In This Issue

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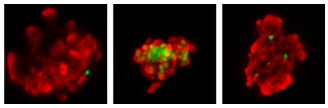
Cdc14 in good repair



Three hours after irradiation, cells lacking Cdc14A (middle) or Cdc14B (right) retain more DNA damage sites (green) than control cells (left).

Cdc14 is an essential regulator of the yeast cell cycle, but its vertebrate homologues appear to be surprisingly dispensable, Mocciaro et al. report. They are required for efficient DNA repair, however.

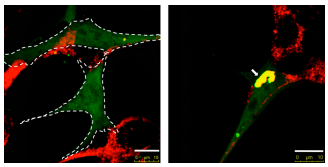
Yeast Cdc14 is a phosphatase that counteracts the cyclin-dependent kinases to control many aspects of the cell cycle including mitotic exit. Vertebrates have at least two versions of the phosphatase that have a similarly wide range of functions according to overexpression and depletion experiments. Cdc14A is thought to control centrosome splitting and cytokinesis, for example, while Cdc14B promotes mitotic exit and activates a DNA damage checkpoint that maintains cells in G2.

Mocciaro et al. were thus surprised to find that deleting either phosphatase from chicken DT40 cells had no obvious effect on cell viability or proliferation. And irradiated cells lacking Cdc14A or Cdc14B still arrested in G2. But the knockout cells took longer to repair the radiation-induced DNA damage. Even without irradiation, cells lacking Cdc14A or Cdc14B had higher background levels of double-strand breaks, indicating that the phosphatases are needed to efficiently mend DNA damage. This function isn't unique to chicken cells because genetically deleting either Cdc14 homologue from human cells also slowed DNA repair.

Human cells lacking Cdc14A or Cdc14B were also viable and passed through the cell cycle without any problems. Although the two isoforms localize to different parts of the cell, it's possible that they redundantly carry out the functions of Cdc14 indicated by previous experiments. The authors now plan to test this by generating double knockout cell lines.

Mocciaro, A., et al. 2010. *J. Cell Biol.* doi:10.1083/jcb.200910057.

Parkin restrictions for damaged mitochondria



Parkin (green) promotes the turnover of damaged mitochondria (red, left), but defective organelles accumulate near the nucleus if Parkin lacks its ubiquitin ligase activity (right).

Mutations that cause Parkinson's disease prevent cells from destroying defective mitochondria, Lee et al. report.

Defects in the ubiquitin ligase Parkin are linked to early-onset cases of this neurodegenerative disorder. The wild-type protein promotes the removal of impaired mitochondria by a specialized version of the autophagy pathway called mitophagy, delivering mitochondria to the lysosomes for degradation. Mitochondria are often dysfunctional in Parkinson's disease, but how Parkin stimulates mitophagy and whether the pathway goes wrong during pathogenesis is unknown.

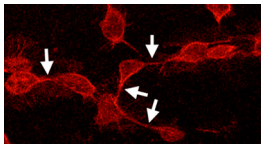
Lee et al. found that cells expressing mutant forms of Parkin failed to clear their mitochondria after the organelles were damaged. Different mutations blocked mitophagy at distinct steps: mitochondria accumulated in the perinuclear region of cells expressing Parkin lacking its ubiquitin ligase activity, for example. The researchers found that ubiquitination of defective mitochondria by Parkin normally recruits the autophagy proteins HDAC6 and p62 to clear these mitochondrial aggregates.

Depolymerizing microtubules or inhibiting the dynein motor protein blocked aggregation and prevented mitochondrial turnover. Transport to the perinuclear region was also blocked by a mutation in Parkin, indicating that this stage of mitophagy is also regulated by the protein.

The clearance of defective mitochondria is therefore similar to the removal of damaged proteins, another autophagic process that goes wrong in Parkinson's disease resulting in the accumulation of toxic protein aggregates. Both pathways rely on microtubules, HDAC6, and p62, says senior author Tso-Pang Yao, providing a common link between the two main features of the neurodegenerative disorder.

Lee, J.-Y., et al. 2010. *J. Cell Biol.* doi:10.1083/jcb.201001039.

A turning point for macrophages



Microtubule arms align when macrophages contact each other (arrows).

Drosophila macrophages have a microtubule "arm" that points them in the right direction and pushes them away from their fellow leukocytes, Stramer et al. reveal.

Fly macrophages disperse themselves around the body during embryogenesis, ready to mount an immune response at the site of a wound. These cells can be observed relatively easily using confocal microscopy, so Stramer et al. developed a fluorescent probe to study the cells' microtubule dynamics as they migrated in living embryos.

The researchers saw that macrophages bundled their microtubules into an arm that pointed to the leading edge of each cell. Wounding the embryos caused macrophages to turn their arms toward the damage before the rest of the cell followed suit, suggesting that the bundles help macrophages polarize and migrate in the direction of their target. The arms also allow the cells to move away from each other: when two macrophages collided, their arms briefly aligned and then collapsed, spurring the cells to retreat in opposite directions. Removing the microtubule arm by expressing the filament-severing protein Spastin or removing the microtubule-stabilizing protein Orbit blocked macrophages' ability to repel each other. The cells still moved but they clumped together instead of dispersing throughout the embryo.

Lead author Brian Stramer now plans to screen for other proteins involved in the process to understand how the microtubule arms sense and redirect colliding macrophages. He also notes that these structures don't exist in cell culture, highlighting the importance of observing cell migration in vivo.

Stramer, B., et al. 2010. *J. Cell Biol.* doi:10.1083/jcb.200912134.