In This Issue

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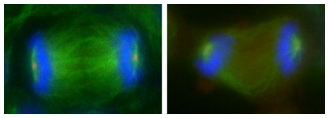
Augmin-ting the central spindle



Fewer interchromosomal microtubules (green) form in anaphase cells lacking augmin (right).

The augmin complex generates new microtubules in anaphase to build the central spindle and complete cytokinesis, Uehara and Goshima report.

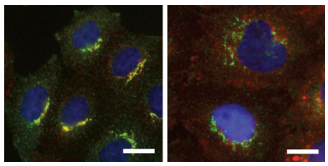
The central spindle forms between segregating chromosomes in anaphase and is required for the subsequent cleavage of cells into two daughters. Whether this structure is formed purely by microtubules recycled from the metaphase spindle or whether new microtubules are also needed is unclear. Uehara and Goshima depolymerized existing microtubules in anaphase cells with nocodazole and a low temperature, and saw that new filaments formed between chromosomes after the drug was removed, generating a functional central spindle from scratch.

Fewer microtubules formed in nocodazole-treated cells lacking augmin, a protein complex required for central spindle assembly and cytokinesis. In metaphase cells, augmin amplifies the number of spindle microtubules by recruiting γ-tubulin to the mitotic spindle to initiate the assembly of new filaments. In anaphase, however, the researchers found that augmin builds upon a combination of preexisting filaments, centrosome-generated microtubules, and/or new filaments nucleated from chromosomes by the protein HURP. HURP was essential for central spindle formation in anaphase cells treated with nocodazole, but was less important in untreated cells that could reuse their metaphase microtubules as templates for augmin amplification.

Without augmin, anaphase cells still assemble some microtubules in their central region, but they can't complete cytokinesis. Senior author Gohta Goshima now wants to investigate why cell cleavage requires augmin-dependent expansion of the central spindle. Of note, one of augmin's subunits is frequently mutated in breast cancer, potentially causing cytokinesis failure and polyploidy.

Uehara, R., and G. Goshima. 2010. *J. Cell Biol.* doi:10.1083/jcb.201004150.

Rab GEFs emerge from their DENN



In the absence of the Rab35 GEF DENND1A (right), Shiga toxin (red) is no longer delivered to the Golgi apparatus (green).

Yoshimura et al. identify a family of proteins that activate different Rab GTPases at specific cell locations to control a variety of membrane trafficking events.

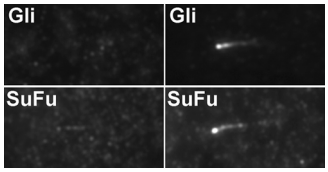
There are 63 human Rabs that control membrane transport, but the guanine nucleotide exchange factors (GEFs) that switch each of them on at specific times and places are unknown for most family members. The handful of Rab GEFs that have been identified are largely unrelated to one another, although a GEF for Rab3 contains a sequence motif found in several other proteins involved in membrane trafficking.

Yoshimura et al. tested the 17 human proteins with this motif—known as a DENN domain—for their ability to activate Rab proteins. Each DENN protein stimulated distinct Rabs involved in different trafficking routes. DENND4, for example, activated Rab10, a key regulator of polarized sorting to the basolateral surface of epithelial cells. DENND2A was found on actin filaments and regulated Rab9's function in transport between late endosomes and the Golgi. In all, the 17 DENN proteins were found to control 10 different Rabs with the DENN domain itself critical for the nucleotide exchange process.

Some of the DENN proteins or their Rab targets are altered in human disease, so the findings should help researchers understand how Rab misregulation contributes to pathogenesis. Yet many Rabs still have no known activator, something senior author Francis Barr hopes to rectify by examining the potential GEF activity of other gene families associated with membrane trafficking.

Yoshimura, S.-i., et al. 2010. *J. Cell Biol.* doi:10.1083/jcb.201008051.

Gli inhibitor pricked by Hedgehog



Gli transcription factors (top) and their inhibitor SuFu (bottom) are recruited to cilia upon Hh stimulation (right).

Tukachinsky et al. reveal how Hedgehog (Hh) signaling in the primary cilium activates the Gli family of transcription factors.

In vertebrates, the Hh pathway begins in the primary cilium, where the Hh ligand binds its receptor Patched, leading to the activation and recruitment of the membrane protein Smoothened (Smo). Pathway activation culminates in the movement of Gli transcription factors into the nucleus. In unstimulated cells, Glis are kept inactive in the cytoplasm by the protein Suppressor of Fused (SuFu), but how Hh and Smo switch on the transcription factors is unknown.

Tukachinsky et al. found that Hh induced the rapid accumulation of both SuFu and Gli in primary cilia, and that this required Smo's activation. Hh also disrupted the interaction between SuFu and Gli. Protein kinase A, an inhibitor of Hh signaling that acts downstream of Smo, blocked SuFu and Gli's ciliary recruitment and preserved their association, suggesting that active Smo normally brings the proteins to cilia to liberate Gli molecules and permit their translocation to the nucleus.

Senior author Adrian Salic now wants to investigate whether Smo acts directly or indirectly on SuFu–Gli complexes and how activated Gli proteins subsequently move from cilia to nuclei—preliminary results indicate that this latter step could involve microtubules. Salic also wants to use quantitative live imaging to follow the ciliary recruitment of SuFu and Gli in greater detail.

Tukachinsky, H., et al. 2010. *J. Cell Biol.* doi:10.1083/jcb.201004108.