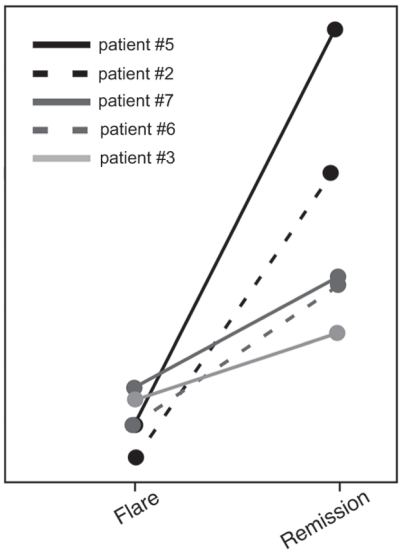


In lupus patients, the number of NKG2D$^+$CD4$^+$ T cells is low during disease flare-ups but surges during remissions.

Immune understudies combat lupus

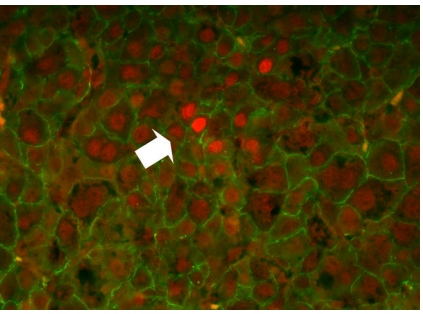
Regulatory T (T reg) cells calm the immune system and thwart attacks on the body's own tissues. On page 793 Dai et al. report that another T cell type performs a similar job and might serve as a backup to impaired T reg cells in autoimmune diseases. The cells could provide a new way to treat diseases such as lupus.

The researchers were investigating a puzzling variety of CD4$^+$ T cells that carries the NKG2D receptor. Previous studies on the cells' functions had given ambiguous results. They seem to protect tumors by quashing immune attacks. In rheumatoid arthritis and Crohn's disease, however, expansions of NKG2D$^+$CD4$^+$ T cells correlate with disease severity, hinting that the cells promote autoimmunity.

Dai et al. straightened out the confusion by showing that the NKG2D-carrying CD4$^+$ T cells normally serve as immune system regulators. These cells recognize self antigens but ignore antigens from pathogens, suggesting that they aren't taking part in antimicrobial defense. They also release an immune-soothing combination of cytokines, including interleukin-10 and TGF-β. This cytokine profile differentiates the cells from other CD4$^+$ T cells that switch on NKG2D only during inflammation and emit pro-inflammatory cytokines such as interferon-γ and TNF-α.

To determine whether these regulators affect autoimmune disease, the team tested blood samples from patients with the juvenile-onset form of lupus, which waxes and wanes in severity. During disease flare-ups, the team discovered, NKG2D$^+$CD4$^+$ T cell numbers plunge, and their abundance rises again during remissions.

Although the cells cannot prevent lupus flare-ups, they seem to alleviate the attacks. T reg cells often malfunction in the disease, but the NKG2D-carrying CD4 T$^+$ cells appear to remain healthy, suggesting that infusions of the cells might quell autoimmune symptoms.



STAT3 (red) levels surge in liver cells lacking both kinds of STAT5.

Flipping the cancer switch

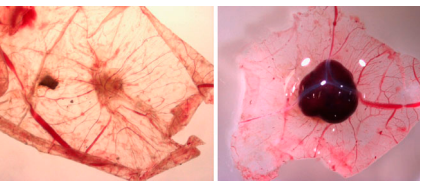
On page 819 Hosui et al. show how a cancer-fighting molecular pathway turns traitor and becomes a cancer promoter. The work clarifies how chronic liver damage can lead to tumors.

Alcoholism and infection by hepatitis viruses can spur liver fibrosis, which often progresses to cancer. In the liver, key functions that go awry in cancer—such as cell survival and proliferation—are under control of growth hormone. In turn, growth hormone acts through STAT5a and STAT5b. These transcription factors are two-faced, encouraging tumors in some tissues but blocking them in others. Whether the two varieties of STAT5 incite fibrosis and cancer in the liver was uncertain.

To find out, Hosui et al. deleted both STAT5 genes from hepatocytes in mice. The researchers discovered that exposure to carbon tetrachloride—which simulates long-term liver damage—triggered fibrosis and tumors in the STAT5-lacking mice but not in controls.

Loss of STAT5 also boosted levels of the fibrosis-stimulating cytokine TGF-β and hiked the amount of activated STAT3, a cousin of STAT5 that fosters an assortment of solid tumors. TGF-β and STAT5 are adversaries, the researchers found. STAT5 cut the amount of TGF-β by reducing its stability. And TGF-β stopped growth hormone from turning on STAT5. As a result, growth hormone is free to switch on STAT3.

The study shows that STAT5 is protective in the liver. The results also suggest an explanation for the link between fibrosis and liver cancer. As fibrosis worsens, the liver pumps out more and more TGF-β, which prevents growth hormone from activating STAT5. Instead, growth hormone flips on STAT3, and cancer results.



Blocking netrin-1 (left panel) reduced neuroblastoma growth in chicks.

Save yourself, cancer cell

Some neuroblastoma tumors are addicts, Delloye-Bourgeois et al. report on page 833. The tumor cells need a steady supply of a molecule called netrin-1, and they get their fix by making the compound themselves. Forcing the cells to go cold turkey could provide a new treatment for neuroblastoma, one of the most common childhood cancers.

Even healthy cells are often poised on the verge of death. Unless so-called dependence receptors receive continual stimulation, the cells kill themselves. One molecule that activates these receptors is netrin-1, a protein that is needed for normal neural development. Previous studies showed that certain breast and lung tumors pump out large amounts of netrin-1, suggesting that they rely on the molecule for survival.

Delloye-Bourgeois et al. now show that netrin-1 is also necessary for neuroblastoma. The most aggressive tumors manufactured extra netrin-1, the researchers found, and production of the molecule

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affected patients' prognosis. Ninety percent of infants with tumors that made little netrin-1 were alive after five years, but only 48% of infants with tumors that produced copious netrin-1 survived that long.

These findings suggest that blocking netrin-1 curbs tumor growth. Indeed, eliminating netrin-1 in tumor cell lines led to their demise. And when the team implanted neuroblastoma tumors into chicken embryos and then neutralized netrin-1, the tumors shrank and were less likely to metastasize.

Cancers sometimes break their dependence on receptor stimulation by jettisoning the receptors. But neuroblastoma tumors didn't do that. Instead, some neuroblastomas feed their own addiction by manufacturing more netrin-1, thus preventing apoptosis. The researchers have recently begun preclinical studies on two netrin-1–blocking compounds that might provide an alternative to chemotherapy and radiation.

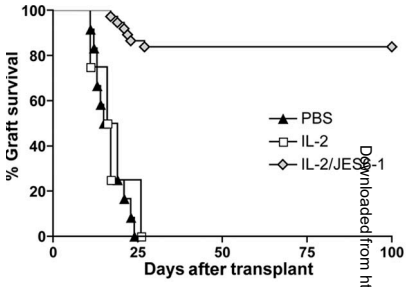
Lasting T reg cell–mediated protection

On page 751 Webster et al. show that an antibody-cytokine combination provides prolonged protection for transplanted foreign tissues without long-term immune suppression. The combination could be a step toward new drugs that deflect attacks on transplanted organs but don't increase vulnerability to infection.

Regulatory T (T reg) cells quell immune attacks, thereby helping to tame autoimmune diseases and prevent rejection of transplanted organs. Injections of T reg cells grown in tissue culture can pacify immune reactions in mice, and many researchers are now seeking ways to coax these cells into replicating in vivo. This group and others had previously shown that T reg cell numbers could be boosted by injecting mice with the T cell growth factor interleukin (IL)-2 and an antibody that reacts with it.

Webster et al. now show that a brief treatment with the cytokine-antibody mixture increases the abundance of T reg cells throughout the body. These fresh T reg cells protected mice from developing EAE, a rodent model of multiple sclerosis, by preventing disease-inducing effector T cells from invading the central nervous system.

When the team transplanted diabetic mice with foreign pancreatic β cells, IL-2/antibody treatment prolonged the survival and function of the transplanted cells, even after nearly all of the induced T reg cells had vanished. How the combo treatment prompts long-term tolerance without causing prolonged increases in T reg cell numbers remains a mystery. In the meantime, for the IL-2/antibody combo to eventually make it to the clinic, scientists need to determine whether the treatment has the same effect on human T reg cells.



IL-2/antibody treatment prolongs the survival and function of β cell transplants.

HIV's cost/benefit analysis

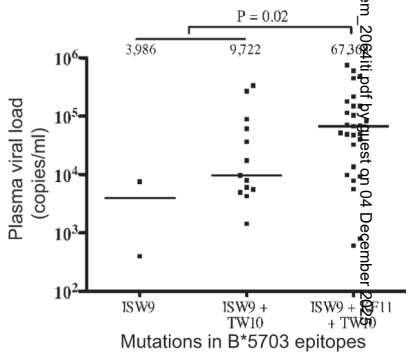
HIV is famous for dodging the immune system, but that elusiveness doesn't come cheap. As Crawford et al. reveal on page 909, mutations that help to conceal the virus from the immune system undermine its ability to replicate.

On the surface of an infected cell, HLA class I molecules show off fragments of viral proteins known as epitopes that alert cytotoxic T cells. Cytotoxic T cells then mobilize an attack on infected cells. How fast an HIV infection progresses depends in part on which versions of HLA class I a person harbors. People with the HLA-B*5703 variant hold virus replication in check longer than people with other HLA alleles. But HIV is slippery. To get around HLA-B*5703, HIV rapidly mutates three residues in its Gag p24 protein.

These mutations erase three of the major epitopes that alert cytotoxic T cells in people with HLA-B*5703, rendering the virus invisible to the immune system. But, as Crawford et al. now show, the virus pays for its invisibility. In culture, the triple mutant viruses replicated 20 times slower than normal.

Despite this handicap, the virus still came out ahead in people with HLA-B*5703. When a virus with only two mutations acquired the third, its abundance in the blood leapt by 10 times. Overall, however, patients with HLA-B*5703 were better off than most—with circulating viral titers about half the average for HIV-infected people.

The team also followed the mutations' impact after transmission by studying Zambian couples in which one person had infected the other. In recipients that lacked HLA-B*5703, the virus gradually lost the mutations, as the benefit of avoiding killer T cells no longer outweighed the cost of reduced replication. But patients unlucky enough to have the HLA type that the virus was already adapted to avoid, sickened rapidly. These data suggest that vaccines should be designed to produce a T cell response against many epitopes, something that experimental human vaccines so far haven't achieved.



The more immune-evading mutations HIV carries, the greater the patient's viral load.