In This Issue

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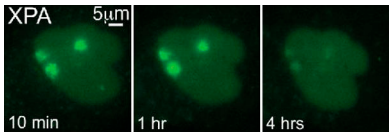
Unfaithful proteins no problem for DNA repair



XPA (green), a protein that helps snip out DNA lesions, accumulates early in the repair process, as this time series shows.

DNA repair proteins constantly bind and let go of DNA damage sites. Luijsterburg et al. discover how these seemingly fickle proteins get the job done.

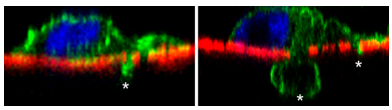
During nucleotide excision repair, ten proteins collaborate to fix DNA, handling separate steps such as recognizing damage, unwinding the DNA, snipping out the marred section, and installing replacement nucleotides. Instead of assembling into a complex beforehand, the proteins come together at the site of damage. So how do the proteins make repairs if they adhere to the complex only for a short time?

Luijsterburg et al. tracked seven of the proteins in cells zapped by ultraviolet light. Repair complexes stuck to DNA for hours, but individual proteins only adhered for tens of seconds. This isn't contradictory, the researchers say. Proteins randomly attach and detach until the right combination is present to catalyze the first repair step. Reshuffling continues until a complex convenes to catalyze the next step, and so on. The result challenges previous findings that complexes assemble in sequence, with each protein staying on after its task is complete.

Luijsterburg et al.'s model suggests a benefit for quick-release proteins. They make it easier to abort the process if repair starts on undamaged DNA, a mistake that can result in mutations. Next up, the researchers say, is determining whether similar mechanisms occur in other processes involving unstable complexes, such as DNA replication and transcription.

Luijsterburg, M.S., et al. 2010. *J. Cell Biol.* doi:10.1083/jcb.200909175.

Skeleton key for metastasis



An actin-rich invadopodium pushes through the basement membrane (red, left), allowing the tumor cell to follow (right).

Cancer cells need all three of their cytoskeletons—actin, microtubules, and intermediate filaments—to metastasize, Schoumacher et al. reveal.

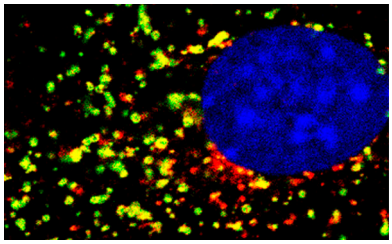
A cancer cell in an epithelial layer is trapped unless it can force through the basement membrane, which cordons off the tissue. Tumor cells start to dissolve the basement membrane with enzymes that build up within extensions called invadopodia. How the different components of the cytoskeleton collaborate to spring the cell remains unclear. To find out, the researchers followed cancer cells as they started their breakout.

Schoumacher et al. found that a tumor cell escapes in three stages. First, stumpy protrusions dig into the basement membrane. These structures then elongate into "mature" invadopodia. Finally, the rest of the cell follows. In culture, crawling cells produce extensions that carry either bundles of actin or an actin mesh. In the cancer cells, both forms of actin were necessary for invadopodia to form and grow. However, microtubules and intermediate filaments were only essential for invadopodia to lengthen.

The researchers suggest a model for this initial step of metastasis. Growing actin bundles push out a protrusion, which the actin mesh stabilizes as it elongates. Only if the invadopodium stretches beyond 5 μm do microtubules and intermediate filaments get involved. Microtubules most likely elongate the invadopodium by delivering materials such as enzymes to the tip. Intermediate filaments, meanwhile, may brace the growing extension.

Schoumacher, M., et al. 2010. *J. Cell Biol.* doi:10.1083/jcb.200909113.

RALT doubles down on EGFR



RALT ushers endocytosed EGFR (red) to lysosomes (green) for destruction.

Frosi et al. describe a new mechanism for turning down epidermal growth factor receptor (EGFR) activity that dispatches the protein for destruction.

Through its kinase activity, EGFR is crucial for cell division, survival, and movement. But faulty or overactive EGFR abets many cancers. Several cellular controls keep EGFR in check. After the receptors are stimulated, for example, endocytosis abducts them from the cell surface. Alternatively, a protein called RALT blocks EGFR's activity by clamping onto its kinase domain. But RALT sometimes follows internalized receptors into the cell, an unexpected behavior because kinase activity is necessary for EGFR endocytosis. Frosi et al. wondered whether RALT could suppress EGFR yet drive its endocytosis.

The researchers discovered that RALT can trigger the receptor's endocytosis by maneuvering it into clathrin-coated pits. To move the receptor into position, RALT connects to two kinds of proteins—AP-2 and the intersectins—that transfer molecules into the pits and allow their maturation into vesicles.

RALT directs EGFR to the lysosomes for digestion. Proteins destined for destruction often carry ubiquitin tags, but the researchers showed that EGFR ubiquitylation wasn't required when RALT was involved. Thus to rapidly decrease EGFR signaling, RALT blocks the receptor's kinase activity. For a slower, longer-lasting effect, it also promotes the molecule's removal and destruction. A key question is RALT's role in cancer—a recent study pegged it as a tumor suppressor in the brain cancer glioblastoma.

Frosi, Y., et al. 2010. *J. Cell Biol.* doi:10.1083/jcb.201002032.