. Tumors became visible about nine months later. As the T cells were unable to keep the cancer cells at bay, the lag until tumor formation might instead stem from the requisite time needed to accumulate additional, proliferation-inducing mutations. The growing tumors did not lose their ability to elicit a T cell response, as injecting them into precancerous mice provoked tumor rejection.

As tumors grew, the defect in cancer-specific T cells spread to all cytotoxic T cells. Proponents of past tumor models attributed this generalized apathy to a threshold level of tumor-derived, T cell-inhibiting molecules that increase as a function of tumor size. The authors ruled out this idea by engineering mice that expressed the oncogene during embryogenesis. T cells in these mice treated the oncogene as "self" and thus allowed tumors to grow unchecked. These tumors did not, however, hamper the ability of other T cells to recognize foreign antigens.

Others have blamed the generalized T cell defects on the suppressive cytokine TGF-β and/or a population of immature myeloid cells that inhibit T cells in vitro. Indeed, mice that turned on the cancer gene had high TGF-β levels and growing numbers of immature myeloid cells at the time they had developed antitumor antibodies. How oncogene-induced antibody responses might lead to TGF-β production and myeloid cell growth remains to be seen. JEM



Large tumors (circles) appear more than a year after mice turn on an oncogene, long after T cells are disabled.

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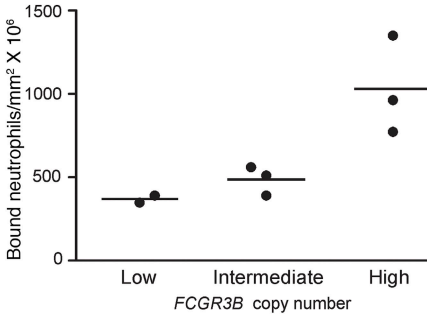
Why less is worse for lupus

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, *FCGR3B*, which encodes the FcγRIIIb 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 *FCGR3B* is not a risk factor for lupus among all populations.

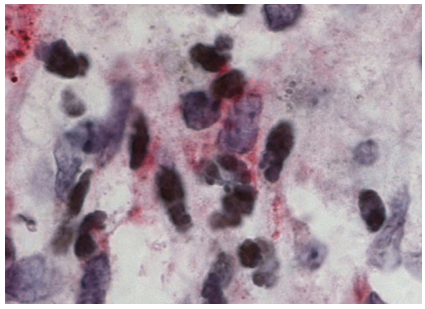
Having more FcγRIIIb receptors, however, doesn't guarantee good health. The group found that a high copy number of *FCGR3B* was associated with vasculitis—a disease in which neutrophils release damaging oxygen radicals in response to cross-linking of FcγRIIIb receptors on blood vessel walls. JEM



Neutrophils with fewer copies of *FCGR3B* bind poorly to IgG complexes.

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.



PTEN deficiency increases collagen deposition and scarring (brown) in injured lungs.

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-β—an inflammatory cytokine that is prevalent in the lungs of IPF patients. JEM

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. JEM