Splicing takes a NAP

Splicing factors, usually associated with RNA polymerase II transcripts, have a temporary home near sites of RNA polymerase I transcription, as shown on page 51 by Bubulya et al.

During interphase, premRNA splicing factors such as the serine arginine–rich (SR) proteins reside in nuclear speckles, along with other pre-mRNA processing proteins. The speckles disassemble during mitosis, and then reform in G1. By viewing speckle reformation, the group finds that SR proteins first make a side trip and gather in nucleolar organizing region–associated patches (NAPs), around areas where rDNA is transcribed.

Inhibiting mRNA transcription prolonged the life of NAPs and also caused SR proteins to accumulate near nucleoli in interphase cells. Without their pre-mRNA transcript targets available, SR protein traffic was backed up at a location it would otherwise move through rapidly.

NAPs contained hypophosphorylated SR proteins, which may self-associate and thus accumulate in patches. NAPs also contained an SR protein kinase, whose activity may release the splicing factors to transcription sites, although it is not clear how active RNA polymerase II might signal to effect such a change. At NAPs, the SR proteins are sequestered from other splicing factors. Their isolation during telophase may be needed for modification or SR complex assembly in reforming daughter nuclei. Why SR proteins choose NAPs for their meeting point remains to be determined.

Export in cystic fibrosis

Cystic fibrosis (CF) often results from the failure of the CFTR chloride channel to hook up with the COPII machinery, based on results from Wang et al. (page 65).

The most common form of CF occurs in response to loss of phenylalanine 508 (F508) in CFTR, resulting in a failure to be exported from the ER. F508 deletion leads to protein misfolding and ER-associated degradation (ERAD). Many groups thus hope to interfere with ERAD to treat CF. But Wang et al. find that the solution may lie elsewhere. “We don’t think less degradation,” says group leader William Balch. “We think more export.”

Export to the Golgi is required for CFTR to get to its functional location on the cell surface. The authors find that this export relies on a conserved di-acidic motif that must be properly presented to Sec24, a component of the COP II coat.

CFTR with mutations in the di-acidic motif were not exported and were less likely to associate with Sec24 in vivo. Recent crystal structures show that F508 lies in a domain adjacent to the di-acidic motif; the loss of F508 and the resulting misfolding may thus hide the sorting motif from Sec24.

Promising small molecule drug candidates for CF might be selected by their ability to improve interactions between Sec24 and the CFTR domain that contains the di-acidic motif. Blocking ERAD, in contrast, may only lead to ER-trapped CFTR, which could trigger ER stress responses.

Talin for presynaptic endocytosis

Talin links integrins to the actin cytoskeleton at focal adhesions. On page 43, Morgan et al. show that talin also links synaptic activity to actin rearrangements.

Synapses are specialized sites of cell adhesion that were recently shown to hold talin. Talin interacts with PIPK1γ, a P(4,5)P2-producing enzyme, which in turn regulates talin and other actin regulatory proteins. The importance of this interaction is now shown at synapses, where P(4,5)P2 also controls clathrin coat dynamics.

The authors interfered with talin–PIP K1γ interactions in the axons of giant lamprey neurons. The interference inhibited the recycling of synaptic vesicles on the presynaptic side. Clathrin-coated pits formed but did not bud off the plasma membrane. These changes were associated with reduced synaptic action networks. The defects are probably due to low levels of P(4,5)P2 resulting from a block in PIP K1γ recruitment to the membrane. The same lab has also recently shown genetically that P(4,5)P2 is necessary for synaptic vesicle trafficking (Di Paolo et al. Nature. 431:415–422).

As P(4,5)P2 production is up-regulated by neuronal depolarization, the authors are now studying how the talin-PIP K1γ interaction is affected by the firing of synapses.