Targeting AID

A dangerously mutagenic protein is targeted to a single genomic site by ssDNA, report Ronai et al. (page 181).

High frequency mutation at the immunoglobulin V region improves antibody affinity and specificity as part of the adaptive immune response. AID (activation-induced cytidine deaminase), which converts deoxycytidines to deoxyuridines, initiates this mutation process. These conversions then induce various error-prone repair mechanisms, increasing the mutation rate further.

AID must be targeted carefully, however, as it is a potent mutagen. Indeed mistargeting of AID-induced mutations is thought to cause B cell lymphomas.

AID’s only in vitro substrate is ssDNA. The team isolated chromatin from B cells undergoing somatic hypermutation (SHM) and found that chromatin- and transcription-dependent ssDNA was present at V regions.

Many genes in B cells are highly transcribed, but the team found that such loci had much less ssDNA than those undergoing SHM. The ssDNA may be short lived during normal transcription but persist at V regions, perhaps due to RNA pol II pausing. Whatever the reason, it seems that the specific abundance of ssDNA at the V region might be one of the chromatin signals for targeting AID. JEM

Activating autoimmunity

Why the body is sometimes attacked by its own immune system is largely a mystery. Work by Hirota et al. (page 41) suggests how an underlying genetic predisposition might combine with an environmental factor—specifically, an unrelated infection—to give rise to rheumatoid arthritis (RA) and possibly other autoimmune disorders.

A mouse model for RA, called SKG, has a single mutation in the ZAP-70 gene that causes an abundance of highly self-reactive T cells to enter the circulation. In a pathogen-free environment these mice are healthy, but when exposed to pathogens the mice develop autoimmune arthritis.

When these mice start to mount an immune response, such as that induced by a pathogen, their antigen-presenting cells (APCs) increase production of the IL-6 cytokine, the team shows. This IL-6 triggers the T cells to proliferate rapidly and differentiate into Th17 cells, which produce vast amounts of the proinflammatory cytokine IL-17. SKG mice that lacked either IL-17 or IL-6 were protected from arthritis.

Some potentially arthritogenic Th17 cells already exist in the pathogen-free mice due to the constant interaction between APCs and T cells. Activation of the Th17 cells is minimal without pathogen, but an increase in IL-6 during an immune response to a microbe, coupled with the constant exposure to self antigens, is just enough to tip these precariously balanced T cells into overdrive.

IL-17 levels have been shown to be high in a number of autoimmune disorders, including RA. Furthermore, mutation of a protein in the same pathway as ZAP-70 is a common genetic risk factor for RA. It is possible, therefore, that similar genetic and environmental factors also come together to produce RA in humans. JEM

Memory maintenance

T cells that remember a previously encountered virus are essential in establishing protective immunity. But some T cells have a longer lifetime, and thus effectively a longer immunological memory, than others. Work by Riou et al. (page 79) might explain why effector memory T cells (TEM) are short lived, whereas central memory T cells (T CM) are maintained in the body long-term.

The longer-lived T CM mainly reside in secondary lymphoid organs such as the lymph nodes, whereas the TEM are found in the peripheral tissues and sites of infection. The exact ontogeny of the two cell types is unknown, but it’s thought that T CM might give rise to the more transient TEM fighters. Regardless of origin, the biological basis for their different life spans was unknown.

Dendritic cells (DCs) were a good starting point, as they are known to produce the T cell survival factor IL-7. The team added dendritic cells to the two memory cell populations and found that the TEM proliferation response was more vigorous, perhaps because IL-7 (and IL-2) more efficiently activated the pro-survival factor STAT5 in T CM.

Even without DCs, T CM were less susceptible to apoptosis. These cells had less active pro-apoptotic transcription factor FOXO3a and lower transcription of its targets. FOXO3a activity is inhibited by phosphorylation, and adding IL-7 or IL-2 to the T CM increased FOXO3a phosphorylation at a particular residue, suggesting these cytokines might promote the long-term survival of T CM by both increasing proliferation and decreasing death. JEM

Pathogens encourage the production of self-reactive T cells, which cause autoimmune arthritis (purple, infiltrating cells).