Battle of the actin junctions

Thomas Stossel is a fervent promoter of his favorite molecule, filamin. "For 25 years I've been saying that this protein is important for making orthogonal actin networks at the leading edge of the cell," he says. "However, recent work has focused attention on a similar structural role for the Arp2/3 complex, which can nucleate actin filaments to form branched structures."

Stossel claims that branching is not sufficient for the formation of a strong actin network capable of pushing out the front of a migrating cell. A highly branched structure can still give way, like a bush that cannot support any significant weight. The cell needs to cross-link the branches together so that they no longer bend under pressure. This, says Stossel, is where filamin comes into the picture.

On page 511, Stossel and colleagues take a closer look at actin filament structure in cells lacking filamin. These cells cannot migrate, and the authors find that they have a dense mat of actin filaments that are almost parallel to each other. The addition of filamin to these cells results in a more open, delicate, and three-dimensional actin network. By immunogold microscopy, many junctions between actin filaments contain filamin, some have both filamin and Arp2/3, and a few have only Arp2/3. With filamin back in the spotlight, Stossel is hoping that he can determine how filamin cross-linking and Arp2/3 nucleation might be coordinated.

Cleaving and migrating

A glycoprotein, more often thought of as an immobilized substrate for crawling over, can also be cleaved to form a soluble signal that promotes cell migration, according to Mechtersheimer et al. (page 661).

The glycoprotein L1 mediates axon guidance and cell migration in the nervous system. Mechtersheimer et al. find that L1 in newborn mouse brain and in certain tumor cells is cleaved. The soluble fragment promotes migration over several substrates, and transfection of CHO cells with an L1 construct enhances migration.

Based on inhibition studies and experiments with mutants, the authors suggest that the metalloproteinase ADAM10 cleaves L1, and the L1 fragment then binds integrins on the same or a nearby cell. Signaling downstream of the integrin probably acts as a general stimulus for migration. ADAM10 can also cleave certain growth factors, thus activating their signaling pathways, which may converge with the L1/integrin pathway. As L1 and ADAM10 are widely expressed, the temporal and spatial regulation of L1 cleavage may involve as yet uncharacterized molecules.

Toxic apoptosis

Bantel et al. report that α-toxin from Staphylococcus aureus can induce apoptosis in immune cells (page 637). This may help the bacterium to immunosuppress the victim and continue proliferating. S. aureus was known to induce apoptosis, but the underlying mechanism was unknown. Bantel et al. find that the inducer is soluble.

Experiments with antibodies and purified proteins indicate that the relevant soluble factor is α-toxin, which forms pores in the target cell membrane.

The α-toxin activates intracellular caspases independently of transmembrane death receptor proteins, and can induce release of cytochrome c from isolated mitochondria. In both cases, however, the mechanism is likely to be indirect. Pores formed by α-toxin are unlikely to be big enough to allow either entry of α-toxin into the cell or exit of cytochrome c from mitochondria. Thus, apoptosis may be triggered by loss of monovalent ions through the plasma membrane pores. In addition, if the bacterium gains access to the inside of the cell, the intracellular α-toxin may form pores in mitochondria that activate a process leading to cytochrome c release.