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.

Defective fat storage

Lyosomal 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.
ES cells mend broken hearts

Heart cells made from embryonic stem (ES) cells improve the function of injured mouse hearts, report Kolossov et al. (page 2315).

Cell replacement is an attractive therapy for heart failure, which is currently treatable only by organ transplant. But which source of cells makes the best starting material has been a matter of debate. Bone marrow cells were reported to provide some improvement in heart failure patients, but their benefit remains controversial. Kolossov et al. found no improvement of heart function when these cells were injected into mice with ischemic heart injury. Cardiomyocytes derived from ES cells, on the other hand, improved the contractility and blood pumping ability of the injured hearts.

The use of ES cells as starting material for this kind of therapy runs the risk of inducing tumors in the recipient due to small numbers of undifferentiated, pluripotent cells in the population. To limit this risk, Kolossov et al. used genetically engineered ES cells that allowed them to select for a virtually pure population of cardiomyocytes. This selection trick, however, would have to be modified to be used in humans, as it introduces foreign DNA into the cells. In the meantime, the team plans to see whether similar success is achievable with ES-derived heart cells in larger animals, in which the contractile forces of heart beats are considerably stronger. JEM

Beating Leishmania’s iron armor

Leishmania parasites that lack an essential iron transporter lose the ability to replicate within macrophages. These parasites persist but do not lead to host pathology, report Chau Huynh et al. (page 2363). Targeting the newly identified LIT1 pathway could be a potential route to leishmaniasis therapy.

Intracellular parasites need iron to grow and multiply, but within the phagolysosome compartment, such parasites inhabit, the supply of iron is limited. Specialized iron transporters had been identified in other intracellular pathogens, but none had been found in Leishmania, until now. Huynh and colleagues searched the Leishmania genome for sequences with similarity to known iron transporters and found a novel gene they call Leishmania iron transporter 1 (LIT1).

Having confirmed that LIT1 behaved as an iron transporter in yeast, the team deleted the gene from Leishmania to see how the bugs would fare in mouse macrophages. By 48 to 72 hours, the number of wild-type Leishmania per phagolysosome compartment had significantly increased. LIT1−/− Leishmania, on the other hand, failed to multiply. Their phagolysosome homes appeared smaller, and the bugs themselves showed signs of degeneration. Whether these bugs would be eventually cleared from the cells is unknown, as macrophages do not survive well in culture beyond 72 hours.

Mice infected with wild-type Leishmania developed skin lesions indicative of cutaneous leishmaniasis. However, when infected with LIT1−/− Leishmania, no lesions appeared. Interestingly, samples from the mice injected with LIT1−/− bugs still contained live Leishmania up to 6 months later, despite the pathology-free status of these mice. Removal of the iron transporter LIT1, thus, obliterates Leishmania’s virulence and renders the bug incapable of replication, yet does not kill it. The team is currently interested in determining the intracellular location of the surviving LIT1−/− bugs and in seeing whether this location allows them to acquire iron by an alternative route. This is an important question—if answered, it could lead to new treatments capable of completely eliminating the parasites from their infected hosts. JEM

ES-derived cardiomyocytes (green) fix a damaged mouse heart.

Replication of Leishmania inside phagolysosome (top) fails when LIT1 is deleted (bottom).