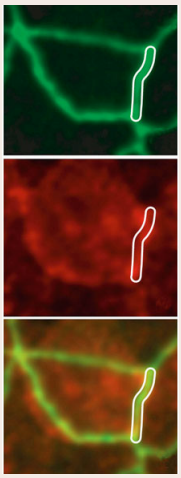
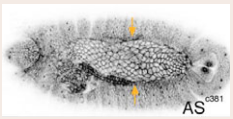
In this issue



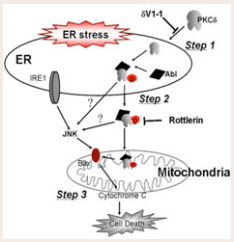
Gα12 breaks up the party

Understanding the regulation and assembly of tight junctions (TJs) is crucial for understanding how epithelial cells form and maintain their polarity, but the mechanisms are poorly defined. In this report, Bradley M. Denker and colleagues (p. 814) investigate the potential role of the G protein subunit Gα12 in regulating TJ assembly in MDCK monolayers. G proteins have been implicated in the regulation of barrier function and TJ assembly, and Gα subunits have been shown to localise to epithelial-cell TJs. The authors previously showed that Gα12 directly interacts with ZO-1, one of the scaffolding proteins of the TJ. Here, they show that Gα12 activation stimulates phosphorylation of ZO-1 and ZO-2 by Src in an Hsp90-dependent manner, leading to dissociation of occludin and claudin-1 from the ZO-1 protein complex, and disruption of TJ integrity. These effects can be blocked by the Src-kinase inhibitor PP2 and the Hsp90 inhibitor geldanamycin. Thrombin (a known agonist for Gα12/Gα13-coupled pathways), acting through Gα12, slows the assembly of TJs. This study provides the first evidence that Gα12 is a negative regulator of TJ assembly.



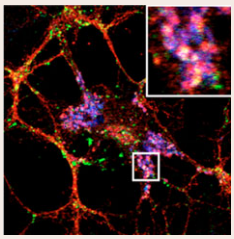
Clearing a Grainy picture

Similar to mammalian skin, the *Drosophila* cuticle maintains the surface barrier defences of the fly, protecting it from the external environment. The Grainy head (Grh) transcription factor is integral to cuticle resilience, and Grh proteins have highly conserved roles in regulating the terminal differentiation of protective epithelia. But could Grh have other functions in these epithelia? Sarah Bray and colleagues (p. 747) investigate whether Grh directly regulates the expression of components of epithelial junctions [called tight or septate junctions (SJs)]. The authors express Grh in the amnioserosa, an epidermal layer in the *Drosophila* embryo that lacks endogenous Grh and SJs. Dorsal closure (a process similar to wound healing) is severely disrupted in the amnioserosa cells, and this defect correlates with ectopic expression of several SJ proteins. Grh-induced expression of these proteins, together with others that contribute to adhesion complexes, probably explains the dorsal-closure-arrest phenotype by promoting enhanced adhesiveness between the dorsal epidermis and amnioserosa cells. This paper provides the first evidence in invertebrates that Grh proteins regulate the genes that encode the epithelial junctional complex.



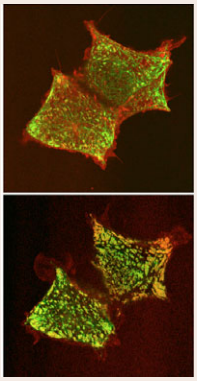
PKCδ-Abl: stressed to death

The unfolded protein response (UPR) is an ER-stress-induced signalling cascade that is activated by the accumulation of misfolded proteins within the ER, and either restores proper protein folding or leads to apoptotic cell death. The mechanism responsible for ER-stress-induced cell death is unclear, but on page 804, Xin Qi and Daria Mochly-Rosen describe a possible role for PKCδ and the receptor tyrosine kinase Abl in culture as well as in an in vivo stroke model. Using a variety of biochemical and imaging studies, the authors implicate the ER-stress-induced apoptosis pathway in Neuro2a cells treated with tunicamycin and also in focal cerebral ischemia in the rat. They report that ER stress induces translocation of PKCδ from the cytosol to the ER, where it binds to Abl. This complex then moves to the mitochondria, where it activates JNK signalling and contributes to ER-stress-induced apoptosis. These results represent a potential mechanism by which cells modulate apoptosis in response to ER stress.



The benefits of recycling

The precise localisation of proteins and lipids to myelin subdomains is crucial for myelin morphogenesis and neuronal function, but how oligodendrocytes regulate this process is largely unknown. Neuronal signals stimulate oligodendrocytes to adjust the relative levels of endocytosis and exocytosis of PLP, the major myelin protein. Eva-Maria Krämer-Albers and colleagues (p. 834) ask whether endocytic trafficking is common to myelin proteins and whether endosomal sorting of myelin components assists in myelin-domain formation. They focus on the myelin-membrane proteins PLP, MAG and MOG, and find that they are all internalised from the plasma membrane before ending up in the myelin sheet. These proteins follow distinct endocytic sorting pathways before being recycled into different regions within the myelin sheets. Biochemical data show that endocytosis of these proteins is required for sorting into distinct myelin-membrane fractions of different densities. Trafficking through the endosomal system, therefore, is an important requirement for sorting into different regions within the myelin sheet. The authors suggest that endocytic sorting and recycling contributes to the mechanism that establishes distinct myelin-membrane domains.



Reversal of SOCE fortune

Depletion of intracellular Ca^{2+} stores leads to the activation of Ca^{2+}-permeable channels in the plasma membrane, a reversible process known as store-operated Ca^{2+} entry (SOCE). The Ca^{2+} that enters through the store-operated channels can then be pumped into stores within the ER to replenish them. Depleted Ca^{2+} stores in the ER stimulate the ER Ca^{2+} sensor Stim1 to rearrange from tubular structures throughout the ER to punctate structures near the plasma membrane, where it activates the SOCE channels. On page 762, James W. Putney, Jr and colleagues investigate the poorly understood mechanism and determinants of the localisation and reversal of Stim1 puncta formation. They show that SOCE is tightly coupled to the formation of Stim1 puncta, because the basis for SOCE termination is the reversal of punctate Stim1 localisation, which, in turn, is dependent on SOCE-dependent store refilling. In addition, they report on the role of the pharmacologic agent ML-9 as a potential antagonist of Stim1-dependent SOCE. These findings provide a molecular basis for the self-regulating nature of the SOCE process.

Development in press

A diaphanous vision of morphogenesis

The changes in cell shape and migration that occur during morphogenesis require coordinated regulation of cell-cell adhesion and of the actomyosin skeleton. Diaphanous (Dia)-related formins – regulators of actin nucleation and elongation – play essential roles in cytokinesis but also regulate cell adhesion, polarity and microtubules. Might they, therefore, be involved in morphogenesis? In a paper published in *Development*, Catarina C. F. Homem and Mark Peifer report that *Drosophila* Dia coordinates cell adhesion and actomyosin contractility during morphogenesis. They show that Dia has a dynamic pattern of expression during fly embryogenesis that is consistent with a role in regulating cell-shape changes. Using constitutively active Dia, they reveal that Dia regulates myosin levels and activity at adherens junctions during cell-shape change. Finally, by reducing Dia function, they show that Dia stabilises adherens junctions and inhibits the formation of cell protrusions. The researchers conclude that, by regulating both actin and myosin, Dia organises the actomysin network at adherens junctions, thereby coordinating cell-shape changes and cell-cell adhesion during morphogenesis.

Homem, C. C. F. and Peifer, M. (2008). Diaphanous regulates myosin and adherens junctions to control cell contractility and protrusive behavior during morphogenesis. *Development* **135**, 1005-1018.