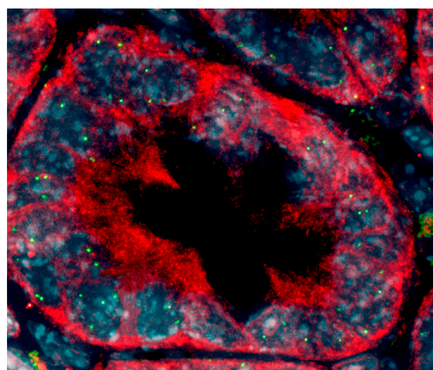
In This Issue



Cells with extra chromosomes (blue), and extra copies of a gene (green), are common in the intestine of mice with an APC mutation.

Starting a tumor off wrong

Aneuploidy is a hallmark of cancer, but the path from mutation to extra chromosomes is unclear. Now, Caldwell et al. help fill this gap, showing that a cancer-causing mutation promotes chromosome doubling by unfastening the mitotic spindle and hindering cell division.

The genome of a cancer cell is a mess, with breaks, rearrangements, and superfluous chromosomes. Many researchers speculate that the genomic instability that leads to aneuploidy and other chromosome chaos starts with tetraploidy, or a duplication of the genome. If so, cancer-spurring mutations should induce tetraploidy early in tumor development. One such mutation, Caldwell et al. suspected, occurs in the mitosis-controlling gene APC. The researchers previously found that APC mutations, which are prevalent in human colorectal tumors, lead to disrupted microtubules and misaligned chromosomes.

To test whether APC mutations promote tetraploidy, the researchers engineered human kidney cells to fashion a faulty version of the protein. The number of cells with two or more nuclei shot up 5 to 10 times. The cytokinetic furrow, which marks cell separation after anaphase, didn't form, and the cells often didn't divide. Moreover, the alteration seemed to unmoor the mitotic spindle, as it often spun or slid out of position.

Intestinal cells from mice that are heterozygous for an APC mutation had similar defects, the researchers found. Their cytokinetic furrows failed to form, their spindles were askew, and they tended to be tetraploid. These defects showed up in cells with no other signs of transformation and that still carried one normal version of APC.

Overall, the study suggests that tetraploidy is an early step toward cancer. Numerous cells in the mutant mice appear to complete this step—by the team's calculations, the small intestine harbored ~100,000 tetraploid cells. Although most of these abnormal cells probably perish, their large numbers might allow cells to try out different chromosome combinations to find one that will allow them to advance toward cancer. JCB

Reference: Caldwell, C.M., et al. 2007. *J. Cell Biol.* 178:1109–1120.

Myosins pull together to move cargo

Two kinds of myosin motors depend on teamwork to keep their cellular cargos rolling, as Dunn et al. show. The finding explains how the molecules, which previous work suggested couldn't move forward, work as haulers.

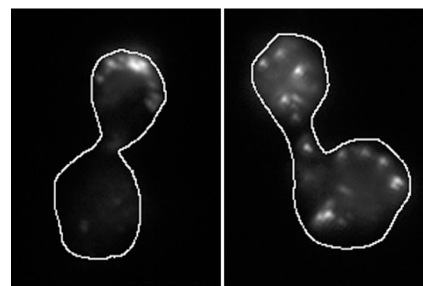
When a yeast cell sprouts a bud, two myosin proteins help furnish the new structure with necessities. Myo2p trucks in organelles and vesicles essential for growth, whereas Myo4p hauls mRNA that helps the bud differentiate from the mother cell. Running on tracks of actin, the proteins seem to keep their cargos moving continuously. That presents a mystery, however, because evidence suggests that the individual myosins are nonprocessive—they let go of the tracks after every power stroke, instead of remaining attached and sliding along.

To resolve that apparent contradiction, Dunn et al. isolated the two myosins and determined that they move differently. Molecules of Myo2p didn't always detach after the power stroke, the researchers found. They were "weakly processive." Several Myo2p molecules latched onto each cargo. At any time, most of them might not be attached to the tracks, but one Myo2p probably will be and can nudge the cargo along. The method makes sense for what Myo2p transports. The vesicles and organelles it totes are large and have room for multiple myosins to hook on.

An individual Myo4p was nonprocessive, but the molecules formed clusters that were processive. A single cluster was able to ferry one molecule of mRNA. Again, the strategy matches the cargo: mRNA has few attachment points for myosins.

The researchers also wanted to determine what accounts for the differences between the two myosins. They created hybrid molecules that carried the tail end of one protein—which attaches to the cargo—fused to the motor portion of the other. A hybrid with the motor of Myo4p and the tail of Myo2p worked like Myo2p, and vice versa. The tail thus dictates myosin's behavior. The researchers now want to investigate how cells integrate pulling by separate motors. JCB

Reference: Dunn, B.D., et al. 2007. *J. Cell Biol.* 178:1193–1206.



Myo4p concentrates labeled mRNA in a yeast bud (left), but the cargo remains dispersed if the cell lacks the myosin (right).

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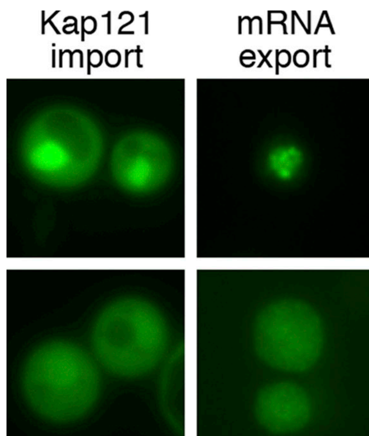


Removing certain FG domains disrupts mRNA export (top row) or protein import (bottom row), but not both.

Going their own way in the NPC

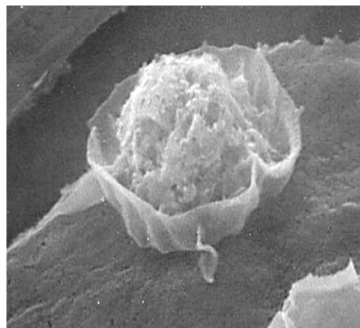
There's more than one way to pass through a nuclear pore, as Terry and Wente show. Different cargos follow different routes through the channels, suggesting a new mechanism for regulating import and export.

A nuclear pore is a bit like a high school hallway, with molecules and their carriers crowding through in both directions. As they make the crossing, carriers attach to sections of pore proteins (Nups) that harbor repeated stretches of phenylalanine and glycine. How binding to these FG repeat domains helps usher cargos through the pores remains controversial.

Three years ago, Wente's group tested the importance of particular FG repeats by making yeast mutants with different combinations of the domains excised. They found that transport doesn't require FG repeats in the filaments that protrude into the cytoplasm and into the basket that hangs from the nuclear side.

To pin down which FG segments are essential, Terry and Wente continued the research with new mutants. The scientists tracked how the loss of certain domains affected mRNA export from the nucleus and protein import via Kapβ carriers. If the removal of an FG domain blocked mRNA from exiting, it didn't necessarily prevent Kapβ cargos from entering, and vice versa. This difference indicates that the two types of cargos follow different paths through the pore. Cells might be able to control what goes in and out by altering FG domains in specific Nups. JCB

Reference: Terry, L.J., and S.R. Wente. 2007. *J. Cell Biol.* 178:1121–1132.


RhoG helps an endothelial cell swaddle a leukocyte in membrane folds.

RhoG welcomes leukocytes

Infection and injury lure leukocytes from the bloodstream, but they first have to traverse a vessel wall to reach the traumatized tissue. As van Buul et al. show, the GTPase RhoG helps the cells make the crossing.

As leukocytes exit a blood vessel, they either pass right through the endothelial cells in the lining or wriggle between them. To get across this layer, a leukocyte first hooks onto the protruding protein ICAM1. An endothelial cell then puckers its membrane to produce a cup that cradles the leukocyte. The molecular events that prompt cup formation remain unclear. The endothelial structures resemble the phagocytic cups that allow cells to gobble pathogens. Because the GTPase RhoG spurs phagocytosis in certain cells, van Buul et al. wanted to determine whether the molecule also promotes construction of endothelial cups.

The researchers found that the binding of a leukocyte to ICAM1 activated RhoG, which congregated at the site of attachment. Knocking down RhoG with RNAi slashed the number of cups that cells fashioned and the number of leukocytes making the crossing.

An activator of RhoG, called SGEF, bound to the cytoplasmic side of ICAM1, suggesting that the molecule might link ICAM1 engagement to RhoG activation. Supporting that hypothesis, RNAi against SGEF decreased cup formation and hindered leukocyte crossing. Still unresolved is how the cups allow a leukocyte to slip through the endothelium. JCB

Reference: van Buul, J.D., et al. 2007. *J. Cell Biol.* 178:1279–1293.

Pol II piece makes and breaks mRNA

"Cradle to grave" describes one protein's relationship with mRNA. As Lotan et al. reveal, the protein helps make mRNA and helps destroy it. The molecule, a piece of RNA polymerase II, might permit cells to coordinate mRNA synthesis and breakdown.

Cells degrade mRNA to eliminate damaged strands and manage protein synthesis. Enzymes first strip off the molecule's tail of multiple adenines. The demolition then sometimes proceeds from the 5′ to the 3′ end, usually in cytoplasmic structures called P-bodies. Or enzymes can chop up the strand in the 3′-to-5′ direction. The RNA polymerase II complex weaves new strands of mRNA, but previous work by the researchers suggested that one of its components, Rpb4p, also helps initiate destruction. However, Rpb4p lacks a site for grabbing RNA, implying that it gets help.

Lotan et al. tested whether that aid comes from Rpb4p's partner, the RNA-binding protein Rpb7p. In yeast with a mutated *rpb7* gene, removal of the adenine tail faltered. Moreover, the researchers found that Rpb7p gathered in P-bodies and was required for destruction of mRNA in the 5′-to-3′ direction. Outside P-bodies, Rpb7p stimulated 3′-to-5′ mRNA breakdown, indicating that it helps orchestrate both mRNA demolition pathways. The next question to answer, the researchers say, is whether Rpb7p links mRNA formation in the nucleus to its destruction in the cytoplasm. JCB

Reference: Lotan, R., et al. 2007. *J. Cell Biol.* 178:1133–1143.

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