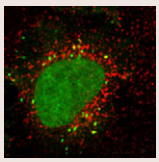
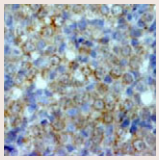
In this issue



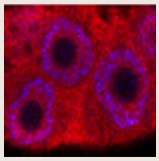
Clathrin joins the autophagosome

Autophagy regulates the turnover of cytosolic components in order to increase the availability of nutrients during starvation or to remove damaged cellular material. More than 30 autophagy-related genes (Atgs), which encode the proteins that are required for the formation of the autophagosomal membranes, have been identified. But an important question remains: which cellular membrane are these structures derived from? The ER, the Golgi network and mitochondria have all been implicated as membrane sources for the autophagosome. On page 1706, Wei Lu and colleagues now provide additional insight by showing that membranes from the trans-Golgi network (TGN) are involved in the formation of autophagosomal structures. They find that an increase in traffic from the TGN to the plasma membrane induces the formation of microtubule-associated protein light chain 3 (LC3)-positive structures, whereas blocking transport from the Golgi complex inhibits autophagosome biogenesis. Furthermore, LC3 binds directly to TGN membranes and, during starvation, LC3-positive vesicles bud from the TGN in a process that requires the clathrin adaptor protein AP1. Together, these results confirm a role for the TGN in autophagosome formation and highlight a role for AP1-mediated clathrin coating of TGN membranes in promoting starvation-induced autophagy.



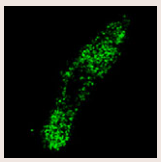
NEDD9 shows tumours how to move

Tumour cells can move in two distinct ways: they can squeeze through pre-existing gaps in the extracellular matrix (ECM) as rounded, amoeboid cells, or invade tissues in an elongated, mesenchymal-type movement by degrading the ECM. Amoeboid-type motility requires actomyosin contractility that is driven by the Rho-associated, coiled-coil-containing protein kinases ROCKI and ROCKII. By contrast, mesenchymal-type invasion in melanoma is initiated by signalling pathways that involve the Crk-associated substrate (CAS) family member NEDD9, the guanine nucleotide exchange factor DOCK3 and the small GTPase Rac1. On page 1814, Chris Marshall and colleagues now describe the molecular mechanism by which NEDD9 promotes mesenchymal and inhibits amoeboid motility. Overexpression of NEDD9 in melanoma cells changes cell morphology from rounded to elongated and enhances invasion into three-dimensional matrices. This effect requires integrin αvβ3. Furthermore, high levels of NEDD9 result in an increase in the phosphorylation of integrin β3 at Tyr785, and the formation of a signalling complex that comprises integrin β3, Src, NEDD9 and CRK. Activation of Src, subsequently, leads to the inhibition of ROCKII- and ROCKII-dependent amoeboid motility. NEDD9, thus, acts as an important signalling component that can drive the switch between the two different forms of tumour cell motility.



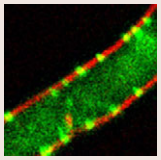
Taking 'PAR-5't in the germline

14-3-3 proteins are evolutionarily conserved regulatory proteins that bind to signalling proteins and affect their stability, activity or cellular localisation. Consequently, they are involved in the regulation of diverse cellular processes, including apoptosis, the cell cycle and the stress response. Here, Simo Schwartz, Jr, Julián Cerón and co-workers (p. 1716) investigate the function of the 14-3-3 protein PAR-5 – which is best known for its role in cell polarity – in the *C. elegans* adult germline, and its impact on the DNA damage response. Worms with decreased *par-5* expression levels contain fewer germ cells and have smaller gonads. In addition, these germline cells contain small, fragmented nuclei, which points to a role for PAR-5 in maintaining genome stability and cell cycle progression. Indeed, the authors report that PAR-5 is involved in DNA maintenance, as depletion of the protein results in the accumulation of DNA damage. Furthermore, they find that PAR-5 is required for cell cycle arrest in response to the S and G2–M checkpoints following replicative stress and ionising radiation, respectively, and that it promotes phosphorylation of the cyclin-dependent kinase Cdk1. Thus, PAR-5 not only has a role in germline proliferation, but also acts in the checkpoint pathway to prevent premature mitotic entry in response to DNA damage.



Dictyostelium rides the Ca^{2+} wave

Aggregation into a multicellular structure is a key step in the *Dictyostelium discoideum* life cycle. During this process, individual cells move towards the aggregation centre in response to cAMP waves. In addition, extracellular Ca^{2+} is important for cellular orientation and motility, and acts as a second chemoattractant. In the search for plasma membrane proteins that facilitate motility and chemotaxis in response to Ca^{2+}, David Soll and colleagues (p. 1770) now describe a role for the inositol 1,4,5-triphosphate receptor-like protein A (IplA) in Ca^{2+} chemotaxis during *Dictyostelium* aggregation. Using three different types of chamber to assess the behaviour of cells in response to chemoattractants, the researchers illustrate that a mutant *iplA*$^{-}$ strain cannot undergo chemotaxis in response to spatial Ca^{2+} gradients. By contrast, loss of IplA function does not affect chemotaxis towards cAMP in vitro. However, when exposed to waves of the chemoattractant generated by wild-type cells, *iplA*$^{-}$ cells portray an inability to reorient themselves towards the aggregation centre at the start of each wave, despite their movement towards cAMP being unaltered. The authors conclude that these findings support the hypothesis that transient Ca^{2+} gradients are required to orient cells towards the aggregation centre prior to the onset of a cAMP wave.



Step-by-step pH response

Fungi initiate specific transcriptional regulatory systems in response to changes in the external pH, which allows them to survive in both alkaline and acidic conditions. In *Aspergillus nidulans*, the *pal/RIM* signalling pathway carries out this function, and Pal proteins interact with components of the endosomal sorting complex required for transport (ESCRT)-III complex. However, the function and site of this interaction have remained unknown. Miguel Peñalva, Herb Arst and co-workers (p. 1784) now show that Pal and ESCRT proteins are assembled at the plasma membrane and dissect the order in which they are recruited. By using mutant strains that lack specific Pal or ESCRT-III components, they investigate changes in protein localization and interaction following an increase in environmental pH. The authors find that pH changes result in the ubiquitylation of the PalF protein, which then recruits the ESCRT machinery. PalC is recruited to these cortical complexes in a manner that depends on the main ESCRT-III component Vps32. This recruitment of PalC, in turn, allows the second Vps32-interacting protein PalA to form part of these complexes. The response to changes in pH is, thus, mediated by the carefully orchestrated assembly of a multimeric signalling complex that depends on the recruitment of ESCRT-III components to the plasma membrane.

From *Development*

miR-125 seals hESC neural fate

MicroRNAs are small non-coding RNAs that have recently emerged as key regulators of embryonic development. In particular, they can coordinate cell fate determination by blocking alternative cell fate choices. In *Development*, Alexandra Benchoua and colleagues report that the microRNA miR-125 contributes to the neural specification of pluripotent human embryonic stem cells (hESCs). By using a culture system that promotes hESC neuralisation, the researchers show that miR-125 is expressed in a time window that is compatible with its role in neural commitment in vitro. They show that miR-125 promotes the conversion of pluripotent cells into SOX1-positive neural precursors by, at least in part, blocking the expression of SMAD4, a key regulator of pluripotent stem cell lineage commitment that promotes non-neural cell fates. Finally, the researchers show that expression of miR-125 is responsive to the level of TGF-β-like molecules. Together, these results identify a central role for miR-125 in the irreversible neural lineage commitment of pluripotent stem cells in response to external stimuli.

Boissart, C., Nissan, X., Giraud-Triboult, K., Peschanski, M. and Benchoua, A. (2012). miR-125 potentiates early neural specification of human embryonic stem cells. *Development* **139**, 1247-1257.