Switching defects

Switching from one antibody isotype to another is a risky business that involves altering and cleaving DNA. B cell lymphomas that are stuck in the riskiest stage suffer repeated mutations and insertions that may further drive oncogenesis, according to Lenz et al. on page 633.

Mature B cells switch from producing IgM to other antibody isotypes during their response to antigen. This process, known as class switch recombination (CSR), is initiated by an enzyme called activation-induced cytidine deaminase (AID). Modification of DNA bases by AID within a so-called switch region leads to DNA cleavage. An intervening sequence is looped out, and two cleaved switch regions are ligated together to create a new gene encoding a new antibody isotype.

The group had previously found that the activated B cell–like (ABC) lymphomas had high expression of AID compared with certain other lymphoma subtypes. They now find that almost two-thirds of the ABC lymphoma cells tested have abnormal CSR events and almost half have internal deletions in a switch region. The switch regions contained as many as 19 independent deletions interspersed with mutations at AID hot spots. The changes could be organized into lineage models, suggesting an ongoing process of aberrant processing.

AID expression is normally a transient phenomenon that occurs as B cells mature. ABC lymphomas, however, are stuck at an intermediate phase of B cell maturation. One consequence is sustained high levels of AID expression. This by itself does not appear to be sufficient to explain the phenotype—another lymphoma subtype expresses almost as much AID but suffers fewer problems with CSR. The AID overexpression in ABC lymphomas may be combined with a defect (as yet hypothetical) in proteins that complete CSR. The frustrated machinery would turn on its own target sites, leading to deletions and mutations rather than a clean class switch.

In one lymphoma, DNA fragments from other chromosomes were inserted into the deletion sites, highlighting the danger inherent in aberrant class switch recombination. Translocations involving cancer-causing genes were also observed, suggesting that defective switching might sometimes further drive oncogenesis in these B cell lymphomas. JEM

Saving myelin from microglia

The blood clotting protein fibrinogen can inadvertently promote multiple sclerosis (MS) when it leaks from the blood into the brain. According to Adams et al. (page 571), it does so by activating microglia and sending these cells into phagocytic overdrive. Interrupting this interaction may yield a treatment for MS that doesn’t interfere with blood clotting.

The neurological dysfunction seen in MS is caused by the destruction of myelin sheaths around axons. This destruction is thought to be driven by T helper (Th)-1 cells, and most of the current treatment protocols are focused on inhibiting their activation and entry into the CNS. But responses to anti–T cell therapy are variable, and inflammatory demyelination can sometimes occur in the absence of T cells.

One feature that all MS lesions have in common is a disruption in the blood–brain barrier and the leakage of fibrinogen into the brain through the damaged endothelia. This results in the formation of fibrin deposits, which are detected even before demyelination. These deposits also overlap with regions where resting microglia have differentiated into phagocytic cells that damage myelin, raising the possibility that clotting proteins activate microglia.

Akassoglou and colleagues had previously shown that fibrinogen promotes disease in mouse models of MS. The team now shows that fibrinogen binds to a macrophage-activating receptor called Mac-1 that is expressed by local microglial cells.

Mice expressing a mutant form of fibrinogen that fails to bind Mac-1 had fewer inflammatory lesions and less severe disease. Blocking the fibrinogen–Mac-1 interaction with an antagonist peptide prevented relapses and further myelin damage in diseased mice and allowed these animals to survive with improved motor function.

Fibrinogen is an attractive target for MS therapy as its appearance in the brain is an early sign of neurodegeneration. Current methods to target fibrinogen involve the use of anticoagulants, but their long–term use increases the risk of hemorrhage. The region of fibrinogen that promotes clotting is, however, distinct from its Mac-1–activating site. Specifically targeting the latter interaction might therefore be a safer option in MS therapy, although it is not yet clear whether T cell–dependent pathways would also need to be blocked. 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 $\frac{0.116}{3.0}$ 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.

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**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 Tregs. 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

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**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

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**Foxy3 deletion in T cells (CD4-Cre) but not thymic epithelial cells (Foxn1-Cre) causes an autoimmune wasting disease.**

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