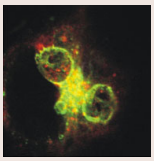
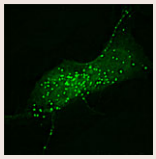
In this issue

By Jane Bradbury



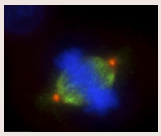
MTMR4 regulates endosomal trafficking

Phosphatidylinositol 3-phosphate [PtdIns(3)*P*] regulates several aspects of the endocytic pathway, including receptor sorting from early endosomes. PtdIns(3)*P* is constitutively synthesized on early endosomes by the phosphoinositide 3-kinase complex hVps34–hVps15; however, the tight control of the cellular levels of PtdIns(3)*P* that is necessary for the regulation of endocytic trafficking must also involve a phosphoinositide 3-phosphatase. On page 3071, Christina Mitchell and colleagues identify MTMR4, a member of the myotubularin family of phosphoinositide 3-phosphatases, as this hitherto mysterious regulator of endocytic trafficking. They show that MTMR4 localizes to early endosomes and to Rab11-positive recycling endosomes in COS-1 cells. MTMR4 knockdown or expression of a catalytically inactive MTMR4 increases the number of PtdIns(3)*P*-decorated endosomes, they report, whereas MTMR4 overexpression delays the exit of the transferrin receptor from early endosomes and its recycling to the plasma membrane. Finally, they show that MTMR4 expression or knockdown also regulates the subcellular redistribution of Rab11 and VAMP3, two proteins that regulate the endocytic recycling compartment. Together, these results identify MTMR4 as a novel regulator of endosomal trafficking that localizes at the interface between early and recycling endosomes.



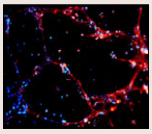
STIM1-ulating store-operated Ca^{2+} entry

Store-operated calcium entry (SOCE) is an important calcium entry pathway in non-excitable cells. Stromal interaction molecule 1 (STIM1) – a transmembrane phosphoprotein located in the endoplasmic reticulum (ER) – is a key regulator of SOCE. When the calcium concentration in the ER falls, STIM1 aggregates and relocates close to the plasma membrane, where it activates store-operated calcium channels – but does STIM1 phosphorylation affect this function? On page 3084, Francisco Javier Martín-Romero and colleagues reveal for the first time that phosphorylation of STIM1 at extracellular-signal-regulated kinases 1 and 2 (ERK1/2) sites modulates SOCE. They identify Ser575, Ser608 and Ser621 as ERK1/2 phosphorylated sites in STIM1, and show that alanine substitution at these target sites or treatment with ERK1/2 inhibitors reduces SOCE in HEK293 cells. 12-*O*-tetradecanoylphorbol-13-acetate activation of ERK1/2, they report, enhances SOCE in cells expressing wild-type STIM1, but not in cells expressing STIM1 with alanine mutations at the ERK1/2 target sites. Finally, alanine mutation of its ERK1/2 target residues reduces STIM1 binding to store-operated calcium channels. Together, these results reveal a mechanism whereby STIM1 phosphorylation modulates SOCE.



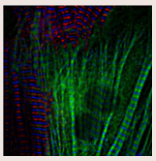
Centrosome regulation SPICEd up

During cell division, a functional, bipolar mitotic spindle is essential for the faithful segregation of chromosomes into daughter cells. Each spindle pole is organized by a centrosome, a microtubule-organizing structure that contains a pair of centrioles surrounded by a proteinaceous matrix called the pericentriolar material. Centrosomes contain numerous uncharacterized proteins, many of which are likely to be involved in the regulation of centrosome duplication during the S phase of the cell cycle. Here (p. 3039), Jens Lüders and colleagues analyze the function of the previously uncharacterized protein SPICE (spindle and centriole protein; also known as CCDC52). The authors show that SPICE is associated with spindle microtubules during mitosis and with centrioles throughout the cell cycle. RNAi depletion of SPICE in human cells, they report, impairs centriole duplication and disrupts mitotic-spindle architecture, spindle-pole integrity and chromosome congression. Occasionally, these severe mitotic defects occur even in cells in which centriole duplication has proceeded normally. The authors propose, therefore, that SPICE is a dual-function regulator that is required for centriole duplication and for the formation of a functional bipolar mitotic spindle.



Angiogenesis: an ERKsome connection

Vascular endothelial growth factor (VEGF) is a potent inducer of angiogenesis (the formation of new blood vessels from endothelial cells) during normal vascular development and during abnormal vascular development in diseases such as cancer. Now, on page 3189, Michael Cross and colleagues report that extracellular signal-regulated kinase 5 (ERK5) is crucial for VEGF-mediated survival and differentiation of endothelial cells. Previous studies have shown that VEGF activates ERK5 and that vascular integrity is disrupted in *Erk5*-null mice. To investigate the physiological role of VEGF-stimulated ERK5 activation in angiogenesis, the authors examine primary human dermal microvascular endothelial cells undergoing proliferation on a gelatin matrix and tubular morphogenesis within a collagen matrix. VEGF induces ERK5 activation in these endothelial cells on both matrices, they report, but only VEGF-stimulated tubular morphogenesis is affected by ERK5 downregulation. Other experiments show that ERK5 is required for VEGF-mediated activation of the serine/threonine protein kinase AKT, and for the subsequent phosphorylation and inactivation of the pro-apoptotic protein BAD. The authors propose, therefore, that ERK5 mediates VEGF-induced endothelial-cell survival during tubular morphogenesis, and suggest that inhibitors designed to target the ERK5 pathway prevent tumour-associated angiogenesis.



Thin filament length regulation

Striated muscles contain overlapping arrays of actin-containing thin filaments and myosin-containing thick filaments. The assembly of these filament systems is tightly regulated to ensure efficient striated-muscle contraction, but the molecular mechanisms underlying this regulation are largely unknown. On page 3136, however, Carol Gregorio and colleagues provide new insights into the regulation of thin filament length in chick cardiomyocytes by showing that the striated-muscle-specific actin-binding protein leiomodin-2 (Lmod2) antagonizes the function of its homologue tropomodulin-1 (Tmod1), a protein that caps the pointed ends of thin filaments. Lmod2 is structurally similar to Tmod1, but contains an extra actin-binding Wiskott–Aldrich syndrome protein homology 2 (WH2) domain. The authors show that Lmod2 competes with Tmod1 for binding to the pointed ends of thin filaments, that overexpression of Lmod2 causes elongation of thin fibres from their pointed end, and that removal of its WH2 domain converts Lmod2 into a pointed-end capping protein. Because Lmod2 transcripts are not detected in the heart until it has begun to beat, the authors suggest that the primary function of Lmod2 is to maintain thin filament lengths in the mature heart by antagonizing Tmod1.

Development in press

Non-muscle myosin II translates cilia polarity

In the brain, cilia on the multiciliated ependymal cells that line the brain ventricles circulate cerebrospinal fluid over the surface of the brain. To generate this directional fluid flow, the ependymal-cell cilia and their basal bodies must be oriented in one direction. This 'rotational' polarity is regulated by the planar cell polarity (PCP) pathway. Recent reports have revealed that the basal bodies are also localized at the anterior of the ependymal cells, but how is this 'translational' polarity established? Using a new method for time-lapse imaging of ventricular walls, Kazunobu Sawamoto and co-workers now show in *Development* that, in mice, the anterior migration of basal bodies in the apical cell membrane during ependymal-cell differentiation establishes translational polarity. Inhibition of the PCP protein Dishevelled, which disrupts rotational polarity, does not affect translational polarity, the researchers report. Instead, their pharmacological and genetic studies identify non-muscle myosin II as a key regulator of translational polarity. Thus, different mechanisms regulate the orientation and distribution of basal bodies in ependymal cells.

Hirota, Y., Meunier, A., Huang, S., Shimozawa, T., Yamada, O., Kida, Y. S., Inoue, M., Ito, T., Kato, H., Sakaguchi, M. et al. (2010). Planar polarity of multiciliated ependymal cells involves the anterior migration of basal bodies regulated by non-muscle myosin II. *Development* **137**, 3037-3046.