

Patients with lupus and type I diabetes have fewer rearrangements in the RS region—a marker of receptor editing.

## Touching up antibodies prevents autoimmunity

Like the first draft of a term paper, the antibody genes of some B cells require revisions. On [page 2985](#), Panigrahi et al. show that this genetic editing is faulty in patients with two kinds of autoimmune disease. The results could lead to new tests and refined treatments for these diseases.

During development in the bone marrow, maturing B cells reshuffle their antibody genes to fashion defenses against a wide variety of pathogens. But these rearrangements can also yield antibodies that target self antigens and provoke autoimmune diseases. To forestall misdirected attacks, self-targeting B cells often undergo further recombination, known as receptor editing, which reshapes their antibody genes.

But receptor editing seems to falter in B cells from patients with autoimmune diseases, Panigrahi et al. report. The researchers gauged the amount of rearrangement in a DNA segment called RS. Although RS doesn't code for part of the antibody, rearrangements there reflect the cell's attempts to fix potentially dangerous antibody genes by reshuffling nearby coding segments. About 30% of patients with lupus or type I diabetes exhibited abnormally low amounts of RS rearrangement, the researchers found. This reduced level of editing might allow self-reactive B cells to escape correction and lead to autoimmune attacks.

Immune tolerance can break down at several points, and reduced receptor editing points to a flaw that develops before B cells exit the bone marrow. Current autoimmune treatments that temporarily deplete B cells are less likely to work in patients with such early-arising problems, the researchers suggest, because the number of self-attacking B cells might quickly rebound. Thus, measuring levels of RS rearrangement might help doctors tailor treatments for patients and allow earlier identification of people prone to autoimmunity.

## The benefits of inflamed arteries

Arterial inflammation can lead to hypertension and heart attacks. But it might also have a good side, according to Tang et al. ([page 3159](#)), permitting vessels to adjust their size to match changes in blood flow.

In response to changing demands for blood flow, arteries alter their size to maintain constant tension in their walls. They enlarge when more blood is needed, for example in response to organ growth; and they narrow when demand for blood flags, such as in the uterine arteries after birth. Previous studies had shown that inflammation spurs remodeling of the vessel wall in atherosclerosis and hypertension, but whether inflammation also triggered the responses of healthy arteries to changes in blood flow was not certain.

To test this idea, the team partially tied off one branch of the carotid artery in mice, cutting blood flow by roughly half. Downstream from this obstruction, the artery narrowed by about 10–15%, and smooth muscle cells disappeared to prevent the vessel wall from thickening. The revamping vessel also showed clear signs of inflammation. Cells of the arterial wall churned out inflammation-promoting cytokines and chemokines, drawing in macrophages and other leukocytes. Destroying the animals' macrophages thwarted the restructuring.

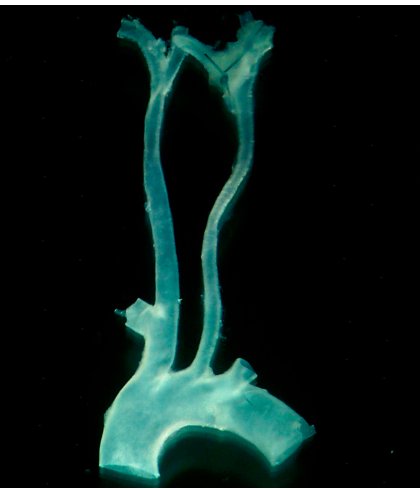
Neither inflammation nor remodeling could occur without MyD88, an adaptor protein necessary for cytokine production in response to IL-1 or Toll-like receptor signals. The researchers also discovered that this type of arterial inflammation clears up after about two weeks, which might explain why previous studies didn't detect it.

## How Notch heals a broken heart

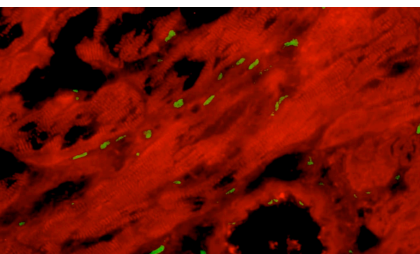
The Notch pathway helps a developing heart get into shape. Croquelois et al. reveal on [page 3173](#) that the pathway also helps a damaged heart reshape itself and keep pumping.

Weakened by a heart attack or the protracted stress of hypertension, the heart rebuilds itself as it struggles to maintain blood flow. To provide more pumping power, cardiomyocytes swell. Some studies suggest that heart stem cells begin proliferating to replace lost cardiomyocytes. Because the Notch pathway helps control self-renewal by other organs, Croquelois et al. thought it might also have a hand in heart remodeling.

When Notch1 was absent, they found, mice with stressed hearts showed signs of over-exuberant repair including thicker ventricular walls, increased fibrosis, and more of the telltale



Carotid arteries shrink in response to reduced blood flow (right artery).



Notch1's absence increases the number of suicidal cells (green) in the stressed heart.

JUN HE AND WANG MIN

proteins fashioned by swollen cardiomyocytes. The mice and their heart muscle cells also had a higher-than-normal death rate. Loss of Notch also spurred more heart stem cells to differentiate. Notch might allow the heart to conserve these cells.

The Notch pathway triggers stem cell proliferation in skeletal muscle, and the pathway short-circuits as we age. The researchers say that it's possible the same deterioration occurs in the older heart, explaining why elderly people are more vulnerable to heart failure.

## Tailoring T regs for self preservation

On [page 3105](#), Lathrop et al. show that different organs carry different combinations of the T cells that forestall autoimmune attacks. The study is the first to demonstrate that the immune system customizes its measures for preventing autoimmunity.

Regulatory T (T reg) cells curtail autoimmunity by stifling assaults from activated T cells. After maturing in the thymus, T reg cells disperse throughout the body. Indirect evidence hints that the immune system adjusts the T reg cell lineup in each organ to match that organ's unique antigen profile. So the liver would harbor more T reg cells that prevent attacks on liver antigens, whereas the stomach would preferentially house those that shelter distinctive stomach proteins. However, researchers hadn't yet shown this immune tuning.

Lathrop et al. gathered T reg cells from the spleen and lymph nodes of mice. The team then sequenced the genes encoding the T cell receptor (TCR), which determines what antigen the cell targets. As the researchers suspected, T reg cells from different locations tended to have different TCRs. The T reg cell population in the lymph nodes draining the intestines was distinct from that of the nodes in the neck and that of the spleen. By contrast, populations of naïve T cells didn't vary from place to place.

One possible explanation for the local differences is that exposure to a particular antigen causes naïve T cells to transform into T reg cells—what's called conversion. To gauge the importance of conversion, the researchers transferred labeled naïve and memory T cells into the mice and determined how many settled down in the spleen and lymph nodes and became T reg cells. The results indicated that conversion furnished only about 4–7% of the overall T reg cells. What might happen instead, the team suspects, is that an assortment of T reg cells arrives in an organ from the thymus, but only those that encounter an antigen they recognize multiply.

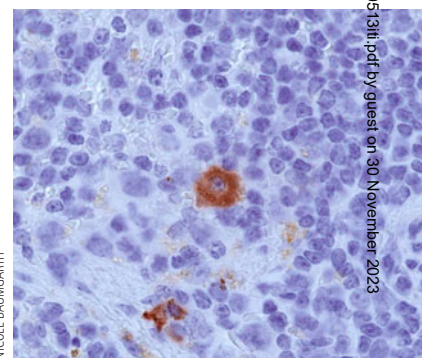
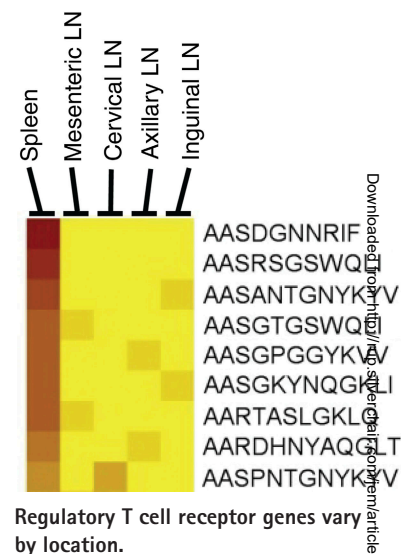
## B cells keep on editing

B cells are famous for rearranging their antibody genes. Contrary to conventional wisdom, this tinkering continues even after the cells leave their birthplace in the bone marrow, Wang et al. reveal on [page 3079](#).

Antibody genes typically undergo several rounds of revision. The gene segments first reshuffle to produce uniquely shaped antibodies. Some B cell genes undergo a further tweak, known as receptor editing, to revamp antibody genes that might lead to attacks on self antigens. The timing of receptor editing is controversial. Most researchers assume it occurs while B cells are maturing in the bone marrow. However, some findings suggest that B cells continue the process even after they relocate to the lymph nodes and spleen.

Wang et al. chanced across fresh evidence while studying the origin of a lymphatic cancer. Whenever it happens, receptor editing involves breaking the DNA and then healing it through a process called non-homologous end-joining (NHEJ). Failure of NHEJ in other situations can lead to cancer-causing chromosome instability, so the researchers wanted to test whether disrupting this type of repair promotes lymphatic tumors.

They created a mouse line in which a key NHEJ gene malfunctions in B cells that have exited the bone marrow. Sure enough, B cell-derived tumors sprouted in the mice. To the researchers' surprise, the cells that gave rise to the tumors had performed not only the initial reshuffling, but also receptor editing, thus supporting the hypothesis that at least some receptor editing occurs outside the bone marrow. The caveat, the scientists say, is that the tumor cells might not duplicate what happens in normal B cells. The benefits of late revisions aren't clear, but they might allow the immune system to further expand its repertoire of antibodies.



B cells (brown) undergo peripheral receptor editing.