A synaptic scaffold quiets T cells

A scaffolding protein at neuronal synapses has found its way to another kind of synapse—the immune synapse, which forms at the interface between antigen-presenting cells and T cells. As shown by Xavier et al. on page 173, this multidomain protein, called Dlg1, tempers the activity of both types of synapses.

On the T cell side of the immune synapse, activated T cell antigen receptors (TCRs) congregate with many cytoskeletal and signaling molecules that spread the word of antigen recognition to the rest of the cell. Recognition of TCR engagement must be transmitted somehow to these other proteins to coordinate their synaptic congregation.

Based on its multidomain structure and role as a scaffold in neuronal synapses and epithelial junctions, Dlg1 seemed a likely candidate for this coordination job in T cells. The authors' localization data support this idea—Dlg1 moves from the cytosol to cortical actin at the immune synapse within five minutes of antigen recognition. There, Dlg is complexed with proteins needed for T cell activation, including a Src kinase, a TCR subunit, and the Cbl ubiquitin ligase, suggesting that it might bring these and perhaps other signaling proteins to the synapse.

Once the complex has assembled, however, Dlg1’s job seems to be to prevent overactivity of T cells, which could potentially cause autoimmune problems. Dlg1 overexpression limited T cell activation, whereas loss of Dlg1 caused an overactive response to antigen.

In flies, Dlg1-like proteins both bring AMPA receptors to synapses and promote their degradation, which requires AMPA ubiquitination. Dlg1 might similarly cause immune receptor down-regulation, possibly via its interaction with Cbl. However, as Dlg1 left synapses within 15 min of TCR engagement, it might instead down-regulate T cell signaling by taking some other synaptic components with it.

Another passenger on chromosomes

Chromosomes are getting crowded. On page 179, Gassmann et al. present their identification of a fourth chromosomal passenger protein. As part of the Aurora B kinase complex, this new protein, Borealin, helps stabilize the mitotic spindle. In a paper soon to appear in Cell, Sampath et al. identify what seems to be the same protein.

Chromosomal passenger proteins, which until now included only Aurora B, INCENP, and Survivin, have several functions during mitosis. As mitosis begins, they are dispersed along chromosomes and phosphorylate histone H3. By metaphase, they gather at centromeres, where they are needed for kinetochore function and to correct spindle attachment errors. Later they move to the spindle midzone and the plasma membrane for cytokinesis.

Borealin (green) moves from metaphase chromosomes (left) to the spindle midzone at telophase (right).

The identification of Borealin in human cells reveals that not all these jobs are done by the same complex. Borealin was found in a complex containing all three other passengers. Some Aurora B, however, associated with INCENP but not Borealin or Survivin. The smaller complex probably phosphorylates histone H3, as loss of Borealin did not affect this Aurora B function.

As is common for passenger proteins, Borealin localization depended on its partners, INCENP and Survivin. Expression of Borealin fragments, in turn, perturbed the localization of other passengers to the centromeres, but did not affect spindle midzone targeting. Different subcomplexes with or without Borealin may thus bring Aurora B to the appropriate places for its various functions.

Cells that were depleted of Borealin, and that therefore mislocalized the other passengers, were delayed in prometaphase and unable to correct errors in spindle attachments to the kinetochore. Many of these cells nonetheless built normal-looking bipolar spindles but, once anaphase began, formed ectopic asters that caused the chromosomes to segregate in several directions. The extra asters seem to derive from the poles, but the reason for their generation remains unclear. This is the first hint that the chromosomal passengers are involved in spindle assembly and function.