In This Issue

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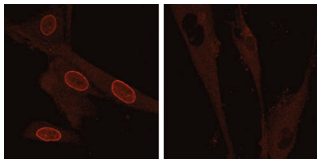
Progerin guilty of size discrimination



Tpr (red) accumulates in the nuclei of cells from a healthy person (left), but it remains in the cytoplasm of cells from an HGPS patient (right).

A mutant protein responsible for Hutchinson-Gilford Progeria syndrome (HGPS) bars large proteins from entering the nucleus, Snow et al. reveal.

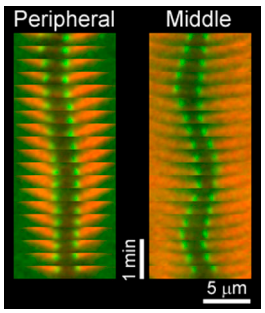
The culprit in HGPS, a fatal disease that resembles premature aging, is Progerin. This defective version of the lamin A protein impairs cells in many ways, including reducing nuclear levels of the RanGTPase. Ran is crucial for nuclear import and export, as it stimulates unloading of cargo that has just entered the nucleus and loading of cargo that's ready to exit. Progerin also impedes the import of Tpr, which forms the basket-like structure on the inner side of nuclear pores. But the mechanism behind this exclusion wasn't clear.

One possibility is that Progerin disrupts the activity of Tpr's nuclear localization sequence (NLS). To test this idea, Snow et al. replaced Tpr's NLS with the localization sequence from the SV40 virus T antigen, a protein that readily enters the nucleus. The modified Tpr was still locked out, however, suggesting that the effect wasn't related to its NLS.

Tpr forms a dimer that weighs in at 535 kD, making it one of the largest proteins to traverse nuclear pores. Snow et al. found that Progerin limits the nuclear import of three other hefty proteins—Tip60, p400, and Orc2. This size effect stems from the reduction in nuclear Ran levels triggered by Progerin. For reasons that are still unclear, large cargoes require more Ran to enter the nucleus. These findings suggest that some cellular defects of HGPS might result from the exclusion of large cargoes, such as multisubunit enzyme complexes, from the nucleus.

Snow, C.J., et al. 2013. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201212117.

Why metaphase chromosomes wander



Sister kinetochores (green dots) at the edge of a PtK1 cell (left) move little, whereas kinetochores near the middle of the cell (right) oscillate.

Civelekoglu-Scholey et al. explain why some metaphase chromosomes shift positions.

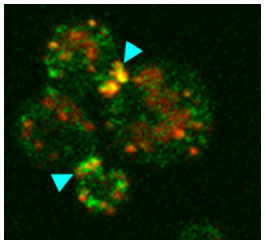
After chromosomes line up at the metaphase plate, sister chromatid pairs often jiggle, sliding a short distance toward one cell pole and then back toward the other. But in some cells, the chromosomes remain stationary until they're ready to separate. Civelekoglu-Scholey et al. focused on PtK1 cells, an unusual case in which chromosomes at the edge of the metaphase plate are immobile, whereas the ones in the central region oscillate.

To explore this difference, the team created mathematical models of chromosome maneuvers in these cells. A model in which molecular motors at the ends of microtubules provide the power couldn't fully explain PtK1 cell chromosome movements. Replacing the molecular motors with dynamic and stretchy connections between microtubules and kinetochores could account for chromosome behavior, however. The researchers assumed that the Ndc80 complex, which couples kinetochores to microtubules, showed so-called bi-phasic detachment, meaning it was more likely to remain connected if it was under moderate tension.

The new model suggests that chromosomes at different locations on the metaphase plate behave differently because of variations in the microtubule-dependent forces that push chromosomes toward the cell equator. The strength of these polar ejection forces increases faster at the edge of the cell than in the middle. This disparity could explain the chromosome movements, the researchers say, because other work has determined that weaker polar ejection forces result in greater oscillations.

Civelekoglu-Scholey, G., et al. 2013. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201301022.

Three's not a crowd for actin nucleators



Bil1 (green) and Bud6 (red) colocalize at the bud necks (arrowheads) of yeast cells.

Graziano et al. reveal a new mechanism for controlling actin nucleation.

Proteins that spur actin assembly often work in pairs. In budding yeast, for example, Bud6 teams up with the formin Bni1 to promote actin cable formation. Researchers are unsure if Bud6 also pairs with Bni1's relative Bnr1. Genetic analyses suggest that Bud6 and Bnr1 combine forces, either directly or indirectly, to induce actin cable growth at the bud neck, but biochemical studies indicate that Bud6 inhibits Bnr1.

Graziano et al. resolved this contradiction, finding that Bnr1 works directly with Bud6 to instigate actin assembly. However, the interaction between the proteins is complicated. The researchers discovered that Bud6 contains a regulatory segment that counteracts its stimulatory effect on Bnr1. Versions of Bud6 containing this region didn't activate Bnr1 but switched on Bni1 in vitro. However, Bud6 variants lacking the regulatory segment stimulated both formins.

How can Bud6 sometimes stimulate and sometimes inhibit Bnr1? Graziano et al. uncovered a new binding partner of Bud6, which they named Bil1, that latches onto the regulatory region and inactivates it, allowing Bud6 to stimulate Bnr1 and actin cable assembly. Although the researchers haven't determined how Bil1 cancels the regulatory segment's inhibition, it might afford the cell more precise control over actin assembly. The study also raises the possibility that other actin-stimulating duos require a similar ignition switch.

Graziano, B.R., et al. 2013. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201212059.