In This Issue

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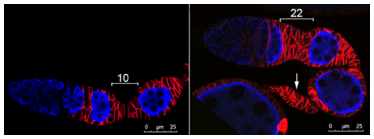
Boi keeps Hedgehog close to home



More follicle cells (red) surround the germ cells (blue) in ovaries lacking the Hh receptor Boi (right).

The Hedgehog receptor Boi limits stem cell proliferation by retaining Hedgehog (Hh) at its source, Hartman et al. report.

In *Drosophila* ovaries, Hh stimulates follicle stem cells (FSCs) to proliferate and form the outer epithelial layer of developing egg chambers. Hh ligand is secreted by apical cells at the anterior end of ovaries, several cell lengths away from FSCs, which express the Hh receptor Patched and downstream components of the signaling pathway such as Smoothened and the transcription factor Ci.

Boi is a coreceptor for Hh, but Hartman et al. found that this protein was expressed on the surface of apical cells rather than on FSCs. Moreover, FSC proliferation increased when Boi was mutated or depleted from apical cells, indicating that the receptor suppresses Hh signaling in *Drosophila* ovaries. In the absence of Boi, apical cells failed to sequester Hh after secreting it, leading to increased amounts of the ligand reaching FSCs. FSC hyperproliferation was reversed by reducing Hh levels or by depleting Smoothened and Ci from the stem cells. Apical cells don't express these downstream effectors, the researchers found, preventing them from being activated when Boi binds Hh.

Senior author Alana O'Reilly now wants to investigate why apical cells limit the signal they send to FSCs by sequestering Hh rather than by decreasing expression of the protein. One possibility is that it enables ovaries to increase FSC proliferation and egg production rapidly in response to environmental changes, allowing flies to lay eggs only when conditions are favorable.

Hartman, T.R., et al. 2010. *J. Cell Biol.* doi:10.1083/jcb.201007142.

Rb gets ERK'd by the competition

ERK MAP kinases disrupt the interaction between lamin A and the retinoblastoma (Rb) protein to drive cell proliferation, Rodríguez et al. report.

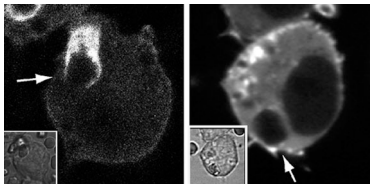
In response to growth factors, active ERKs enter the nucleus and stimulate cell cycle entry and progression by several different mechanisms. One of ERK's earliest actions is to bind lamin A at the nuclear periphery, where it phosphorylates and releases the transcription factor c-Fos. Rodríguez et al. noticed that the ERK-binding site on lamin A overlapped with the binding site for the Rb tumor suppressor, which inhibits cell cycle entry by sequestering the E2F family of transcription factors.

Both ERK1 and ERK2 competed with Rb for binding to lamin A, the team found, and displaced the tumor suppressor into the nucleoplasm, where it was phosphorylated and inactivated. ERKs lacking kinase activity could also dislodge and switch off Rb if they were constitutively targeted to the nucleus by a nuclear localization signal. Displacement of Rb by ERK led to increased cell proliferation and enhanced transformation, effects that were reversed by overexpressing lamin A.

Senior author Piero Crespo now wants to identify the kinase responsible for inactivating Rb once the tumor suppressor has been evicted from its binding site at the nuclear envelope. Rb is known to be phosphorylated by cyclin-dependent kinases 2, 4, and 6, but these kinases are still inactive when ERK first arrives in the nucleus to stimulate cell cycle entry. Crespo also wants to determine whether any disease-related mutations in lamin A dysregulate the cell cycle by disrupting the protein's interactions with Rb or ERKs.

Rodríguez, J., et al. 2010. *J. Cell Biol.* doi:10.1083/jcb.201004067.

PIPs propel phagosomes



Phagosomes formed via the CR3 receptor assemble an actin comet tail (arrow, left), whereas FcγR phagosomes do not (right).

Bohdanowicz et al. describe how different phosphatidylinositol phosphates (PIPs) promote actin polymerization on specific phagosome membranes to move the organelles through the cell.

Cells recognize phagocytic cargoes using distinct receptors, and engulf them in actin-rich pseudopods. Actin disassembles once the phagosome has internalized, but Bohdanowicz et al. noticed that a second wave of actin polymerization occurred on phagosomes formed by the phagocytic receptor CR3, forming "comet tails" that propelled the vacuoles through the cytoplasm. Phagosomes formed by a different receptor, FcγR, didn't induce a second burst of actin assembly.

Comet tail formation required the small GTPase Rac1 and the PIP $PI(3,4,5)P_3$, both of which accumulated on CR3 phagosome membranes. $PI(3,4,5)P_3$ was generated by class I PI3-kinases, which phosphorylated the precursor phospholipid $PI(4,5)P_2$. Yet $PI(3,4,5)P_3$ accumulation and comet-tail formation also required the production of PI(3)P by class III PI3-kinases. This monophosphorylated PIP displaced an inositol 5-phosphatase from phagosomes, allowing their membranes to accrue $PI(4,5)P_2$ and $PI(3,4,5)P_3$.

Why do only CR3 phagosomes form a comet tail? Bohdanowicz et al. found that phagosomes formed by this receptor retained PIP5-kinase, whereas FcγR phagosomes did not. PIP5-kinase generates $PI(4,5)P_2$ as a precursor for $PI(3,4,5)P_3$. Forcing PIP5-kinase onto FcγR phagosomes induced these vacuoles to accumulate $PI(3,4,5)P_3$ and assemble comet tails.

Senior author Sergio Grinstein now wants to investigate why PIP5-kinase preferentially localizes to CR3 phagosomes. The specific assembly of actin on these vacuoles may help them mature faster, potentially explaining why cargoes—such as the pathogen *Mycobacterium tuberculosis*—can have different fates depending on the phagocytic receptor that internalizes them.

Bohdanowicz, M., et al. 2010. *J. Cell Biol.* doi:10.1083/jcb.201004005.