In This Issue

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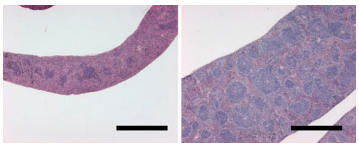
Both routes to cell death necessary



When Bim can't hook to Bax (right), reduced apoptosis leads to a larger spleen than in controls (left).

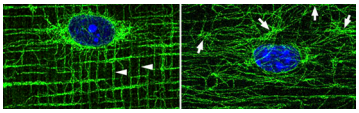
Bak and Bax are killers that can dispatch a cell in no time—once they switch on. Mérino et al. have discovered that two different explanations for the activation of these apoptosis-promoting proteins are both partly right.

Once Bak and Bax flip on, the cell is done for. Mitochondria begin to leak, spilling apoptosis-stimulating molecules that eventually cause cell death. Proteins that carry the BH3 domain, like Bim, trigger apoptosis, but researchers have clashed over how these proteins work. Some scientists argue that certain BH3 proteins turn on Bak and Bax by direct binding. Other researchers support an indirect activation model, in which BH3 proteins neutralize pro-life molecules such as Bcl-2 and Bcl-x_L, which normally suppress Bax and Bak. So far, in vitro studies have been inconclusive.

Mérino et al. performed the first in vivo study on Bim, engineering mice to produce the protein with various modifications to its BH3 domain. Bim normally controls blood cell homeostasis, so the researchers used white cell counts and spleen weight as gauges of cell suicide. If the indirect hypothesis is correct, you'd expect that mice carrying Bim versions unable to grab and switch off all the pro-survival proteins would show less apoptosis than normal. But if only indirect activation is important, you'd expect that Bim variants that can neutralize all of the pro-survival molecules but can't activate Bax would have normal levels of apoptosis. However, cell death decreases in both animals. The researchers conclude that both routes are necessary to explain how Bim engages Bax and Bak. The findings might help refine cancer drugs that emulate BH3-carrying proteins.

Mérino, D., et al. 2009. *J. Cell Biol.* doi:10.1083/jcb.200905153.

Dystrophin makes a new connection



The tidy microtubule lattice of a normal muscle (left) turns into a tangle when dystrophin is missing (right).

Dystrophin, the protein absent in Duchenne muscular dystrophy, is better at networking than researchers realized. The protein's links to two kinds of cytoskeletal components are well known, and now Prins et al. demonstrate that dystrophin also fastens to microtubules.

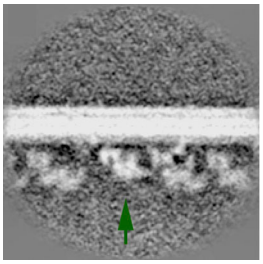
With its fragile plasma membrane, a muscle cell lacking dystrophin can die from mechanical stress. Although dystrophin is a middleweight in comparison, it resembles the heavyweight cytolinker proteins that keep cells in shape by hitching membrane-spanning proteins to the cytoskeleton. Previous studies have shown that it hooks up with transmembrane proteins and two parts of the cytoskeleton—intermediate filaments and actin—but researchers haven't demonstrated a connection to microtubules.

Prins et al. showed that dystrophin and microtubules coincide at costameres, portions of the cytoskeleton that reinforce the plasma membrane in muscle cells. The researchers also observed that microtubules and dystrophin sediment together if dystrophin sports a putative microtubule-binding domain, but not if the domain is missing. Dystrophin also stabilizes microtubules forced to depolymerize by cold. And when cells lack the protein, microtubule networks snarl.

The findings suggest that dystrophin does function like the cytolinkers, providing structural support for muscle cells in part by stabilizing or organizing microtubules. As a result, muddled microtubules might be responsible for some of the defects of muscular dystrophy.

Prins, K.W., et al. 2009. *J. Cell Biol.* doi:10.1083/jcb.200905048.

Chlamydomonas does the lopsided wave



The arrow indicates where a crossbridge extends from doublet 1 of *Chlamydomonas*' flagellum.

Not all flagella look alike, at least if you zoom in close enough. Bui et al. have identified structural quirks in the *Chlamydomonas* flagellum that might account for the alga's swimming style.

When a sperm wriggles, its flagellum undulates symmetrically like a crawling snake. When *Chlamydomonas* zips along, by contrast, it appears to do the breast stroke, as its twin flagella reach forward and then pull back. *Chlamydomonas*' flagella sport the standard "9 + 2" structure of nine microtubule doublets surrounding a central pair. The trick has been to find a structural imbalance in these flagella that could explain why the movements of extension and retraction are asymmetric.

Bui et al. used electron cryotomography to take a close look at the flagellum and found that microtubule doublet 1 was the oddball. Dynein arms typically link neighboring microtubule doublets. When these arms pull, adjacent doublets slide past one another, and the flagellum flexes. But doublet 1's inner dynein arm is missing one of the molecules that is usually present in other doublets. Bui et al. hypothesize that this difference slows the sliding between doublet 1 and its neighbors, doublets 2 and 9.

The researchers also found more interconnections between microtubule pairs—including a strong bridge between doublets 1 and 2—than previously identified. The final picture the team concludes, is that doublets 9, 1, and 2 differ from the three doublets that lie on the opposite side of the shaft. That disparity might yield asymmetrical motion when the alga swims.

Bui, K.H., et al. 2009. *J. Cell Biol.* doi:10.1083/jcb.200903082.