In This Issue

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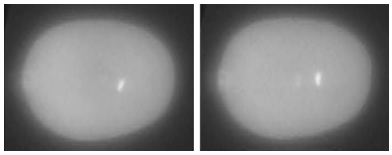
Licensing factors lose their credentials



As anaphase progresses (left to right), more and more Mcm3 protein (glowing dots) attaches to the DNA.

Sonneville et al. reveal how *C. elegans* embryos control replication licensing factors to promote efficient DNA duplication while preventing the genome from being copied more than once.

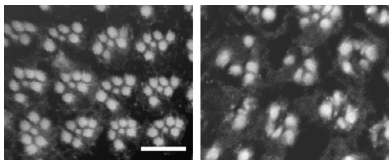
A cell starts preparing to duplicate its DNA before it has finished dividing. Beginning in anaphase, the cell flags replication origins where DNA replication will commence. Licensing factors cooperate to mark replication origins by clamping the Mcm2–7 complex around the DNA. Once a cell has tagged a large number of replication origins, it shuts down licensing before S phase so that each section of DNA will be duplicated only once.

Using live-cell imaging, Sonneville et al. followed the dynamics of licensing factors in *C. elegans*. The researchers propose that the specific behavior of the proteins makes licensing more efficient. Two of the main licensing factors, the origin recognition complex (ORC) and CDC-6, attach to DNA independently, potentially speeding up replication licensing. And the binding of the Mcm2–7 proteins to DNA encouraged the release of CDC-6 and the ORC, allowing them to move on and mark other origins.

Sonneville et al. also determined how a cell curtails replication licensing to stop double duplication of its DNA: the cell expels CDC-6 and ORC from the nucleus during interphase, a process that required the nuclear export factor XPO-1. Depleting this molecule slowed removal of CDC-6 and ORC components from the nucleus and allowed DNA rereplication.

Sonneville, R., et al. 2012. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201110080.

n-Syb makes a dangerous delivery



Compared with those in a wild-type fly eye (left), photoreceptor neurons degenerate in an eye lacking n-Syb (right).

A protein essential for neurotransmitter release also helps neurons trash old proteins and protects against neurodegeneration, Haberman et al. reveal.

Neuronal synaptobrevin (n-Syb) is a SNARE protein that promotes membrane fusion, helping neurotransmitter-carrying vesicles to release their contents at the synaptic terminal. Another protein found on these vesicles, the v-ATPase pump that shuttles protons into the vesicle interior, appears to forestall neurodegeneration. Loss of V100, a key component of the ATPase, kills neurons in the *Drosophila* eye. The ATPase is part of a "sort-and-degrade" mechanism that dispatches vesicles that contain worn-out membrane proteins to the lysosome for destruction.

Haberman et al. found that fly eye neurons lacking n-Syb gradually died. Their synaptic terminals filled not with exocytic vesicles containing neurotransmitters but with endosomes carrying undegraded membrane cargo, suggesting that n-Syb also contributes to the sort-and-degrade mechanism.

n-Syb–deficient neurons teemed with vesicles that carried inert forms of cathepsins, enzymes that slice up proteins. Cathepsins are so destructive that they only switch on in the acidic interior of late endosomes, lysosomes, or autophagosomes. Haberman et al. think that n-Syb helps deliver cathepsin-containing endosomes from the Golgi and ER to the lysosome or late endosomes. Thus, by promoting the destruction of worn-out proteins, n-Syb prevents neurodegeneration. The researchers now want to investigate whether breakdown of this protective system can trigger neurodegenerative diseases.

Haberman, A., et al. 2012. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201108088.

DGK-α keeps integrins close to the edge

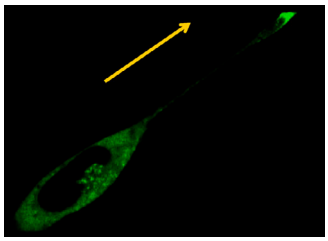


IMAGE COURTESY OF ELENA RAINERO

Rab-coupling protein (green) gathers at the tip of the pseudopod of an invasive tumor cell.

Like a car with snow tires, metastasizing cancer cells often carry integrins that provide better traction. Rainero et al. reveal how a lipid-converting enzyme helps the cells mobilize these integrins.

Integrins continually cycle to and from the plasma membrane. Invasive cancer cells that carry mutant forms of p53 often bias the process, increasing the recycling of the α5β1 integrin that offers a better grip on the fibronectin fibers found in tumors. To make this change, mutant p53 requires the Rab-coupling protein (RCP), which connects α5β1 integrins to the Rab GTPases that promote membrane recycling. In turn, RCP links up with a lipid called phosphatidic acid (PA).

Rainero et al. found that diacylglycerol kinase α (DGK-α), an enzyme that makes PA, helps cancer cells to get moving. Tumor cells that were short on DGK-α didn't recycle α5β1 integrin and didn't penetrate into slabs of extracellular matrix.

In metastasizing tumor cells, vesicles sporting RCP are tethered to the tips of the advancing pseudopods. Few of these vesicles built up if DGK-α was absent, however, indicating that vesicle tethering requires PA. The researchers found that the particular tumor cells they studied didn't boost levels of DGK-α in order to metastasize. Instead, the team thinks that DGK-α permits cancer cells to move following the acquisition of p53 mutations. By manufacturing PA that binds to RCP, DGK-α enables the tumor cells to tether vesicles containing α5β1integrins close to the plasma membrane, where the integrins can readily recycle.

Rainero, E., et al. 2012. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201109112.