In this issue

**Next ER exit after the bend**
Proteins that are destined to reside in the plasma membrane or in the extracellular space move from the endoplasmic reticulum (ER) to the cell surface through the secretory pathway. Transport from the ER to the Golgi complex involves the coat protein complex II (COPII) as well as a number of accessory proteins. COPII vesicles form at so-called ER exit sites (ERES), which are morphologically distinct from the surrounding ER. Using high-resolution live imaging and genetic manipulation, Akiko Nakanoh and co-workers (p. 3412) now provide new insight into how transport from the ER to the Golgi is organised in *S. cerevisiae*. They illustrate that ERES are numerous COPII- and Sec16-containing punctate structures that are preferentially located at sites of high membrane curvature, namely the tubular ER and the edges of ER sheets. Depleting cells of proteins that stabilize ER morphology results in the redistribution of ERES to the remaining areas of high curvature. Furthermore, the authors show that, despite the lack of stacked Golgi cisternae in budding yeast, the cis-Golgi is found in the vicinity of ERES and that changes in ER morphology and ERES distribution affect the dynamics of Golgi cisternae. Thus, the geometric features of the ER are crucial determinants of the distribution of ERES and the connection between the ER and the Golgi.

**Domains BAR-e functional diversity**
BAR (for Bin/Amphiphysin/Rvs)-domain-containing proteins are involved in numerous cellular processes through their ability to bind to and deform membranes. It had previously been proposed that proteins with a BAR, N-BAR or F-BAR domain are involved in membrane invagination and tubulation, and that 1-BAR-domain-containing proteins mediate filopodia formation. However, more recent work has shown that SLIT-ROBO Rho GTPase-activating protein 2 (srGAP2), which contains an F-BAR domain, can induce filopodia-like membrane protrusions. Here, Franck Polleux and co-workers (p. 3390) provide further evidence for the functional diversity of F-BAR domains by investigating the differential effects of the related srGAP1, sgAP2 and srGAP3 on membrane deformation. They demonstrate that srGAP2 is more effective at inducing filopodia formation in non-neuronal cells than the other two proteins. In cortical neurons, these differences are even more pronounced: whereas the F-BAR domains of srGAP2 and srGAP3 induce cellular protrusions, the F-BAR domain of srGAP1 inhibits filopodia formation. Furthermore, the F-BAR domain of sgAP2, but not that of srGAP1 or srGAP3, localises to the distal end of filopodia and is more mobile in the plasma membrane. This work reveals that, even within a single protein family, BAR domains can exhibit substantial functional diversity.

**Less oxygen, more fat**
Hypoxia results in the activation of hypoxia-inducible transcription factors (HIFs) and distinct changes in gene expression that allow cells to adapt to reduced oxygen conditions. One of the adaptive changes induced by HIF1 is the switch from oxidative to glycolytic metabolism through the upregulation of specific genes. Little is known, however, about the way in which hypoxia influences lipid metabolism. George Simos and colleagues (p. 3485) now investigate HIF1-mediated changes in lipid metabolism in response to reduced oxygen concentrations and discover a role for lipin 1 (LPIN1) in this process. In different cells of non-adipocyte origin, hypoxia results in the nuclear accumulation of the HIF regulatory α subunit, HIF1-α, as well as an increase in triglyceride synthesis and lipid droplet formation. These effects are accompanied by increased levels of the phosphatidate phosphatase lipin 1. The authors show that the human LPIN1 promoter contains a conserved, functional HIF-responsive element (HRE) and that HIF1 binds directly to the LPIN1 promoter to upregulate its expression. By contrast, expression of lipin 2, which is the main hepatic isoform of this protein, is not affected by hypoxia. Together, these results highlight a molecular mechanism that involves HIF1 and lipin 1, and results in lipid accumulation in response to hypoxia.

**Stable connections need Rac1**
Cell–cell adhesion is not only necessary for tissue formation, but is also essential for the barrier-function of epithelia and endothelia. Furthermore, tumorigenic transformation and metastasis are associated with a dysregulation of cell–cell adhesion. Small GTPases, including RhoA, Rac1 and Cdc42, regulate the formation and loss of cell–cell contacts. But which signals do they activate to achieve this regulation? On page 3430, Peter Hordijk and colleagues now provide new insight into the role of Rac1 in promoting cell–cell contact maturation. Rac1, through its C-terminal domain, associates with the E3 ligase NEDD4 (for neural precursor cell expressed developmentally downregulated 4). Furthermore, activated Rac1 and NEDD4 colocalise at epithelial cell–cell contact sites. Depleting cells of NEDD4 impairs the formation of adherens and tight junctions, and reduces the transepithelial electrical resistance. The researchers further delineate the signalling pathway that links Rac1 and NEDD4 with junction maturation, by showing that NEDD4 ubiquitylates the adaptor protein dishevelled-1 (DVL1), which is a known negative regulator of cell–cell contacts. On the basis of these observations, they propose that Rac1 – through activating NEDD4, which in turn induces DVL1 ubiquitylation and degradation – increases the stability of cell–cell contacts.

**Obscuring(g) fly muscles**
The thick myosin filaments of adult muscle are crosslinked to each other. These links are important in maintaining proper filament alignment when the muscle contracts and stretches, and previous work has shown that the M-line is particularly prone to distortion under stress. On page 3367, Belinda Bullard and colleagues now show that obscurin (also known as Unc-89) is involved in stabilizing the M-line in the *Drosophila* indirect flight muscle. They find that obscurin is expressed throughout development, as well as in the adult fly, and that it is recruited to the forming M-line of sarcomeres. Flies that lack obscurin develop normally, but myosin assembly in the indirect flight muscle is impaired in the pupa, and adult flies are unable to fly. Furthermore, indirect flight muscles have an irregular structure in the absence of obscurin: the myofibrils are narrower, the H-zone is misplaced or absent and the M-line is missing. The asymmetry of the thick filaments in the absence of obscurin results in abnormal length and polarity of thin filaments in indirect flight muscles. Taken together, these observations highlight an important role for obscurin in the assembly of the thick filaments in *Drosophila* indirect flight muscle, which is required for the generation of the correct sarcomere symmetry and muscle function.

**Mim2 makes mitochondria**
All proteins that are located in the mitochondrial outer membrane (MOM) are encoded by nuclear DNA and must, therefore, be inserted into the membrane following translation on cytosolic ribosomes. Mitochondrial import 1 (Mim1) has been shown to be involved in the insertion of several single-spanning and all multi-spanning proteins into the MOM. But are additional proteins involved in this process? Here, Doron Rapaport and co-workers (p. 3464) describe a new protein, Mim2, that is involved in the biogenesis of helical MOM proteins in yeast. Mim2, which has no homologue in higher eukaryotes, is an integral membrane protein of the MOM, whose N-terminus faces the cytosol. Mim1 is known to form part of a large oligomeric complex. In immunoprecipitation experiments, the authors show that Mim2 directly interacts with Mim1 and is also a component of this complex. Deleting the *MIM2* open reading frame results in severe growth reduction, abnormal mitochondrial morphology and reduced levels of certain MOM proteins. Furthermore, the researchers demonstrate that yeast lacking Mim2 are severely hampered in their ability to import some helical proteins into the MOM and that this results in a global defect in protein import into these organelles as a result of the defective assembly of the translocase of the outer mitochondrial membrane (TOM) complex.