**XBP-1 image overhaul**

The development of antibody-secreting plasma cells is crippled in the absence of the transcription factor XBP-1 (X-box binding protein). Based on the role of XBP-1 in the endoplasmic reticulum (ER) unfolded protein response (UPR), it was speculated that the ER needs this protein to cope with the ramped-up protein production that accompanies plasma cell differentiation. On page 505, Tirosh and coworkers show instead that XBP-1 controls immunoglobulin synthesis posttranslationally, independently of its role in orchestrating the UPR.

The UPR is a signaling system that ensures proper folding, processing, and degradation of proteins in the ER. When protein production exceeds the ER’s quality control capacity, XBP-1 drives the expression of additional proteins, such as chaperones and degradative enzymes that help to absorb the extra workload.

The prevailing explanation for the XBP-1 requirement in plasma cell development—that the ER otherwise becomes lethally clogged with excess immunoglobulin protein—is called into question by the new data from Ploegh’s group. The study shows that protein degradation in the ER was intact in the absence of XBP-1, suggesting that the ER quality control pathway in B cells does not require XBP-1. Instead, XBP-1 was required for the sustained synthesis of IgM in primary B cells. This defect was specific for IgM heavy chain protein, as synthesis and trafficking of other proteins were unaffected.

**Water-clogging antibodies**

Autoantibodies produced during a severe variant of multiple sclerosis (MS) latch on to water channels in the brain, according to Lennon and colleagues on page 473.

Optic–spinal MS (or neuromyelitis optica, NMO) is a severe demyelinating disease that affects the spinal cord and optic nerves and is often misdiagnosed as classical MS, despite the absence of typical MS-like brain lesions. This group recently described an antibody that was present in the serum of up to 70% of patients with NMO, but was never found in patients with classical MS. The antibody bound to an unidentified antigen prominent at the blood–brain barrier.

Lennon and her colleagues now identify the target of the antibody as the water channel aquaporin-4 (AQP4). AQP4 is the most abundant water channel in the brain and is concentrated in the astrocyte membranes that border the blood–brain barrier. The expression of this protein is increased in patients with epilepsy and certain brain tumors, probably accounting for the associated brain edema that can limit blood flow and deprive the brain of oxygen.

Lennon suspects that the consequences of the antibody’s binding to AQP4 in the brain are twofold. The binding might directly alter the function of the water channel, triggering swelling. The antibodies might also trigger complement activation, which could then initiate the robust inflammatory reaction that is characteristic of early NMO.

Aquaporins are also abundant in the kidney, where they are required for normal water retention and urine concentration. Indeed, the anti-AQP4 antibodies from the NMO patients reacted with kidney tissue. It remains a mystery why these patients do not develop renal abnormalities.

The authors now plan to test whether AQP4-specific antibodies can trigger an NMO-like disease in mice. In the meantime, they have shown that these antibodies provide a useful diagnostic tool to distinguish NMO patients from those with conventional MS, as the diseases call for distinct treatment strategies. JEM