TCR chain gangs

T cell receptors (TCRs) band together to detect minute amounts of antigen, according to Schamel and colleagues on page 493. Their new work shows that TCRs are expressed on the surface of resting T cells either individually or in groups. The grouped TCRs, but not the solitary receptors, were triggered by low dose antigen, suggesting that these receptors must cooperate when antigen is scarce.

Whether TCRs exist as solitary entities or whether they group together is a long-standing matter of debate. Previous studies have failed to uncover evidence of grouped (multivalent) TCRs, but this may have resulted from dismantling of the groups as a result of overly harsh purification techniques.

In the new study, Schamel et al. gently coaxed the TCRs from the cell membrane using a mild detergent, allowing the receptors to retain both their native conformation and any associations with neighboring membrane proteins. They discovered that up to 50% of TCRs expressed by naive T cells associated with other TCRs and formed linear multivalent chains on the cell surface. Only the multivalent TCRs became phosphorylated in response to low doses of antigen, which might explain how T cells can detect and respond to rare antigenic peptide–MHC complexes amidst a sea of self peptide–MHC pairs. The authors suggest that preexisting clusters of TCRs may allow the responding TCR to facilitate phosphorylation of its neighbor, triggering a chain reaction and making the most of an otherwise weak signal. The research teams are now looking for multivalent TCRs on activated and memory T cells. They suspect that a higher proportion of multivalent TCRs on these cells might in part explain these cells’ increased responsiveness to antigen. JEM
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.

Electron micrograph of a mature plasma cell showing extensive endoplasmic reticulum. Reproduced from Bosman et al. (1969. J. Exp. Med. 129:1029–1044).

Despite the drop in IgM protein production, IgM heavy chain transcripts were not decreased in XBP-1–deficient cells, suggesting that XBP-1 affected translation. Although the mechanism is not yet clear, Ploegh suspects that XBP-1 might drive the expression of microRNAs that regulate translation, similar to those that control gene expression during neuronal development in worms and cell fate decisions in developing hematopoietic cells.

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.