Text by Ben Short
bshort@rockefeller.edu

Deciding what to eat

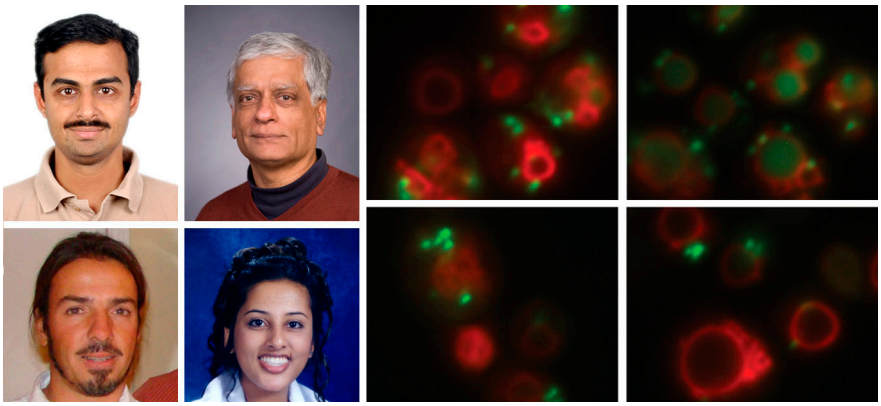
A signaling pathway directs cells to degrade peroxisomes while leaving other organelles untouched.

Cells adapt to their surroundings by generating new organelles when needed and degrading them when they become damaged or superfluous. Many organelles, including the ER and mitochondria, are turned over by autophagy—the "self-eating" pathway in which cytoplasmic contents are engulfed in a double-membraned vesicle and transported to the lysosome to be broken down and recycled. But, just like people, cells have to watch what they eat and ensure only the right organelles are degraded. Manjithaya et al. now reveal the signaling pathway that specifically stimulates the destruction of peroxisomes (1).

Because peroxisomes contain the enzymes necessary for catabolizing fatty acids, yeast grown on oleate produce extra peroxisomes to exploit this carbon source. But switching the yeast to glucose-containing medium renders these peroxisomes redundant. In a process called pexophagy, cells dismantle their excess peroxisomes using their autophagic machinery (2). "But how do you take a nonselective process like autophagy and make it only eat peroxisomes?" asks Suresh Subramani, from the University of California, San Diego.

Subramani and colleagues have identified factors that control the selective destruction of peroxisomes, including a protein called Atg30 that targets the organelles to the autophagy pathway (3). Little is known about the signaling events that control pexophagy, however, so Manjithaya et al. screened for yeast kinase mutants that couldn't eliminate their peroxisomes after switching from oleate to glucose media (1). The researchers discovered that the mitogen-activated protein kinase (MAPK) Slt2p was essential for peroxisome turnover. "Our assay was pexophagy-specific but we were concerned that this might be a general signaling pathway for all autophagic processes," says Subramani. "We were really excited to find that Slt2p didn't affect general autophagy or the selective removal of other organelles."

Focal Point



(Clockwise from top left) Ravi Manjithaya, Suresh Subramani, Shveta Jain, and Jean-Claude Farré identify a yeast MAP kinase cascade that, together with hexose sugars, induces cells to degrade their peroxisomes via a selective form of autophagy. Cells grown on oleate (top left) produce peroxisomes (green) to metabolize the fatty acid, but these organelles are superfluous in the presence of glucose (top right) and so are targeted to the vacuole (red) for destruction. Yeast lacking the MAP kinase Slt2p still form peroxisomes on oleate (bottom left) but can't degrade them in response to glucose (bottom right).

Slt2p is at the bottom of a signaling cascade activated by damage to the yeast cell wall (4). All of the upstream kinases in the pathway were also required for pexophagy, as was Mid2p—a cell surface protein that senses cell wall integrity and initiates signaling to Slt2p. But what does the cell wall have to do with peroxisome turnover?

In fact, activating the MAPK pathway wasn't sufficient to induce pexophagy. The team thinks that simultaneous activation of protein kinase A (PKA) by the entry of hexoses, such as glucose, into yeast cells is also required for peroxisome removal. The presence of glucose stimulates PKA by up-regulating cAMP levels and, Subramani speculates, activates Mid2p by inducing changes in the glycosylation pattern of cell wall proteins. The coincidence of these two signals causes cells to destroy their peroxisomes. "You don't want to trigger pexophagy by mistake," Subramani explains, "so you need signaling through both of these pathways."

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How does Slt2p promote pexophagy? Manjithaya et al. found that peroxisomes were still engulfed into double-membraned "pexophagosomes" in cells lacking Slt2p, suggesting that this MAPK controls a later step in the pathway, such as transport to, or fusion with, the vacuole (the yeast equivalent of lysosomes). Although MAPKs often target transcription factors, Subramani thinks that Slt2p regulates pexophagy more directly by phosphorylating a protein on the pexophagosome surface. "That makes our task more difficult as it's likely to be a novel substrate," he adds. "But at least we know where to start looking."

Subramani is also interested in how the MAPK and hexose-sensing pathways are integrated, and to what extent this regulation is conserved across evolution. He suspects that the process may ultimately be linked to human disease—defects in both peroxisome biogenesis and autophagy contribute to a variety of disorders. "These are important proteins," Subramani says. "As we start to look at selective organelle turnover, there will be disease connections that we'll need to explore."

1. Manjithaya, R., et al. 2010. *J. Cell Biol.* doi:10.1083/jcb.200909154.
2. Farre, J.C., et al. 2009. *Curr. Opin. Cell Biol.* 21:522–530.
3. Farre, J.C., et al. 2008. *Dev. Cell.* 14:365–376.
4. Levin, D.E., et al. 2005. *Microbiol. Mol. Biol. Rev.* 69:262–291.