In This Issue

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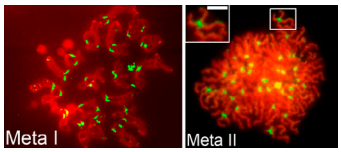
Frog oocytes evade the checkpoint



Chromosomes (red, with centromeres labeled green) from nocodazole-treated oocytes transition successfully from homologous pairs in metaphase I (left) to sister chromatid dyads in metaphase II (right).

Shao et al. reveal that *Xenopus* eggs have no spindle assembly checkpoint (SAC) to prevent them from entering anaphase with misaligned chromosomes.

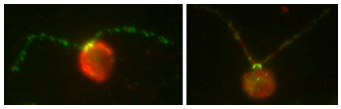
In most dividing cells, the SAC prevents anaphase onset by keeping the ubiquitin ligase APC/C inactive until all chromosomes are correctly attached to the metaphase spindle. In frog oocytes, however, the APC/C is activated before the first meiotic spindle is assembled, suggesting that the SAC may not regulate anaphase initiation in these cells.

To test this idea directly, Shao et al. developed a way to analyze the state of meiotic frog chromosomes. In oocytes treated with microtubule-depolymerizing drugs such as colcemid, the first meiotic spindle was disrupted, but homologous chromosomes separated into individual pairs of sister chromatids without delay, indicating that the oocytes had progressed into meiosis II as normal. When colcemid was removed, oocytes reassembled their spindles, and, just like control oocytes, they arrested in metaphase II before completing the second meiotic division in response to a fertilization signal.

To confirm their findings, the researchers then analyzed oocytes with monopolar meiotic spindles—an abnormal architecture that triggers the SAC in mitotic cells. Frog eggs with monopolar spindles completed both rounds of meiosis with normal timing, however, supporting the idea that these cells have no SAC. Senior author Johné Liu now wants to investigate what other signals may regulate anaphase onset in *Xenopus* oocytes.

Shao, H., et al. 2013. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201211041.

The BBSome's export duty



In comparison to a wild-type cell (left), a cell lacking BBS4 (right) accumulates PLD (red) in its cilia (green).

Lechtreck et al. describe how a protein complex linked to human disease helps export signaling proteins out of cilia.

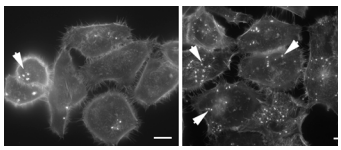
Bardet-Biedl syndrome (BBS) is associated with mutations in several cilia proteins, seven of which form a complex called the BBSome. In model organisms from mice to the green alga *Chlamydomonas*, the loss of BBS proteins causes various signaling proteins to either accumulate in or disappear from cilia, suggesting that the BBSome regulates the export and/or import of ciliary proteins.

Lechtreck et al. found that, in algae lacking BBS4, the signaling enzyme phospholipase D (PLD) gradually accumulated to 150 times its level in wild-type cilia, changing the ciliary membrane's lipid composition. Reintroducing wild-type BBS4 induced the rapid removal of excess PLD from cilia, demonstrating that the BBSome is involved in PLD export. The BBSome doesn't work alone, however. The BBSome moves up and down cilia in association with both retrograde and anterograde intraflagellar transport (IFT) particles. Algae lacking retrograde IFT proteins also accumulated PLD in their cilia, despite the presence of intact BBSomes.

Lechtreck et al. therefore think that the BBSome acts as a cargo adaptor linking PLD and other proteins to retrograde IFT particles as they move out of cilia. BBS proteins weren't required for PLD's entry into cilia, but whether the BBSome imports other cilia proteins remains unclear. The enzyme carbonic anhydrase 6, for example, disappeared gradually from BBS4 mutant cilia, suggesting that its loss could be an indirect consequence of defective export rather than a direct result of impaired import.

Lechtreck, K.F., et al. 2013. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201207139.

Hypoxia takes invadopodia up a Notch



The increase in actin-rich puncta shows that a cancer cell line forms more invadopodia in low-oxygen conditions (right) than when oxygen levels are normal (left).

Díaz et al. describe how several signaling pathways combine to enhance cancer cells' invasive capabilities.

Cancer cells form actin-rich protrusions called invadopodia, which degrade the extracellular matrix and potentially allow tumors to invade surrounding tissue. Tumor cells are often deprived of oxygen, and hypoxia can promote invadopodia formation in vitro. But how this pathway is regulated is unclear.

Díaz et al. found that the transcription factor HIF-1α, which is stabilized in low oxygen conditions, was required for hypoxia-induced invadopodia formation. Hypoxia and HIF-1α are known to activate Notch signaling, another pathway that promotes cancer cell invasion. Blocking Notch activation prevented hypoxia from inducing invadopodia.

But how does Notch signaling promote invadopodia formation? Díaz et al. found that hypoxia and Notch activation boosted the level of ADAM12, a metalloprotease that sheds growth factors from the outer surface of cells. Conditioned medium collected from control hypoxic cells—but not from cells lacking ADAM12—could induce invadopodia in oxygen-rich cells, indicating that ADAM12 releases an invadopodia-promoting factor from oxygen-deficient cancer cells. That factor turned out to be HB-EGF, a soluble ligand for the EGF receptor.

Because Notch signaling is dependent on cell contact and HB-EGF is a paracrine signaling molecule, hypoxic cancer cells may therefore induce invadopodia in both neighboring and distant tumor cells, coordinating their collective invasion. ADAM12 was up-regulated in hypoxic regions of lung tumors, suggesting that this pathway may also operate in vivo, a possibility that lead author Begoña Díaz now wants to investigate.

Díaz, B., et al. 2013. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201209151.