

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.

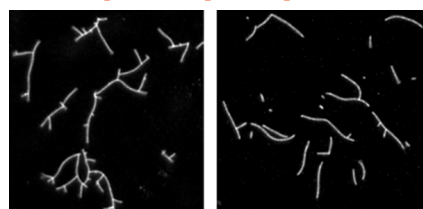
Xia et al. used an ovarian cancer cell line that is resistant to the autophagy inhibitor spautin-1 or an upgraded version of this molecule. After screening more than 8,200 compounds, they found that quizartinib was the most effective at restoring the cells' vulnerability to either of the autophagy blockers. 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.

Treating cancer cells with quizartinib alone inhibited glycolysis and activated macroautophagy, the best known type of autophagy in which the cell digests a large portion of its contents. In contrast, cells that received both compounds couldn't initiate macroautophagy, but they switched on chaperone-mediated autophagy, a selective form of the process that eliminates individual molecules.

Xia et al. noticed that cells that had activated chaperone-mediated autophagy were low on ATP, so they determined which proteins the process was destroying. One of its targets was the enzyme hexokinase II, which is crucial for glucose metabolism and is often overexpressed in cancer cells. By eliminating hexokinase II, quizartinib and the autophagy inhibitor may prevent cancer cells from metabolizing absorbed glucose and mobilizing stored nutrients. The study provides evidence that combining an FLT3 inhibitor with an autophagy blocker could be a new way to treat cancer. Xia, H.-g., et al. 2015. *J. Cell Biol.* <http://dx.doi.org/10.1083/jcb.201503044>

Phospholipid prunes actin branches



This time-lapse series shows that actin filaments "de-branch" in the presence of cortactin and PI(3,5)P₂.

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 fusion

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.

What controls cortactin's activity isn't clear. Hong et al. investigated the role of the phospholipid PI(3,5)P₂, which is present on late endosomes and lysosomes and helps manage vesicle trafficking.

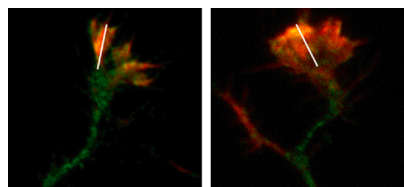
The researchers found that cortactin uses its N-terminal actin-binding region to latch onto PI(3,5)P₂ and that this interaction led to the release of cortactin from actin filaments. When the researchers curbed PI(3,5)P₂ synthesis, cortactin accumulated on late endosomes and actin turnover slowed.

In vitro, cortactin promoted the formation and stabilization of actin branches. However, the addition of PI(3,5)P₂ reduced cortactin's effects. In cells, live imaging showed that PI(3,5)P₂ promoted turnover of endosomal actin if cortactin was present.

The results suggest that PI(3,5)P₂ reduces the stability of branched actin by bumping cortactin from endosomes.

Hong, N.H., et al. 2015. *J. Cell Biol.* <http://dx.doi.org/10.1083/jcb.201412127>

Hsc70's trip to the tip



Trio (green) and F-actin (red) in an unstimulated axon growth cone (left) and one stimulated by netrin-1 (right).

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.

DeGeer, J., et al. 2015. *J. Cell Biol.* <http://dx.doi.org/10.1083/jcb.201505084>