In This Issue

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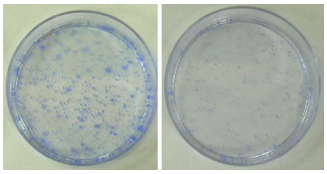
SIRT1 takes down tumors



Cells that make c-Myc proliferate in culture (left), but not when SIRT1 is present (right).

Yuan et al. have identified another anti-cancer effect of the "longevity" protein SIRT1. By speeding the destruction of the tumor promoter c-Myc, SIRT1 curbs cell division.

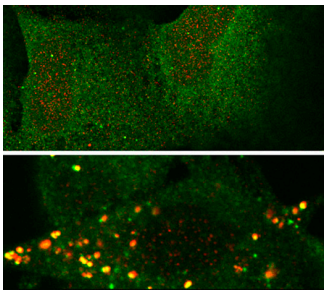
The yeast and nematode equivalents of SIRT1 are fountains of youth that stretch lifespan. Whether SIRT1 slows aging in mammals isn't certain, but it's beneficial in other ways. The protein tunes up metabolism, reducing blood levels of glucose and insulin, and might forestall neurodegenerative illnesses such as Alzheimer's disease and ALS. Given its pro-life credentials, you might expect SIRT1 to inhibit cancer. And several studies suggest that it does. But other work indicates that the protein aids tumors. For example, SIRT1 chops off acetyl groups, which can inactivate the tumor suppressor p53.

Yuan et al. determined SIRT1's effect on the transcription factor c-Myc, whose expression surges in many breast, colon, and liver cancers. The two proteins are tangled in a regulatory loop, the team found. c-Myc latched onto SIRT1's promoter, spurring cells to manufacture more SIRT1. In turn, SIRT1 detached acetyl groups from c-Myc, hastening its breakdown. To test SIRT1's effects on tumor growth, the researchers implanted cancerous cells expressing c-Myc into nude mice that lack immune defenses. Boosting production of SIRT1 blocked tumor formation.

How deacetylation of c-Myc sparks its destruction is still a mystery. The researchers say that the results don't necessarily conflict with studies suggesting that SIRT1 is pro-tumor. Whether SIRT1 promotes or prevents cancer probably depends on the situation.

Yuan, J., et al. 2009. *J. Cell Biol.* doi:10.1083/jcb.200809167.

Autophagosomes meet before they eat



A control cell (top) contrasts with a cell without COPI (bottom), where immature autophagosomes have accumulated.

Hungry cells sometimes digest a portion of their contents inside structures called autophagosomes. Razi et al. identify a key step in autophagosome maturation, showing that it depends on early stages in the endocytic pathway that enables cells to absorb necessities from their surroundings.

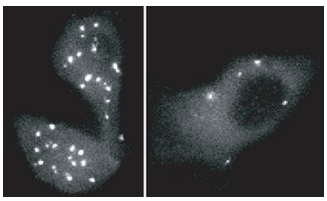
An autophagosome is like a miniature stomach that uses enzymes to dissolve macromolecules and organelles. The process of self-eating, known as autophagy, recaptures macromolecules and clears away potentially toxic protein tangles. But before an autophagosome can start digesting, it has to combine with endosomes and lysosomes that provide the necessary enzymes. Researchers knew that maturing autophagosomes fuse with late endosomes, which are far along in the endocytic pathway and break down absorbed material. But they didn't know whether the youthful autophagosomes also merge with early endosomes that harbor freshly imbibed molecules.

To find out, Razi et al. deleted components of the coatomer complex COPI, which is necessary for endosome function. Loss of COPI disrupted early endosomes, reducing absorption and processing of two molecules taken in via the endocytic pathway. COPI's absence also gave cells indigestion: immature, nonfunctional autophagosomes built up in the cells.

The results suggest that to start working, an autophagosome has to fuse not just with late endosomes, but also with early endosomes. What the autophagosome gains from the rendezvous is a question for future studies. But the researchers suspect that early endosomes provide the molecular pump that helps acidify the autophagosome's interior.

Razi, M., et al. 2009. *J. Cell Biol.* doi:10.1083/jcb.200810098.

When cancer cells can't let go



The invadopodia (glowing dots) speckling a cell lacking FAK (left) are rare on a control cell (right).

Like a climber scaling a rock face, a migrating cancer cell has to keep a tight grip on the surface but also let go at the right moment to move ahead. Chan et al. reveal that the focal adhesion kinase (FAK) coordinates these processes to permit forward movement.

Crawling cancer cells send out extensions called invadopodia. By releasing enzymes that dissolve the extracellular matrix (ECM), invadopodia clear a path for the cell to wriggle through. As they move, cancer cells get traction by temporarily attaching to the ECM through focal adhesions. FAK spurs focal adhesions to disengage, and it is more abundant in metastatic tumors. Whether FAK also regulates invadopodia was unknown.

When Chan et al. removed FAK, breast cancer cells were much less invasive. But to the team's surprise, the FAK-lacking cells sprouted extra invadopodia. The cells also sported large focal adhesions that were particularly sticky. The protein Src serves as FAK's helper. FAK and Src work together to phosphorylate tyrosines in proteins such as paxillin, which then disassemble the focal adhesion. But the team found that in cells missing FAK, the phosphorylated proteins accumulated in the invadopodia. Src's localization reflects this difference. In control cells, Src accumulated in focal adhesions. In FAK's absence, Src headed to the invadopodia.

The work suggests that FAK controls movement by balancing the number of invadopodia that create a path for migration and the number of focal adhesions that hold the cell back. The next question, the researchers say, is how FAK and Src integrate these events to promote invasion.

Chan, K.T., et al. 2009. *J. Cell Biol.* doi:10.1083/jcb.200809110.