In This Issue

Build actin at the right place, right time

Cells explore their environment by sending out filopodia and lamellipodia. These protrusions encounter extracellular matrix components that encourage adhesion and cell spreading through actin polymerization. On page 881, DeMali et al. show how sites of cell adhesion specifically attract actin-polymerizing proteins, thus linking adhesion to protrusion.

Adhesion and actin polymerization are coordinated by an interaction between proteins essential for both. DeMali et al. identified an association between vinculin, a protein found in focal complexes, and the Arp2/3 actin nucleation and remodeling complex. Induction of lamellipodial formation (e.g., by EGF) or integrin clustering (e.g., by fibronectin) stimulated the binding of vinculin to Arp2/3. The strongest association required signaling effects downstream of PI3K, including Rac1-induced activation of Arp2/3 and a PIP2-induced conformational change in vinculin.

Binding recruited Arp2/3 to focal complexes at the leading edge of migrating cells. This recruitment might ensure that components of the focal complex are hooked to the cytoskeleton, which should help in the maturation of focal complexes into focal adhesions. Cell spreading and lamellipodial formation were diminished in cells that expressed a mutant version of vinculin that does not bind to Arp2/3.

The Arp2/3 complex was not found in mature adhesions, where the actin linkages were fully formed. The Arp2/3 complex binding site on vinculin is in a region used by several other proteins, including VASP, that might displace Arp2/3 in mature adhesions. The transient nature of the Arp2/3 association with vinculin should help concentrate new actin polymerization only at the newest adhesions, and might explain why the interaction had not been detected previously.

Mads at the nuclear pore

Two recent studies in mammalian cells have shown that spindle checkpoint proteins can be found at the nuclear pore during interphase and that nucleoporins localize to kinetochores during mitosis. A new study on page 807 by Iouk et al. provides the first functional connection between kinetochores and nuclear pores through spindle checkpoint proteins and suggests that the two structures were linked long before vertebrates evolved.

Iouk et al. found budding yeast checkpoint proteins Mad1p and Mad2p at the nuclear pore complex (NPC). The Mad proteins interacted with a subcomplex of the NPC that contained, among other nucleoporins, Nup53p. The use of deletion strains indicated that Mad2p is linked to the NPC by its association with Mad1p, which in turn is bound to the Nup53p-containing complex. Unlike in vertebrates, which break down the nuclear envelope during mitosis, Mad1p remained at the NPC. The rearrangements were unexpected, considering that the NPC remains intact during mitosis in yeast, and may be indicative of other events, including regulation of nuclear transport. Checkpoint activation also resulted in the phosphorylation of Mad1p and the release of Mad2p, which, unlike Mad1p, moved to kinetochores.

The authors speculate that the NPC may serve as a scaffold for the formation of certain checkpoint protein complexes. This function may be mediated by Mad1p, which is essential for checkpoint function, although it did not appear to leave the NPCs. Cells lacking Nup53p had reduced levels of Mad1p and Mad2p at the NPC, and very little Mad2p made its way to kinetochores. This did not prevent checkpoint activation, however, which is reminiscent of the recent demonstration in mammalian cells that the checkpoint can be activated with few or no Mad proteins at the kinetochore.