In This Issue

Starving tumors eat metabolic enzyme

Xia et al. describe a way to force cancer cells to destroy a key metabolic enzyme they need to survive.

Autophagy helps cancer cells survive the stressful environment inside a tumor. However, blocking the process doesn’t kill cancer cells, so researchers have been looking for a way to make cells vulnerable to autophagy shutdown.

Xia et al. used an ovarian cancer cell line that is resistant to the autophagy inhibitor spautin-1 or an upgraded version of this molecule. After screening more than 8,200 compounds, they found that quizartinib was the most effective at restoring the cells’ vulnerability to either of the autophagy blockers. Quizartinib inhibits FLT3, a receptor tyrosine kinase that spurs growth and differentiation of hematopoietic precursor cells.

The team found that quizartinib and the improved version of spautin-1 killed tumor cells from a variety of cell lines while leaving noncancerous kidney cells unscathed.

Phospholipid prunes actin branches

A rare membrane phospholipid helps control actin branching on endosomes, Hong et al. show.

Branched actin filaments promote several steps in the endocytic pathway, such as vesicle formation and the formation of endosomal tubules. This type of actin is very dynamic, a property that’s important for its function. However, researchers are still working out how cells fine-tune its stability. The protein cortactin gathers on branched actin networks, enhancing formation of new branches and stabilizing nascent ones.

Hsc70’s trip to the tip

The chaperone Hsc70 shepherds a key guanine exchange factor to the tips of growing axons, DeGeer et al. show.

As the nervous system takes shape during development, netrin-1 helps steer elongating axons in the right direction. After netrin-1 stimulates the receptor DCC on the axon tip, the Rho GTPase Rac1 causes the axon to extend. The guanine exchange factor Trio switches on Rac1, but researchers haven’t figured out what transports Trio within the growth cone so that it can activate Rac1 in the right location.

DeGeer et al. found that Trio pairs up with Hsc70, a member of the heat shock protein family. Depleting Hsc70 reduced the amount of Trio that reached its proper position at the edge of the growth cone, and the axons of Hsc70-deficient cells didn’t extend in response to netrin-1. The team also discovered that Hsc70 must be able to function as a chaperone for Trio to switch on Rac1, the first time this dependence has been demonstrated for a GTPase regulator.

To test Hsc70’s function in vivo, the researchers expressed a defective form of the protein in the brains of 14-day-old embryonic mice. Three days later, cortical neurons showed growth abnormalities in the animals. For instance, certain axons that normally extend to the corpus callosum, the bridge between the brain’s hemispheres, didn’t reach the structure.

Hsc70 is abundant in neurons during development, and the findings suggest that the protein hooks onto Trio and delivers it to the tips of axons. Once there, Trio can activate Rac1 and promote axon growth. The study raises the possibility that Hsc70 also offers rides to other Rho family exchange factors.