In This Issue

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New Twist on cell migration

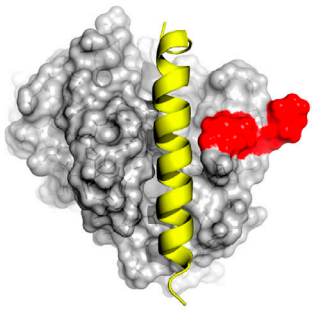
Instead of packing the dishes and submitting a change of address form, a cell that is about to move replaces its surface proteins, revamps its cytoskeleton, and alters its shape. Lander et al. show that one enzyme serves as a master controller for this process.

A cell's pre-move preparations are referred to as the epithelial–mesenchymal transition (EMT). Embryonic cells undergo EMT before they relocate during develoment, as do tumor cells that are about to metastasize. Researchers are still working out how cells regulate EMT so that the molecular and behavioral changes occur in concert and at the right time. Thus far, they have shown that the transcription factors Slug, Snail, Twist, and Sip1 help activate EMT. In turn, the enzyme Partner of paired (Ppa) adjusts the levels of Slug and Snail, triggering their ubiquitination so that they can be destroyed by the proteasome.

Lander et al. discovered that Ppa also controls cellular quantities of Twist and Sip1 by promoting their ubiquitination. Thus Ppa regulates all four of the EMT-triggering transcription factors, despite their structural differences. Using the same protein to manage Slug, Snail, Twist, and Sip1 may ensure that the transcription factors work in synchrony and that their effects can be shut down simultaneously. The work also suggests that it might be possible to curtail metastasis by targeting Ppa to disrupt EMT.

Lander, R., et al. 2011. *J. Cell Biol.* doi:10.1083/jcb.201012085.

Bak activators get in the groove



A model shows how a portion of the activator Noxa (yellow) settles into the groove on Bak.

The protein Bak belongs to a molecular hit squad that spurs apoptosis. Dai et al. reveal that Bak has to make the right connection before it can kill cells.

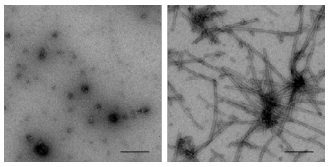
Bak and its cousin Bax dispatch their victims by perforating the outer membrane of mitochondria, permitting cytochrome *c* to escape. Researchers think that a family of proteins called BH3-only proteins control this function of Bak and Bax. The leading hypothesis is that some BH3-only proteins, known as direct activators, bind to Bak or Bax and induce them to oligomerize, thereby switching them on. Another group of BH3-only proteins, the sensitizers, latch onto antiapoptotic relatives of Bak and Bax and prevent them from inhibiting activation.

To nail down the details of Bak's activation, Dai et al. followed its interactions with BH3-only proteins in vitro. They found that the protein bound to three direct activators but not to one of the sensitizers. Unlike Bax, which loiters in the cytoplasm until it's needed on the mitochondrion, Bak remains on the mitochondrial membrane. The researchers showed that a lipid milieu wasn't necessary for binding between BH3-only proteins and Bak, although it did strengthen the link between the partners.

The researchers also showed that only a transient interaction between BH3-only proteins and a groove on Bak was required to trigger Bak's oligomerization. Bak couldn't kill cells if the team prevented this brief interaction. Scientists still need to determine the structures of the Bak and Bax oligomers and how they enable the proteins to puncture the mitochondrial membrane.

Dai, H., et al. 2011. *J. Cell Biol.* doi:10.1083/jcb.201102027.

SUMO defeats protein aggregates



Unsumoylated α-synuclein aggregates into fibrils (right), whereas sumoylated α-synuclein doesn't (left).

Sumoylation might prevent the protein aggregations that typify Parkinson's disease (PD), Krumova et al. report.

Insoluble protein clusters are the hallmarks of several neurodegenerative diseases. In PD, neurons harbor clumps of the protein α-synuclein. What triggers these protein pileups remains obscure. A possible clue for PD came when researchers overexpressed α-synuclein in human kidney cells and found that the protein was modified by the addition of the small, ubiquitin-like molecule SUMO. Since sumoylation generally boosts the solubility of proteins, the result raised the possibility that SUMO proteins affect the aggregation of α-synuclein.

Krumova et al. tested whether sumoylating purified α-synuclein hindered it from clustering into fibrils, filaments similar to those detected in neurons of PD patients. If all of the α-synuclein molecules in a solution were sumoylated, no fibrils appeared. And even if only 10% of the molecules were sumoylated, fibril formation slowed dramatically.

SUMO molecules typically attach to two sites on α-synuclein, the researchers found. Compared with controls, cells that produced α-synuclein mutants lacking these two sites contained more protein clusters and were more likely to die by apoptosis. The scientists then genetically altered rats to manufacture the α-synuclein mutants specifically in neurons. Cell death surged in the substantia nigra, the brain region where large numbers of neurons perish in PD patients. But whether sumoylation goes awry in these patients remains unknown.

Krumova, P., et al. 2011. *J. Cell Biol.* doi:10.1083/jcb.201010117.