Synapse too exclusive for CD148

A phosphatase gets squished out of the immunological synapse, thus preventing premature down-regulation of T cell immune responses, as demonstrated by Lin and Weiss on page 673.

The immune responses mounted when T cell receptors (TCRs) are engaged by antigens are initiated by tyrosine kinases and lead to cytokine production and T cell proliferation. One protein that is up-regulated in T cells during immune responses is CD148, a large transmembrane tyrosine phosphatase. CD148 has been shown to inhibit immune responses elicited when TCRs are stimulated with soluble anti-TCR antibodies. But Lin and Weiss now show that this down-regulation is normally delayed by the architecture of T cell contacts with antigen-presenting cells (APCs).

In the more biologically relevant context of B cells used as APCs, CD148 is still up-regulated after antigen presentation. But the authors find that it is excluded from the site of contact between the T cell and the APC (known as the immunological synapse), and thus fails to prevent the immune response.

The bulky glycosylated extracellular domain of CD148 prevents it from entering the synapse, as the distance between the membranes of the T cell and APC is so small that proteins larger than four immunoglobulin domains are probably too large to enter. So CD148 cannot reach its substrates until the two cells disengage. In the experimental system, immune responses were inhibited only after 8 h of TCR stimulation. This timing gives T cells enough time to produce cytokines and begin proliferation programs, while preventing autoimmunity that might result from inappropriately prolonged responses.

Excluding CD148 (red) from the synapse (green) keeps immune responses going.

G-proteins for spindle geometry

On page 623, Yu et al. demonstrate that unequal cell division in fly embryos results from two apical complexes that somehow affect microtubule dynamics.

Unequally sized daughter cells are created in fly neuroblasts by the formation of a longer half spindle in the apical side of the cell. Yu et al. demonstrate that the production of this asymmetric spindle is regulated through the distinct activities of two subunits of the heterotrimeric G-protein complex.

By isolating mutant embryos lacking the Goi subunit, they show that this subunit is part of one of two redundant apical protein complexes—one including Goi and Pins, and the other including Par6 and atypical protein kinase C. Loss of both apical pathways results in a symmetric spindle and thus equally sized daughter cells. In wild-type neuroblasts, astral microtubule formation seems to be asymmetrically associated with the apical but not basal centrosome. But if both apical pathways are abolished, astral microtubules form over both centrosomes, suggesting that some normally apically localized molecule can stabilize the association of astral microtubules with the cell cortex.

Loss of a different G-protein subunit, Gβ13F, disrupts the localization of components from both apical pathways. Thus, although Gβ13F is found both apically and basally, it seems to control the localization of the apical components.

BubR1 checks in with CENP-E

A kinetochore protein plays both sides of the checkpoint field, according to Weaver et al. on page 551. They show that CENP-E, a mitotic checkpoint-silencing protein, also stimulates the amount of checkpoint inhibitor released from an unattached kinetochore.

The mitotic checkpoint is the major mechanism preventing chromosomal loss during mammalian mitosis. Unattached kinetochores generate an inhibitor that blocks the destruction of proteins whose loss is required for initiating chromosome segregation. The chromosomal kinesin CENP-E helps to silence checkpoint signaling by promoting stable bipolar kinetochore attachments to spindle pole microtubules. The checkpoint can be activated in the absence of CENP-E when most of the chromosomes are misattached (as occurs when microtubules are destabilized). But Weaver et al. show that if only one or two chromosomes are not correctly attached (as probably occurs at least transiently in most normal cells preparing for mitosis), cells lacking CENP-E fail to mount a checkpoint and thus produce aneuploid daughter cells.

The checkpoint fails without CENP-E because the checkpoint-activating protein BubR1 is not recruited to kinetochores and because its kinase activity is not stimulated. The group shows that CENP-E binds to BubR1 and activates its autophosphorylation during mitosis. Thus, by activating its binding partner BubR1, CENP-E amplifies the basal checkpoint signal produced at individual kinetochores.