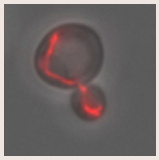
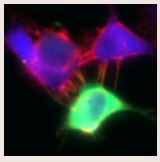
In this issue



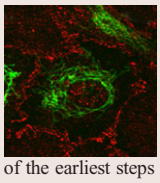
New insights into mitochondrial lipid homeostasis

The yeast mitochondrial outer membrane (MOM) protein Mdm10 has been shown to have important roles in different aspects of mitochondrial function, including mitochondrial biogenesis and mitochondrial lipid homeostasis – a role it exerts as a component of the so-called ER-mitochondria encounter structure (ERMES). Consequently, *mdm10*Δ mutants show severe growth defects. However, because the functions of Mdm10 are related and interlinked, its primary role in mitochondria remains unclear. In this study (p. 3563), Doron Rapaport, Kai Stefan Dimmer and co-workers perform a systematic screen for suppressors of the growth phenotype in *mdm10*Δ cells. They find two new proteins with, thus far, unknown functions, which they call Mdm10 complementing proteins 1 and 2 (Mcp1 and Mcp2, respectively). Both Mcp1 and Mcp2 localise to mitochondrial membranes. Mcp1 is a MOM protein, with its C-terminus facing the intermembrane space, whereas Mcp2 is an integral protein of the mitochondrial inner membrane. They find that overexpression of Mcp1 and Mcp2 rescued mitochondrial morphology, and restored mitochondrial phospholipid and ergosterol homeostasis in *mdm10*Δ cells. The authors also show that there are genetic interactions between *MCP1* or *MCP2* and other ERMES components, and their findings suggest that the ERMES complex is also involved in mitochondrial ergosterol homeostasis. Taken together, these data provide new insights into the mechanism of lipid homeostasis in mitochondria.



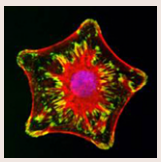
Htt aggregates travel through tunneling nanotubes

The misfolding and aggregation of proteins is a common hallmark of neurodegenerative disorders, such as Alzheimer's, Parkinson's and Huntington's disease. The latter is caused by genetic expansion of the huntingtin (*Htt*) gene, which results in the addition of tracts of polyglutamine (polyQ) to the protein, leading to toxic HTT aggregates in the brain. Recently, intercellular propagation of protein misfolding has emerged as an important means for the spreading and transmission of these diseases. However, little is known with regard to how HTT aggregates progress through the brain. Chiara Zurzolo and colleagues (p. 3678) now investigate the capability of mutant HTT fragments to transfer between co-cultured neuronal cells in primary neuronal culture. They demonstrate that HTT aggregates formed in donor cells are spontaneously transferred to receiving cells; this transfer appears to be an active transport mechanism that requires cell–cell contact. Interestingly, the authors find HTT aggregates in tunneling nanotubes (TNTs), which they had previously shown to be involved in the spreading of prions. They show here that their numbers increase when cells express mutant, but not wild-type HTT fragments. On the basis of these data, the authors suggest that TNTs provide an efficient mechanism for the transfer of polyQ aggregates between neuronal cells, which might also be exploited to develop new avenues for the therapeutic intervention of different neurodegenerative diseases.



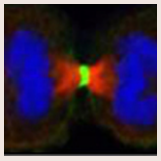
Drebrin: crucial at cell–cell contacts

Cell–cell contacts are essential for the integrity of the vascular endothelium and ensure that the tissue is able to withstand the forces associated with vascular flow. However, the exact molecular events underlying the formation of endothelial cell–cell junctions are still unresolved, although it is known that one of the earliest steps is the recruitment of nectin to adherens junctions. Nectins are transmembrane proteins that form trans-dimers with nectins from adjacent cells and so establish the initial cell–cell connection. It has been proposed that afadin then interacts with and stabilises nectin. On page 3756, Stefan Linder and colleagues now demonstrate that drebrin, which binds to F-actin, has a crucial role in anchoring nectin to the cortical actin cytoskeleton. They show that knockdown of drebrin leads to reduced transendothelial resistance and to a rupture of endothelial monolayers under conditions that mimic vascular flow; this is accompanied by a loss of nectin at junctions and its subsequent degradation. Using different biochemical and imaging approaches, the authors decipher the molecular interactions underlying the stabilisation of nectin: the polyproline region of drebrin binds to the PR1-2 region of afadin, and afadin recruits nectin through its PDZ domain. Therefore, being able to bind to both F-actin and afadin, drebrin facilitates the stabilisation of nectin at the endothelial junction and helps to preserve its integrity under vascular flow.



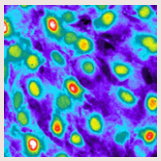
A new type of focal adhesion in the lung

Focal adhesions (FAs) form at the site of contact between the leading edge of a cell and the extracellular matrix; they originate from focal complexes of integrins, talin and focal adhesion kinase, which then mature into FAs through the addition of other factors and assembly of actin bundles. In the lung, alveolar epithelial cells (AECs) are responsible for gas exchange and are exposed to considerable mechanical forces, such as strain during breathing and shear stress caused by blood flow. Jonathan Jones and colleagues, therefore, reasoned that the mechanical requirements of the lung might be reflected in the adherence of individual lung epithelial cells, and on page 3746, they investigate this further in cultured primary AECs. Interestingly, they find that in some cells, FAs are arranged in two concentric circles, one FA ring that is located at the cell periphery (pFAs) and another located centrally in the cell (cFAs). In addition, when AECs are plated onto micropatterned surfaces, assembled cFAs mirror the cell shape. Furthermore, cFAs associate with actin arrays and with keratin filaments and, unexpectedly, are more dynamic than pFAs, as assessed by fluorescence recovery after photobleaching. The authors also show that cFA assembly requires plectin, because its depletion abolishes the double-ring arrangement of FAs with a concomitant reorganisation of the cytoskeleton. Therefore, the mechanical environment in the lung might give rise to unconventional FAs in AECs with unique composition and functions.



How supervilin guides the cleavage furrow

Cytokinesis is the final step of cell division, which physically disconnects two daughter cells, and myosin II drives the ingression of the cleavage furrow until abscission. The different steps of mitosis are regulated by mitotic kinases, such as polo-like kinase (PLK1), but it remains unclear how PLK1 regulates the activation of myosin II at the equatorial cortex and ingression of the cleavage furrow. In this work (p. 3627), Takeshi Senga and colleagues set out to address this question by screening for new PLK1 substrates that are essential for cytokinesis. They find that the actin- and myosin-II-binding protein supervillin (SVIL) is a new PLK1 substrate, and is required for completion of cytokinesis. SVIL has been previously described to be necessary for cytokinesis, but the molecular mechanisms underlying its role were unknown. The authors now show that SVIL is phosphorylated at Ser238 by PLK1, which promotes the localisation of SVIL to the central spindle and its association with the spindle factor PRC1 (protein regulator of cytokinesis 1). Furthermore, using a phosphorylation site mutant of SVIL and a mutant that lacks the myosin-binding region, they demonstrate that PLK1-mediated phosphorylation of SVIL is required for the activation of myosin II and accurate furrowing. These results suggest that SVIL functions as a scaffold that connects the central spindle to the contractile ring, and activates myosin II to guide the cleavage furrow in the restricted zone at the division plane.



P2 receptor networks make sense of ATP

Extracellular ATP signals through two families of cell-surface P2 receptors, the P2Y family of G-protein-coupled receptors and the P2X family of ligand-gated cation channels, whose activation by ATP, in many cases, results in elevation of Ca^{2+} in the cell. Several P2 receptor subtypes with varying affinities for ATP are expressed simultaneously in a number of tissues; however, the biological significance of such an extensive P2 receptor network remains unclear. Jeff Dixon and co-workers (p. 3615) now use osteoblasts as a model system to gain insight into this question. They find that Ca^{2+} signalling is activated by an extremely wide range of ATP concentrations that spans six orders of magnitude. The authors demonstrate that low concentrations of ATP (1 nM to 100 µM) act through P2Y receptors and result in a transient elevation of Ca^{2+}, which in turn leads to only a brief nuclear localisation of nuclear factor of activated T-cells, cytoplasmic 1 (NFATC1) – a transcription factor that promotes osteoblast differentiation and is regulated by cytosolic Ca^{2+} – but without the expression of NFAT target genes. By contrast, high concentrations of ATP (300 µM to 10 mM) act through P2X7 and elicit sustained Ca^{2+}-mediated NFATC1 signaling with a subsequent robust expression of NFAT target genes. These data suggest that an ensemble of P2Y and P2X receptors allow cells to sense ATP over a wide range of concentrations and to transduce this input into distinct cellular signals.