In This Issue

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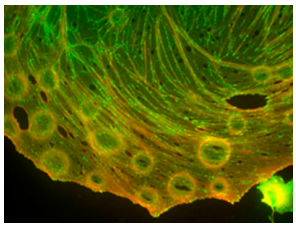
Smooth muscle cells put their best podosome forward



Rings of podosomes sprout from a smooth muscle cell lacking key microRNAs.

Two microRNAs keep smooth muscle cells on a leash. Now, Quintavalle et al. have uncovered a molecular pathway that sets the cells free and might worsen the arterial buildup of atherosclerosis.

When sedentary smooth muscle cells start crawling, they can cause trouble. The cells pile into the vessel lesions that form during atherosclerosis, and they can spur restenosis, the re-narrowing of an artery after an angioplasty or insertion of a stent. Previous studies have shown that two microRNAs, miR-143 and miR-145, prevent cells from switching to the mobile form. But researchers didn't know what controlled the microRNAs.

Quintavalle et al. created mice that lack miR-143 and miR-145. In a culture dish, a smooth muscle cell begins its journey by extending a membrane "foot" called a podosome. Using immunoelectron microscopy, the team identified smooth muscle podosomes in aortic tissue from the mice, the first time the structures have been spotted in vivo. The researchers showed that the microRNAs normally halt podosome extension, in part by down-regulating protein kinase C ϵ, PDGF receptor α, and fuscin.

Quintavalle et al. teased out the molecular pathway that unleashes smooth muscle cells. The circuit begins with platelet-derived growth factor (PDGF), which is overactive in patients with atherosclerosis and restenosis. PDGF activates Src, which reduces levels of the microRNAs by inhibiting p53. One of p53's tasks is spurring production of miR-143 and miR-145.

The results suggest the microRNAs as a potential treatment for atherosclerosis—though researchers first have to develop a practical way to deliver the molecules to vascular cells. The work also raises the question of whether these microRNAs shackle cancer cells, which crawl with podosome-like structures called invadopodia.

Quintavalle, M., et al. 2010. *J. Cell Biol.* doi:10.1083/jcb.200912096.

Ataxia's double hit

A fly larva carrying a faulty human β-III–spectrin gene hoists its paralyzed hindquarters, a maneuver called a tail flip.

The neurodegenerative disease spinocerebellar ataxia type 5 (SCA5) damages nerve cells in two ways. Lorenzo et al. report that the defective protein responsible for the disease cuts the number of synaptic terminals and snarls traffic inside neurons.

SCA5 results from a faulty gene for β-III–spectrin. The disease targets the cerebellum's Purkinje cells, which control coordination. How the mutant protein damages neurons remains uncertain. β-III–spectrin stabilizes synapses, suggesting that synapse deterioration might doom the cells. But the protein also helps the adapter protein dynactin hitch cargoes to dynein motors, pointing to a disruption of intracellular transportation.

The team found support for both mechanisms. They engineered fruit flies to carry a mutated β-III–spectrin gene. Fly larvae with the mutated gene had paralyzed tails. At the neuromuscular junctions where nerves and muscles meet, the larvae showed fewer presynaptic terminals.

The researchers next tracked the movement of synaptic vesicles in axons from the animals. Vesicles from flies that made the faulty β-III–spectrin were slower and more likely to change direction, and thus traveled shorter distances. Other neurodegenerative diseases, including Alzheimer's disease and amyotrophic lateral sclerosis, involve faulty transport, and the results indicate that SCA5 does too.

The two mechanisms might have a common link, the researchers suggest. The complex containing β-III–spectrin, dynactin, and dynein might not just haul cargoes. At the synapse it might snag microtubules that strengthen the membrane and prevent degeneration.

Lorenzo, D.N., et al. 2010. *J. Cell Biol.* doi:10.1083/jcb.200905158.

IFT proteins go off the rails

Flagella and cilia serve as molecular highways. Sedmak and Wolfrum have for the first time tracked down several key proteins involved in this transport. They also discovered the proteins in cells that have neither cilia nor flagella, indicating that the molecules have additional functions.

Traffic in cilia and flagella runs in both directions. Kinesin motors haul cargo up, while dynein molecules ferry it down. Crucial for this movement are intraflagellar transport (IFT) proteins, which researchers think cluster into complexes. However, where the individual IFT proteins settle in the cell and what they do are unclear.

Using immunoelectron microscopy, Sedmak and Wolfrum pinpointed five IFT proteins in photoreceptor cells from the retina. The photoreceptor cell's outer segment harbors light-sensitive pigments. All the active organelles reside in the inner segment of the cell. The connecting cilium is the only cytoplasmic bridge through which cargoes can pass between the segments.

The researchers found that the five IFT proteins didn't always occur together, suggesting that they perform different tasks during intraflagellar transport. For example, at the base of the connecting cilium, cargoes leave the microtubules that transported them through the inner segment and switch to the cilium for the trip to the outer segment. Three of the IFT proteins clustered at this transfer station, slightly apart from the other two. This separation might indicate that the two protein bunches load different cargoes onto the cilium. Another difference involves the protein IFT20, the only one that appeared in the Golgi apparatus. Its job could include sorting molecules destined for the cilium.

To the researchers' surprise, when they checked the dendrites of neurons that don't carry cilia or flagella, they also spotted IFT proteins on cargo vesicles. Last year, a study found the proteins in T cells, which also lack the structures. These findings broaden the range of cells that rely on IFT proteins and suggest that they also take part in non-ciliary transportation.

Sedmak, T., and U. Wolfrum. 2010. *J. Cell Biol.* doi:10.1083/jcb.200911095.

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