In This Issue

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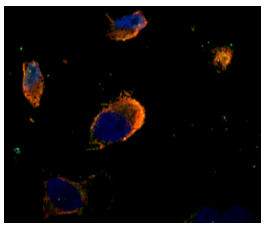
TCAF1 puts a chill on prostate cancer



TRPM8 (red) and TCAF1 (green) colocalize at the plasma membrane.

The partner of a cold-sensing ion channel prevents prostate cancer cells from migrating, Gkika et al. reveal.

The ion channel TRPM8 detects low temperatures, but it occurs in parts of the body that aren't exposed to the cold, such as the prostate and bladder, suggesting that it has other roles. The protein is overexpressed in prostate tumors and other cancers, and the researchers previously determined that it curbs migration of prostate cancer cells.

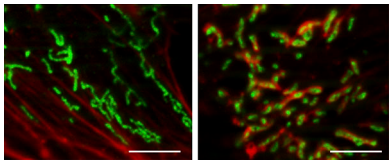
Gkika et al. looked for proteins that interact with TRPM8. Two of its partners were previously uncharacterized proteins that the authors named TCAF1 and TCAF2. The researchers found that TCAF1 and TCAF2 help TRPM8 move into the plasma membrane. However, the proteins have opposite effects on TRPM8's activity. TCAF1 stimulates the channel, whereas TCAF2 shuts it down. The difference appears to lie in TCAF1's tail, which, unlike TCAF2's, sports a domain that is homologous to PI3K.

TCAF2 levels were the same in normal and cancerous cells. But like TRPM8, TCAF1 was overexpressed in prostate cancers that hadn't spread, whereas in metastatic prostate cancer cells the levels of TRPM8 and TCAF1 plunged, likely as a side effect of the treatment the patients had received to suppress androgen production.

The researchers found that TCAF1 slowed migration of prostate cancer cells in vitro but that TCAF2 stimulated cell motility. The work suggests that TCAF proteins regulate TRPM8 and possibly other TRP channels, functioning like the accessory subunits that control the activity and location of voltage-gated channels.

Gkika, D., et al. 2015. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201402076.

Actin is good at long division



Actin (red) and mitochondria (green) remain separate in control cells (left), but actin gathers on the organelles when they are stimulated to divide (right).

F-actin helps mitochondria divide by polymerizing on the organelles, Li et al. show.

The GTPase Drp1 forms spirals around mitochondria to cut the organelles in two. Studies suggest that actin also has a role in mitochondrial division and recruitment of Drp1. The mechanisms, however, remain unclear.

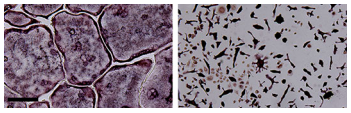
Li et al. found that F-actin polymerizes on the outer mitochondrial membrane in cultured cells but doesn't extend into the organelles. When the researchers spurred mitochondria to divide by putting them under stress, F-actin amassed on the organelles. However, latrunculin B, which prevents actin polymerization, curtailed this accumulation. Actin therefore gathers on mitochondria when they are ready to split.

The proteins cortactin and cofilin and the Arp2/3 complex—all of which spur actin to branch— also collect on mitochondria, Li et al. found. Depleting any of these factors led to extra-long mitochondria but didn't alter the rate of organelle fusion, suggesting that actin branching promotes mitochondrial division.

In cells lacking Drp1, extra cortactin, cofilin, and Arp2/3 accumulated on mitochondria. In cells lacking either cortactin or cofilin, mitochondria carried excess Drp1. Mitochondria are abnormally long in both types of cells, suggesting that Drp1 accumulation and F-actin polymerization are necessary for mitochondrial fission. But how actin polymerization helps Drp1 cleave mitochondria remains unknown.

Li, S., et al. 2015. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201404050.

No substitute for β3 integrin



Osteoclasts from a mouse that lacks Dap12 and αvβ3 integrin (right) don't measure up to normal osteoclasts (left).

Thanks to some big-boned mice, Zou and Teitelbaum determined how osteoclasts get along without a key signaling protein.

Osteoclasts continually break down bone as part of the skeleton's normal repair and regeneration. When an osteoclast attaches to bone, the cell's cytoskeleton rearranges to form a tight seal. A signaling complex that contains αvβ3 integrin detects bone and triggers this cytoskeletal reorganization. Another component of the complex is Dap12. The bones of mice lacking the αvβ3 integrin are only slightly more dense than normal, as are the bones of mice lacking Dap12. The skeletal effects of Dap12 loss might be minimal because another protein, FcRγ, can substitute for it.

Zou and Teibelbaum examined the bones of mice lacking Dap12 and β3 integrin. They expected that the animals would have marginally thicker bones than mice deficient in only one of the proteins. Instead, the double knockout mice had massive, dense bones. Their osteoclasts were puny, attached weakly to bone, and showed a distorted cytoskeleton.

In contrast, the bones of mice missing β1 integrin and Dap12 were no different from the bones of mice lacking Dap12 alone. That result suggested that FcRγ requires β3 to replace Dap12. The researchers tested this idea by determining whether the signaling complex transmits a "dissolve bone" message, a sign that it has been activated. FcRγ and its co-receptor OSCAR send this signal in osteoclasts lacking Dap12 but not in cells missing Dap12 and β3.

The osteoclast signaling complex therefore comes in two forms. One version usually includes Dap12 and αvβ3 integrin, but β1 can stand in for β3. The other combination includes FcRγ instead of Dap12 and can't function unless it contains β3.

Zou, W., and L. Teibelbaum. 2015. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201410123.