In This Issue

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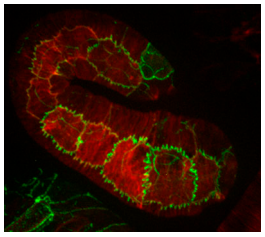
SRGP-1 drives cell junctions round the bend



Overexpressing SRGP-1 (green) causes dramatic outward projections of the intercellular junctions of embryonic epidermal cells.

An F-BAR domain protein bends the plasma membrane to promote the formation of intercellular adhesions, Zaidel-Bar et al. report.

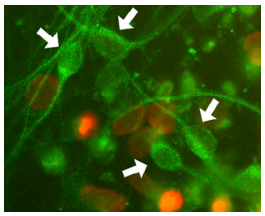
BAR (Bin1, Apmphiphysin, and RVS167) family proteins curve membranes inward or outward to facilitate endocytosis, filopodia formation, and other membrane movements. Zaidel-Bar et al. found that a *C. elegans* F-BAR protein, SRGP-1, localized to the junctions between neighboring worm cells, and that these adhesions formed more slowly in the protein's absence. Nevertheless, SRGP-1 was dispensable for embryogenesis unless the worms also carried mutations in key junctional components like α-catenin: when both junctions and SRGP-1 were compromised, embryos died because neuroblasts and epidermal cells failed to seal up holes and enclose the embryos' outer surface. A truncated version of SRGP-1, containing just the protein's F-BAR domain and a junctional targeting sequence, was sufficient to rescue these embryonic defects.

In most cases, F-BAR domains are thought to pull membranes inward, but Zaidel-Bar et al. found that overexpressing SRGP-1 had the opposite effect, pushing out the plasma membranes and junctions of epidermal cells so that they protruded into their neighbors.

Lead author Ronen Zaidel-Bar thinks that this activity might facilitate the formation of intercellular adhesions by increasing the area of contact between adjacent cells. He now wants to investigate the four human homologues of SRGP-1 and their potential function in epithelial and endothelial cell adhesion.

Zaidel-Bar, R., et al. 2010. *J. Cell Biol.* doi:10.1083/jcb.201005082.

Cells find an alternative exit



Rb family–knockout cells express a neuronal protein (green) but don't take up a marker of proliferating cells (red).

Mammalian cells can arrest and differentiate even in the complete absence of Rb family proteins, Wirt et al. reveal.

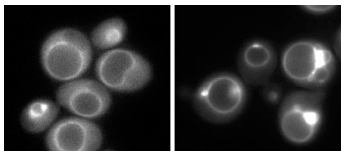
The retinoblastoma (Rb) tumor suppressor and its close relatives p107 and p130 arrest cells in G1 by binding and inactivating E2F transcription factors, blocking transcription of E2F target genes required for cell cycle progression. The Rb family is also thought to influence cell fate and promote terminal differentiation. To investigate the extent to which the Rb family is required for these processes during development, Wirt et al. generated mouse embryos lacking all three family members.

Triple knockout embryos died surprisingly late in embryogenesis, surviving until mid-gestation with normal-looking organs and embryonic patterning. Nevertheless, most wild-type cells are still proliferative at this point in embryogenesis, so Wirt et al. generated teratomas (embryonic stem cell tumors) to examine the Rb family's effect on cell cycle exit and terminal differentiation. Like wild-type teratomas, tumors lacking all three Rb proteins contained multiple different lineages and cells that had successfully exited the cell cycle. Triple knockout embryonic stem cells could also arrest and differentiate into specific cell types in vitro.

This suggests that Rb proteins have a regulatory rather than essential function in most differentiation pathways. Less clear is how some cells manage to arrest in the absence of the Rb family. Many E2F targets were still down-regulated in triple knockout cells, suggesting that atypical E2Fs, which repress genes independently of Rb, might control this alternative cell cycle exit route. If so, says author Julien Sage, activating atypical E2Fs might slow the growth of tumors carrying mutations in the Rb pathway.

Wirt, S.E., et al. 2010. *J. Cell Biol.* doi:10.1083/jcb.201003048.

How Vps41 HOPS between tethering functions



In the absence of Yck3 (right), Vps41 relocalizes from vacuoles to endosomes.

Cabrera et al. reveal how phosphorylation alters the membrane-tethering activity of Vps41, allowing the protein to operate in two distinct trafficking pathways.

Vps41 is part of the HOPS complex that controls transport to the yeast vacuole from two different sources, tethering either endosomes or Golgi-derived AP-3–coated vesicles to the vacuolar membrane. The vacuolar kinase Yck3 may help the HOPS complex discriminate between these pathways by phosphorylating Vps41. In the absence of Yck3, Vps41 accumulates on endosomes and targets them to the vacuole successfully, but it doesn't function in the delivery of AP-3 vesicles to the vacuole.

Cabrera et al. discovered that Yck3 phosphorylates Vps41 in a membrane-binding motif called an amphipathic lipid-packing sensor (ALPS). The ALPS is an α-helical structure that inserts into highly curved membranes. Insertion of the Vps41 ALPS into endosomal membranes masks a binding site for the AP-3 coat, the team found, preventing the fusion of AP-3 vesicles with endosomes but allowing Vps41 to deliver endosomes to the vacuole. Once at the vacuole, however, Yck3 phosphorylates Vps41 in its ALPS motif. Cabrera et al. found that this helped release the motif from membranes, making Vps41's AP-3–binding site available to tether AP-3 vesicles to the vacuole.

Yck3 therefore switches Vps41 from its function in endosome–vacuole fusion to its role in AP-3 vesicle delivery. Author Christian Ungermann now wants to investigate if similar principles apply to other tethering processes and to determine what happens after Vps41 recognizes the incoming AP-3 vesicle—the vesicle must quickly shed its coat to allow vacuole fusion to proceed.

Cabrera, M., et al. 2010. *J. Cell Biol.* doi:10.1083/jcb.201004092.

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