Weapons of self–destruction

Patients with systemic lupus erythematosus (SLE) do not get rid of self-attacking B cells even when in symptom-free remission, report Yurasov et al. (page 2255).

Patients with SLE suffer from chronic inflammation mainly of the connective tissues and organs. Treatment with immunosuppressants or cytotoxic drugs relieves the symptoms of SLE by depleting B cells, but these patients in remission are prone to frequent flare-ups.

During normal B cell development, checkpoints identify and destroy cells that make antibodies against the self. Previous studies revealed high levels of self-reactive antibodies in patients with SLE compared with healthy people, but whether these cells persist in symptom-free remission patients was unknown.

Yurasov et al. used ELISA to look at the reactivity of individual B cell antibodies. They compared individual B cells from patients in remission with those from symptomatic patients as well as healthy individuals. Although patients in remission had fewer self-reactive B cells than symptomatic patients (34.25% versus 44.4%), they still had considerably more than healthy individuals (19.7%). The B cells analyzed by the team were “naive” and thus immature, suggesting that checkpoint failures early in B cell development are the cause of self-reactive antibodies in SLE.

The persistence of self-reactive B cells in remission patients might explain the occasional flare-ups and also suggests that, although the symptoms of SLE might disappear in remission, the faulty checkpoints remain. JEM

Creating the right environment

Like baby chicks, stem cells need a nest—a niche within the body where they reside and self-renew. Oguro et al. (page 2247) find that, for blood stem cells, this nest is built by the same gene silencer that also helps them self-renew.

This silencer is Bmi1, which turns off two cell cycle inhibitor genes, Ink4a and Arf, to promote the self-renewal of hematopoietic stem cells (HSCs). Oguro et al. showed that defective HSC self-renewal in Bmi1-deficient mice can be restored by deletion of these cell cycle regulators, as previously observed in neural stem cells. But the new results show that HSC levels gradually decline as these mice age.

The authors wondered whether the progressive HSC problem might be due to defects in the HSC niche—the bone marrow microenvironment. Indeed, they found that development of the spongy meshwork structure of bone marrow in mice lacking Bmi1 was severely impaired and failed to support renewal of wild-type HSCs. The defects suggested that Bmi1 might be required for normal growth of the niche cells. The group showed that the proliferation of bone-forming osteoblasts was impaired in the absence of Bmi1. These findings fit well with previous reports that osteoblasts are important components of the HSC niche.

The defective niche was not rescued by deletion of Ink4a and Arf. Nest building in the bone marrow is therefore likely to require silencing of other Bmi1 targets. The team is currently searching for what those targets might be. JEM

Defective fat storage

Lysosomal storage disorders prevent the proper action of some natural killer T (NKT) cells, according to Gadola et al. (page 2293).

NKT cells recognize glycosphingolipid (GSL) antigens presented on the surface of various cell types. Recognition of endogenous GSL antigens leads to the positive selection of NKT cells in the thymus. Once in the periphery, NKT cells can induce an immune response if presented with GSLs of foreign origin. The overaccumulation of GSLs in lysosomes is a common feature of lysosomal storage disorders. Here, Gadola and colleagues show that this congestion impairs the intracellular processing and presentation of GSLs in the antigen-presenting cells of mouse models of lysosomal storage disorders.

The authors reasoned that, given their reliance on GSLs for selection, NKT cells might be impaired in the disease model mice. They found that, although the mice had normal NKT cells in terms of development and function, the numbers of these cells were dramatically reduced compared with wild-type mice. The simplest explanation for the low numbers, says coauthor Frances Platt, is that the impaired presentation of endogenous GSLs in the thymus leads to fewer NKT cells making it through the positive selection stage.

The mouse models differ in the particular lysosomal component affected, but they all accumulate GSL in their lysosomes. It will thus be interesting to determine whether the broad spectrum of human GSL storage disorders also lack NKT cells and whether this defect could help explain in part the clinical heterogeneity of these disorders. JEM