

## Rab35 drives exosome secretion

**T**he GTPase Rab35 regulates the release of small vesicles called exosomes from the surface of glial cells, say [Hsu et al.](#)

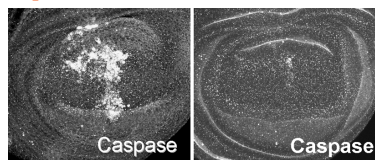
Exosomes are formed in the lumen of specialized endosomes called multivesicular bodies (MVBs), which fuse with the plasma membrane to secrete the vesicles extracellularly. The process was first described as a way for differentiating reticulocytes to quickly discard their unwanted cellular contents. In other cell types, exosomes have signaling functions or mediate the transfer of mRNAs between cells. Oligodendrocytes secrete a lot of exosomes, but their role in the central nervous system isn't clear—partly because molecules controlling the vesicles' release haven't been identified.

Because Rabs and their accessory proteins regulate membrane trafficking, Hsu et al. investigated their function in exosome

secretion by screening all 38 Rab GTPase-activating proteins (GAPs). Five GAPs inhibited exosome release from oligodendrocytes, including three closely related proteins that all switched Rab35 to the inactive, GDP-bound state. Knocking down Rab35 or expressing a dominant-negative version of the GTPase also blocked exosome secretion. Rab35 prepared MVBs for exocytosis by docking them to the plasma membrane.

Both Rab35 and MVBs were found in the myelin compartment of oligodendrocytes, which enwraps and insulates nerve cell axons. This suggests that exosomes released from glial cells could communicate with neighboring neurons. Senior author Mikael Simons is also interested in a possible connection to multiple sclerosis (MS): an abundant component of glial cell exosomes is a myelin protein called PLP—a common autoantigen in MS patients. [Hsu, C., et al. 2010. \*J. Cell Biol.\* doi:10.1083/jcb.200911018.](#)

## Epithelial cells on death Rho



Apoptosis (marked by caspase staining) is increased in imaginal disc cells lacking moesin (left) but is blocked if Rho1 is also reduced (right).

**C**ortical localization of the small GTPase Rho1 activates the JNK signaling pathway to kill *Drosophila* epithelial cells, [Neisch et al.](#) reveal.

Cell death by apoptosis is elevated in flies missing the epithelial

protein moesin, which organizes the apical cortex of cells, partly by linking the plasma membrane to the underlying actin cytoskeleton. Moesin also regulates Rho1, but the GTPase's contribution to apoptosis was unclear.

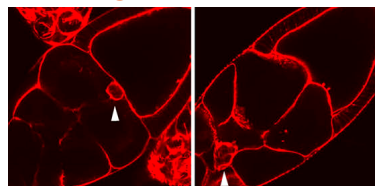
Neisch et al. saw that plasma membrane levels of Rho1 were increased in fly epithelia lacking moesin, and that removing one copy of the GTPase rescued the cells from apoptosis. In addition,

overexpressing Rho1 boosted cell death by up-regulating the pro-apoptotic gene *hid*. The authors then investigated the JNK signaling pathway, which can promote apoptosis in *Drosophila* imaginal disc epithelia. The pathway was activated in the absence of moesin, and inhibiting different steps of the signaling cascade blocked Rho1-induced death. Rho1 activated JNK signaling through an interaction with an upstream kinase called Slipper, but surprisingly, this association was independent of whether Rho1 was bound to GTP or GDP.

Recruitment of Rho1 and Slipper to the cell cortex was essential to triggering apoptosis in cells lacking moesin, as the two proteins formed a complex with other components of the JNK signaling pathway. The next step, says senior author Richard Fehon, is to determine how moesin limits the amount of Rho1 at the cell membrane and whether this is controlled developmentally. One possibility is that moesin binds a GTPase-activating protein to switch off Rho1 and decrease its membrane association.

[Neisch, A.L., et al. 2010. \*J. Cell Biol.\* doi:10.1083/jcb.200912010.](#)

## MIM gives cells a sense of direction



Border cells (indicated with arrowheads) fail to reach the large oocyte in egg chambers lacking MIM (right).

**C**ompetition between pro- and anti-endocytic proteins steers cell movement by polarizing the activity of guidance cue receptors, say [Quinones et al.](#)

During *Drosophila* oogenesis, a cluster of

border cells migrates across the flies' egg chamber toward the oocyte. This movement is guided by EGF and PDGF, which primarily activate their receptors at the border cells' leading edges. Quinones et al. found that this localized signaling and directional movement is disrupted in border cells lacking the protein missing-in-metastasis (MIM).

MIM is part of the BAR protein family, whose members normally promote endocytosis by linking membrane curvature to

changes in the actin cytoskeleton. But Quinones et al. found that EGF receptor internalization was increased in the absence of MIM suggesting that, unlike its relatives, MIM inhibits endocytosis. MIM competed with the pro-endocytic BAR protein endophilin for binding to the actin-polymerizing factor cortactin. Cortactin drives endocytosis when bound to endophilin, and mutations in the protein also disrupt border cell migration. But cells lacking both cortactin and MIM migrated properly. Normal EGF receptor endocytosis was also restored, suggesting that the balance of pro- and anti-endocytic factors is critical for localizing signaling activity and guiding cell migration.

Other cell types also lost their bearings in the absence of *Drosophila* MIM. These cells all respond to different cues, so competition between MIM and other BAR proteins may be a general mechanism by which cells steer to their destinations. The authors now want to investigate how MIM affects the migration of cancer cells, because the protein is missing or up-regulated in a variety of human tumors. [Quinones, G.A., et al. 2010. \*J. Cell Biol.\* doi:10.1083/jcb.200910136.](#)