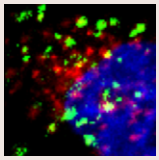
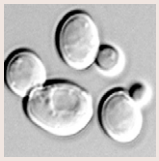
In this issue



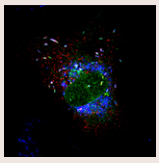
Atg14L snaps up endocytic role

Autophagy – lysosome-mediated degradation of intracellular constituents within double-membrane autophagosomes – shares several vesicle-trafficking components with the endocytic pathway. Now, Jae Jung and co-workers (p. 4740) report that the autophagy protein beclin 1-associated autophagy-related key regulator (ATG14, also known and hereafter referred to as Atg14L) is a multivalent trafficking effector that regulates the maturation of endosomes as well as the formation of autophagosomes. Atg14L interacts with beclin 1, a component of the phosphatidylinositol 3-phosphate kinase class III complex that induces autophagosome membrane nucleation. To further delineate the biological functions of Atg14L, the authors screen for Atg14L-interacting partners by using a yeast two-hybrid system. They report that Atg14L binds to the SNARE effector protein SNAPIN – SNARE complexes drive membrane fusion in the endocytic pathway – and that this interaction accelerates endosomal maturation in mammalian cells without affecting autophagic degradation of cargo. The authors also show that knockdown of *ATG14* in HeLa cells delays the late stage of endocytic trafficking and that expression of wild-type Atg14L or of a beclin-1-binding mutant but not of a Snapin-binding mutant rescues this phenotype. These and other results provide new insights into the crosstalk between autophagic and endocytic vesicle trafficking in eukaryotes.



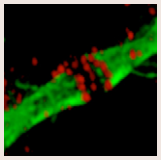
Shapely ER and mitochondria pair up

The endoplasmic reticulum (ER) is a dynamic network of sheets and tubules that extends throughout the cytoplasm, and that makes close contacts with other organelles. Proteins that maintain the complex structure of the ER include the reticulons Rtn1p and Rtn2p, and the reticulon-like protein Yop1p in *Saccharomyces cerevisiae*, as well as the atlastin family of proteins – dynamin-like GTPases in mammalian cells and their functional homologue in yeast Sey1p. Surprisingly, yeast cells that lack ER-shaping proteins grow as well as wild-type cells, even though they contain fewer ER tubules. To gain insights into the role of ER morphology in cell physiology, William Prinz and co-workers screen for mutations that cause poor growth in yeast cells that lack ER-shaping proteins (p. 4791). They authors report that cells that lack members of the ER–mitochondria encounter structure (ERMES) complex – which maintains functional contacts between the ER and mitochondria – as well as ER-shaping proteins have severe growth defects, reduced ER to mitochondrial phospholipid transfer and an altered mitochondrial phospholipid content. Together, these results reveal an unexpected role for ER-shaping proteins in maintaining functional contacts between the ER and mitochondria, and suggest that the shape of the ER at ER–mitochondria contact sites affects lipid exchange between these organelles.



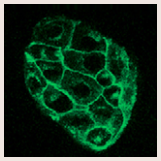
Weibel-Palade body Rabs identified

Weibel-Palade bodies (WPBs) are endothelial-cell-specific secretory vesicles whose cargo molecules are essential in blood vessel abnormalities, such as thrombosis and inflammation. Despite the importance of WPBs, little is known about the mechanisms that mediate their secretion. On page 4780, Savvas Christoforidis and colleagues investigate the involvement of Rab GTPases in the exocytosis of WPBs. Groups of organelle-specific Rab proteins are known to orchestrate the dynamics of various intracellular and secretory vesicles but, so far, only Rab27a and Rab3d (the so-called exocytic Rab proteins) have been found on WPBs. Now, in an unbiased screen for WPB-associated Rabs, the authors show that, in addition to Rab3 and Rab27, Rab15 (previously identified as an endocytic Rab), Rab33 (localized in the Golgi complex) and Rab37 (another exocytic Rab) are present on the WPB-limiting membrane in human umbilical vein endothelial cells. By using RNA interference, the authors show that only Rab3, Rab27 and Rab15 are required for exocytosis, and that Rab15 cooperates with Rab27 in the secretion of WPBs. Finally, they report that the Rab27-specific effector and tethering factor UNC13D (also known as Munc 13-4) is also an effector for Rab15 and required for WPB exocytosis. These findings pave the way for a comprehensive understanding of the mechanism by which Rab GTPases control WPB exocytosis.



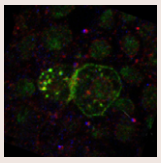
Wnt5a sets the stage for the final cut

The Wnt family of secreted ligands regulates various cellular functions by activating at least two signalling pathways. β-catenin-dependent Wnt signalling is known to be involved in the G1–S transition during mitosis; but is β-catenin-independent Wnt signalling also involved in cell-cycle regulation? On page 4822, Akira Kikuchi and colleagues report that Wnt5a signalling, which activates this second Wnt signalling pathway, controls cytokinesis. The authors have previously reported that Dishevelled 2 (Dvl2), a mediator of Wnt signalling, is localized to the midbody (the microtubule-enriched bridge that connects the two daughter cells during cytokinesis). Now, they show that the Wnt receptor Frizzled 2 (Fz2) also localizes to the midbody in dividing cells of human cell lines. Fz2 localization in the midbody is similar to that of CHMP4B, a subunit of the endosomal sorting complex required for transport III (ESCRT-III) – ESCRT proteins have been implicated in cytokinesis. Moreover, depletion of Wnt5a, its receptors or of Dvl increases multinucleated cells and destabilises the midbody microtubules, which leads to the mislocalisation of CHMP4B. The authors propose, therefore, that Wnt5a-mediated β-catenin-independent signalling regulates cytokinesis by ensuring that ESCRT-III is positioned correctly in the midbody for abscission, the final stage of cytokinesis.



KLF4 helps epithelial cells scatter

Hepatocyte growth factor (HGF; also known as scatter factor) induces epithelial cell scattering, a process that involves the loss of cell-to-cell junctions and the acquisition of motile and invasive mesenchymal features by epithelial cells, and underlies HGF-induced invasive growth in several human tumours. Now, on page 4853, Chia-Che Chang and colleagues propose that Krüppel-like factor 4 (KLF4), a zinc-finger transcription factor involved in cell proliferation, differentiation and self-renewal, mediates the effect of HGF on cell scattering. The authors show that HGF upregulates *KLF4* expression and induces scattering in HepG2 hepatocellular and MDCK epithelial cells through activation of the mitogen-activated protein kinase kinase/extracellular-signal-regulated kinase (MEK/ERK) pathway and induction of early growth response protein 1 (EGR1). By contrast, knockdown of *KLF4* in these cell lines inhibits HGF-induced E-cadherin expression and cell scattering. EGR1 binds directly to the *KLF4* promoter to induce *KLF4* transcription, report the authors. Moreover, EGR1-induced KLF4 binds to the *KLF4* promoter in order to create a positive feedback loop that sustains KLF4 expression and cell scattering. These findings provide new insights into the molecular mechanisms underlying cancer progression and might facilitate the development of cancer therapies that target this crucial process.



Intracellular traffic signals for Notch

Notch signalling is involved in numerous processes during development and throughout adult life, and its activation is tightly regulated in time and space. Yet, the Notch receptor and its ligands (e.g. the ligand Delta) are widely expressed; so what are the mechanisms that allow one cell to send Notch signals and another to receive them? Because endocytosis and recycling of both Notch and its ligands are essential for the accurate regulation of Notch activation, intracellular trafficking has recently emerged as a regulator of Notch signalling. To learn more about this regulatory mechanism, Stéphanie Le Bras, Roland Le Borgne and colleagues (p. 4886) have undertaken a tissue-specific dsRNA screen to target 418 genes that are potentially involved in endocytosis and endolysosomal recycling. Induction of dsRNAs that target 113 of these genes in the *Drosophila* sensory organ lineage (where Notch signalling regulates the acquisition of binary cell fate) resulted in gain or loss of Notch signalling phenotypes in adult sensory organs and, for 26 of the genes, changed the steady-state localization of Notch, Sanpodo (a Notch co-factor) and/or Delta in the pupal lineage. Overall the authors identified 11 genes that encode previously unknown regulators of Notch signalling. Further analysis of these genes should, therefore, provide new insights into the regulation of Notch signalling.