The nesprin–IF connection

The nucleus is linked to the cytoplasmic intermediate filament (IF) network, say Wilhelmsen et al. (page 799), by a relative of the nesprin actin-binding proteins.

Nesprin-1 and -2 connect the outer nuclear membrane to the actin cytoskeleton. Now, a third nesprin is identified that lacks actin-binding abilities but instead links to IFs. This linkage requires plectin, a keratin-binding protein, as a go-between. The authors show that nesprin-3 recruits plectin to the nuclear perimeter, where both proteins are colocalized with keratins, a type of IF.

Plectin, in addition to its nuclear localization, has also been found at hemidesmosomes, where it links IFs to a matrix-bound integrin. The two linkages imply a continuous IF network from the matrix to the nucleus. Nesprins interact with inner nuclear membrane proteins that are associated with lamins, which in turn influence chromatin and transcription factors. So, tug on a cell, and it is even possible that this long linkage might bring about transcriptional changes with far more speed than could any signaling pathway.

Nuclear links to the cytoskeleton are more traditionally thought of as essential for nuclear positioning. Proper nuclear alignment might be especially important in multi-nucleated cells, such as skeletal muscle fibers. The authors are knocking down nesprin-3 levels in muscle satellite cells to test this possibility. JCB

Out with the active β-catenin

A highly active subset of β-catenin is specifically expelled from the nucleus by RanBP3, according to Hendriksen et al. on page 785. This active pool is just a tiny fraction of total β-catenin, but should be the focus of future studies on Wnt signaling.

Wnt signals are converted into changes in gene expression by β-catenin, which turns on the TCF/Lef transcription factors. In a search for nuclear β-catenin–interacting proteins, the authors picked up RanBP3 in a pull-down assay. As RanBP3 is a cofactor for CRM1-mediated nuclear export, the logical next step was to look at β-catenin export.

Nuclear levels of total β-catenin were not affected by RanBP3, but the authors found a more specific target. A very small, almost invisible, fraction of β-catenin—the active dephosphorylated form—was relocated from the nucleus to the cytoplasm upon RanBP3 overexpression. Only by using tumor cell lines with unusually high levels of active β-catenin were the authors even able to detect this pool in situ.

As a result of the export, Wnt signals were unable to activate their transcription programs. By contrast, fly embryos lacking active RanBP3 had developmental defects associated with too much Wnt (presumably from too much active nuclear β-catenin). RanBP3 overexpression in frog embryos had the reverse effect. The authors do not yet know whether endogenous RanBP3 levels increase to inhibit Wnt signaling, as required during differentiation, for example.

RanBP3 is a cofactor for the CRM1 exporter, but β-catenin export was independent of CRM1. Perhaps RanBP3 accompanies β-catenin through a different export pathway. Alternatively, RanBP3 might compete for DNA binding sites that retain active β-catenin in the nucleus. JCB

Localized oxidation

Despite their bad reputation, free radicals are also beneficial—they are used as second messengers in proliferation, apoptosis, and migration. Oxidants are promiscuous, however, and must be harnessed to modify only specific proteins. One way specificity is achieved in migration, based on findings from Wu et al. (page 893), is by localizing the oxidase with other motility proteins at the leading edge.

Wu and colleagues found that the NADPH oxidase is localized to focal complexes—transient integrin clusters at the front of migrating cells. The oxidase is brought to these sites by the TRAF4 adaptor and Hic5, a paxillin relative. Disruption of TRAF4–Hic5 interactions that are expected to delocalize the oxidase reduced cell migration, suggesting that the oxidation of a focal complex protein is necessary for motility. This target turns out to be PTP-PEST, a focal complex phosphatase that blocks migration by inactivating the Rac1 GTPase. Phosphatases, including PTP-PEST, are easily inhibited by oxidants, as their catalytic cysteine residues need to be in a reduced state to transfer phosphates.

As oxidation of PTP-PEST activates Rac1, and Rac1 is known to activate the oxidase, the authors have identified a new positive feedback loop that might help amplify shallow gradients of chemoattractants.

This function of TRAF4 in localizing the oxidase might explain why flies and mice mutant in TRAF4 have defects in dorsal and neural tube closure, respectively, as both phenotypes are caused by cell migration failures. JCB