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In This Issue

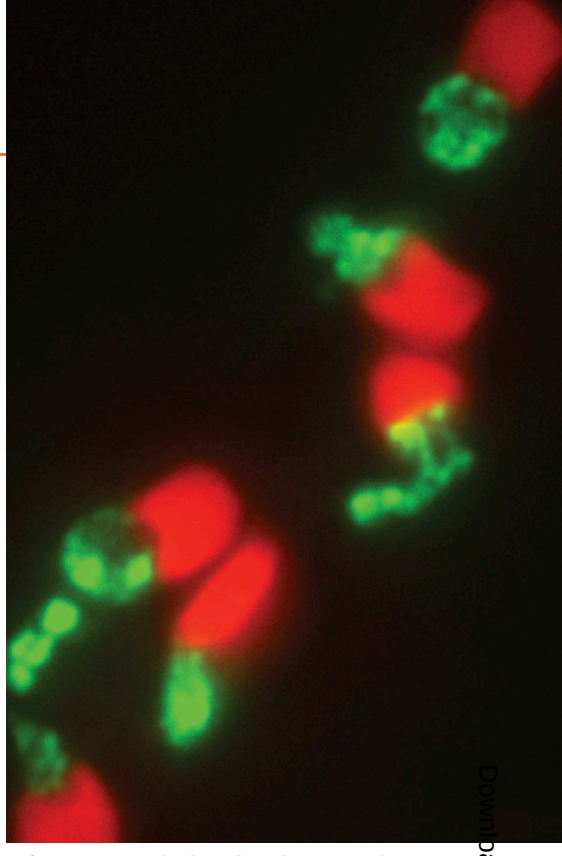
Caching killer carbs

Plants and protists may not have a nervous system, but they can help elucidate the mechanism of a fatal neurodegenerative disease, as Gentry et al. reveal on page 477. The organisms helped researchers pin down the function of a protein suspected of sparking destructive carbohydrate accumulations.

Lafora disease is a fatal form of epilepsy whose symptoms usually begin between the ages of 10 and 20. In neurodegenerative diseases such as Parkinson's and Alzheimer's, globs of insoluble proteins amass in neurons. But in Lafora disease, neurons harbor clumps of insoluble carbohydrates similar to amylopectin, a component of starch. Several mutations can trigger the illness, including glitches in the gene for laforin. This protein carries two key modules: one that grabs carbohydrates, and a second that slices off phosphate groups. Although mouse models develop the symptoms of Lafora disease, researchers still don't understand how their faulty laforin protein elicits neurological damage.

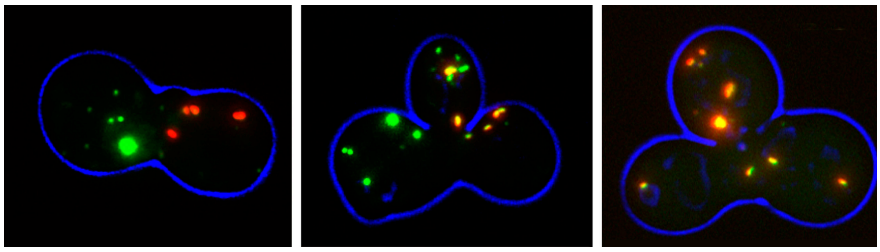
Gentry et al. thus went hunting for other laforin-making organisms. They trolled protist genomes and pinpointed genes for laforin in organisms as different as the pathogen behind toxoplasmosis and a type of red alga. Previously, researchers had thought that only vertebrates manufacture the protein. Like human laforin, the protist version grips carbohydrates and lops off a phosphate. Where laforin hangs out has been a mystery, but the researchers determined that, in one type of protist, it congregates around starch granules.

The team also found that plants carry an unrelated protein with the same function, known as SEX4. *Arabidopsis* plants with a defective form of SEX4 built up excess starch. The presence of proteins with the same job in such a range of organisms suggests that phosphate removal is crucial for breaking down insoluble carbohydrates. Why persistent phosphates lead to carbohydrate buildup remains unclear. The scientists now want to investigate whether the carb clusters from patients with Lafora disease carry excess phosphates. JCB



Laforin (green) dephosphorylates starch granules in this red alga.

Splitting the difference on peroxisomes



A peroxisome protein (green) spreads (left to right) from the ER of one yeast cell to the peroxisomes (red) of a mating partner.

The question of whether cells manufacture new peroxisomes from scratch or cleave existing organelles has divided researchers. On page 399, Motley and Hettema show that yeast opt for the second mechanism, only turning to synthesis if they run out of the organelles.

Packed with enzymes, peroxisomes are essential for defusing cellular toxins—a shortage of the organelles triggers the lethal disorder Zellweger syndrome. Before a cell divides, it duplicates its stock of peroxisomes, half of which it then parcels out to its daughter cell. But research on how cells fashion more peroxisomes has produced contradictory results. Some work suggests that new structures bud from the endoplasmic reticulum. Other findings suggest that new peroxisomes form when existing ones split. A third explanation is that cells rely on both mechanisms.

To sort through these possibilities in yeast cells, Motley and Hettema attached GFP to a protein segment that directs molecules to the peroxisomes. They briefly switched on production of the combination, then shut it off and followed what happened through several rounds of cell division.

If yeast relied on ER budding to produce new peroxisomes, the researchers reasoned, the number of labeled peroxisomes per cell should decline as new, nonlabeled structures emerged from the ER. If cells relied on the fission of existing peroxisomes, however, the number of labeled structures should remain the same, but their brightness should decline as peroxisomes repeatedly halved their store of GFP. The second possibility was correct, Motley and Hettema discovered.

The researchers then devised a new technique to temporarily trap a peroxisome membrane protein in the ER until yeast cells mate. The team found that the ER did furnish some peroxisome membrane components. However, yeast cells only used ER budding to produce new peroxisomes when they had none of their own. Motley and Hettema conclude that the ER is continually releasing preperoxisomes, but they usually merge with existing organelles. Only if the cell lacks peroxisomes will these structures mature. The researchers suspect that the cells prefer fission to make peroxisomes because it's faster than ER budding. JCB

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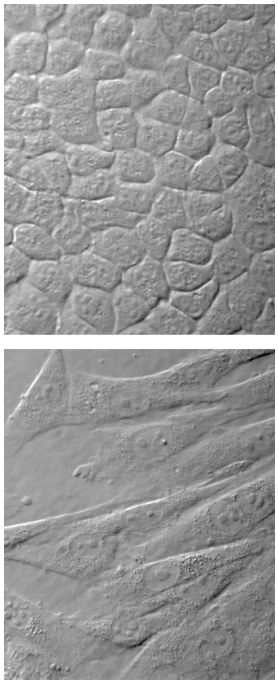


Cancer cells (top) exposed to TGF-β grow and elongate as they undergo EMT (bottom).

Small cancer cells don't stray

Wanderlust is what makes cancer cells deadly. On page 437, Lamouille and Derynck show that anticancer drugs already in clinical trials might have an unexpected benefit by turning the rogue cells into homebodies.

Cancer cells often enlarge and crank up protein synthesis, presumably to support their racing metabolism. Before they metastasize, the cells undergo a transformation known as the epithelial–mesenchymal transition (EMT). They reorganize their skeleton, stretch out, and break connections with their neighbors. After they've completed the transition, cells dissolve the extracellular matrix that restrains them and start spreading. EMT is prodded by increased expression of the cytokine TGF-β via the Smad pathway, which regulates gene transcription.

TGF-β also acts through a separate pathway that increases protein synthesis, the researchers found while studying cultured breast cancer cells. Dosing the cells with TGF-β spurred them to get bigger and boost translation while undergoing EMT.

The speed of protein synthesis is controlled by the mTOR pathway, which Lamouille and Derynck found was activated by TGF-β in these cancer cells. In turn, the researchers discovered, mTOR was under the control of a pathway initiated by PI3 kinase rather than Smads.

The drug rapamycin, which blocks mTOR, prevented cells from bulking up and boosting protein production, but it didn't forestall EMT. It did, however, rein in the cells, probably by loosening the surface attachments that cells use to crawl. These findings indicate that although tumor cells undergo EMT before they move, the two events can be separated.

That distinction suggests a strategy for thwarting metastasis. Researchers have so far focused on blocking TGF-β to short-circuit EMT. But drugs that shut down mTOR might keep cancer cells at home even if they don't stop EMT. The researchers are now testing whether rapamycin analogues restrain cancer cells in animals. If they do, the good news is that similar compounds are already in clinical trials. JCB

Separate and unequal Deltas

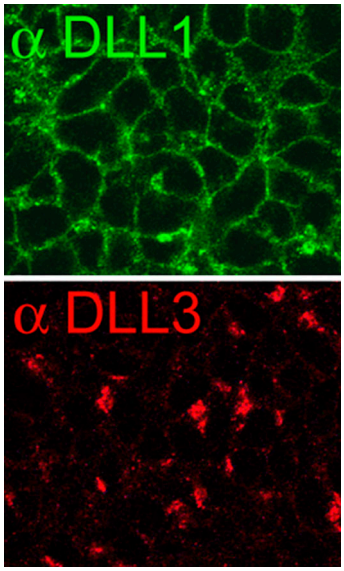
Two key developmental proteins that once appeared to be molecular twins perform different jobs and work in different parts of the cell, as Geffers et al. show on page 465.

Among its many functions, the Notch pathway helps orchestrate the formation of somites that give rise to the vertebral column and other structures. The pathway appears to be full of redundancy. For example, mice carry four Notch genes and three for the Delta proteins that interact with the pathway. The jobs of two of the Delta proteins, DLL1 and DLL3, have remained unclear. Initial studies suggested that the proteins are interchangeable. But individually deleting the proteins, which are made in the same part of the mesoderm, induces different developmental defects, and a recent study suggested that DLL3 interferes with DLL1.

To sort through the confusion, Geffers et al. replaced one or both copies of the *Dll1* gene with a short but functional version of the *Dll3* gene. Mice lacking DLL1 die as embryos. The researchers found that mice that manufacture DLL3 instead of DLL1 also perished during embryogenesis, indicating that one protein cannot substitute for the other.

The team also gauged whether one protein inhibits the activity of the other by examining mice with three copies of *Dll3* and one of *Dll1*. Animals with only one copy of *Dll1* display some skeletal flaws. If the proteins were antagonists, the scientists reasoned, animals with the extra DLL3 should show even more severe abnormalities. But these mice were no worse off.

The researchers confirmed their findings by tracking Notch after its activation. When Notch switches on, its intracellular tail detaches and spirits the signal to the nucleus. Levels of this tail piece did not increase in embryos lacking DLL3, the scientists determined. DLL3 thus does not interfere with Notch activation.



DLL1 (top) studs the surface of the cell, whereas DLL3 (bottom) collects in the interior.

So what is DLL3 doing? The researchers are still not sure, but they discovered that most of the protein lurked inside the cell, mainly in the Golgi apparatus, rather than on the surface, where DLL1 resided. The Golgi location suggests that, instead of triggering Notch, DLL3 has some other, undiscovered role in the pathway. JCB