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 non-apoptotic 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](#)

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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).