Fusion at the front

Neurite extension is dependent on the growing neurite’s ability to get longer rather than fatter. Sakisaka et al. (page 17) now show that a protein called tomosyn works in a complex to help focus membrane growth to the tip of growing neurites.

As neurites grow, traveling vesicles are prevented from fusing willy-nilly to the plasma membrane first by their attachment to microtubule highways. Where those highways terminate—at the back of the growth cone—is where tomosyn takes over as a fusion inhibitor. With fusion prevented, the vesicles find their way to the actin cytoskeleton, which distributes them to the leading edge of the growth cone.

Sakisaka et al. found that, in growing neurites, tomosyn localizes at the rear of the growth cone. This area appears to be analogous to the rear of a locomoting cell. In both situations, Rho activates ROCK. The authors found that activated ROCK can, at least in vitro, phosphorylate syntaxin-1, making it a much better binding partner for tomosyn. The SNARE protein SNAP-25 also joins the complex, leading to inhibition of membrane fusion.

Consistent with this suggested function in inhibiting membrane fusion, overexpressing tomosyn in neurons resulted in stunted neurites and prevented proper transport of proteins to the cell surface. Killing tomosyn expression via RNAi caused neurites to branch out excessively.

Signals that induce neurite retraction, such as LPA, activate ROCK throughout the growth cone. This resulted in distribution of tomosyn—and presumably inhibition of fusion—throughout the growth cone. Actin contractility should then be free to reel in the existing plasma membrane as the neurite retracts.

Anti-angiogenesis is anti-actin

Blood vessel growth is suppressed by several proteins—such as endorepellin—that are anti-angiogenic only after they are generated as fragments of larger proteins. Now, Bix et al. (page 97) report two surprises of endorepellin action: it exerts its effects via an integrin that collagen I uses to promote angiogenesis; and it may operate via a heat shock protein to disassemble actin structures needed for motility.

Endorepellin is a COOH-terminal fragment of perlecan, a heparan sulfate proteoglycan that acts as a cofactor for proangiogenic factors such as FGF. The authors found that a segment of endorepellin was enough to prevent endothelial cell migration and formation of capillaries, and that it acted by disrupting the actin cytoskeleton and attachment sites. They found that the major functional receptor for endorepellin was α2β1 integrin, one of the collagen receptors. Treating cells with endorepellin resulted in clustering of α2β1 integrin, and these integrin clusters colocalized with collapsed actin bundles. As reorganization of actin filaments is crucial to cell migration and capillary morphogenesis, the authors reason that endorepellin halts these processes by taking apart actin filaments and focal adhesions.

Collagen I binding to integrin α2β1 decreases cAMP levels and the activity of protein kinase A, but endorepellin binding to the same integrin triggers the opposite results. Endorepellin binding also activates FAK, p38MAPK, and phosphorylation of Hsp27. FAK activation has been associated with disassembly of focal adhesions, and results with inhibitors suggest that the transient phosphorylation (or subsequent destruction) of Hsp27 may somehow prompt the disintegration of actin filaments.

Early steps in angiogenesis include proteolysis of matrix to make room for growing vessels. This proteolysis probably liberates protein fragments such as endorepellin, which damp down angiogenesis so that it does not become overactive.