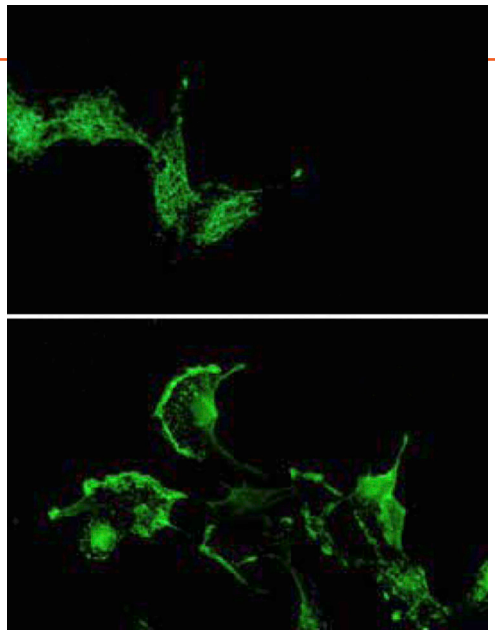
In This Issue



Phosphorylation of threonine-2256 causes NG2 (green) to migrate from the cell's upper surface (above) to its front edge (below).

Go forth or multiply

A cell can move and reproduce, but it usually can't do both simultaneously. As Makagiansar et al. report on page 155, the pattern of phosphorylation on a membrane proteoglycan helps determine whether cells grow or go. The phosphorylation differences direct the molecule to distinct parts of the cell membrane.

Even cancer cells have to slow down before they can divide, as do normal progenitor cells such as those that spawn oligodendrocytes in the brain. Evidence suggests that NG2, a proteoglycan in the cell membrane, enables cells to choose which action to perform. Cancer cells and progenitor cells manufacture NG2, for example, but most other cells don't.

Three years ago, the researchers showed that affixing a phosphate to a particular amino acid in NG2 changed cell behavior. Specifically, phosphorylating the threonine at position 2256 spurred cells to crawl. Makagiansar et al. wanted to discern what happens after phosphorylation of another threonine, found at position 2314.

This addition inhibited movement. The researchers also discovered that whereas phosphorylation of threonine-2256 checked cell proliferation, phosphorylation at the other position promoted it. The difference in function might stem from a shift in location.

Instead of signaling directly, NG2 relays its messages through β1 integrin. The team showed that, after phosphorylation of threonine-2256, NG2 and β1 integrin clustered at the front edge of the cell. But after phosphorylation of threonine-2314, NG2 and β1 integrin gathered in small spikes on the cell's upper surface. Overall, the results indicate that phosphorylation at each site triggers a contrasting response from the cell. If both sites were modified, threonine-2256 seemed to prevail, and the cell got going.

The researchers now hope to work out how phosphorylation at the two sites nudges NG2 into different locations. One possibility is that phosphorylation alters how NG2 interacts with scaffolding molecules such as MUPP1 and GRIP1 that control signaling interactions in the cytoplasm. JCB

The juvenile salivary glands (green) stick around in this pupa with a mutation in the CBP gene.

Death comes for the salivary gland

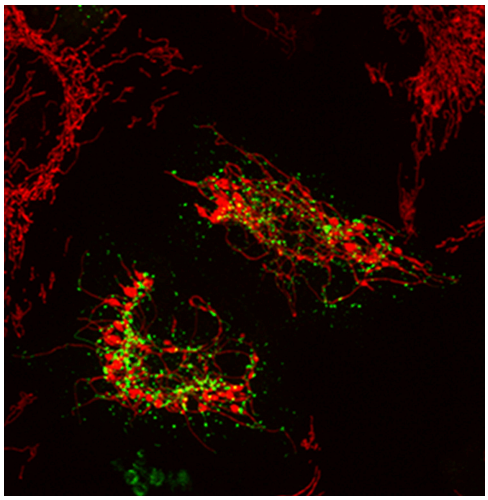
As it morphs from a squirming maggot into a buzzing adult, a fruit fly jettisons its juvenile salivary glands. On page 85, Yin et al. show how the insects get rid of a protective protein, allowing the glands to break down at the right time. The research helps clarify how certain tissues prepare themselves to die.

During metamorphosis, a larva's obsolete internal organs degenerate, and replacements sprout. Surging quantities of the steroid hormone ecdysone spur the salivary glands and other juvenile structures to melt away. Researchers have mapped out some of the molecular details of this deterioration. Ecdysone cranks up several genes, including one called *reaper*, that trigger salivary gland cells to perish. But getting rid of the glands requires one more change: elimination of a protein called *diap1*, which shields salivary cells. How a fly-to-be cuts the levels of *diap1* on schedule was unknown.

To find out, the researchers screened the insects for mutations that allowed the youthful salivary glands to persist. They found three such glitches in the transcriptional coactivator CBP. The scientists assumed that faulty CBP spared the salivary glands by preventing the activation of *reaper* and other killer genes. Instead, Yin et al. determined, CBP slashed the amount of *diap1* shortly before pupation.

Although the decline in *diap1* primed the salivary glands to die, enough of the protein remained to spare cells from *reaper*. A second surge of ecdysone triggered salivary cells to purge the vestiges of *diap1* without using CBP, and the glands deteriorated. This two-step process ensures that the salivary glands don't disappear prematurely, the researchers speculate. They now want to pin down how CBP influences *diap1*. CBP normally helps switch genes on rather than off, so it probably works by activating another gene that curtails *diap1* production. JCB

Text by Mitch Leslie
mitchleslie@comcast.net



Mitochondria (red) are stickier in cells that make faulty MARCH5 (green).

Mitochondria on the MARCH

Breaking up isn't hard to do for mitochondria, which are continually separating and merging. On page 71, Karbowski et al. pinpoint a protein that prods the organelles to go their own way.

Cells carefully control mitochondrial fusion and fission, and an imbalance between the processes can be disastrous. For example, a faulty fusion-promoting protein triggers dominant optic atrophy, the leading cause of inherited blindness. Researchers know more about the regulation of fusion and fission in yeast than in mammals. But they do know that one of the mammalian proteins essential for mitochondrial breakup is Drp1.

Karbowski et al. pinpointed another, called MARCH5, which colocalizes with Drp1. Although two studies published last year suggested that MARCH5 promoted mitochondrial fusion, the scientists now find the opposite. When they altered cells to produce a defective version of the protein, mitochondria stuck together to form extra-long networks instead of breaking apart. The researchers also observed this abnormal elongation when they added RNAi against MARCH5.

The protein normally spreads out around the mitochondrial membrane, but the mutant MARCH5 clumped. These clusters trapped Drp1. These findings suggest that MARCH5 spurs mitochondrial splitting by helping to direct Drp1 to the future separation site. MARCH5 is a ubiquitin ligase that works by attaching a ubiquitin molecule to its target. The researchers' next move is to track down that target. JCB

No way to treat a tumor

On page 93, Yuneva et al. provide bittersweet news for efforts to turn cancer cells' big appetite against them. Contrary to previous work, the study shows that a sugar shortage snuffs out normal cells as well as cancer cells. But the results bolster another nutritional target: the amino acid glutamine.

The idea that cancer cells hunger for glucose is more than 50 years old. In the 1990s, researchers showed that glucose depletion kills rodent cells that carry an overactive form of the cancer-promoting gene *MYC*. Nontransformed cells survived.

Tumors also need plenty of glutamine, and two drugs that disrupt metabolism of the amino acid reached clinical trials but have since proved toxic. Some scientists question whether scarcity of either nutrient is lethal to human tumors: cancer cells synthesize their own glutamine, and some tumors switch to alternative food sources if glucose runs out. Yuneva et al. wanted to nail down whether the nutrients are essential for cells with overactive *MYC*.

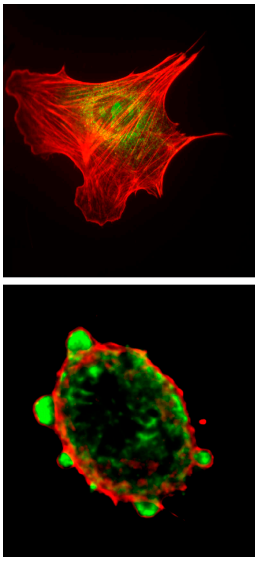
To their surprise, the researchers found that, unlike rodent cells, human cells were killed by glucose deprivation whether or not extra MYC was present. By contrast, shutting off the glutamine supply had a stronger effect on MYC-overproducing cells. The results suggest that glutamine deprivation as a cancer treatment—which researchers have abandoned—deserves a second look. The findings don't show that glucose deprivation is a bust, the authors caution. Instead, they say, scientists need to carefully compare the intricacies of metabolism in normal and cancer cells before they can predict whether such treatments will work. JCB

p53 hits the brakes

Crawling cells shift into high gear after they lose the tumor suppressor protein p53, as Gadea et al. report on page 23. The work reveals that the same flaw that allows cancer cells to divide uncontrollably also increases their mobility.

Most cancer cells sport faulty versions of p53, which normally halts the cell cycle or triggers apoptosis in response to DNA damage. The researchers and other groups had previously shown that deleting p53 gets cells moving in two-dimensional cultures. Gadea et al. tested for the same effect in more realistic, three-dimensional cultures.

The researchers found that crawling mouse embryonic fibroblasts came in two varieties. If they carried working p53, the cells were elongated and sluggish. But if p53 was absent, they were rounder and slithered six times faster. This speedier movement required RhoA GTPase and its downstream enforcer, ROCK.



A p53-expressing fibroblast (top) is outrun by a fast crawler lacking p53 (bottom).

Inactivating p53 in melanoma cells that normally carry a functional version of the protein increases their invasiveness, confirming that p53 loss can accelerate the dispersion of cancer cells. The results suggest that cancer treatments that restore p53 activity bring an added benefit by reining in the rogue cells. JCB