Gfi-1 also dampens the cells’ tendencies toward the Th17 and T reg cell lineages. Gfi-1 inhibited production of IL-17 and blocked the expression of CD103, which is found on certain T reg cells. In a model of autoimmunity, mice that lacked Gfi-1 developed a preponderance of CD103-expressing T reg cells, thus delaying the onset of disease.

The protein prevented gene expression by binding to loci in the genes encoding IL-17 and CD103. Gfi-1 binding triggered histone modifications—most likely via its known interaction with the LSD1 histone demethylase—thus turning off gene expression. Gfi-1 expression was repressed by the cytokine TGFβ, which drives Th17 and T reg cell differentiation, allowing induction of those cells when needed.

Examining expression of Gfi-1 in various human infections may help explain why the balance of cell types can sometimes be tipped in the wrong direction.

**Virus-friendly Th17s**

On page 313, Hou et al. expose a traitor. Cells producing the cytokine interleukin (IL)-17 protect a virus instead of their host. These results may help explain how chronic viruses, like HIV, establish a long-term foothold.

High levels of IL-17–secreting helper T (Th17) cells coincide with a number of chronic infections, but their role in disease pathogenesis is variable. Th17 cells help protect the body against certain bacterial infections, but they exacerbate tissue damage in autoimmune diseases. Hou et al. now catch IL-17 helping virus-infected cells survive.

Antigen-presenting cells infected with the CNS-invading virus Theiler’s murine encephalitis virus (TMEV) drove naive T cells toward a Th17 cell fate by secreting IL-6, show the authors. In turn, the IL-17 produced by those cells up-regulated anti-apoptosis genes, allowing infected cells to skirt suicide as well as assassination by killer T cells.

Other groups have shown that IL-6 promotes Th17 responses by triggering a positive feedback loop with IL-17. Here the authors show how TMEV manipulates that loop. Mice that produced higher levels of IL-6 and IL-17 after infection developed more severe disease than did resistant mice, in which protective Th1 responses predominated. Overproduction of IL-17 has been reported during early HIV infection in humans and herpes simplex virus in mice. Now that Hou et al. reveal that IL-17 promotes viral infection, chances are it’s playing a similarly insidious role in other chronic infections.

**Bound to arthritis**

Among the autoantibodies detected in patients with rheumatoid arthritis, none indicate the disease as reliably as those that bind to citrullinated proteins. On page 449, Uysal et al. now suggest that these popular biomarkers not only signal the presence of disease, but help to induce it.

The inflamed cartilage and soft tissue in arthritic patients’ joints consist mainly of type II collagen. Previous studies showed that those collagenous proteins are partially citrullinated—in other words, some of their arginine residues have been replaced by citrulline. The presence of antibodies targeting citrullinated proteins diagnoses arthritis with 99% accuracy. And because they are often detected before arthritic symptoms set in, Uysal et al. suspected that they might help generate joint destruction.

The authors now confirm the disease-inducing role of antibodies targeting citrullinated collagen epitopes. Injecting these antibodies into normal mice resulted in disease, and injecting them into arthritic mice worsened disease. According to Uysal et al., disease induction relates to how these antibodies bind their target.

By assessing the crystal structure of one antibody–citrullinated protein complex, the authors show that the antibody recognizes citrulline, rather than some other part of the modified protein. This direct binding suggests that the antibodies might cross-react with other proteins known to be citrullinated in arthritic joints, such as fibrinogen and fillagrin, thus exacerbating inflammation.

The numbers of citrulline-specific antibodies may soar soon after citrullinated proteins evoke an immune response. Mixed in with these antibodies are others that react to noncitrullinated collagen epitopes. The authors speculate that the latter antibodies might present collagen epitopes to T cells. And in turn, collagen-specific T cells could provide help for B cells that recognize either modified or unmodified collagen, creating a vicious cycle that culminates in collagen attack and cartilage destruction.

Why citrulline triggers an immune response in the first place and why that reaction is joint-specific in arthritis remain key questions. Because citrullinated proteins lurk behind several other human diseases, such as psoriasis and multiple sclerosis, understanding how these antibodies interact with their targets may help unravel the pathenogenicity of multiple maladies.