In This Issue

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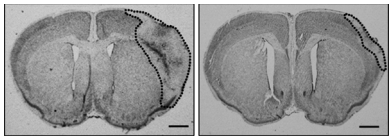
B23 steals to stop cell-killing pair



Larger lesions (outlined) form in the brains of mice engineered to produce faulty B23 (left) than in mice that overproduce normal B23 (right).

A cell-protecting protein saves neurons by breaking up a lethal molecular couple, Lee et al. reveal.

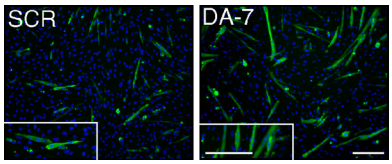
Stress can be deadly for a neuron. It triggers the cell to manufacture nitric oxide, which reacts with glyceraldehyde-3-phosphate dehydrogenase (GAPDH) and causes this enzyme to latch onto another protein, SIAH1. The GAPDH–SIAH1 tandem then slips into the nucleus and kills the cell by ubiquitylating various targets. But stress can also unleash a countervailing pathway, Lee et al. learned.

The researchers were searching for binding partners for the protein B23/nucleophosmin, whose functions include promoting cell survival. The GAPDH–SIAH1 complex turned out to be one of those partners. The team discovered that B23 can swipe nitric oxide from GAPDH and that nitrosylated B23, which showed enhanced binding to SIAH1, prevented GAPDH and SIAH1 from hooking up.

That interference saved cells. Lee et al. engineered cultured neurons to overproduce a normal version of B23 or a mutant version that can't bind to SIAH1. When they stressed the cells by adding the neurotransmitter NMDA, the researchers found that neurons that contained normal B23 were more likely to survive than were cells with the mutant version. Mice expressing mutant B23 unable to bind SIAH1 developed larger brain lesions in response to NMDA than did control mice, and the lesions were even smaller in mice that overproduced normal B23. These findings suggest that stress activates a cell-killing pathway but also indirectly spurs a cell-sparing pathway. How a neuron balances the two pathways to determine whether it lives or dies remains unclear.

Lee, S.B., et al. 2012. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201205015.

microRNA's big role in preventing tumors



Immature muscle cells transfected with seven miRNAs (right) differentiate into myotubes (green) more readily than control cells (left).

Like a second lock on a door, a team of microRNAs (miRNAs) provides a backup layer of protection against cancer, Marzi et al. show.

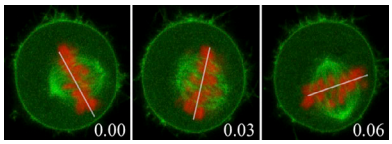
The levels of many miRNAs plummet in cancer cells. Studies suggest that this decline promotes cell division and makes tumors more aggressive, but researchers haven't worked out how. Marzi et al. suspected that the loss of miRNAs might be harmful because they normally combine forces with regulatory gene pathways to keep cell proliferation in check.

They tested the idea by engineering terminally differentiated muscle cells to express the oncogene E1A, which spurs the cells to "unspecialize" and reenter the cell cycle. E1A counteracts the tumor suppressor gene Retinoblastoma (Rb), and the team found that many of the genes that E1A induces foster cell division and are usually suppressed by Rb.

An independent layer of tumor suppression emerged when the team measured E1A's effects on more than 300 miRNAs. They identified 56 miRNAs whose levels changed upon E1A expression; E1A suppressed miRNAs that are normally produced during differentiation and unleashed miRNAs that induce proliferation. The researchers found that most of the miRNAs involved in differentiation were expressed independently of Rb and were instead regulated by the transcription factors Myc and MyoD. Seven of these miRNAs curbed division of immature muscle cells and stimulated their differentiation. The researchers conclude that these miRNAs constitute a distinct regulatory mechanism that curbs cancer development.

Marzi, M.J., et al. 2012. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201206033.

Dynein's helper not so helpful



When excess dynein reaches the cortex of cells overexpressing Gαi$_1$, the spindle oscillates, as indicated by the changing position of chromosomes over time (white lines).

A protein complex anchors dynein during mitosis but doesn't help the motor protein pull, Kotak et al. show.

The location of the mitotic spindle determines where animal cells divide and thereby decides the developmental fate of the resulting daughter cells. Proper spindle positioning requires a ternary complex of proteins that is thought to anchor dynein to the cortex beneath the cell membrane, where the molecular motor can maneuver the spindle into position. But previous research hadn't confirmed that dynein works at the cell membrane or determined whether the ternary complex serves as more than an anchor for dynein and has a more direct role in positioning the spindle.

HeLa cells overexpressing one ternary complex component, Gαi$_1$, recruited extra dynein to the cell cortex, resulting in exaggerated spindle movements. Cells expressing a version of Gαi$_1$ unable to bind to the membrane, however, lacked cortical dynein and carried misplaced spindles that barely moved, suggesting that membrane-anchored dynein is necessary for positioning the spindle.

To determine if cortical dynein is sufficient to orient the spindle, the researchers directed dynein to the plasma membrane by expressing the dynein-interacting portion of the ternary complex protein NuMA fused to a membrane-targeting motif. Cells expressing this construct showed excess spindle movements even in the absence of the ternary complex, suggesting that cortical dynein can adjust the spindle's location and that the ternary complex's primary function is to localize dynein to the right place at the right time.

Kotak, S., et al. 2012. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201203166.