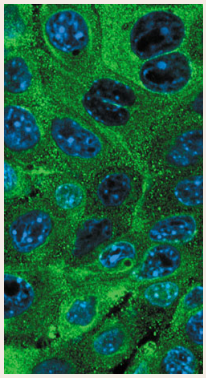
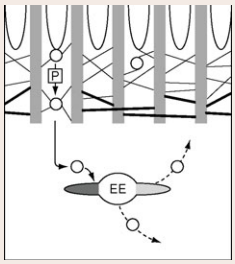
In this issue

by Jane Bradbury



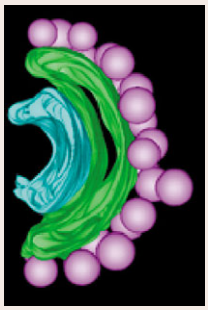
Signalling cystic fibrosis severity

Cystic fibrosis (CF), which affects the lungs and epithelia from other tissues, is caused by mutations in the cyclic-AMP-activated Cl^- channel CFTR. The severity of the disease, however, varies widely between patients with the same CFTR mutation and must therefore be influenced by additional factors. On p. 1320, Stephen Shears and colleagues identify ITPK1, a kinase that produces the signalling molecule inositol 3,4,5,6-tetrakisphosphate [Ins(3,4,5,6)P_4], as a potential modifier. Using an airway-epithelial-cell model, the authors show that Ins(3,4,5,6)P_4 inhibits Ca^{2+}-dependent Cl^- secretion – this is upregulated in CF and partly compensates for the CFTR defect. They also show that Ins(3,4,5,6)P_4 levels are reduced in murine tracheal CF epithelial (MTE) cells because of reduced expression of *ITPK1*. Furthermore, they note that ITPK1 is localized at the apical membrane of MTE cells, close to the Ca^{2+}-dependent Cl^- channels that its product inhibits. The authors suggest, therefore, that variability in *ITPK1* expression may contribute to CF severity by affecting how well the Ca^{2+}-dependent Cl^- channels compensate for loss of CFTR.



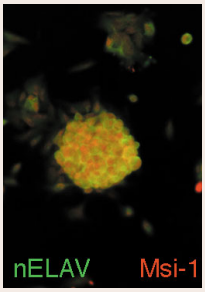
The spectrin haunting endocytosis

Many mature epithelia have apical brush borders made from densely packed microvilli. These are supported by F-actin bundles linked by a terminal web of spectrin and myosin II. How the vesicles that maintain the brush border move through this dense network is unclear. On p. 1361, Matthew Phillips and Graham Thomas propose that brush border spectrin – β_{Heavy}-spectrin – helps vesicles to make this journey, showing that it is required for early endosome recycling in *Drosophila* intestinal cells. They show that endosomes bearing the GTPase Rab5 are defective in the cuprophilic cells of the larval midgut of *karst* mutants, which lack functional β_{Heavy}-spectrin. They also find that brush borders and early endosomes from these mutants lack the apical H^+ V-ATPase that is normally present. This loss seems to disrupt normal acid secretion from the cuprophilic cells. Finally, the authors use epistasis experiments to place β_{Heavy}-spectrin between dynamin and Rab5-dependent endosome activities, which leads them to propose that spectrin 'primes' newly internalized proteins so that they can navigate the terminal web and enter the recycling pathway at the early endosome.



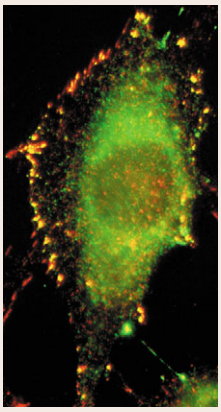
SNAREd by phospholipase D

Vesicle fusion is important for many cellular processes, including membrane trafficking, endo/exocytosis and yeast sporulation. During sporulation, vesicles gather on the spindle pole bodies and fuse to form prospore membranes around the daughter nuclei. Aaron Neiman and co-workers now reveal that Spo14p – the major yeast phospholipase D (PLD) – and its product phosphatidic acid (PA) promote the fusion process (see p. 1406). The authors show that, in cells that lack Spo14p or cells that express catalytically inactive Spo14p, prospore precursor vesicles accumulate on the spindle pole bodies but fail to fuse. Similar accumulations occur in cells that lack the SNARE protein Sso1p or the partially redundant SNAREs Sec9p and Spo20p. The authors show that PA recruits Spo20p to precursor vesicles but that PA-independent targeting of Spo20p to these vesicles does not restore prospore membrane formation in Spo14p-deficient cells. They conclude that PA is not only important for SNARE targeting but also has other roles in the fusion process. Since PLD has been implicated in regulated exocytosis in mammalian cells, it may play similar roles in membrane fusion in higher organisms.



Stem cells in an RNA bind

The proliferation and differentiation of neural stem cells (NSCs) is partly controlled by RNA-binding proteins (RBPs). While the RBP Musashi 1 (Msi1) prolongs NSC proliferation by translationally repressing its target RNAs, neural ELAVs (nELAVs) induce neuronal differentiation by stabilizing and/or promoting translation of transcripts that contain an AU-rich element (ARE). Some data indicate that Msi1 and nELAVs are expressed sequentially during mouse brain development but, on p. 1442, Antonia Ratti and co-workers report that these proteins are actually co-expressed in the neurogenic region of the adult mouse brain where NSCs reside. They show that nELAV proteins bind to *Msi1* RNA through an ARE and that the nELAV family member HuD stabilizes *Msi1* RNA in vitro and increases its translation in vivo. The authors propose that nELAVs stimulate *Msi1* expression as part of a multistep molecular cascade that leads from proliferating NSCs to differentiated neurons. The nELAV/*Msi1* pathway may thus represent a potential therapeutic target for the enhancement of neurogenesis in treatment of neurodegenerative disorders.



PTP route to mature attachment

Adhesion of cells to the extracellular matrix is important for tissue formation, transmembrane signal transduction and cell migration. How cell-matrix adhesion sites form is largely unknown, however. Carlos Arregui and colleagues now throw new light on the process by implicating protein tyrosine phosphatase 1B (PTP1B) in the maturation and stabilization of these adhesion sites (see p. 1233). They use GFP-labelled PTP1B D181A, a substrate-trapping mutant of PTP1B that forms stable enzyme-substrate complexes, to visualize the subcellular localization of PTP1B. The authors' results indicate that PTP1B is associated with the external face of the ER and punctate structures (foci) at the distal tips of immature cell-matrix adhesion sites. Intriguingly, they also suggest that PTP1B is targeted to these structures by ER tubules that are projected towards cell-matrix adhesion sites by microtubules. In addition, Arregui and colleagues observe that maturation of the foci is impaired in PTP1B-null cells. PTP1B could therefore be required for adhesion site maturation and, consequently, the stabilization of lamellae during cell migration.

Development in press

β-Catenin: it takes two

β-Catenin signalling is important for several stages of vertebrate neural development. Early on, it is essential for the formation of the dorsal organiser, a neural-tissue-inducing and dorsalising signalling centre; later, it promotes posterior and ventral fates. In a paper published in *Development*, Bellipanni and colleagues examine the multiple roles of β-catenin in neural development in more detail in the zebrafish model. They identify a new β-catenin gene (*β-catenin-2*), whose expression is reduced by a maternal-effect mutation (*ichabod*) that produces embryos lacking notochord, head and trunk neurectoderm. The authors use RNAi to show that β-catenin-2 – but not the previously studied β-catenin-1 – is needed for dorsal organizer formation. Later in development, however, the two β-catenins function redundantly to repress neurectoderm formation – in the absence of both, zebrafish form an abnormal tuft-like projection of neurectoderm with an apparently appropriate anteroposterior pattern. Overall, the researchers conclude that different β-catenins can have different, and sometimes opposing, roles at different points during neural development.

Bellipanni, F., Varga, M., Maegawa, S., Imai, Y., Kelly, C., Pomrehn Myers, A., Chu, F., Talbot, W. S. and Weinberg, E. S. (2006). Essential and opposing roles of zebrafish β-catenins in the formation of dorsal axial structures and neurectoderm. *Development* **133**, 1299-1309.