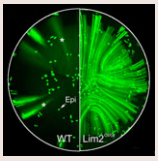
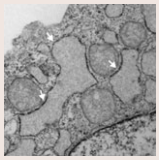
In this issue



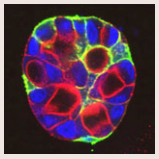
Focusing in on lens syncytia

Within the lens of the vertebrate eye, macromolecules can move from cell to cell through a poorly characterised process known as the large molecule diffusion pathway (LMDP). To explain this movement, it has been proposed that the lens contains syncytia (the product of multiple cell-cell fusion events) – but how are these syncytia structured, and what might be their role in light focusing in the eye? To address these questions in living, intact lenses, Steven Bassnett and colleagues (p. 1607) express GFP in lens epithelial cells in young mice, and track its movement between cells. The authors show that macromolecules preferentially traffic between lens cells that lie within a single stratum of the lens cortex (and are, therefore, of a similar age). They next examine the role of the lens plasma-membrane protein Lim2, which has been proposed to mediate intercellular communication in the lens. They show that, in mice lacking Lim2, the LMDP is not established and syncytia do not form. Moreover, regions of partial cellular fusion are common in wild-type lenses, but are rare or absent in Lim2-deficient mice. The authors conclude that the lens contains several overlapping Lim2-dependent syncytia that form a unique 'stratified syncytium', and propose several ways in which intercellular protein diffusion within the strata might promote light focussing by the lens.



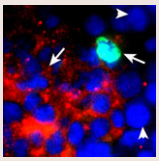
UPR: new paths to ER expansion

In response to increased demand on the protein-folding capacity of the ER, cells trigger the unfolded protein response (UPR) – a series of pathways that suppresses the flow of polypeptides into the ER and upregulates the expression of ER proteins such as chaperones. Recently, Joseph Brewer and colleagues showed that the UPR transcriptional activator XBP1 also increases synthesis of phosphatidylcholine (PtdCho; a key ER lipid) and expansion of the ER; now, on page 1626, they show that ATF6α, another UPR transcriptional activator, can also promote these changes. Using transmission electron microscopy, the authors demonstrate that the ER is enlarged and distended when a constitutively active form of ATF6α is expressed in cells in culture. Importantly, ATF6α-driven membrane expansion occurs even in the absence of active XBP1. They go on to show that the overexpression of active ATF6α induces PtdCho biosynthesis; notably, ATF6α modulates the activity of PtdCho biosynthetic enzymes differently than XBP1. The authors conclude that both XBP1 and ATF6α can induce ER expansion and lipid biosynthesis through methods that are at least partially distinct. Their data underscore the emerging complexity of the UPR and its related signalling pathways.



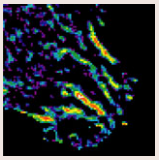
Going apical with PAR-3

PAR-3 and the aPKC–PAR-6 complex – which are crucial proteins for establishing apicobasal polarity in epithelial cells – are thought to regulate the establishment of the apical domain, as well as the maturation of epithelial junctional structures such as tight junctions (TJs). The molecular mechanisms that underpin their roles have been unclear, although it has recently been shown that PAR-3 can regulate TJ development without interacting with aPKC–PAR-6. By contrast, Shigeo Ohno and colleagues (p. 1595) now show that apical-domain formation requires an interaction between PAR-3 and aPKC–PAR-6. The authors show that, in MDCK cells, knocking down PAR-3 inhibits exocytic delivery of apical proteins to the plasma membrane and eventually results in apical-domain mislocalisation; moreover, the cells fail to form normal cysts in 3D culture, and instead develop cysts that have multiple lumens. These defects can be rescued by wild-type PAR-3, but not by a PAR-3 mutant that cannot interact with aPKC. They next observe that, in depolarised MDCK cells, aPKC and PAR-6 (but not PAR-3) accumulate on apical vacuoles, and that these are targeted to PAR-3-containing primordial cell-cell contact sites as repolarisation progresses. Thus, the authors conclude, the formation of a PAR-3–aPKC–PAR-6 complex is necessary for apical-domain establishment.



DSV2: at the heart of cell-cycle exit?

In mammals, myocardial infarction (MI) leads to the formation of diseased heart tissue – however, the heart lacks the ability to replace this myocardium with newly divided cardiomyocytes because adult cardiomyocytes do not undergo cell division. Little has been known about the mechanisms regulating cell-cycle exit in cardiomyocytes but, as Kishore Pasumarthi and colleagues (p. 1563) now show, a splice variant of cyclin D2 (D2SV) might have an important role. The authors first demonstrate that endogenous D2SV is highly expressed in embryonic myocardium – where it localises to micro-aggregate structures – but not in the adult heart. Moreover, in mouse embryonic cardiomyocytes, endogenous D2SV expression is inversely correlated with cell-cycle activity, and enforced expression of D2SV leads to cell-cycle exit. The authors next demonstrate that D2SV aggregates are retained in the Golgi, ER and lysosomes, and that cells containing D2SV aggregates are subject to ER stress. Importantly, they show that D2SV aggregates also contain other cell-cycle proteins such as cyclins and cyclin-dependent kinases. They therefore propose that the sequestration of cell-cycle proteins is the mechanism by which D2SV induces cell-cycle exit. Their data shed light on cell-cycle control in cardiomyocytes, and hint at potential therapeutic strategies for MI.



α4 integrin: making it complex

The integrin α4β1 – which, like other integrins, spans the plasma membrane and connects cells with the extracellular matrix – is particularly important for leukocyte migration during the immune response, and defects in the α4 subunit are associated with several diseases. The α4 cytoplasmic domain is known to interact directly with the focal-adhesion protein paxillin; however, many aspects of α4-dependent migratory signalling remain unclear. Now, Martin Humphries and colleagues (p. 1654) identify a novel α4-containing signalling complex, and show how it affects known pro-migratory signalling pathways. The authors show, using FRET, that the α4 cytoplasmic domain interacts directly with 14-3-3ζ at adhesion contacts in CHO-B2 cells; moreover, this interaction depends on the phosphorylation of α4 at S978 (the paxillin-α4 interaction depends on phosphorylation at a distinct site on α4, S988). The authors next present evidence that an α4–14-3-3ζ–paxillin ternary complex exists in vitro and at adhesions in cells. Notably, they show that the ternary complex is required for localised activation of the pro-migration GTPase Cdc42 at the leading edge and for directed cell movement (although the association of α4 and paxillin alone is sufficient for the activation of Rac1). Their results elucidate a new mechanism of α4β1 signalling.

Development in press

Sugar-coated stop signs for neurons

Proper neuronal migration is crucial for development of the vertebrate nervous system, but how do neurons know when to stop migrating? In a paper published in *Development*, Hitoshi Okamoto and colleagues shed light on this question and report that some neuronal progenitors in zebrafish fail to stop migrating at their normal position when the sugar fucose is not synthesised correctly. By screening for mutants in which motor nuclei of the vagus nerve do not form properly, the authors identify a gene (towhead) that encodes GDP-mannose 4,6-dehydratase (GMDS), a key enzyme in the fucosylation pathway. Accordingly, the authors detect fewer fucosylated glycans than normal in towhead mutant embryos. Fucosylation has been reported to regulate Notch signalling, but the authors show that this signalling pathway is not altered in towhead mutants. They also demonstrate that, for correct migration, GMDS is not required in vagus motor neuron progenitors, but instead is required in the surrounding epithelial cells. They propose, therefore, that fucosylated glycans on epithelial cells modulate the migration of vagus motor neuron progenitors.

Ohata, S., Kinoshita, S., Aoki, R., Tanaka, H., Wada, H., Tsuruoka-Kinoshita, S., Tsuboi, T., Watabe, S. and Okamoto, H. (2009). Neuroepithelial cells require fucosylated glycans to guide the migration of vagus motor neuron progenitors in the developing zebrafish hindbrain. *Development* **136**, 1653-1663.