Research Roundup

A fatal break up

Apoptosis can be short-circuited by inhibiting a protein that stimulates mitochondria to split. The finding suggests that mitochondrial fission is indispensable for programmed cell death.

Most mitochondria are not the solitary, kidney bean–shaped objects you see in the textbooks, says Richard Youle (National Institute of Neurological Disorders and Stroke, Bethesda, MD). Instead, the organelles have an active social life, often linking up to form long, interconnected chains, and then sometimes splitting apart again. During apoptosis, however, networks of mitochondria shatter into small, “punctiform” blobs. The mitochondria of a dying cell also spill their guts, dumping proteins such as cytochrome c that further drive apoptosis.

To discover what spurs mitochondrial fission, Youle and colleagues focused on a protein called Drp1, a member of a class of proteins known as dynamin that are involved in endocytosis and vesicle formation. In a healthy cell, Drp1 loiters in the cytosol and regulates the division of mitochondria. But the authors found that during apoptosis, Drp1 swarms to the mitochondria, concentrating at the sites where the organelles tend to cleave. Youle believes that these Drp1 complexes hasten mitochondrial breakup. Blocking Drp1 not only slows the splitting of mitochondrial networks, it also prevents release of cytochrome c and thwarts apoptosis. The researchers plan to probe how Drp1 works and why its actions change once apoptosis begins. “It works in healthy cells to regulate mitochondrial dynamics,” Youle says, “the question is how does it change from its normal function to its proapoptotic function.”


In the nick of time

Like romance, politics, and batting, cell division requires good timing. Now, a molecular switch that sets the pace for the early part of the cell cycle has been discovered. The switch is novel because it revs up one pathway, while blocking another that may accelerate the cell cycle.

A team led by Richard Assoian of the University of Pennsylvania (Philadelphia, PA) already knew that progression through the cell cycle depended on the protein cyclin D1. Induced during the middle of the G1 phase, cyclin D1 activates a cyclin-dependent kinase that advances the cell through the rest of that phase. Thus, cyclin D1 is vital to the timing of the cell cycle, says Assoian. “We view it as the event that sets the clock for the balance of the events that occur during G1 phase.” But how does the cell ensure that the cyclin D1 gene turns on at the right time?

Assoian and colleagues determined that the master switch was a protein called Rho, which performs two functions. Rho is required for the activation of ERK MAP kinases, which are necessary for cyclin D1 expression in the middle of the G1 phase. The other function showed up when the authors inhibited Rho. Cyclin D1 turned on earlier in G1 phase, stimulated by an alternative pathway that Rho normally keeps silent. How Rho exerts control over the two pathways remains a mystery, Assoian says. He adds that the second pathway might allow the cell to shorten G1 phase and grow faster, although that possibility is unproven. “Rho might allow the cell to decide which pathway to turn on.”

Slide this way

When cells of the slime mold Dictyostelium sense cAMP, they get the urge to merge, steering toward the source of the chemical and fusing into a slimy blob. By observing labeled cAMP receptors on traveling slime mold cells, Masahiro Ueda (Osaka University, Osaka, Japan) and coworkers were able to document differences in receptor activity between the “front” and “back” ends. The paper marks one of the first uses of a new technique for resolving and monitoring individual molecules.

To label the individual cAMP receptors, the authors fused cAMP molecules to an orange fluorescent dye called Cy3 and then exposed the slime mold cells to the compound. Using a total internal reflection fluorescence microscope, they could track and count the receptors on the cell surface that had bound to the glowing cAMP. “This technique can reveal the dynamics of the individual signaling molecules in living cells,” says Ueda.

The observations confirm previous reports that the migrating cells are polarized. Although there were about the same number of receptors at each end, 12% more receptors were bound to cAMP at the anterior end than at the posterior end. The investigators also found that the receptors at the anterior end released their cAMP more quickly. How the cells become polarized remains a mystery, Ueda says. However, polarity apparently develops independent of the cAMP gradient. “It will be important to determine how cells initially form such a polarity in receptor states and whether chemoattractant gradients can modify it,” Ueda says.


Staying connected

Learning spurs axons in the brain to grow and connect with other neurons. However, scientists know little about what maintains these connections, which sometimes last a lifetime. A new study reveals that a protein known as p190 RhoGAP stabilizes the axon. The authors report that p190 works by stiffling a built-in “retraction pathway” that causes axons to shrink.

Liqun Luo of Stanford University, Palo Alto, CA, and colleagues investigated p190’s function in the Drosophila mushroom body, the part of the brain responsible for olfactory learning and memory. When they inhibited p190 in neurons, the axon branches shrank or even disappeared. They got the same results by activating the RhoA pathway, which p190 normally blocks. “The idea that in mature neurons there is a pathway whose job is to destroy the axon is surprising,” says Luo.

The authors did not look for behavioral abnormalities in flies with inactivated p190. The results suggest, however, that regulation of the protein may have a role in the neural rewiring responsible for learning and memory, Luo says. p190 may also be linked to two other proteins that are necessary for memory formation or storage: Src and integrin. Since Src and integrin likely inhibit p190, their effects on memory may stem from changes in neuronal structure rather than changes in synapse function, says Luo.