In This Issue

**cGMP steers axons home**

On page 489, Schmidt et al. identify a second messenger that helps to steer growth cones. Without this cGMP-directed guidance system, sensory axons lose their way during development.

Axonal pathfinding and cyclic nucleotide second messengers have been linked by recent in vitro studies showing that cGMP protects growth cones from collapse induced by repulsive cues. Now, Schmidt et al. show that cGMP is required for axon guidance in vivo, at least in sensory neurons.

To decipher cGMP function during axon growth in vivo, the group deleted the effector kinase cGKI. This effector kinase was expressed in embryonic sensory axons in wild-type mice, suggesting that sensory neurons might be affected in the deletion mice. Wild-type sensory axons traveled to the spinal cord, where they formed T-like branches and extended in both directions. Axons lacking cGKIA had difficulties performing this task.

Rather than splitting evenly at the branch point, axons in the mutant mice preferred to extend in one direction. They continued to grow toward the center of the spinal cord, but the branching defects resulted in fewer sensory axons there. The errors had significant physiological effects, including dampened pain reflexes, as measured by electrical stimulation of in vitro spinal cord preparations.

How cGMP signaling is transduced, both upstream and downstream of cGKIA, remains unknown. The kinase sits in lamellipodia and filopodia of the growth cone, well-placed to shift the trajectory of the growing axon when it encounters the appropriate guidance factors. The group is now looking for guidance factor receptors that activate adenylate cyclases (and thus increase cGMP levels). cGMP activation of cGKIA might change the growth cone direction by triggering remodeling of the actin cytoskeleton, by phosphorylating the actin-organizing protein VASP, for example.

---

**ECM communicates with MMP**

The extracellular matrix (ECM) orchestrates its own destruction, according to results by Gálvez et al. (page 509).

Many different proteins, such as collagen (COL), fibronectin (FN), and gelatin (GEL), make up the basement membranes and connective tissues of ECM-rich tissues. Their degradation by membrane-type matrix metalloprotease 1 (MT1-MMP) is required for cell migration. But it now appears that ECM proteins are not passive victims in this process—they influence the location and activity of the protease by recruiting the help of cell adhesion receptors.

Using MT1-MMP fused to GFP in endothelial cells, Gálvez et al. noted that the protease had an unusual association with β1 integrin at cell–cell contact sites on β1 integrin–dependent substrates (e.g., FN and COL). This association induced by ECM-mediated integrin clustering somehow blocked internalization of MT1-MMP, possibly through integrin signaling. Endocytosis of MT1-MMP was recently shown to be necessary for its substrate (as on GEL) or wound-induced migration. In migrating cells, MT1-MMP relocalized to motility-associated (such as filopodia), where it associated with α,β3 integrin. MT1-MMP internalization proceeded, thus allowing MMP activation. MT1-MMP activity and its association with integrins were both necessary for maximum cell migration.

The localization of MT1-MMP at cell contact sites indicates that it may have functions not previously considered. Although it is inactive at this site, the authors speculate that MMPs could be activated at the onset of cell migration and cleave adhesion receptors to ease the separation of the close-knit endothelial cells. Transmigrating leukocytes might also stimulate MMP activity at cell contacts to allow cell passage through the endothelium.