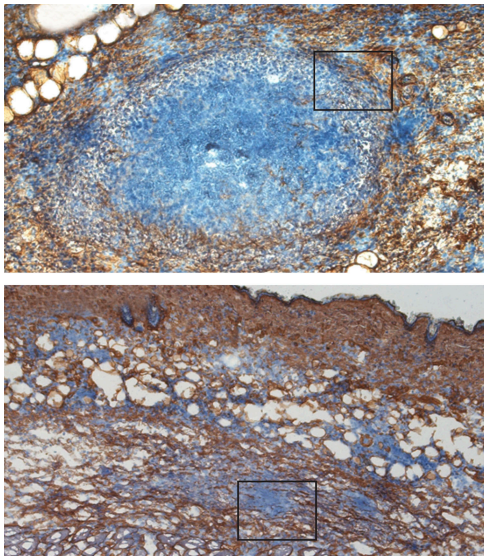


Granulomas (blue) do not form when mice lack the collagen-building protein SPARC (bottom).

Disadvantages of a SPARCling defense

Giving infecting bacteria a little freedom early on can be good for the host, according to a new study by Rotta et al. (page 657). Confining the bugs too quickly, they find, can tie up the immune cells that need to spread the word.

Certain bacteria, such as *Mycobacterium tuberculosis* and *Salmonella*, are quickly surrounded by macrophages, dendritic cells, and other immune cells that seal off the invaders from surrounding tissue. The convergence of these cells creates immune cages—or granulomas—that contain several extracellular matrix proteins, including SPARC, which enhances collagen assembly.

Rotta et al. now find that SPARC-induced collagen prevents *Salmonella*-laden dendritic cells from slipping out of granulomas to the nearest lymph node to alert T cells. In mice infected through the skin with an attenuated strain of *Salmonella*, bacteria were hemmed in by a SPARC-enhanced granuloma within a day. After 9 days, however, the bacteria breached the fortifications. In the resulting absence of bacterium-killing T cells, the bugs rapidly spread out into other organs, and the animals soon died.

SPARC-deficient mice, on the other hand, never formed granulomas when they were infected with this crippled strain of *Salmonella*. Immune cells found the infection site but failed to coalesce because SPARC-formed collagen was absent, thereby allowing dendritic cells to reach lymph nodes. The mice thus fought off this initial infection and survived a later challenge with a virulent strain of *Salmonella*.

The immune system's knee-jerk reaction in trapping bacteria right away might be initially protective for widely infecting bugs that invade via the airways or the blood rather than the skin. The current findings suggest that antibacterial vaccines injected through the skin might be more effective if they are coinjected with a SPARC-blocking molecule. JEM

Less naive with age

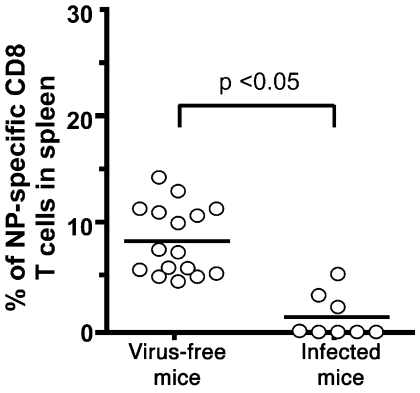
An aged immune system has experienced $CD8^+$ T cells to combat old enemies but is missing some of the fresh $CD8^+$ T cells that are also needed, according to Yager et al. (page 711).

The $CD8^+$ T cell pool is finite and in flux throughout an individual's lifetime. Each infection strengthens the numbers of T cells specific to that infecting microbe. In time, the T cell pool thus becomes skewed: the large number antigen-specific clones decreases the number and diversity of remaining naive T cells.

Yager et al. now show that this age-related shrinking of the naive T cell pool results in a loss of the ability to respond to epitopes for which there were a low number of precursors to start with. In young mice, $CD8^+$ T cells specific for a particular influenza nucleoprotein (NP) epitope were at least ten times less frequent than those specific for other flu epitopes. This NP-specific naive T cell population was greatly reduced in most old mice. Age-related decay of the thymus, which maintains the naive T cell repertoire, may be at least partly to blame: young mice with a surgically removed thymus experienced similar declines in their naive T cell pool.

The resulting inability of the old mice to mount a strong immune response against the NP epitope weakened their ability to protect themselves against different flu strains. Older flu-infected mice that had the fewest NP-specific T cells were least adept at fighting off a second infection with a different flu strain, even though these mice had plenty of T cells directed against other flu epitopes. Why non–NP-specific T cells fail to protect the mice is unclear.

The findings suggest that current efforts to boost flu-fighting power in the elderly with vaccines carrying multiple T cell epitopes might misfire, as the naive T cells that would respond to these vaccines are missing. As the preferential loss of low frequency naive T cells is probably not unique to the flu, prolonging thymic function and vaccinating against as many microbes as possible before the thymus deteriorates too far might be better strategies. JEM



Old mice that fight off a second strain of the flu (left column) have more NP epitope–specific T cells than do mice that stay infected (right column).

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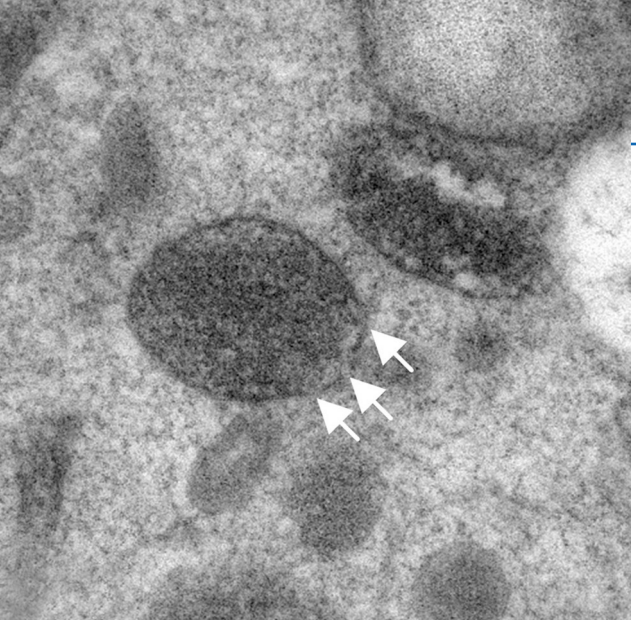


Cathepsin D leaks out of the punctured membranes (arrows) of a granule and triggers neutrophil apoptosis.

Granules live and let die

Healthy eating and sleeping habits prolong human life, but neutrophils leave their longevity in the hands of granules, say Conus et al. (page 685).

Neutrophils that ingest bacteria die after killing their prey, thereby reining in their inflammatory effects. The authors wondered whether neutrophil granules, which are loaded with enzymes and chemicals that kill the bacteria, also kill the neutrophils.

Conus et al. now find that granules release cathepsin D, a protease known to cause nonapoptotic death in other cell types. In neutrophils, however, cathepsin D activated an apoptotic cascade by cleaving caspase-8. Because cathepsin D is only active in acidic environments, how it snips caspase-8 in the neutral cytosolic pH is unclear. Perhaps the spilling of the acidic contents of the granules lowers the pH nearby.

The granules released cathepsin D when their membranes were punctured by reactive oxygen species (ROS)—inflammatory byproducts that gradually build up in cells. Neutrophils from humans who lack an ROS-generating enzyme therefore lived longer.

Neutrophils from patients suffering from sepsis—a prolonged system-wide inflammation—also lived longer than normal neutrophils. Their granules were kept intact by neutrophil survival cytokines, which are produced during inflammation, until ROS levels rose high enough to supersede the cytokine effects. What skews the balance between these cytokines and ROS in septic patients is not known, but the development of therapies that artificially rupture the granules might help speed their recovery. JEM

Regulatory T cell brakes

On page 565, Haxhinasto et al. pinpoint the signaling roadblock that stops $CD4^+$ T cells from turning into regulatory T (T reg) cells.

Some T reg cells develop directly from thymic progenitor cells, but others seem to be converts that were once $CD4^+$ T cells. These potentially inflammatory $CD4^+$ T cells turn into immune-suppressing T reg cells when they simultaneously bind antigen and the cytokine TGF-β. The mechanism that flips this switch was unknown.

T reg cells have less PI3K/Akt signaling, which promotes T cell proliferation and survival. The authors now find that the suppression of Akt allows $CD4^+$ T cells to convert. Activated $CD4^+$ T cells that were forced to express Akt were unable to turn on T reg cell–specific genes, including the transcription factor Foxp3. The expression of Akt did not, however, prevent the development of T reg cells from immature thymic T cells that had already turned on *Foxp3*. Foxp3 levels in these T reg cells were stable, perhaps because the gene becomes fixed in an active state by chromatin modifications.

The perpetual activation of Akt leads to overactive T cells that can trigger autoimmunity and the rejection of transplanted organs. Blockade of Akt signaling using the drug rapamycin can prevent organ rejection. The group found that activated, rapamycin-treated $CD4^+$ T cells expressed Foxp3 and other T reg cell–specific genes, suggesting that the drug helps replace offensive T cells with defensive T reg cells. JEM

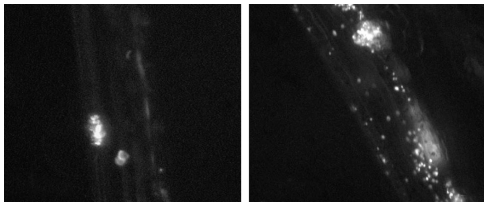
Clotting linked to a memory maker

A chemical that boosts our ability to learn and remember also boosts blood clotting, say Morrell et al. (page 575).

The learning chemical, glutamate, is released at neuronal synapses, where it activates neurons by binding to ion channel receptors. Glutamate is also abundant in the blood—particularly in clot-forming platelets—but its function outside the brain was unknown.

Morrell et al. now find that glutamate increases platelet activation and clumping. Glutamate treatment increased the expression of clot-inducing adhesion molecules on platelets that were activated with thrombin—a blood enzyme that becomes activated during infection or injury. The platelets carried glutamate receptors, which flood the cell with sodium ions when stimulated. Sodium triggers a structural change in thrombin receptors, which might enhance their affinity for thrombin. Mice lacking glutamate receptors and those treated with drugs that block them were slow to form clots.

The authors speculate that, like neurons, activated platelets form synapses with neighboring platelets into which they spew glutamate. The high glutamate concentration within these spaces might keep the cells stuck together and further enlarge the clot by snaring more platelets, which then add to the glutamate pool. Drugs that block glutamate receptors might be potentially useful in preventing stroke, heart attacks, and other diseases that can be triggered by clots. JEM



Mice injected with glutamate receptor–blocking drugs (left) form fewer clots (spots).