For neurons, overexcitement is deadly. To avoid this, brain cells must sop up unneeded neurotransmitters from the synapse through membrane-bound transporters. If these transporters fail, neurons and other brain cells get excited to death—a phenomenon that may contribute to brain damage during stroke and Alzheimer’s disease.

Indeed, brain deterioration after stroke is associated with elevated levels of glutamate—the major excitatory neurotransmitter in the mammalian central nervous system (CNS)—in the plasma and cerebral spinal fluid. One possible explanation for this glutamate build-up, reported by Mallolas and colleagues on page 711, is a mutation in the gene encoding the glutamate transporter protein EAAT2.

This mutation—a single adenine (A) to cytosine (C) change in the EAAT2 promoter—was equally prevalent in healthy individuals and stroke patients. But among stroke patients, those with the mutated C allele had higher plasma levels of glutamate and were more likely to suffer from post-stroke neurological problems than those with the A allele.

The A-to-C mutation changed a binding site for the activating transcription factor AP-2 into a binding site for the repressor GCF2—a swap that inhibited promoter activity in transfected rat brain cells. Whether the mutant promoter decreases EAAT2 expression in the human brain, as would be predicted, remains to be tested.

Clot control

Blood clots are needed to patch vessel injuries. But clot size must be carefully controlled, as oversized clots (thrombi) can plug up blood vessels. The combined action of protease inhibitors, which inactivate clotting factors, and fibrin-cleaving enzymes, which dissolve the fibrin meshwork of the clot, keeps clot size in check. On page 767, Chauhan and colleagues find that another enzyme—the metalloprotease ADAMTS13—is also required to limit clot size.

ADAMTS13 chops up ultra-large multimers of von Willebrand factor (UL-VWF), the blood protein that tethers platelets to injured blood vessels. The importance of dicing up UL-VWF became clear when defects in ADAMTS13 were identified as the cause of the life-threatening disease thrombotic thrombocytopenic purpura (TTP). In patients with TTP, small clots—composed largely of platelets and VWF—form in vessels, eventually breaking free and clogging downstream vessels. What instigates clot formation in these patients is unknown, although infections are often associated with the onset of TTP symptoms.

A collaborating group recently created a mouse model of TTP by making mice that lack ADAMTS13. In these mice, newly released UL-VWF remained stuck to the vessel wall for longer than normal, snaring passing platelets and forming long strings that wave in the bloodstream. When injected with a vessel-damaging bacterial toxin, the ADAMTS13-deficient mice developed a TTP-like disease, with unstable VWF platelet–rich clots forming in their veins.

Now, Chauhan and colleagues show that ADAMTS13 not only inhibits the initial adhesion of platelets to the vessel wall, but also limits the growth of platelet-containing clots. In the deficient mice, spontaneous clots formed and injury-induced clots grew larger and faster than in normal mice. Treating the mice with recombinant ADAMTS13 dissolved injury-induced clots, suggesting that ADAMTS13’s clot-busting power could potentially be harnessed for the treatment of thrombotic conditions such as heart attacks and strokes.
Unhurried NK cells

Naive T cells race around lymph nodes in search of their specific antigens but, according to a study on page 619, natural killer (NK) cells are in less of a hurry. Bajénoff and colleagues provide the first glimpse of NK cells in live lymph nodes, revealing slow moving cells that form long-lasting contacts with dendritic cells (DCs).

In recent years, intravital imaging has shown that T cells dart rapidly around lymph nodes in search of their rare cognate antigens, making fleeting contacts with DCs as they go. An encounter with a cognate antigen delivers a stop signal that triggers stable T cell–DC interactions, during which the T cell presumably receives activating signals.

Bajénoff and colleagues used the same technology to show that NK cells move at a more leisurely pace than T cells—a pace that is unaltered by infection. The reason for this lethargy is a matter of speculation, but might reflect both the clonal nature of NK cells and the diversity of ligands that activate these cells. In other words, unlike T cells, NK cells needn’t look far for their activating signals.

Also unlike T cells, NK cells form long-lasting contacts with DCs in the absence of antigen. These prolonged interactions, the authors suggest, might provide the NK cells with survival signals. Indeed, recent studies showed that interleukin (IL)-15—an essential NK cell survival factor—must be presented in trans, with the cytokine binding to its receptor on one cell type (the DC) and acting on another (the NK cell).

Infection with *Leishmania major* caused lymph node NK cells to secrete the T helper type 1 (Th1)-promoting cytokine interferon-γ (IFN-γ) and congregate with CD4+ T cells—a positioning consistent with the requirement for NK cell–derived IFN-γ in the development of a protective Th1 response against *L. major.* JEM

Dividing with IL-7

The cytokine interleukin (IL)-7 is well known to promote T cell survival and homeostatic proliferation of T cells, with the signals required for the latter being less well understood. A study by Li et al. (page 573) now shows that IL-7 induces T cell proliferation by triggering the degradation of the cell cycle inhibitor p27kip1.

The surprising aspect of this study was not that a growth cytokine induces cell division by disposing of p27kip1—this occurs in many cell types—but that T cells have a unique way of getting rid of this protein. In most cell types, growth signals trigger the phosphorylation of p27kip1. Once phosphorylated, p27kip1 becomes bound by a Skp2 (S phase kinase-associated protein 2)-containing ubiquitin ligase complex that marks the inhibitor for proteasomal degradation.

Li and colleagues now show that p27kip1 levels were increased in T cells starved of IL-7, triggering cell cycle arrest. Although the level of Skp2 protein in these cells declined in the absence of IL-7, this decrease did not account for build-up p27kip1. Instead, the stabilization of p27kip1 required PKCθ (protein kinase C θ), a protein not previously implicated in cell cycle control. The PKCθ-dependent stabilization of p27kip1 probably requires an intermediate protein, as p27kip1 has no apparent phosphorylation site for PKCθ. The authors are now in search of that intermediate.

Why do T cells destroy p27kip1 in their own way? One hint may lie in the requirement of IL-7 for the recombination of the T cell receptor (TCR) locus during T cell development in the thymus. Developing T cells might have devised a way to avoid activating Skp2 in response to IL-7, as a recent study showed that Skp2 also induces the degradation of Rag2, the enzyme that catalyzes TCR recombination. JEM
Lulling septic shock to sleep

A sleep-inducing neuropeptide can also inhibit lethal septic shock, according to Gonzalez-Rey and colleagues on page 563. This natural neuropeptide—called cortistatin—curbed the production of cytokines and inflammatory mediators that trigger organ failure and vascular collapse in mice exposed to lethal doses of bacteria.

Many neuropeptides that regulate activity in the central nervous system (CNS) double as regulators of inflammation. The stress hormone neuropeptide Y, for example, controls both metabolism and heart rate via the CNS and cytokine production by macrophages in the periphery. Cortistatin is no exception—it was originally described as a sleep-promoting hormone produced in response to circadian rhythms, but was recently shown to be produced by activated immune cells.

But the consequences of cortistatin production by immune cells had not been investigated. Gonzalez-Rey and colleagues now show that cortistatin treatment shuts down the synthesis of cytokines and inflammatory mediators by macrophages and protects mice against septic shock. Immune cells produce cortistatin during infection—probably as a means of keeping inflammation in check—but levels of endogenous cortistatin may be too low to shut down cytokine production in the face of a massive bacterial infection.

Cortistatin’s close relative somatostatin (which is used to treat certain neuroendocrine cancers) also inhibits cytokine production by macrophages. But somatostatin is not produced by immune cells and, in this model, did not protect against sepsis. If cortistatin, like somatostatin, proves safe in humans, it may be an effective way to treat patients who have septic shock.

T reg cells get specific

Naturally occurring regulatory T (T reg) cells suppress T cell–driven autoimmunity and chronic inflammation. Although the origin and function of these cells has been widely studied, the specificity of their T cell receptors (TCRs)—whether for self or foreign antigens on target cells—remains a matter of debate. Prevailing opinion comes down on the side of self-antigen. But now Suffia and colleagues (page 777) show that a majority of these T reg cells, at least those that congregate at the site of chronic parasite infection in mice, recognize the bug, not the mouse.

In earlier work, the group showed that this kind of T reg cell accumulated in the skin of mice infected with the parasite *Leishmania major*, thus hampering the response of effector T cells and allowing the bug to settle in for the long haul. They now show that most of these T reg cells are parasite specific, as they divided extensively when exposed to *L. major*-infected dendritic cells.

Unlike self-reactive T reg cells, which are thought to circulate throughout the body, these parasite-specific T reg cells stayed put, inhabiting the infected skin and nearby draining lymph node, but not venturing to distant sites. This localization probably reflects a dependence on antigen for survival, as the T reg cells rapidly died off when the infection was eliminated. The strict corraling of the antigen-specific T reg cells makes sense, says senior author Yasmine Belkaid, as escape of these cells could cause systemic immunosuppression.

These data do not suggest that self-reactive T reg cells don’t exist, but rather prove that antigen-specific ones do. Belkaid suspects that localized bug-specific T reg cells are a common feature of chronic infections with pathogens that have coevolved with the host. These parasites might have become adept at activating T reg cells as a way to help ensure their survival.