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

Switching defects

Switching from one antibody isotype to another is a risky business that involves altering and clearing 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

Activated B cell–like (ABC) lymphomas have a higher rate of intraswitch deletions compared with other lymphomas.