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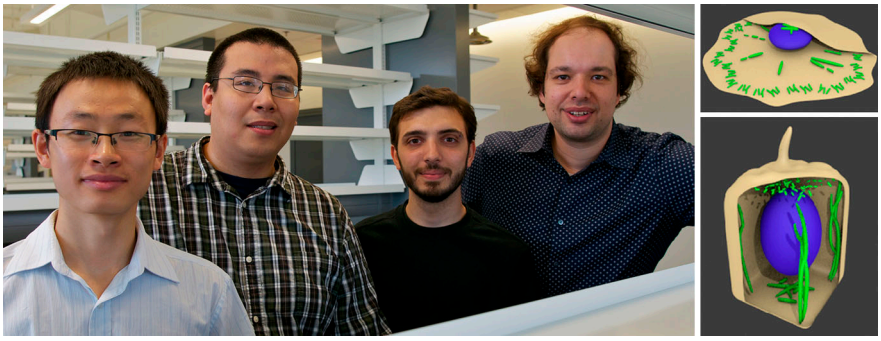
Microtubules follow septins' guidelines

Septin filaments direct the reorganization of microtubules during epithelial polarization.

Focal Point



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(Left to right) Xiaobo Bai, Daniel Hwang, Jonathan Bowen, Elias Spiliotis, and Dheeraj Roy (not pictured) reveal that septin GTPase filaments guide the reorganization of microtubules during epithelial polarization. Septins control both the direction and—by inhibiting depolymerization—the dynamics of microtubule growth. The cartoons at right show the progressive rearrangement of septin filaments (green) as a flat MDCK cell (top) polarizes into a columnar epithelial cell (bottom). In the absence of these filaments, microtubules aren't directed to the apical regions of the cell.

The microtubules inside an epithelial cell undergo dramatic rearrangements when the cell becomes part of a polarized epithelial sheet. On its own, an epithelial cell is flat, and its microtubules radiate out from the centrosome. But, after forming contacts with neighboring cells, an epithelial cell rises up into a columnar shape, and its microtubules form a more complex network: microtubule bundles run from the top to the bottom of the cell, while meshworks of shorter tubulin filaments underlie both the apical and basal membranes. Bowen et al. reveal that this reorganization is guided by another cytoskeleton—the network of filaments formed by the septin family of GTPases (1).

Septins form hetero-oligomers with each other that can assemble into filaments and other higher-order structures (2), and they have previously been shown to associate with subsets of microtubules (3, 4). "But people haven't paid much attention to the septin–microtubule connection," says Elias Spiliotis from Drexel University in Philadelphia, PA. "We know they're associated, but we don't know what this means for microtubule organization and dynamics."

Spiliotis and colleagues decided to investigate how septins affect microtubule remodeling during the polarization of MDCK epithelial cells (1). When MDCK cells first contact each other, their microtubules convert from a radial array into a diverse network that includes long microtubule bundles near the nucleus, which Bowen et al. found were associated with septin filaments. Knocking down septin 2 reduced the appearance of both the septin filaments and the perinuclear microtubule bundles. In addition, shorter septin filaments were associated with the ends of peripheral microtubules, which failed to properly target to the cell cortex in the absence of septin 2.

> "[Septin filaments rise up] like an Amish barn raising."

Septins might organize perinuclear and peripheral microtubules by regulating their dynamics. Indeed, knocking down septin 2 increased the frequency and duration of microtubule "catastrophes"—when microtubules shrink—suggesting that septin filaments promote the growth of microtubules by inhibiting their depolymerization.

Septins also control the direction of microtubule growth. By simultaneously imaging septin filaments and microtubule plus ends, Bowen et al. found that microtubules grew along septin filaments in both the perinuclear and peripheral regions of the cell. Microtubule ends often collided with septin-decorated microtubules and redirected their growth in line with these filaments. In the absence of septin 2, microtubules failed to align and become entangled in a disorganized network.

Spiliotis and colleagues then looked to see whether septin 2 depletion disrupted microtubule organization in fully polarized epithelial cells. In the absence of septin filaments, microtubule plus ends no longer concentrated in the apical region of columnar MDCK cells, as they did in wild-type cells. But how might septins guide microtubules to the apical domain? Bowen et al. followed the movement of septin filaments during epithelial polarization and found that the septin–microtubule bundles initially found around the nucleus gradually rose up to extend vertically from the top to the bottom of columnar MDCK cells.

"It's like an Amish barn raising where pillars are pulled up to support the house," explains Spiliotis. "In epithelial cells, we think that other microtubules use these vertical filaments as a way to direct themselves to the apical domain to establish the apical microtubule meshwork." An important feature of septin filaments is that they are much more stable than other cytoskeletal elements such as microtubules or actin filaments. "That allows them to act as a scaffold to organize things in space," Spiliotis points out.

Spiliotis now wants to investigate how septin filaments control the direction and dynamics of microtubule growth. "We think that septins may interact with motor proteins associated with microtubule plus ends," he says. Another intriguing line of research involves exploring whether septins' effects on microtubule organization explain why tumor cells overexpressing septins are more resistant to microtubule-targeting drugs (5).

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3. Spiliotis, E.T., et al. 2008. *J. Cell Biol.* 180:295–303.
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