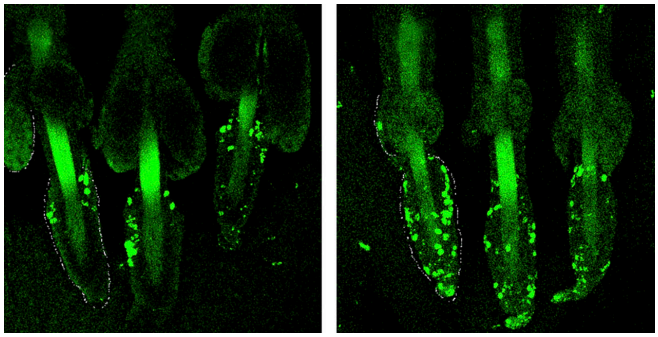
# In This Issue

## Stem cell slowdown

Stem cells become sluggish in a disease that resembles premature aging, as Espada et al. show. The work is the first in vivo study to link the disease to stem cell abnormalities.

In some ways, children with Hutchinson-Gilford progeria syndrome (HGPS) resemble their grandparents. They lose their hair, their bones weaken, and they develop atherosclerosis, which usually kills them as teenagers. HGPS patients manufacture a defective version of lamin A, a key component of the nuclear lamina. Two years ago, Paola Scaffidi and Tom Misteli strengthened the link between aging and HGPS, showing that healthy people accumulate faulty lamin A at the edge of the nucleus as they age. One hypothesis suggests that mutant lamin A causes some infirmities of HGPS and aging by hampering stem cells.



**Slowly dividing follicle stem cells (green specks) are more abundant in mice lacking Zmpste24 (right).**

Espada et al. tested this idea using a mouse model of HGPS. The animals fashion faulty lamin A because they lack an enzyme, Zmpste24, that helps trim the protein into its functional form. The team first measured the abundance of the skin's follicle stem cells, which promote wound healing and hair growth. To the researchers' surprise, the Zmpste24-deficient mice harbored more of these stem cells than did controls. However, these more numerous cells were reluctant to divide. In culture, stem cells from the mutant mice spawned smaller colonies than did cells from normal animals.

The researchers also found that abnormal lamin A disrupts the Wnt/β-catenin pathway that helps control the proliferation of stem cells. Zmpste24-lacking mice contained less of the active form of β-catenin and less cyclin D1, one of the division-promoting targets of the pathway.

Last month, Scaffidi and Misteli reported that mutant lamin A disrupted differentiation of mesenchymal stem cells (Scaffidi, P., and T. Misteli. *Nat. Cell Biol*. doi:10.1038/ncb1708). However, Espada et al. found that the follicle stem cells differentiated normally.

The mutant mice didn't show increased apoptosis by stem cells. But the suicide rate was higher among neighboring cells, whose signals nudge the stem cells to divide. The researchers conclude that abnormal lamin disrupts not just stem cells but also the surrounding cells that help control their behavior. The next step, the researchers say, is to look for similar defects in other stem cell types, such as hematopoietic stem cells. JCB

Espada, J., et al. 2008. *J. Cell Biol.* 181:27–35.

## Career change for a mitotic protein

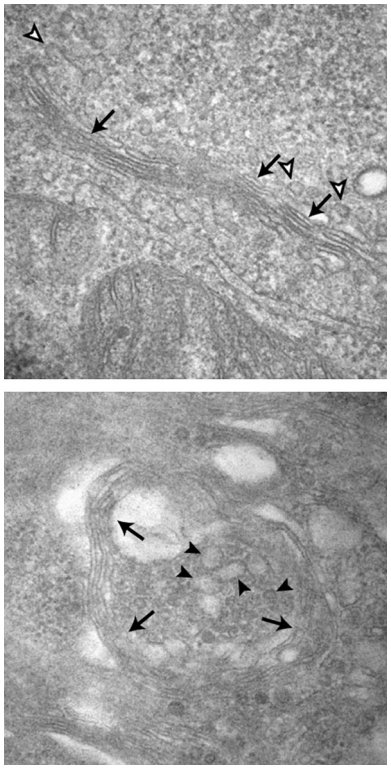
Mitosis involves more than parceling out chromosomes. A daughter cell also inherits part of the Golgi apparatus and ER from its parent cell. Nakajima et al. reveal that a protein once thought to dictate when a cell enters mitosis helps ensure that these organelles get passed on.

Conventional wisdom about the protein Myt1 held that it works with another protein called Wee1 to delay mitosis. Evidence for that view includes the fact that the proteins phosphorylate and inhibit Cdc2, a take-charge molecule that instigates mitosis when it enters the nucleus from the cytoplasm. Moreover, previous studies of yeast and human cells showed that overexpression of Myt1 prevents mitosis.

Nakajima et al. found otherwise when they used RNAi to cut Myt1 and Wee1 levels in human cells. Although cells low on Wee1 hurried into mitosis, the loss of Myt1 had little effect on mitotic timing. But Myt1 did perform a key job, the researchers discovered. During prometaphase, the Golgi apparatus fractures into thousands of tiny vesicles, some of which travel into the daughter cell and reassemble into a new Golgi apparatus. The breakup occured in cells missing Myt1, but the reunion did not. Instead of its normal folded ribbon shape, the Golgi apparatus in postmitotic, Myt1-lacking cells consisted of clustered vesicles and short or elongated tubes. Whether these defects hamper the Golgi is not clear.

Myt1 might also get the ER back into shape at the end of mitosis. Although researchers don't know all the changes that the ER undergoes during mitosis, the network appeared abnormal in Myt1-depleted cells that had just divided, Nakajima et al. found. The tubes were thicker than usual, and the cisternae that are normally scattered around the cell concentrated at its edge. Myt1 targets the B1 and B2 cyclins, which team up with Cdc2. The researchers conclude that by blocking these Cdc2/cyclin combinations, Myt1 allows the Golgi apparatus and ER to reform as mitosis concludes. JCB

Nakajima, H., et al. 2008. *J. Cell Biol.* 181:89–103.



**The Golgi apparatus's layered look (top) is lost without Myt1 is (bottom).**

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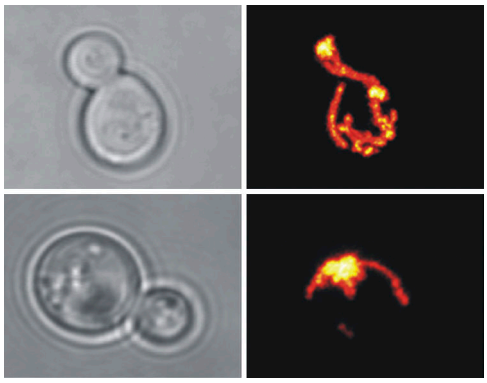


**During budding, glowing mitochondria remain stuck in the parent cell if Myo2's tail is mutated (bottom).**

## Hauling tail

Solving a long-standing mystery, Altmann et al. have discovered that mitochondria get around a yeast cell in style. The organelles ride on the tail of a myosin molecule known as Myo2.

Mitochondria are always on the move. They change positions within the cell, come together to fuse, and split apart. During cell division or budding, they migrate into the daughter cell. The organelles scoot along actin filaments, but what powers them has stumped scientists. Prime candidates are myosin motors, which attach to actin and tow vacuoles and other organelles. But the evidence for the myosins' involvement in mitochondrial movement is mixed. Yeast strains with mutations in certain myosin genes show no abnormalities in mitochondrial structure or distribution. However, researchers have detected hesitant mitochondria in yeast with a mutant form of the myosin Myo2.

To clarify Myo2's contribution, Altmann et al. turned to yeast cells in which the level of Myo2 can be reduced by treating the cells with the antibiotic, doxycycline. The organelles normally link up to form a network. But in cells grown with the antibiotic, they clumped or curled into rings, suggesting disrupted movement. Altmann et al. found that isolated mitochondria lacking functional Myo2 cannot bind to actin filaments. The team then tested whether Myo2's tail, which carries vacuoles and other organelles, also hauls mitochondria. In yeast with mutations in the Myo2 tail, the researchers observed mitochondrial clumping. When a cell with one of these tail mutants sprouted a bud, few mitochondria moved in, Altmann et al. found. They conclude that mitochondria travel by boarding Myo2's tail. Up next: determining how Myo2 attaches to the mitochondrial surface. JCB

Altmann, K., et al. 2008. *J. Cell Biol.* 181:119–130.

## Neurons on life support

Neurons are high maintenance, requiring a continuous supply of nurturing molecules. A shortage of one of these molecules might underlie one of the most common causes of dementia, Van Damme et al. report.

Unlike Alzheimer's disease, frontotemporal lobe dementia (FTLD) usually strikes people who are under the age of 65. Their fatal illness devastates the brain's frontal lobe, causing symptoms such as apathy and personality changes, or the temporal lobe, resulting in impaired speech or comprehension. Two years ago, researchers showed that some FTLD patients carry mutations in the gene for progranulin, a secreted protein that takes part in everything from tumor growth to inflammation. These glitches often reduce mRNA levels, suggesting that the disease stems from insufficient progranulin. But researchers knew little about progranulin's effects on the nervous system or how reduced levels could promote brain deterioration.

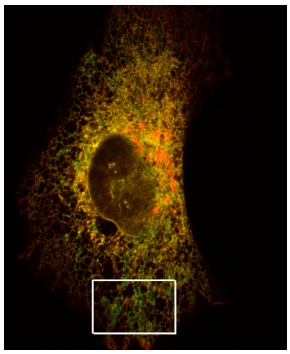
Van Damme et al. first determined whether progranulin levels are lower in FTLD. Samples of cerebrospinal fluid from patients contained much less progranulin than did samples from controls. To gauge the impact of this reduction, the team cultured rat neurons from the brain and spinal cord. Progranulin boosted their survival by up to 39%. After secretion, progranulin often gets snipped into multiple pieces, each of which might have a separate function. The researchers determined that one of these segments exerted the same cell-saving effect as full-sized progranulin. The findings point to progranulin as a potential treatment for FTLD. JCB

Van Damme, P., et al. 2008. *J. Cell Biol.* 181:37–41.

## Short proteins got no reason to leave

A cell uses a simple trick to keep certain proteins from leaving the ER: it bars them from the organelle's exits. Ronchi et al. show how cells determine which proteins to keep out.

Proteins due to be exported from the cell enter the ER, where they get bundled into vesicles that spirit them to the Golgi apparatus. One way that the ER prevents its resident proteins from departing by the same route is to exclude them from exit sites. But researchers didn't know what characteristics get a protein banished. Ronchi et al. suspected that the ER sorts proteins by their transmembrane domain (TMD).



**The distributions of proteins with a long (red) and short (green) transmembrane domain don't overlap.**

To test the idea, the researchers altered human cells to manufacture two proteins that were identical except for their TMD, which was 22 amino acids long in one molecule and 17 in the other. The team had previously shown that the longer protein leaves the ER, while the shorter one stays behind. The new work shows that the 17–amino acid protein tended to avoid the ER exit sites. The longer protein, however, moved into and out of the sites, and a small amount of it accumulated there.

Where each protein ends up might depend on which lipids it associates with, the researchers speculate. Because its TMD is longer and more hydrophobic, the 22–amino acid version might seek stiffer lipid domains, which could gather at the exit sites. The shorter protein, by contrast, would fit in better with less orderly, thinner portions of the membrane. JCB

Ronchi, P., et al. 2008. *J. Cell Biol.* 181:105–118.

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