In This Issue

Huntington's disease protein extends its reach

The mutant protein that causes Huntington's disease doesn't just wreak havoc inside the nucleus. It also makes trouble in the cytoplasm, as Wang et al. show.

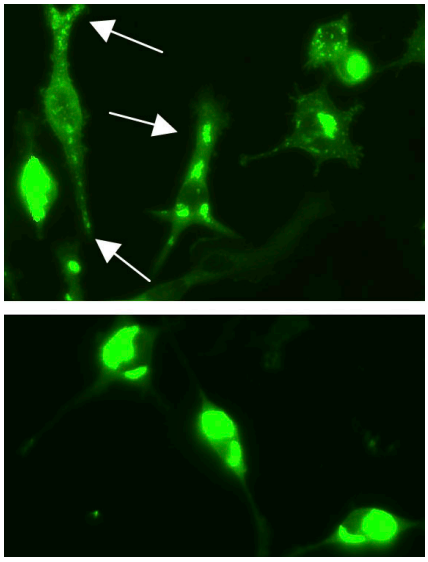
The symptoms of Huntington's disease—which include personality changes and jerky movements—stem from damage triggered by a version of the protein huntingtin that sports extra copies of the amino acid glutamine. The abnormal protein forms globs in the nuclei of brain cells and stifles transcription of necessary genes. Smaller clumps of huntingtin also lurk in the cytoplasm, but researchers weren't sure whether these could injure neurons.

To find out, Wang et al. produced an intracellular antibody, or intrabody, that preferentially targeted mutant huntingtin in the cytoplasm. In rat brain cells that produce mutant huntingtin, nuclei break up and neurites—extensions that connect to neighboring cells—deteriorate. But both of these defects were less common when the authors engineered the cells to produce the intrabody.

The researchers then scaled up from cells to whole animals and asked whether the intrabody eased symptoms in mice that make mutant huntingtin. The team injected a virus carrying the intrabody gene into the striatum, a brain area devastated in the disease. Compared with controls, the injected animals had less difficulty walking and were better able to keep their balance on a slowly revolving rod. However, their life span didn't increase, possibly because the intrabody protects only one of the brain regions injured by faulty huntingtin.

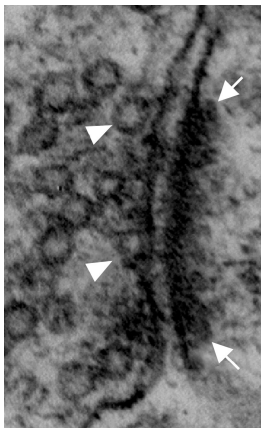
Intrabody-making cells harbored less mutant huntingtin in neurites than did control cells, the team found. The intrabody appears to promote attachment of ubiquitin molecules that spur destruction of the rogue molecules.

Because symptoms are less severe when the intrabody ties up mutant protein in the cytoplasm, the researchers conclude that nonnuclear huntingtin is responsible for some ill effects of the disease. How cytoplasmic huntingtin causes harm remains uncertain, however. JCB



Cytoplasmic clumps of mutant huntingtin (arrows, top) are smaller in cells that produce an internal antibody (bottom).

Wang, C.-E., et al. 2008. *J. Cell Biol.* doi:10.1083/jcb.200710158.



Vesicles ready for release (arrows) cluster at a synapse in a hippocampal neuron.

Slow synapses in schizophrenia?

The hallucinations, delusions, and confused thinking of schizophrenia might result from sluggish synapses, as Chen et al. reveal. The team found that neurotransmitter release slowed in mice missing a protein that's also scarce in many schizophrenia patients.

Scientists have long suspected that synaptic transmission is faulty in schizophrenia. Clues to the mechanism might come from schizophrenia susceptibility genes, one of which codes for the synaptic protein dysbindin. Although scientists haven't identified any dysbindin mutants in schizophrenia patients, lower levels of the protein in two brain areas, the hippocampus and the prefrontal cortex, might produce the disease's symptoms. Chen et al. tested mutant mice that lack dysbindin (known as "sandy" mice) to determine how loss of the protein alters synaptic transmission.

Transmission across the synapse involves the release of neurotransmitter vesicles. The researchers first asked whether vesicle release in general was affected in sandy mice, by studying the animal's adrenal gland cells—commonly used models for vesicle dynamics. Applying a technique called amperometry, which detects discharge of individual vesicles, the team found that although vesicles were larger than normal in sandy mice, vesicle release took longer and the odds of a particular vesicle unloading its contents were lower. The researchers then saw a similar pattern in hippocampal neurons from sandy mice: larger vesicles but tardy release.

Neurotransmitter vesicles poised for release line up on the presynaptic side of the neuron. But neurons from sandy mice showed fewer of these vesicles than did control cells. The changes Chen et al. identified could impair a neuron's ability to relay a message. The next step is to determine whether synapses in schizophrenia patients show similar changes. JCB

Chen, X.-W., et al. 2008. *J. Cell Biol.* doi:10.1083/jcb.200711021.

Text by Mitch Leslie
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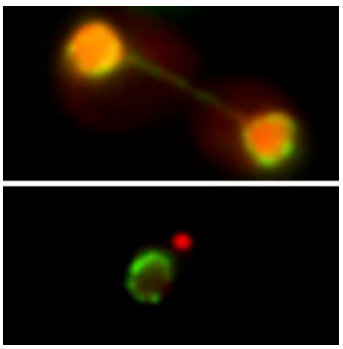
Dieting yeast clean house

When a yeast cell hunkers down for hard times, it kicks its proteasomes out of the nucleus, as Laporte et al. show.



Proteasomes (red) are scattered around the nucleus of a dividing cell (top), but cluster in the cytoplasm when the cell is quiescent (bottom).

The cell's garbage disposal, the proteasome, digests proteins that are damaged or no longer needed. In dividing yeast, proteasomes in the nucleus help drive the cell cycle by demolishing regulatory proteins such as cyclins at crucial times. But yeast spend much of their lives in a nondividing state prompted by food scarcity. Laporte et al. tracked what happens to proteasomes during this quiescence.

Hungry yeast ejected proteasomes from the nucleus and stashed them in previously undescribed cytoplasmic structures that the researchers dubbed proteasome storage granules. Whether the exiled proteasomes were functional wasn't clear. But when the cells found a meal, the proteasomes returned to the nucleus, the team found.

Laporte et al. speculate that a cell stores its proteasomes, instead of breaking down and then resynthesizing them, so it can quickly fire them up after quiescence and clear damaged proteins that have built up in the nucleus. Whether mammalian cells relocate their proteasomes is an open question. Proteasomes do bunch up in certain diseases, but these congregations might not be comparable to the granules, the researchers note. Pinning down what happens to proteasomes in mammalian cells might provide clues about the origin and growth of cancer, since most of the cells in our bodies are in a nondividing state similar to yeast quiescence. Moreover, many cancer cells depend on proteasome activity to continue multiplying. JCB

Laporte, D., et al. 2008. *J. Cell Biol.* doi:10.1083/jcb.200711154.

Synapse crowd control

New work from Leal-Ortiz et al. shows how a protein helps neurons fine-tune synapse sensitivity. The protein reduces synapse responsiveness by detaining another protein that holds down neurotransmitter-containing vesicles.

Like paratroopers ready to jump, vesicles line up at a neuron's presynaptic membrane, waiting for an action potential to arrive. Behind this so-called active zone, many more vesicles remain in reserve. Leal-Ortiz et al. wanted to nail down the function of a giant protein called Piccolo, which researchers suspect helps shape the active zone and serves as a scaffold for other proteins.

The team used RNAi to eliminate the protein from cultured neurons. Synapses between the cells formed normally even when Piccolo was absent. But the neurons released neurotransmitter vesicles more readily after stimulation than did cells with Piccolo.

A protein called Synapsin 1a straps reserve vesicles to the cytoskeleton. To move forward to the active zone, the vesicles need to sever their bonds. Piccolo appeared to limit this movement by regulating the mobility of Synapsin 1a. In cells without Piccolo, Synapsin1a was more likely to drift away from the synaptic terminal, allowing the reserve vesicles to break free. How Piccolo keeps Synapsin1a close to the active zone is the next question to be answered, say the authors. JCB

Leal-Ortiz, S., et al. 2008. *J. Cell Biol.* doi:10.1083/jcb.200711167.

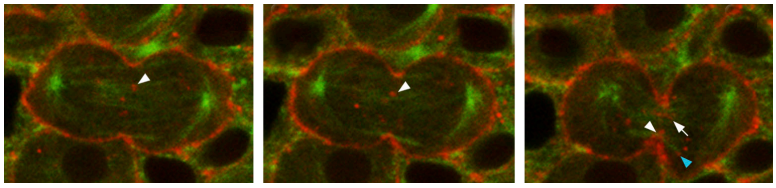
Actin hitches a ride to the cleavage furrow

When it comes to efficient packing and shipping, FedEx doesn't have anything on a dividing cell. As Albertson et al. report, the cell bundles two ingredients needed for division and then speeds them along a microtubule highway to their destination.

Cell division begins when a structure called the contractile ring tightens, creating a furrow that expands to eventually cut the cell in two. Deepening the furrow requires a continual supply of actin filaments, which drive constriction of the contractile ring, as well as a supply of new membrane. Where the fresh actin filaments come from has puzzled researchers. One possibility is that actin monomers already in the furrow polymerize. Alternatively, cells could truck in preformed filaments. How cells target new membrane to the furrow was also unclear.

Both components travel together, Albertson et al. discovered when they followed fluorescently labeled vesicles in *Drosophila* embryo cells. The researchers observed tagged vesicles sliding toward the furrow and embedding in its edge. Actin rode on the outside of the vesicles. During mitosis, microtubule bundles at the center of the cell combine to form a structure called the central spindle. The vesicles and their actin cargo cruised to the cleavage furrow along these microtubules. Presumably, one of the motor proteins attached to the vesicles dragged them along. The researchers now want to determine which motor powers the vesicles. JCB

Albertson, R., et al. 2008. *J. Cell Biol.* doi:10.1083/jcb.200803096.



Time-lapse images show packages of actin (red, arrows) at the cleavage furrow of a dividing cell.