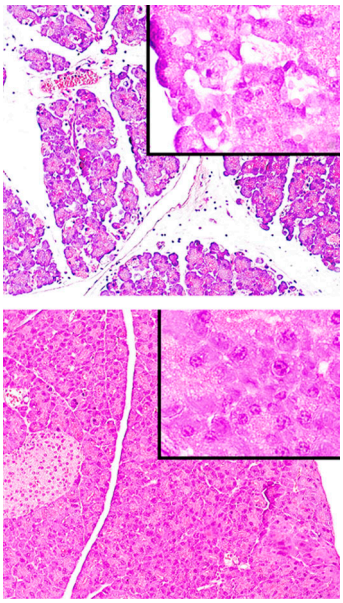
In This Issue



Pancreatic tissue from a control mouse shows damage from pancreatitis (top), but tissue from a mouse that can't instigate autophagy is healthy (bottom).

Cellular self-eating promotes pancreatitis

To survive tough times, cells sometimes resort to a form of self-cannibalism called autophagy. But as Hashimoto et al. reveal, autophagy can have a down side, destroying the pancreas by prematurely activating a digestive enzyme.

In autophagy, a vesicle swallows a portion of cytoplasm and ferries it to the lysosome for digestion. The process is often beneficial, allowing hungry cells to recycle molecules, for example. However, the researchers previously discovered that in mice with pancreatitis the level of autophagy in pancreatic cells surges. Pancreatitis occurs when the enzyme trypsin dissolves cells from within. Normally, pancreatic cells fashion and discharge an inactive form of trypsin called trypsinogen, which remains inert until it reaches the small intestine. But if trypsinogen converts to trypsin before its release, it can damage or kill a pancreatic cell. Hashimoto et al. tested whether autophagy promotes this early activation by delivering trypsinogen to the lysosome, where enzymes turn it on.

The researchers gave mice injections of the compound cerulein, which spurs pancreatitis. Control animals suffered severe damage to the organ, which harbored numerous deteriorating cells. But rodents that lack a gene necessary for autophagy displayed almost no symptoms. To determine whether autophagy promotes trypsinogen activation, the team dosed pancreatic cells from both types of mice with cerulein. Cells from the autophagy-impaired animals carried much less activated trypsinogen than did cells from controls.

In rodents capable of autophagy, cerulein injections triggered much higher levels of trypsin activity in pancreatic tissue than did shots of saline, confirming that autophagy switches on the enzyme. The study is the first to reveal that autophagy can initiate a disease. The next step, the researchers say, is determining what triggers pancreatic cells to start eating themselves. JCB

Hashimoto, D., et al. 2008. *J. Cell Biol.* doi:10.1083/jcb.200712156.

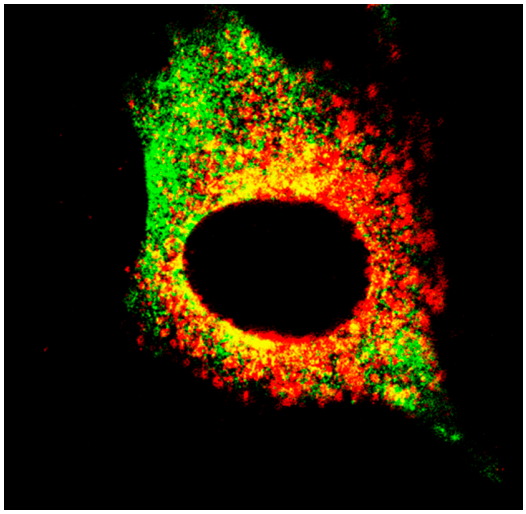
Alzheimer's protein controls calcium's ins and outs

Two enzymes that help manufacture amyloid β, the protein that accumulates in the brain in Alzheimer's disease, also take on another job. As Green et al. report, the enzymes, known as presenilins, help set calcium levels inside cells by activating a pump protein.

Presenilins partner with other proteins to create the enzyme γ-secretase, which helps snip amyloid β into shape. Faulty presenilins trigger a rare, early-onset variant of Alzheimer's disease (AD) that strikes patients who are under 65 yr old. Presenilins might also help dictate how much calcium enters and exits the ER, which serves as the cell's storehouse for the ion. For instance, ER calcium release skyrockets in cells from patients with early onset AD. And in cells lacking one of the presenilins, the ER contains less calcium than normal. These results suggest that the presenilins help regulate SERCA, the protein that pumps calcium into storage.

To test that possibility, Green et al. eliminated both presenilins from cells and found that their cytoplasmic calcium levels were higher than normal. The scientists also measured how rapidly frog eggs shuttled a controlled influx of calcium ions into the ER. Engineering the eggs to manufacture presenilins, which they don't normally make, accelerated calcium pumping into the ER.

The location of presenilins and SERCA reflects their close relationship, the team found. Presenilins not only settle alongside SERCA in the ER, they attach to the pump protein. Green et al. also discovered a link between amyloid β and SERCA: increased SERCA activity translated into higher amyloid β production. SERCA might exert this effect by prodding γ-secretase, the team concludes.



Presenilin (red) and SERCA (green) cozy up in this fibroblast.

The results show that along with forming part of the protein-slicing γ-secretase complex, presenilins are crucial for regulating intracellular calcium homeostasis. Both functions allow the enzymes to exert control over amyloid β formation. JCB

Green, K.N., et al. 2008. *J. Cell Biol.* doi:10.1083/jcb.200706171.

Text by Mitch Leslie
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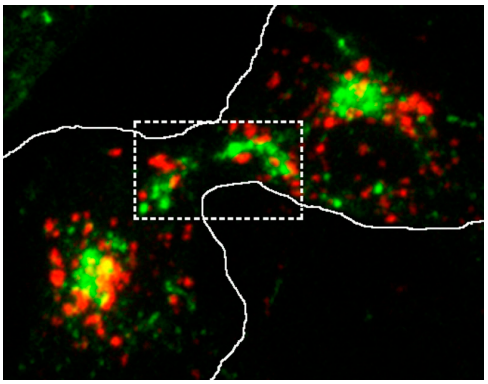
How cells make local calls

Broadcast a message over a loudspeaker, and you can't be sure who will hear it. But whisper the message into the friend's ear, and you can be sure it got through. Cells follow a similar strategy when they transmit signals with reactive oxygen species (ROS), as Chen et al. show. By positioning the sender and recipient molecules near each other, cells ensure efficient communication.

ROS are best known as destructive byproducts of metabolism that might cause aging. But cells also use the molecules to carry messages. The mystery is how cells direct ROS to their targets, since some ROS can diffuse throughout the cell, potentially reacting with any molecules they encounter.

Proximity is the key, Chen et al. found. They tracked down the signal-relaying molecule NADPH oxidase 4 (Nox4), which produces the ROS hydrogen peroxide. The protein was stationed in the endoplasmic reticulum near another protein called PTP1B, which slows division of endothelial cells by turning down the epidermal growth factor receptor (EGFR). The team showed that Nox4 was oxidizing and shutting down adjacent PTP1B molecules. Using an antioxidant that homes in on the ER, for instance, the team could block EGFR signaling, indicating that oxidation of PTP1B had been prevented. An antioxidant that remains in the cytoplasm, however, had no effect on the receptor. The results suggest that by keeping Nox4 and PTP1B close together in the ER, cells make it easier for ROS signals to travel between them. One question the researchers now want to answer is what activates Nox4 in the first place. JCB

Chen, K., et al. 2008. *J. Cell Biol.* doi:10.1083/jcb.200709049.



Golgi-derived vesicles (green) amass at the cleavage furrow.

Daughter cells share duties

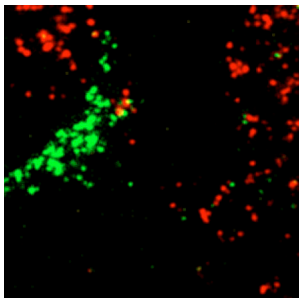
There's no sibling rivalry during cell division. Goss and Toomre show that during cytokinesis both daughter cells pitch in to supply new membrane.

Researchers suspect that during cytokinesis, fresh membrane shuttles to the junction between the two daughter cells. Where the membrane comes from has puzzled researchers. A previous study using spinning disc confocal microscopy suggested that only one daughter cell provides it. However, that study didn't track individual membrane vesicles.

Goss and Toomre were able to do just that by capturing images 60 times faster. They found that vesicles from both daughter cells leave the Golgi apparatus and cruise to the cleavage furrow, accumulating there. Although other potential sources of membrane, including endosomes, also collect near the furrow, they remain aloof from the Golgi-derived vesicles that will ultimately fuse with the cell membrane.

With total internal reflection fluorescence microscopy, the team observed individual vesicles from both daughter cells merging with the plasma membrane at the cleavage furrow. However, the results don't necessarily conflict with the previous study, the researchers say. They note that they also observed an asymmetric stage in which only one cell appears to direct vesicles to the cleavage furrow. JCB

Goss, J.W., and D.K. Toomre. 2008. *J. Cell Biol.* doi:10.1083/jcb.200712137.



In fused cells, there's little mixing between the two kinds of mitochondrial DNA (red and green).

Mitochondrial DNA stays home

Mitochondria stow their DNA in structures called nucleoids. As Gilkerson et al. reveal, nucleoids are selfish and don't share their DNA with each other. The results might help explain some quirks of mitochondrial inheritance and support a proposed treatment strategy for illnesses caused by defects in the organelles.

A nucleoid can house up to 10 copies of a mitochondrion's genome. One reason that the structures intrigue researchers is that they might help control how the DNAs get parceled out when mitochondria divide. To understand mitochondrial DNA inheritance, researchers need to resolve whether nucleoids swap DNA. The question has remained unanswered because of the difficulty of tracking individual mitochondrial DNAs.

To overcome that problem, Gilkerson et al. fused two kinds of cells, each of which carried a different mitochondrial genome. In the merged cells, the researchers found, labeled versions of the two types of mitochondrial DNA rarely appeared together, suggesting that the nucleoids weren't mingling their contents. Stingy nucleoids could explain why cells that harbor a variety of mitochondrial genomes sometimes lose DNA diversity as they divide and sometimes don't. The outcome might depend on whether the DNAs in a particular nucleoid are uniform or varied. The results also offer support for plans to treat mitochondrial diseases by nudging cells to eliminate defective DNA. The lack of swapping will make it easier to purge faulty mitochondrial genomes, the researchers say. JCB

Gilkerson, R.W., et al. 2008. *J. Cell Biol.* doi:10.1083/jcb.200712101.