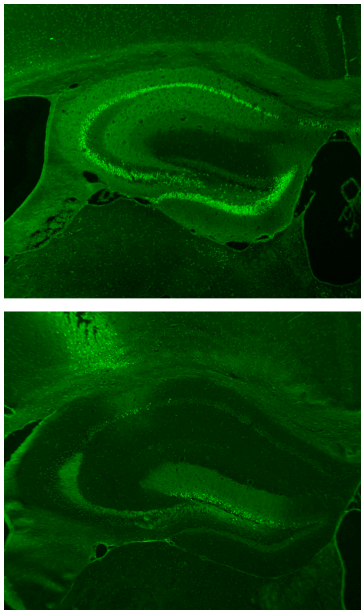
In This Issue



After stimulation of NMDA receptors, prion-lacking mice suffer more damage to the hippocampus (top) than do mice with prions (bottom).

Prions show their good side

One function of prions, the Jekyll-and-Hyde proteins behind illnesses such as Creutzfeldt-Jakob disease (CJD) and mad cow disease, has been identified by Khosravani et al. The proteins calm brain cells, preventing them from dying of overexcitement.

Only when a prion folds incorrectly does it trigger brain-ravaging diseases like CJD. The normally shaped version, which all body cells carry, presumably performs an important task, but researchers haven't been able to pin it down. One hint comes from mice lacking the gene for prion protein. The animals are healthy, if somewhat forgetful. After a stroke or seizure, however, they suffer more severe brain damage than do control mice. Some of their brain neurons are also hypersensitive. These abnormalities implicate NMDA receptors, which respond to the neurotransmitter glutamate and to the drug NMDA. Overstimulation of NMDA receptors can allow lethal amounts of calcium into neurons.

Khosravani et al. tested whether normal prions dampen the activity of NMDA receptors. The researchers electrically stimulated slices of brain tissue from prion-making and prion-lacking mice. The same stimulation causes cells from rodents that don't harbor prions to respond more vigorously. The scientists saw similar results when they used NMDA to prod brain neurons. The drug provoked longer-lasting currents in the cells without prions. The cells paid a price for their excitability. Neurons from the prion-lacking rodents were more likely to die after a dose of NMDA than were cells from control mice.

The results from Khosravani et al. suggest that normal prions might exert their protective effect on neurons by switching off a particular subset of NMDA receptors that contain a subunit called NR2D. The work also suggests a mechanism for the brain damage caused by prion diseases. Malformed prions coax normal molecules to misfold. As the amount of normal protein falls, neurons lose their protectors and become more vulnerable to death by overstimulation. JCB

Khosravani, H., et al. 2008. *J. Cell Biol.* doi:10.1083/jcb.200711002.

When cells make a meal of themselves

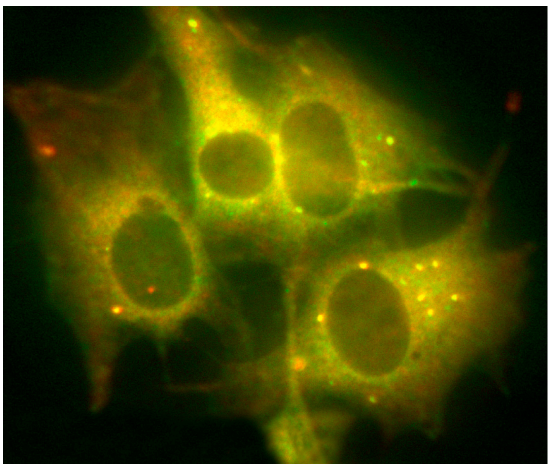
Cells take recycling to the extreme. If they run low on food, they digest and reuse some of their own cytoplasm. Hara et al. have discovered a key protein that helps get this process started.

This cellular self-eating is called autophagy. A membrane pouch known as an autophagosome forms inside the cell and swallows some cytoplasm. The autophagosome then hauls its contents to a lysosome for digestion. Researchers have teased out many of the molecular details of autophagy in yeast. But they know much less about how it works in mammals.

Hara et al. probed the function of two mouse kinases, ULK1 and ULK2. The proteins are homologous to a yeast protein that's vital for autophagy, but researchers weren't sure whether they performed the same job in mice. Hara et al. found that nonfunctional versions of ULK1 and ULK2 blocked autophagy and that the normal proteins clung to the membrane of autophagosome precursor compartments.

The team also captured one of ULK1 and ULK2's accomplices, FIP200. This protein gets around: it blocks tumor growth, hinders cell movement, helps control cell size, checks cell cycle progression, and prevents apoptosis. FIP200 bound ULK1 and ULK2 and ensured these proteins retained their kinase activity, the researchers found. Furthermore, mouse cells that lacked FIP200 demonstrated that this protein was also essential for autophagy.

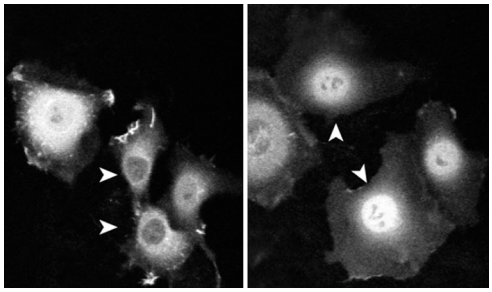
How does a protein with so many responsibilities choose which one to perform? Hara et al. think that its choice of partner dictates its function. The team concludes that if FIP200 combines with ULK1 and ULK2, it helps instigate an early step of autophagy. But why this protein partnership whets a cell's appetite for itself remains unknown. JCB



In starving cells, ULK1 and ULK2 gather on incipient autophagosomes (yellow dots).

Hara, T., et al. 2008. *J. Cell Biol.* doi:10.1083/jcb.200712064.

Text by Mitch Leslie
mitchleslie@comcast.net



Rac1 (white) is in the cytoplasm for G1 (left) but heads to the nucleus for G2 (right).

Rac1 takes a trip

Whether a cell is on the move or tangling with invading bacteria, the enzyme Rac1 is on the job. Michaelson et al. add another task to the hard-working molecule's resume. It shuttles into and out of the nucleus to help induce mitosis.

By reshaping the actin cytoskeleton, Rac1 prompts cells to crawl, polarize, or form adherens junctions with their neighbors. It also switches on genes and controls the activity of an antipathogen enzyme. Although researchers had observed Rac1 in the nucleus when it was overexpressed, they thought that the enzyme exerted most of its effects from the cytoplasm.

But Michaelson et al. found that Rac1 enters and departs from the nucleus at particular points in the cell cycle. The protein builds up in the nucleus during the G2 phase. By the next G1 phase, it's back in the cytoplasm. Rac1's entry into the nucleus promoted cell division, the team found. Conversely, a Rac1 variant that can't access the nucleus hindered mitosis.

What directs Rac1 into the nucleus at G2 isn't clear. The team's findings suggest that to hold Rac1 in the cytoplasm, cells attach a prenyl lipid group to the protein's tail. However, the researchers also showed that much of the Rac1 that reaches the nucleus carries the prenyl group. The researchers speculate that a protein chaperone might cover up the lipid and allow Rac1 to make its move.

Why Rac1 enters the nucleus is also mysterious. It might arrive to activate some of the molecular machinery of mitosis. Alternatively, cells could be exiling the protein from the cytoplasm because many of its functions, such as promoting junction formation and cell spreading, hamper division. JCB

Michaelson, D., et al. 2008. *J. Cell Biol.* doi:10.1083/jcb.200801047.

Tag team at the telomeres

It takes two crews of proteins to keep the telomeres in fine fettle, as Kim et al. show.

TRF1 and TRF2 are just two of the proteins that ensure that a cell's telomeres remain long and structurally sound. Another protein, TIN2, links up with both molecules and with other proteins to form complexes that help maintain the telomeres. However, researchers weren't sure whether TRF1 and TRF2 worked together in the same complex.

When Kim et al. netted TIN2-containing complexes from nuclear extracts of human cells, they found that TRF1 and TRF2 usually separated. TRF1 turned up in what the scientists dubbed complex A, and TRF2 appeared in complex B. Further evidence that TRF1 and TRF2 go their own way came when the researchers altered cells that produce normal TIN2 to also make either of two TIN2 mutants. One of the mutants, which can't attach to TRF1 but can latch onto TRF2, bound to and broke up the B complexes. The second mutant, TIN2, which can't hook onto TRF2 but can bind to TRF1, disrupted A complexes.

The work indicates that the A and B complexes perform different jobs. The tail of a telomere doubles over on itself, a process called capping. Complex B appears to control capping, whereas complex A might help the telomere keep in shape. However, the researchers say they still haven't ruled out the possibility that the A and B complexes combine. The team also discovered that disrupting the B complex was lethal for cells missing the antitumor protein p53, which is absent from many cancer cells. That finding points to drugs that break up the complex as a possible treatment for cancer. JCB

Kim, S.-h., et al. 2008. *J. Cell Biol.* doi:10.1083/jcb.200710028.

CENP-E goes fishing for microtubules

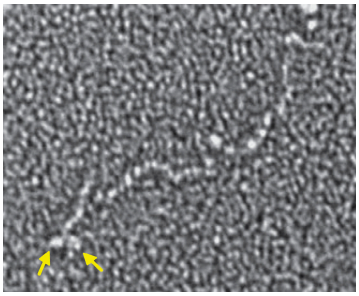
The first close-ups of a protein that's crucial for lining up the chromosomes during mitosis have been snapped by Kim et al. Their work might clarify how chromosomes retain connections to the microtubules that help move them around.

Microtubules attach to a mitotic chromosome at the kinetochore, a structure at the chromosome's midsection. Kinetochores have to keep a grip on microtubules that are lengthening and shortening, but scientists don't understand how they do it. Kim et al. came up with a possible explanation while investigating the role of CENP-E, an essential microtubule motor that clings to the kinetochore.

CENP-E is tricky to purify, but Kim et al. isolated enough of the protein to scrutinize under the electron microscope. The images show that the protein contains two motors at the end of a long, springy strand. When the researchers tested the protein's pulling ability, they found that it was 50 times slower than any other molecular motor. However, CENP-E was sticky, sometimes hanging onto microtubules for more than 20 minutes.

The protein thus has flexibility, reach, and tenacity. These attributes, the authors suggest, allow CENP-E to anchor to the kinetochore with one end, while the other, motor-carrying end gropes around and grabs microtubules. Once it's gotten a grip, its ability to slide keeps the chromosome attached to the shrinking or lengthening microtubule. JCB

Kim, Y., et al. 2008. *J. Cell Biol.* doi:10.1083/jcb.200802189.



A stretched out CENP-E molecule sports two molecular motors (arrows).