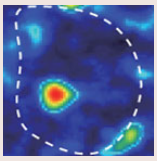
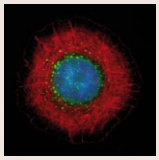
In this issue

By Jane Bradbury



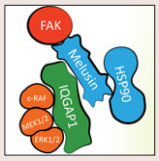
ATP makes an exit at caveloae

ATP is not only the major provider of energy in the cell but also functions as an autocrine and paracrine signalling molecule. Its release in response to mechanical and biochemical stimuli regulates cellular function by activating purinoreceptors, such as P2X ion channels and G-protein-coupled P2Y receptors on the cell surface. For example, vascular endothelial cells lining the inner surface of blood vessels release ATP in response to shear stress, which results in a Ca^{2+} influx and increased Ca^{2+}-induced signal transduction. It is well known that this process is important for the regulation of vascular function, but the mechanism behind the ATP release remained unclear. Here, Joji Ando and colleagues (p. 3477) use a biotin–luciferase protein construct that they attach to the surface of cultured endothelial cells to assess the release of ATP in real time. They find that exposure of cells to shear stress causes the nucleotide to be released in two distinct ways: diffusely and in a highly localised pattern. This localised ATP release occurs in caveolin-1-rich regions of the membrane and knockdown of caveolin-1 expression using siRNA inhibits this process without affecting the more diffuse release of the nucleotide. Furthermore, ATP release at caveolae results in a rapid increase in intracellular Ca^{2+} concentration at these specific locations and propagation of this signal throughout the cell in form of a Ca^{2+} wave.



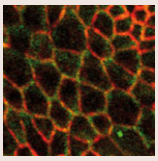
Clathrin waves on lamellipodia

Lamellipodia are plasma membrane protrusions that define the leading edge of migrating cells. The formation of branched actin networks, which is mainly controlled by the activity of the Arp2/3 complex, provides the force required to form lamellipodia. In mammalian cells, three Wave proteins, which are embedded in multiprotein Wave complexes, are the major activators of the Arp2/3 complex at the leading edge of cells. Now, on page 3414, Alexis Gautreau and co-workers have undertaken a combined proteomics and genomics screen in *Drosophila* cells to look for new regulators of the Scar/Wave complex (SWC; in *Drosophila*, Wave is referred to as Scar) during lamellipodium formation. The authors identify clathrin heavy chain (CHC, a protein that is best known for its involvement in membrane traffic) as a protein that binds to the SWC and that regulates lamellipodium formation. They report that these two properties of clathrin are conserved in mammalian cells. Notably, this new role for clathrin is uncoupled from its conventional role in membrane trafficking. Finally, the authors show that CHC promotes the recruitment of the SWC at the plasma membrane. They propose, therefore, that CHC regulates lamellipodium formation independently of its role in membrane trafficking by bringing the SWC to the plasma membrane.



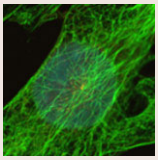
Melusin heartens ERK activation

Aortic stenosis (narrowing of the aortic valve in the heart) causes pressure overload, a pathological condition that can lead to heart failure. ERK1/2 signalling is a key pathway in cardiomyocyte hypertrophy and survival in response to pressure overload and other stress stimuli. Now, on page 3515, Mara Brancaccio, Guido Tarone and colleagues describe how ERK1/2 signalling is activated in the mouse heart. The authors show that melusin – a muscle-specific chaperone protein that can activate ERK1/2 signalling in the heart and that also binds the Hsp90 chaperone protein – forms a supramolecular complex with the mitogen-activated protein kinases (MAPKs) c-Raf, MEK1/2 and ERK1/2. Melusin-bound MAPKs, they report, are activated in mouse hearts by aortic banding, a surgical intervention that mimics pressure overload. Moreover, focal adhesion kinase (FAK) and IQGAP1 (a scaffold protein for the ERK1/2 signalling cascade) are also part of the melusin complex and are required for melusin-dependent ERK1/2 activation in response to pressure overload. The authors propose, therefore, that melusin, by interacting with FAK, IQGAP1, c-Raf, MEK1/2 and ERK1/2, regulates the MAPK pathway, and thus cardiomyocyte hypertrophy and survival, both through its own chaperone activity and through Hsp90 recruitment.



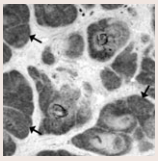
Crumbs keeps PI3K in check

The polarised architecture of epithelial cells is crucial for tissue development and integrity. Variations in plasma membrane lipid composition are involved in epithelial polarity, and the apical domain contains primarily PtdIns(4,5)P_2, whereas the basolateral membrane is characterised by high levels of PtdIns(3,4,5)P_3. But how is this difference maintained? On page 3393, Patrick Laprise and colleagues provide an answer by showing that the transmembrane protein Crumbs, the small GTPase Rac1 and PI3K fine-tune the membrane lipid composition in polarised epithelial cells. They show that in the *Drosophila* embryo, active PI3K results in the activation of Rac1 and that this, in turn, enhances PI3K activity. Furthermore, they find that Crumbs regulates polarity by interfering with this positive-feedback loop. By limiting the activity of PI3K and Rac1, Crumbs has an important role in limiting the production of PtdIns(3,4,5)P_3 in the apical membrane. The researchers also show that overexpression of constitutively active Rac1 results in decreased Crumbs expression and a highly restricted apical domain. Thus the system is additionally fine-tuned by the inhibition of Crumbs activity in the apical domain by the Rac1–PI3K module. These data shed light on the mechanisms involved in establishing epithelial polarity and highlight that these signals need to be carefully balanced to obtain the correct cellular arrangement.



Apaf1 balances life and death

The pro-apoptotic protein Apaf1 (apoptotic protease activating factor 1) forms the core of the apoptosome and is a crucial component of the mitochondria-dependent death pathway. Paradoxically, Francesco Cecconi and colleagues (p. 3450) now report that, by regulating centrosome morphology and function, Apaf1 also has a pro-survival role. By analysing *Apaf1*-depleted cells, the authors show that Apaf1 loss induces defects in the centrosome, the major microtubule organizing centre in animal cells. These defects impair centrosomal microtubule nucleation and cytoskeleton organization, thereby affecting mitotic spindle formation, cell migration and mitochondrial network organization. As a result, *Apaf1*-depleted cells are more fragile and have a lower stress response threshold than wild-type cells. Apaf1 regulates centrosome maturation, the authors report, by controlling the recruitment of HCA66 (hepatocellular carcinoma antigen 66) to the centrosome; HCA66, a positive regulator of Apaf1-dependent apoptosis, is also required for the stability of the γ-tubulin small complex that helps to form the pericentriolar material in the centrosome. Together, these results suggest that Apaf1 is a pro-survival protein, as well as a pro-apoptotic protein. Thus, Apaf1 could help to regulate the equilibrium between cell death and survival.



BMP puts the brakes on miR-21

In the skin, bone morphogenetic proteins (BMPs) control hair follicle morphogenesis and keratinocyte differentiation and act as potent tumour suppressors. Many cellular processes in the skin are also regulated by changes in the expression of specific microRNAs (miRs), and previous studies have shown that signalling pathways and miR expression are closely linked. Here, Natalia Botchkareva and co-workers (p. 3399) provide evidence for crosstalk between BMP signalling and miR-21 and elucidate the role of miR-21 in the regulation of several BMP targets. They find that stimulation of primary mouse keratinocytes results in a marked decrease in miR-21 expression. By contrast, the levels of miR-21 are increased in transgenic mice overexpressing the BMP4 antagonist noggin. Furthermore, miR-21 downregulates the expression of the BMP target genes *Pten*, *Pdcd4*, *Timp3* and *Tpm1* and prevents BMP4 from inducing their expression. Because the proteins encoded by these genes are tumour suppressors, the authors propose that the anti-tumorigenic activity of BMPs is, in part, mediated by downregulation of miR-21, which is further supported by the observation that miR-21 interferes with the inhibitory effects that BMP4 exerts on keratinocyte proliferation and motility.