In This Issue

Centrosome-free basal MT organization

epithelial microtubules (MTs) rely on the cortex and each other to create stable organized patterns, as shown by Reilein et al. (page 845).

MTs are normally organized by centrosomes in animal cells. But in polarized epithelial cells, centrosomes are busy building the primary cilium under the apical membrane, leaving basal MTs to fend for themselves. Reilein and colleagues wanted to know how this dynamic yet stable basal network forms.

Epithelial cells are especially tall, so imaging their basal MT network is difficult. Reilein thus called upon an old technique that John Heuser referred to as “unroofing”—she got rid of the apical and lateral membranes to clear her view of the basal cytoskeleton.

What was uncovered was a network of mostly immobile MTs, with a few MTs growing or shrinking until they made contact with other MTs or with the cortex. Both the plus and minus ends of MTs were stabilized at these contacts, presumably by MT plus-end binding proteins (such as APC, Clip170, or EB1) or perhaps by ß-tubulin at the minus end.

Treadmilling, bundling, and MT motor–based movements—features that create MT networks in other noncentrosomal systems—were rare or absent in the basal networks. The authors thus supposed that MT–MT and MT–cortex interactions might be sufficient to create this organization.

To test their hypothesis, the group developed a computational model. They had already shown that cortex-associated adenomatous polyposis coli (APC) organizes new MTs, so they included in their model random sites of APC-mediated MT interactions, as well as MT–MT interactions and default MT dynamic instability. They found that the creation of a stable pattern from these inputs required only one additional parameter—that MTs contacting either another MT or the cortex be rescued from dynamic instability.

During their imaging, the group had noticed basal membranes whose MT network was somehow destroyed and then recreated de novo. They compared these actual forming networks with the model versions and got uncannily similar results. Now, the authors need to identify definitively the MT-stabilizing proteins that lie at MT–MT and MT–cortex contact sites. JCB

Simple sensing in fibroblasts

Fibroblasts are like the dumb cousins of neutrophils when it comes to gradient sensing. On page 883, Schneider and Haugh show that fibroblasts need stricter instructions and apparently lack the sophisticated signaling loops that are found in neutrophils.

Neutrophils take small differences in chemoattractant levels at the front and back of the cell and amplify them, via GTPase-driven positive feedback loops, into large differences in 3’ phosphoinositide (PI) production that drive the polarization of cytoskeletal changes. Neutrophils also adapt quickly to uniform chemoattractant levels by returning 3’ PI to near basal levels (possibly through global inhibition of 3’ PI production, as seen in Dictyostelium).

PDGF-stimulated fibroblasts, by contrast, do not adapt, prompting the authors to wonder how this sensing mechanism works. The team formulated a mathematical model to describe the simplest possible mechanism of this gradient sensing: PDGF-bound receptors activate PI3K locally, which creates 3’ PI; receptors compete for limiting amounts of PI3K; but no global regulatory mechanisms or feedback loops are included.

This basic model correctly predicted the PDGF gradient-sensing behavior of fibroblasts under all tested conditions. It also highlighted some differences from neutrophils. For one, fibroblasts have a much narrower range of chemoattractant concentrations (~20 fold) within which they will respond well. They also require steeper gradients than do neutrophils. No evidence for the involvement of positive feedback loops was found.

Each sensing mechanism is well-suited to its owner. Neutrophils are like heat-seeking missiles tracking elusive bacterial invaders over long distances; they must respond and adapt quickly to directional changes. PDGF gradients direct fibroblasts into wounds from the adjacent tissue on a much longer time scale, during which the gradient orientation does not change. Desensitization of PDGF signaling through PI3K would be detrimental, as these pathways also control survival and proliferation.

PDGF is perceived by a receptor tyrosine kinase, whereas neutrophils sense chemoattractants via G-protein–coupled receptors. The two receptor types might elicit diverse responses via distinct PI3K isoforms, as suggested by recent reports. JCB

Fibroblasts use simple local 3’ PI (green) production to respond to PDGF (red) gradients.