Re-redefining Foxp3 function

Liston et al. (page 475) report that a transcription factor that protects mice against autoimmunity is required for regulatory T cell (T reg) function only, and not for thymic epithelial cell function, as previously reported.

Mutations in the Foxp3 gene have been identified as the basis of autoimmune syndromes in both mice and men. This was thought to be due to a failure in the development of immune-suppressing T reg cells, which has been shown to require Foxp3.

However, a recent study indicated that Foxp3-lacking bone marrow cells do not cause autoimmunity when transferred into mice that lack T cells but express Foxp3 in their thymic stroma (JEM 202:1141). This suggested that Foxp3 also functioned in non–T cells, and that the autoimmunity suffered by Foxp3-deficient animals might be due not to defective T regs but to a defective thymic epithelium.

To Liston et al., a function for Foxp3 outside of T regs sounded suspicious, as Foxp3 had previously been extensively characterized as being specific to T regs. They have now specifically deleted Foxp3 in T cells. This targeted deletion caused the same full-blown autoimmunity as seen in Foxp3-negative mice. The deletion of Foxp3 in the non–T cell populations of the thymus, however, did not cause disease.

The authors also show that, in normal mice, Foxp3 is not expressed in thymic epithelia but is limited to T reg cells alone. Although these results redefine Foxp3 expression, the reason for the disparity between the two papers remains unclear. JEM

Heavy metal for a troubled heart

Including more copper in your everyday diet could be good for your heart, according to a study on page 657. Jiang et al. now find that dietary supplementation of copper offsets the effects of stress on an overworked heart by preventing its enlargement.

Copper-carrying proteins disarm oxygen radicals and power electron transport. Humans with copper deficiency have increased cholesterol levels, clot formation, oxidative tissue damage, and heart disease. Cardiac tissue biopsies of heart attack victims show a great reduction in copper levels.

In mice with stress-induced heart disease, the team now shows, increased heart size and decreased heart function can both be restored to normal levels by a small increase in the daily intake of copper, even when the stress stimulus is maintained. But without the copper supplement, stressed mice suffer heart failure after two months.

The authors show that mice receiving dietary copper supplements have increased activity of a transcription factor called HIF-1α, leading to increased production of the vascular endothelial growth factor (VEGF) protein, which promotes angiogenesis. Blocking VEGF activity inhibits the ability of copper to reverse heart enlargement and dysfunction. It is not clear, however, how angiogenesis helps decrease muscle mass or how copper gets pushed out of the heart during stress.

The human equivalent of the beneficial dose of copper used in this study is ~3.0 mg/day. The current recommended daily intake for humans, however, is only 0.9 mg/day. Increasing copper intake may be a cheap way to reduce mortality associated with heart disease. JEM

Translated to death

An effective alarm leads to an effective response. On page 525, Tellam et al. show that increased translation of a viral protein results in a more effective display of epitopes to T cells and thus a better immune response.

Most viral epitopes are derived not from long-lived stable proteins but from defectively translated and rapidly degraded intermediates. More translation should lead to more intermediates and thus more epitope presentation. However, this link has not been convincingly shown with identical proteins that have different translation efficiencies.

Tellam and colleagues compared cells translating either EBNA1 from Epstein–Barr virus (EBV), or a mutant version of EBNA1 that lacked EBNA1’s self-inhibiting sequence and was therefore translated more rapidly.

Cells expressing the normal EBNA1 generated very few epitopes and failed to activate T cells. In contrast, cells expressing the mutant EBNA1 produced a large number of epitopes, possibly due to the production of more defective products, and primed a strong T cell response.

EBV evades the immune response by minimizing EBNA1 translation and thus presentation; EBNA1 also inhibits its own degradation so that normal levels of protein are maintained. In EBV–associated cancers, increasing EBNA1 translation rates by targeting EBNA1’s self-inhibiting sequence may lead to increased epitope presentation and thus improve the efficacy of cancer therapies using anti-EBV T cells. JEM