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.