In This Issue

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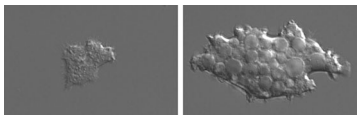
WASH cleans up after sloppy eaters



A wild-type *Dictyostelium* (left) contrasts with one lacking WASH (right), which is crammed with vesicles containing indigestible dextran.

Carnell et al. have discovered a new job for actin. In social amoebas, actin helps recycle a valuable protein before the cell throws out its garbage.

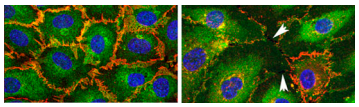
Dictyostelium is not a picky eater. So sometimes the social amoeba gobbles something it can't digest, such as yeast or the cell walls of certain bacteria, and ends up spitting out its meal. In this process, the lysosome that harbors the indigestible material switches from acidic to neutral and converts into a postlysosome that eventually jettisons its contents through exocytosis. A layer of polymerized F-actin coats the lysosome as it neutralizes, but an open question was actin's function during the transformation.

Carnell et al. discovered the answer while studying the role of a lysosomal protein called WASH that regulates actin polymerization. Exocytosis stalled in slime mold cells lacking WASH. If the cells consumed large amounts of indigestible dextran, they ballooned and sported huge lysosomes that couldn't be expelled. Without WASH, lysosomes didn't neutralize, and cells didn't accumulate the large, actin-covered vesicles that form when several postlysosomes fuse before exocytosis.

Removing WASH also prevented cells from recycling V-ATPase, a protein complex that attaches to the lysosome and maintains the high acidity inside. The researchers think that WASH's role on the lysosome is to attract actin that ushers V-ATPase (and presumably other molecules) into recycling endosomes. V-ATPase is large and costly to make, so the cell gains by recycling it from the lysosome rather than misdirecting it to the plasma membrane.

Carnell, M., et al. 2011. *J. Cell Biol.* doi:10.1083/jcb.201009119.

Caveolin-1 says NO to permeability



Endothelial cells normally stick together (left), but thrombin opens gaps between them (arrowheads, right).

Proteins and other substances can cross the endothelial layer that lines a blood vessel via two routes. Caveolin-1 is essential for both, Siddiqui et al. show.

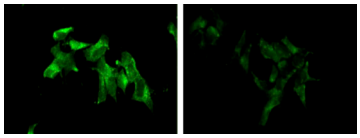
Researchers already knew that caveolin-1 was necessary for transcellular protein trafficking, in which macromolecules such as albumin enter an endothelial cell from the bloodstream and exit on the tissue side. Caveolae swallow these molecular travelers and bundle them into vesicles that wend through the cell. In an alternative pathway, known as the paracellular route, molecules slip between the cells of the endothelial layer, passing through the adherens junctions that fasten adjacent cells together. Previous work showed that adherens junctions become permeable in mice lacking caveolin-1, suggesting that the protein helps seal the junctions.

Siddiqui et al. dissected the molecular chain of events that connects caveolin-1 to adherens junction integrity. Loss of caveolin-1 activated the enzyme eNOS, which spawns nitric oxide (NO) that reacts to form peroxynitrite. In turn, peroxynitrite modifies the adherens junction protein p190RhoGAP-A, preventing it from inhibiting RhoA. Activated RhoA then tweaks the cytoskeleton at adherens junctions, making them leaky. The researchers found that they could reseal the junctions by blocking eNOS or RhoA activity.

The inflammation-promoting enzyme thrombin also tampers with adherens junctions through this pathway, Siddiqui et al. found. An open question, they say, is whether such disruption allows fluid buildup and migration of inflammatory cells across the endothelial layer, both of which are characteristic of inflammation.

Siddiqui, M.R., et al. 2011. *J. Cell Biol.* doi:10.1083/jcb.201012129.

Noncoding RNA to blame for bad editing



The alternative KCNIP4 splice variant Var IV (green) is prevalent in cells that make extra 38A (left) but rare in control cells (right).

Massone et al. pinpoint a small RNA that spurs cells to manufacture a particular splice variant of a key neuronal protein, potentially promoting Alzheimer's disease (AD) or other types of neurodegeneration.

Like a movie with an alternate ending, a protein can come in more than one version. Although scientists have identified numerous proteins and RNAs that influence alternative splicing, they haven't deciphered how cells fine-tune the process to produce specific protein versions. Four years ago, researchers identified a set of 30 small, noncoding RNAs manufactured by RNA polymerase III, which they suspected help regulate gene expression.

Massone et al. determined the function of one of the RNA snippets, known as 38A, that hails from an intron in the gene that encodes the potassium channel–interacting protein (KCNIP4). KCNIP4 latches onto the potassium channel Kv4, and together they ensure that neurons fire in a characteristic slow, repeating pattern. The researchers found that 38A spurs cells to produce a splice variant of KCNIP4, Var IV, that disrupts this current, potentially leading to neurodegeneration.

KCNIP4 normally interacts with γ-secretase, the enzyme complex that helps generate β-amyloid (Aβ), a protein that accumulates in the brains of AD patients. But Var IV can't make the connection, possibly disturbing Aβ processing. Supporting that notion, the researchers found that levels of 38A were more than 10 times higher in brain cells from AD patients than in controls. 38A also hiked output of the more dangerous Aβ isoform, Aβ 1-42.

Massone, S., et al. 2011. *J. Cell Biol.* doi:10.1083/jcb.201011053.