Axons miss turning signals if they do not have the Arp2/3 complex to slow them down, according to Geraldine Strasser, Lorene Lanier (University of Minnesota, Minneapolis, MN), and colleagues.

Arp2/3 forms short, branched actin filaments in lamellipodia to drive movement in fibroblasts. Axons, however, do not need Arp2/3 activity for forward momentum, as the authors show that axons are longer if Arp2/3 is inhibited. But these axons did not change direction in response to guidance cues. They passed straight over inhibitory signals rather than turning away.

Longer axons usually have very stable microtubules, but the long Arp2/3-less axons had overly dynamic microtubules.

Their instability may impair the coordination of actin and microtubule networks that is needed for growth cone turning. “The microtubules are out of control,” says Lanier. “Like on a highway, if you go too fast, you might see the exit, which is the turning cue, but you might not respond in time.”

Arp2/3 was found at the center of growth cones rather than the periphery, where it lies in fibroblasts. A highly branched central actin network might be a physical barrier to microtubules, thus slowing their growth just enough for a timely response to actin changes.

Reference: Strasser, G., et al. 2004. Neuron. 43:81–94.

Death takes a holiday

At times, the DIAP-1 anti-apoptotic protein is not what it seems. Erika Geisbrecht and Denise Montell (Johns Hopkins School of Medicine, Baltimore, MD) show that, in the fly ovary, this caspase inhibitor is needed for cell migration but not survival.

Montell’s group studies border cells in the fly egg chamber, which migrate to help establish the sperm entry site. Rac activity is needed for this; so to identify more players, the group screened for proteins that restore migration when Rac activity is reduced. They found DIAP-1. Although DIAP-1 is essential for cell survival in the embryo, its loss in the ovary caused migration defects but not cell death.

Extra actin or profilin, presumably leading to increased actin polymerization, also compensated for the loss of Rac. DIAP-1 may also promote actin polymerization. To block apoptosis, DIAP-1 inhibits the fly caspase-9 homologue, called Dronc. Dronc is probably the DIAP-1 target in border cell migration as well, as reducing its activity suppressed the loss of Rac. Possible Dronc substrates include Rac and actin, which are cleaved by caspases during apoptosis, or profilin.

The unexpected identification of DIAP-1 as a suppressor emphasizes the importance of random screens. “The whole point is to find something that you can’t even imagine would be involved,” says Montell. Tumor cells that manage to increase their levels of DIAP-1-like proteins could gain both a survival advantage and the ability to migrate.

Reference: Geisbrecht, E., and D. Montell. 2004. Cell. 118:111–125.

Running Mad-ly into mitosis

Two spindle checkpoint proteins work away from the kinetochore to regulate mitotic timing, based on work from Patrick Meraldi, Viji Draviam, and Peter Sorger (MIT, Cambridge, MA). This control may kick in even before a kinetochore is assembled.

The mitotic checkpoint—controlled by Mad1, Mad2, Bub1, BubR1, and Bub3—delays anaphase by inhibiting APC until all kinetochores are properly attached to the spindle. Because inhibition of Mad2 leads to an accelerated mitosis and a precocious anaphase, it has been assumed that the checkpoint itself also regulates mitotic timing.

But Mad2 does not represent all of its kinetochore partners. “The assumption was that all were required for the checkpoint, so all would be needed here too,” says Meraldi. But the authors found that only Mad2 and BubR1 delay anaphase even in cells with properly aligned chromosomes. The others monitor only gross problems with kinetochore attachments.

Mad2 and BubR1 could be prevented from binding to kinetochores and yet still regulate mitotic timing. In cells where mitosis requires nuclear breakdown, checkpoint proteins need to find their way to kinetochores after breakdown, leaving a window of time when the spindle checkpoint is not active. “APC could be held in check with this cytoplasmic function of Mad2/BubR1,” says Meraldi. Now, the group needs to determine how this function is inactivated.

Reference: Meraldi, P., et al. 2004. Dev. Cell. 7:45–60.