

Research Roundup

Plasma membrane in Golgi costume

Stretching cells hold tight by allowing integrins to sidestep the Golgi, suggest Hans Schotman, Leena Karhinen, and Catherine Rabouille (University Medical Centre, Utrecht, Netherlands). The group uncovers a specialized section of Golgi-like plasma membrane that draws in integrins directly.

The hybrid membrane appeared in remodeling epithelial cells that cover the developing fly oocyte. The cells begin as columns that attach to each other at the sides and to the matrix on their basal side. But as the oocyte grows, the cells are stretched and flattened. The group found that these forces pulled the cells apart slightly, exposing the matrix to membrane that was previously attached to other cells.

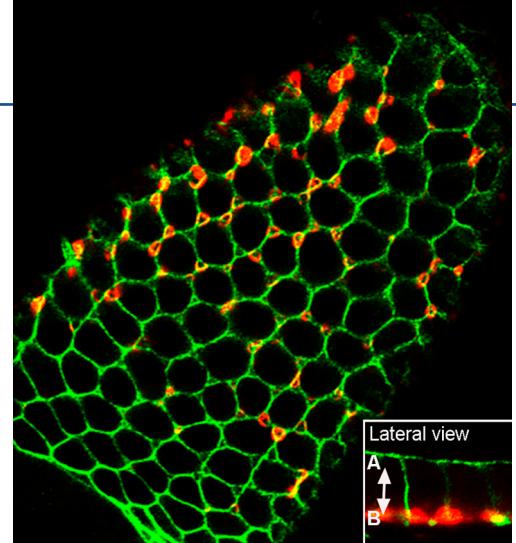
This newly matrix-adjacent membrane soon harbored GRASP, which is normally a bona fide Golgi marker. As the epithelial cells were pulled apart, *grasp* RNA was translated near the exposed membrane region. Two other Golgi proteins, GM130 and Gos28, were also found in this membrane region. “Our idea is that the plasma membrane is disguising itself as the Golgi,” says Rabouille, “so that carriers from the ER fuse there instead of with the Golgi.”

These lured carriers, the group imagines, harbor integrins that attach the membrane to the matrix. Insertion of one integrin subunit into these membrane sections was indeed insensitive to inhibitors of Golgi transport. And in the absence of GRASP, the integrin was instead retained within the cell. The resulting lack of adhesion caused epithelial disorganization.

It is not clear why the cells do not use the standard Golgi trafficking pathway. Posttranslational modifications that occur at the Golgi can make integrins less sticky. Bypassing this organelle might thus create more adhesion for these highly stressed cells.

The *Dictyostelium* version of GRASP has been shown to drive another unusual secretion pathway, which sends proteins directly from the cytosol to the extracellular space. Rabouille’s group now wants to determine how the fly bypass is activated; since integrins are thought to be mechanosensors, they might trigger their own retargeting in response to stretching. **JCB**

Schotman, H., et al. 2008. *Dev. Cell.* 14:171–182.



The *grasp* RNA (red) is translated near membrane regions that are being pulled apart from neighboring cells and newly attaching to the matrix.

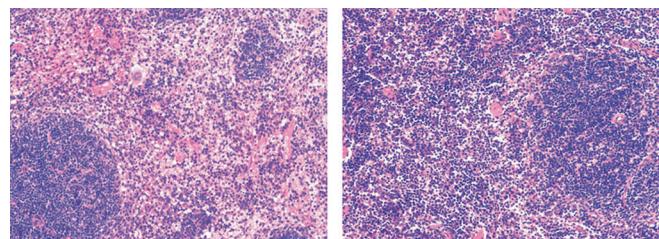
Rb turns up mitochondria

New results suggest that escape from the cell cycle is hooked to mitochondrial performance, say Vijay Sankaran, Stuart Orkin, and Carl Walkley (Harvard Medical School, Boston, MA). The group finds that both escape and performance are controlled by Rb in differentiating red blood cells.

The precursors to red blood cells, like many cell types, must stop proliferating before they can differentiate. Previous work showed that the precursors of red blood cells must also boost mitochondrial activity, perhaps to generate enough ATP for the impending onslaught of globin synthesis. In the new work, the authors reveal that Rb-mediated exit from the cell cycle allows differentiation by providing this mitochondrial boost.

In several cell types, Rb is necessary for the transition from G1 to S phase. But reports on its function in red blood cell development were conflicting. Sankaran et al. eliminated some of the complications that afflicted previous studies by knocking out Rb activity only in the cell lineage that produces red blood cells in mice.

The mutant precursors failed at a late stage of differentiation, when exit from the cell cycle is needed. Gene expression patterns revealed that S phase genes were maintained at high levels in the mutants. Several of these genes were targets of the E2F transcrip-

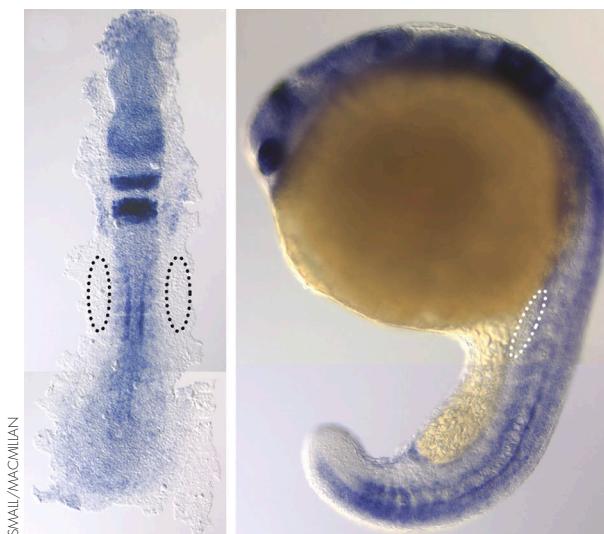


Red blood cell precursors proliferate uncontrolled when they lack Rb (right) and enough mitochondrial activity to differentiate.

tion factor—a known substrate of Rb’s inhibitory powers. As a result, whereas normal precursors escaped proliferation at this G1 stage, the mutants pushed forward into another S phase.

Loss of Rb also impaired mitochondrial biogenesis, electron transport, and oxidative phosphorylation. These pathways were up-regulated just before differentiation in normal precursors but remained flat in the mutants.

One transcription factor that promotes mitochondrial biogenesis in muscle and fat, called PGC, was reduced in the Rb mutants. The authors imagine that PGC levels are kept low by the mutant cells’ high levels of S phase cyclin-dependent kinases, one of which has been shown to block PGC function. **JCB**
Sankaran, V., et al. 2008. *Genes Dev.* 22:463–475.



Primordial germ cells (in circles) avoid CXCR7 (blue), which soaks up SDF-1 guidance cues.

Sopping up chemokine

As a sponge-like receptor sops up excess chemokine to refine the path for migrating primordial germ cells, based on findings from Bijan Boldajipour, Harsha Mahabaleshwar, Erez Raz (Center for Molecular Biology of Inflammation, Münster, Germany), and colleagues.

During development, germ cell precursors are drawn by gradients of the SDF-1 chemokine toward the gonads, where they will form the germ line. Zebrafish embryos have two SDF-1 receptors, CXCR4b and CXCR7, but the new results reveal that only CXCR4b leads the germ cells directly. CXCR7 was instead found on surrounding somatic cells, where it soaked up SDF-1.

The CXCR7 receptor and its bound SDF-1 ligand were taken into cells in endosomes. Rather than activate migratory signaling pathways, the receptor simply seemed to bring its ligand to lysosomes, where it is probably degraded.

Migrating germ cells avoided regions where CXCR7 sopped up SDF-1. The group suspects that the intake by CXCR7 allows conversion of the changes in SDF-1 mRNA expression patterns into differences in the protein pattern.

"To begin with," says Raz, "SDF-1 is expressed broadly throughout the embryo," drawing in the widely dispersed precursors. As development proceeds, he says, "SDF-1 expression becomes more restricted, and the old info must be quickly erased as cells draw nearer to their destination. If the ligand isn't cleared, it will reach unusually high levels, and the gradient will be disturbed." Such problems were seen in embryos lacking CXCR7, in which germ cells were unable to polarize or migrate. They were similarly immobilized when extra SDF-1 was expressed throughout the embryo. **JCB**

Boldajipour, B., et al. 2008. *Cell*. 132:463–473.

Variety in leading edge actin

Actin filaments lie in a wide range of orientations in the leading edge of a migrating cell, according to images from Stefan Koestler, Victor Small (Austrian Academy of Sciences, Vienna, Austria), and colleagues. What looks like disorder might help organize both protrusion at the front and retraction behind.

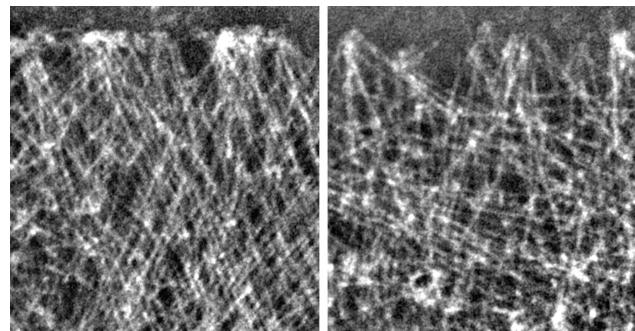
The work casts doubt on the textbook view of the network in the very front of a migrating cell, known as the lamellipod. In this view, the actin filaments branch off one another at consistent 70° angles. Small's group has been questioning this model for years, worried that fixation techniques might introduce branch-like artifacts by causing the filaments to collapse.

In the new work, the authors tried to avoid these problems by using a stronger fixative and drying the samples directly in a negative stain. Live cells were first viewed using light microscopy to determine whether lamellipodia were protruding, pausing, or retracting. They were then immediately fixed and examined by EM.

Protruding lamellipodia, the images revealed, contained actin filaments that hit

the plasma membrane at a wide range of angles, varying from 15° to 90°. During pauses, more filaments aligned more nearly parallel to the membrane. Small thinks the rearrangement comes naturally as the cell front slows its forward movement. "As cells slow, some actin filaments stop growing, but others are still polymerizing. Those filaments have to change orientation," he says, since their growing plus ends are tracking along the membrane.

The change might create an organization of filaments that maintains the retracting cell edge by lying parallel to it. It might also help construct the cytoskeleton just behind the lamellipod, in the lamella, where contractile bundles are built from myosin and antiparallel actin arrays. In an upcoming *JCB* paper, Small and colleagues show that actin bundles from filopodia also contribute to contractile bundles in the lamella.



Actin filaments sit at various angles to the plasma membrane in protrusions (left), but more are parallel to the membrane during pauses (right).

"What we're saying," Small explains, "is that lamellipodia and filopodia are filament factories not only for protrusion but also for constructing the cytoskeleton behind. One way to get antiparallel filaments in the lamella is by reorienting those at the front."

Although Small hopes to change how people envision the lamellipodial actin array, he knows more work is yet to be done. "We haven't disproven branching yet," he says. "We'll need 3D imaging to put the nail in that coffin. But what we've seen makes the branching model unlikely." **JCB**

Koestler, S.A., et al. 2008. *Nat. Cell Biol.* doi:10.1038/ncb1692.