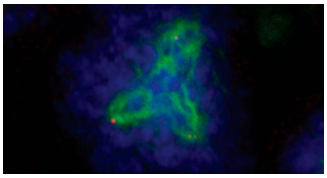
In This Issue

Text by Mitch Leslie
mitchleslie@comcast.net

Aki1 helps centrioles stay tight



When Aki1 is missing, a cell makes multipolar spindles (green).

Duplicated centrioles are codependent, remaining attached until the end of mitosis. An unlikely protein helps hold the structures together by enlisting one of the tethers that connects sister chromatids, Nakamura et al. show.

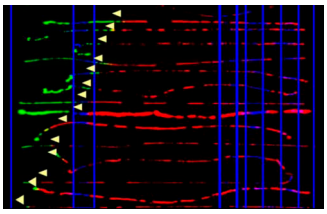
Replicated pairs of centrioles relocate to opposite ends of a dividing cell, but the members of each pair remain linked until the end of mitosis. Researchers are starting to unravel how cells control this connection and have already found overlap with the mechanisms that join and part sister chromatids. Centrioles harbor some members of the cohesin complex that lashes chromatids together. The enzyme separase, which cleaves sister chromatids, also splits up centriole pairs.

Nakamura et al. discovered that centrosomes harbor the protein Aki1, which is involved in epidermal growth factor signaling. But when they investigated further, the team found that Aki1 also promotes centriole togetherness. In cells lacking the protein, centriole pairs divorce prematurely, resulting in multipolar spindles. These cells trip the spindle checkpoint and eventually commit suicide.

The cohesin component Scc1 prevents centrioles from splitting too soon, the researchers showed. Aki1 sticks to Scc1 and another cohesin component, SA-2. The results suggest that Aki1 helps direct Scc1 to the centrosome, where it can fasten centrioles together. The next step, the researchers say, is determining why Aki1 helps connect centrioles but not sister chromatids.

Nakamura, A., et al. 2009. *J. Cell Biol.* doi:10.1083/jcb.200906019.

No copying allowed



The smooth transition between early (red) and late-replicating (green) segments shows that replication origins in the heavy chain TTR were silent.

Guan et al. suggest a function for mysterious DNA segments that are scattered throughout the mammalian genome. The segments curtail most or all replication within their boundaries and might allow cells to fine-tune the pace of DNA duplication.

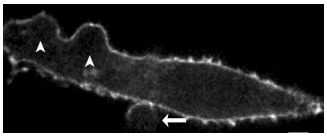
Different parts of the genome replicate at different times in S phase. Some sections start the process early, whereas others procrastinate. A third category contains the temporal transition regions, or TTRs, that start replicating at the beginning of S phase but don't finish until late. How cells control the timing of TTR duplication is unknown. A possible clue comes from the gene locus for the antibody heavy chain. In embryonic stem cells, these genes are located within a TTR. But early in B cell development, the TTR appears to vanish, and the entire locus replicates early. This indicates that the TTR harbors latent replication origins that can be turned on. Guan et al. wanted to discover how.

Genes that are being transcribed typically duplicate before inactive ones. To test whether transcription affects TTR replication, Guan et al. inserted gene-containing DNA segments into the heavy chain TTR of stem cells and switched them on. Although the insertions were expressed, sometimes at a high level, they didn't change the TTR's replication schedule. Increasing histone acetylation, a marker of working genes, also had no effect. Even when the researchers slipped replication origins from another locus into the TTR, DNA duplication rarely began.

In effect, the heavy chain TTR is a replication dead zone where origins remain quiet except during specific developmental events. The repression mechanism remains unclear, but the researchers suggest that a TTR's status could depend on higher-order chromatin structure or its position in the nucleus. TTRs could serve as speed bumps during DNA copying, preventing the early starting sections from overshooting and causing premature duplication of the laggards.

Guan, Z., et al. 2009. *J. Cell Biol.* doi:10.1083/jcb.200905144.

Rules of phagocytic attraction



Just three minutes into phagocytosis, PIP5K has departed from this cell's two phagosomes (arrowheads).

The relationship between a key phagocytic enzyme and its target is deeper than physical compatibility, Fairn et al. show. Electrical attraction also brings the two molecules together.

During phagocytosis, actin filaments polymerize to extend the cell's pseudopods and then depolymerize when the target has been surrounded. A key controller of these changes is the membrane phospholipid $PI4,5P_2$. It builds up at growing pseudopods and spurs actin to lengthen. Later, it disappears from the base of the forming phagosome, an essential step for the completion of phagocytosis. The kinase PIP5K manufactures $PI4,5P_2$ from another lipid known as PI4P. Fairn et al. tackled the question of how cells manage PIP5K's location and activity.

Because the enzyme's structure isn't known, Fairn et al. modeled its morphology on a similar protein. Their results indicated that one face of PIP5K bristles with positive charges. The inner portion of the plasma membrane, where much of a cell's PI4P resides, is negatively charged, suggesting that electrical attraction, not just structural specificity, draws PIP5K to its substrate.

Supporting the idea, PIP5K molecules let go when the cells' inner membrane charge was diminished. Mutant PIP5K molecules carrying less positive charge also avoided the membrane.

The researchers conclude that an electrostatic switch controls PIP5K's location. Their scenario suggests that the enzyme trails PI4P to the membrane and makes $PI4,5P_2$ to trigger pseudopod extension. However, another enzyme called PLC-γ begins destroying the negatively charged $PI4,5P_2$, weakening the attraction between the membrane and PIP5K. The enzyme drops off, decreasing $PI4,5P_2$ synthesis. With less of the phospholipid at the membrane, actin fibers collapse and phagocytosis can wrap up.

Fairn, G.D., et al. 2009. *J. Cell Biol.* doi:10.1083/jcb.200909025.