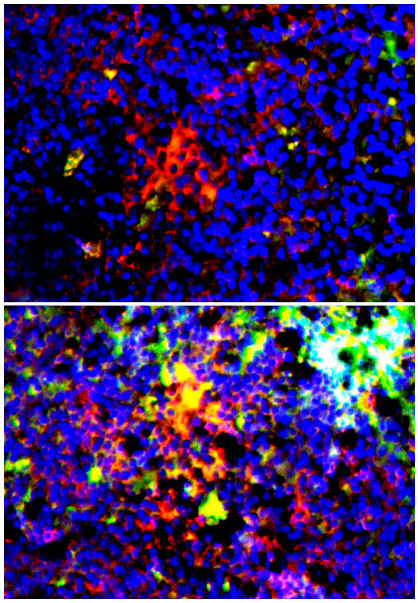


The destruction (top) of TRAF2 (green) via SOCS2 (red) is blocked in mice treated with proteasome inhibitors (bottom).

New targets for aspirin

On page 1077, Machado et al. reveal a new way in which aspirin reins in inflammation—it triggers the destruction of proinflammatory signaling proteins.

Aspirin's power was initially attributed to its inhibition of proinflammatory lipids called prostaglandins—a discovery that won the Nobel Prize in 1982. Later, aspirin was also shown to beef up levels of lipids called lipoxins, which help resolve inflammation by blocking NF-κB activation and the recruitment of inflammatory cells.

Lipoxins were recently found to activate SOCS2, a protein that blocks signals from growth hormone receptors by targeting downstream signaling proteins to the proteasome. To determine whether SOCS2 also blocks inflammatory signals, Machado et al. fished for its binding partners among molecules that transmit innate immune receptor signals.

They now find that SOCS2 binds TRAF2 and TRAF6—adaptor proteins that are required for cytokine production by activated dendritic cells (DCs)—and seems to target them to the proteasome. Treating mice with aspirin decreased DC levels of cytokines and TRAF2 and TRAF6—effects that were mitigated by proteasome inhibitors. The same effects were not found in DCs from SOCS2-deficient mice.

Mice treated with a proteasome inhibitor after parasitic infection beat the bug but died from inflammatory damage. The deadly inflammation probably resulted from prolonged signaling via TRAF2 and TRAF6, as inflammation in SOCS2-deficient mice was severe even without the inhibitor. Infected mice that were left untreated resolved the inflammation and survived the infection.

Because proteasome inhibitors also block the degradation of IκB—the molecule that holds NF-κB in check—they are being developed as alternatives to aspirin, which can cause stomach problems and other side effects. But the current findings suggest that this strategy might be counterproductive. JEM

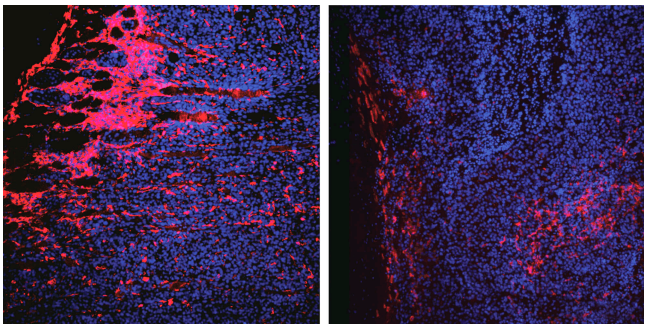
Spreading instead of growing

A protein previously hailed as a tumor suppressor has a sinister agenda, according to Rolny et al. (page 1155). Although this false savior, semaphorin 3B (SEMA3B), tells tumor cells to stop growing, it then sends them on their way to grow elsewhere.

Semaphorins were initially identified as extracellular navigation signals for growing axons. Some of them are now known to enhance tumor progression by increasing the growth of blood vessels that feed the tumor. SEMA3B, however, is thought to be a tumor suppressor because it also inhibits tumor cell proliferation.

Rolny et al. now find that this suppression comes at a potentially fatal price. Most tumor suppressors are either absent or expressed at low levels in cancerous tissues. But the group found high levels of SEMA3B in many cancer cell lines and in metastatic tumors from patients. Although SEMA3B inhibited the proliferation of these tumor cells in vitro, the poor prognosis of these patients suggested that SEMA3B signaling might have detrimental effects in vivo.

To test this hypothesis, the authors engineered human tumor cells in which SEMA3B expression was controlled by a drug-inducible promoter and injected these cells into the skin of immune cell-depleted mice. Drug-treated mice had smaller skin tumors but developed secondary lung tumors, suggesting that SEMA3B induced metastasis.



Infiltration of macrophages (red, left) into tumors is blocked when tumors are treated with anti–IL-8 antibody (right).

The authors found that SEMA3B inhibited growth and simultaneously triggered metastasis by activating the signaling kinase p38. p38 then activated a cell cycle inhibitor and induced tumor cells to secrete IL-8, a cytokine known to induce leukocyte chemotaxis. The IL-8–secreting tumors were full of infiltrating macrophages, which are thought to spur metastasis by producing soluble factors such as VEGF. Blocking the release of IL-8 in response to SEMA3B, the group found, blocked the metastasis of these tumors. JEM

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A trick presentation

On page 1201, Huang et al. find that an antigen-presenting protein suffers from an identity crisis: it looks like MHC class I but behaves like MHC class II.

This molecule, MR1, is recognized by a subset of gut-roving T cells. When MR1 carries the right antigen, these T cells suppress gut inflammation, but the identity of that antigen is a mystery. Because MR1 is structurally similar to MHC class I molecules, which usually pick up proteasome-processed peptides in the ER, MR1 was thought to do the same.

This notion is now disproved by Huang et al., who show that MR1-expressing cells treated with proteasome inhibitors or lacking ER peptide–loading chaperones can still activate these T cells. Instead, they found, MR1 picked up its antigens in endosomes, where MHC class II molecules get theirs.

MR1 bound to a chaperone called the invariant chain, which ferries MHC class II molecules from the ER into endosomes. There, it bound another chaperone, called DM, which loads them up with peptides. MR1-expressing cells that lacked the invariant chain were unable to activate gut T cells, whereas high levels of this protein increased their activation.

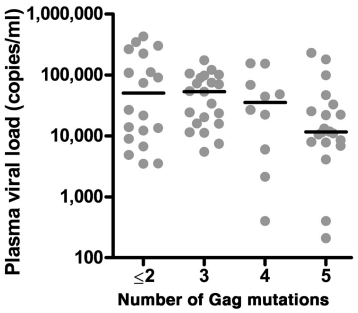
The immune-suppressing ability of MR1-activated T cells suggests that they might prevent the gut from attacking its helpful resident flora. The authors therefore speculate that the MR1 ligand might be derived from one or more of these residents. JEM

Weakening HIV

One person's fight against an HIV infection can decrease the virus's ability to threaten its next victim, say Goepfert et al. (page 1009). Mutations that help the virus survive in one host decrease its ability to replicate in the next.

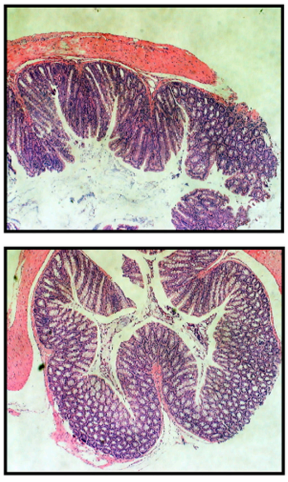
HIV mutations that help the virus bypass the host's immune system often fall within *gag*. This gene is a favorite target for mutations because, for some reason, Gag epitopes that are presented by HLA B alleles create the most productive immune response. But Gag is also critical for viral replication. The infected individual doesn't benefit from replication-dampening *gag* mutations, as the virus still escapes from cytotoxic T cells.

Goepfert and colleagues now find, however, that the resulting decreased replication may benefit the patient's sexual partner. Their study of 114 couples found that individuals who were infected by partners with certain HLA B alleles had much lower viral levels when more than five *gag* mutations were present. Viral levels were lowest in newly infected individuals who did not have the same type of HLA B alleles as their partners, perhaps because the recipients' T cells efficiently targeted non-Gag epitopes of the mutated virus.



HIV levels are lower in patients infected with viruses carrying 5 HLA B–associated Gag mutations.

At least five *gag* mutations were needed to reduce viral load significantly. This threshold might explain why a T cell vaccine that induces immune responses against two Gag epitopes failed in a recent trial. Better results might be gained by targeting more epitopes. JEM



Autoimmune colitis (top) caused by homeostatically proliferating CD8⁺ T cells is resolved in mice injected with anti–IL-6 antibody (bottom).

Dangers of restocking T cells

Refilling an empty niche with proliferating $CD8^+$ T cells can cause autoimmune disease, say Tajima et al. (page 1019).

Infusion of naive T cells into an environment where there are few native T cells—such as in patients undergoing cancer therapy—spurs two kinds of proliferation. T cells activated by non-self-peptide/MHC complexes proliferate rapidly, whereas those activated by self-peptide/MHC in the presence of cytokines such as IL-7 and IL-15 proliferate slowly. $CD4^+$ T cells that proliferate by these methods have previously been shown to drive the inflammation seen in several autoimmune diseases.

Tajima et al. now find a new variation in homeostatic proliferation of $CD8^+$ T cells that also induces autoimmunity. In gut lymph nodes of T cell–deficient mice, injected $CD8^+$ T cells proliferated rapidly in response to IL-6. This inflammatory cytokine was found at high levels in these lymph nodes, perhaps due to their proximity to the bacterium-laden gut.

The mice developed a thicker gut epithelium and lost weight—signs of an autoimmune disease called colitis. T cell–injected mice treated with an IL-6–blocking antibody or with bacterium-depleting drugs, however, remained healthy.

The proliferating T cells secreted several inflammatory cytokines, including IL-17. The IL-17 alone seemed to be responsible for the colitis, as mice injected with T cells that were unable to produce IL-17 remained healthy. If these IL-17–producing $CD8^+$ T cells are found in patients suffering from diseases such as colitis, the anti–IL-6 antibody might be a good therapeutic option. JEM