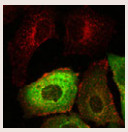
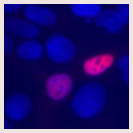
In this issue



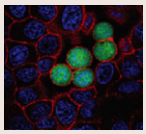
Re-routing endosomal traffic

Cell-surface molecules can be recycled directly through a rapid sorting endosomal pathway or indirectly by accessing the endosomal recycling compartment (ERC) in the pericentrosomal region of the cell. Members of the Rab11 GTPase protein family, which are key regulators of membrane trafficking through the ERC, are enriched at the cytosolic face of this compartment; in addition, a Rab11 effector protein known as FIP3 is important for the structural integrity and subcellular localisation of the ERC. On page 181, Mary McCaffrey and colleagues provide new findings that clarify the role of FIP3 in endosomal trafficking. They report that FIP3 forms a ternary complex with Rab11a and a subunit of cytoplasmic dynein 1, dynein light intermediate chain 1 (DLIC-1). The FIP3–DLIC-1 interaction occurs in peripheral regions of the cell and precedes minus-end-directed microtubule-mediated transport of endosomal cargo (in which cytoplasmic dynein participates as a motor protein). If a truncation mutant encompassing the DLIC-1-binding region of FIP3 is expressed, proteins that are normally recycled through the ERC cannot access this compartment. Finally, microscopy experiments show that the Rab11a–FIP3–DLIC-1 complex moves from the periphery of the cell towards the centrally located ERC. The authors conclude that this ternary complex mediates transport from peripheral sorting endosomes to the pericentrosomal ERC.



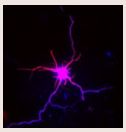
PPARγ catches the nucleocytoplasmic shuttle

Peroxisome proliferator-activated receptor-γ (PPARγ) is a nuclear hormone receptor that regulates cellular responses through both direct DNA binding and its ability to interact with and sequester proteins such as NF-κB and STAT transcription factors. However, recent evidence indicates that PPARγ is also present in the cytoplasm under some conditions. Andreas von Knethen, Bernhard Brüne and colleagues (p. 192) now characterise a mechanism by which PPARγ subcellular localisation can be regulated in cell lines and primary mouse macrophages. They first show that the phosphorylation of PPARγ at two serine residues by casein kinase II is required for PPARγ export from the nucleus to the cytoplasm. Second, they find that PPARγ export depends on a nuclear export receptor known as CRM1, and that the GTPase Ran and its co-factor RanBP3 are involved. Third, they show that ERK1 activity is also required for PPARγ nuclear export because ERK1 phosphorylation of RanBP3 permits a CRM1-RanBP3 interaction that enhances the binding of CRM1 to its cargo. Given that other mechanisms for PPARγ nuclear export have previously been reported, these data indicate that several different export mechanisms might regulate the cytoplasmic localisation of this protein in a context-dependent manner.



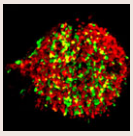
Triggers from tumour-cell neighbours

Many of the genetic mutations that occur in transformed cells have been well characterised, but less is known about how interactions between transformed cells and surrounding untransformed cells might also influence carcinogenesis. Yasuyuki Fujita and colleagues recently reported that the signalling pathways and cellular respones of RasV12-transformed epithelial cells are altered in the presence of untransformed cells. On page 171, this group now examines how the behaviour of cells transformed by another oncogene, Src, is influenced by their untransformed neighbours. The authors report that the interfaces between untransformed cells and cells transformed by either Ras or Src are remarkably similar, despite the fact that Ras and Src have different cellular roles. Similar to RasV12-transformed cells, the presence of untransformed neighbours causes Src-transformed cells to activate several signalling pathways and leads to their apical extrusion, which involves the activities of MAPK and myosin II. However, several differences – such as marked enhancement of focal-adhesion-kinase activation and tyrosine phosphorylation around the entire cortex of Src- but not RasV12-transformed cells – indicates that the promotion of apical extrusion by untransformed neighbours occurs by both overlapping and distinct mechanisms. How transformed cells sense their untransformed neighbours awaits elucidation in future studies.



Wee1: preventing polarity

Wee1 is a well-characterised cell-cycle checkpoint kinase that regulates mitotic entry in dividing cells. On page 286, Andreas Püschel and colleagues uncover a novel effect of Wee1 on cell polarity in post-mitotic neurons that is regulated by the kinases SadA and SadB (SadA/B). They show that Wee1 is expressed and has a functional role early during the development of hippocampal neurons when cells have several undifferentiated neurites, but that its expression declines later as the cells become polarised and form a single axon. If high Wee1 expression is maintained during later stages of differentiation, cell polarity is disrupted: instead of forming a single axon, developing neurons form multiple neurites that are positive for axonal markers and in some cases also for dendritic markers. But how is Wee1 expression regulated? In contrast to Wee1, the expression of SadA/B (which are known to be involved in axon formation) increases during later stages of neuronal development. SadA physically interacts with Wee1 and mediates an inhibitory phosphorylation at Ser642, which is necessary for the decrease in Wee1 expression. Accordingly, developing neurons from *Sada*$^{-/-}$*Sadb*$^{-/-}$ mouse embryos continue to express Wee1 and are subsequently abnormal. Therefore, the authors conclude, SadA/B regulate Wee1 activity and expression in developing neurons, which thereby determines proper neuronal cell polarity.



Quick on the uptake: prion proteins

Prion disease is thought to be caused by changes in the conformation of normal cellular prion protein (PrP^{C}) to an infectious PrP^{Sc} isoform, which induces neurotoxicity in PrP^{C}-expressing cells. A physical interaction between PrP^{C} and PrP^{Sc} stimulates this conformational change, so investigating PrP uptake and cellular localisation is crucial to obtain a better understanding of the pathology of prion disease. Roger Morris and colleagues previously reported that PrP binds to low-density lipoprotein receptor-related protein 1 (LRP1), which has two high-affinity ligand-binding sites (clusters 2 and 4). In a follow-up study (p. 246) they now show that both PrP^{C} and PrP^{Sc} interact only with LRP1 ligand-binding cluster 4, and that PrP^{Sc} appears to out-compete PrP^{C} for binding to this site. Furthermore, the kinetics and outcome of PrP^{Sc} endocytosis differ from that of PrP^{C}: PrP^{Sc} is endocytosed more rapidly and targeted to lysosomes, whereas PrP^{C} is recycled back to the cell surface. These differences, the authors propose, might be explained by differences in the size of the oligomers formed by the two PrP isoforms. As PrP^{Sc} binding and uptake is decreased by inhibiting the expression of LRP1, the authors propose that preventing the interaction between PrP^{Sc} and LRP1 ligand-binding cluster 4 might be effective for limiting prion disease.

Development in press

Islet cell development under Rfx6's wing

Each type of pancreatic islet cell produces a different hormone. For example, beta cells produce insulin, whereas alpha cells produce glucagon. In mouse embryos, the transcription factor neurogenin 3 (Ngn3) controls endocrine cell-fate decisions in multipotent pancreatic progenitor cells, but how does it mediate this effect? In a paper published in *Development*, Gerard Gradwohl and colleagues identify the winged helix transcription factor Rfx6 as a novel Ngn3-dependent regulator of islet-cell development in mice and zebrafish. They show that mouse Rfx6 and its zebrafish orthologue *rfx6* are expressed in islet progenitor cells and in all developing and adult islet cell types. Furthermore, loss-of-function experiments in zebrafish indicate that the differentiation of *glucagon*-, *ghrelin*- and *somatostatin*-expressing cells is blocked at the progenitor stage in the absence of Rfx6, whereas *insulin*-expressing cells differentiate normally but fail to form compact islets. This new information about the Ngn3-controlled genetic program during pancreas development might facilitate efforts to produce functional beta cells from human embryonic stem cells for the treatment of type 1 diabetes.

Soyer, J., Flasse, L., Raffelsberger, W., Beucher, A., Orvain, C., Peers, B., Ravassard, P., Vermot, J., Voz, M. L., Mellitzer, G. and Gradwohl, G. (2010). Rfx6 is an Ngn3-dependent winged helix transcription factor required for pancreatic islet cell development. *Development* **137**, 203-212.