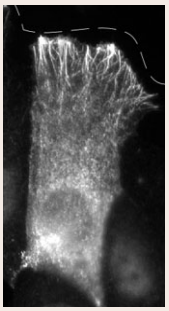
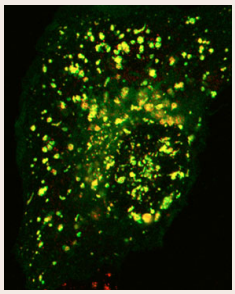
In this issue

by Jane Bradbury



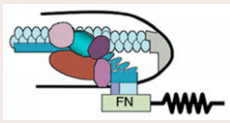
AMER1 puts APC in its place

The tumour suppressor protein APC, which is mutated in most colorectal cancers, prevents tumorigenesis by inhibiting Wnt signalling. It also regulates cell adhesion and migration through interactions with the plasma membrane and microtubules. Jürgen Behrens and co-workers now identify a novel membrane-associated protein, AMER1, that recruits APC to the plasma membrane (see p. 3738). They show that localization of AMER1 to the plasma membrane depends on two lipid-binding domains in its N-terminus and that AMER1 interacts with the armadillo repeat domain of APC. Overexpression of AMER1, they report, increases APC levels, recruits APC to the plasma membrane and prevents interaction of APC with microtubules. Conversely, knocking down AMER1 by RNAi increases the association of APC with microtubules and disrupts intercellular junctions. This work provides exciting new information about how the subcellular distribution of APC (and consequently its regulation of Wnt signalling, cell migration and cell-cell adhesion) is controlled. Moreover, it reveals how mutations in AMER1, which turns out to be identical to WTX, a tumour suppressor mutated in Wilms tumours, might promote tumorigenesis.



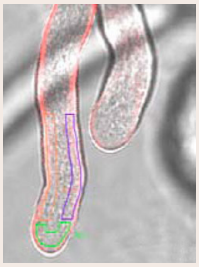
Lysosomal hideaway for ATP receptors

Extracellular ATP regulates biological processes throughout the nervous, immune and circulatory systems. Its effects are mediated by P2 purinergic receptors in the plasma membrane, including the $P2X_4$ receptor, a ligand-gated ion channel. On p. 3838, Ruth Murrell-Lagnado and colleagues report that lysosomal sequestration and exocytosis regulate this receptor. They show that endogenous $P2X_4$ receptors in rat microglia, endothelial cells and macrophages localize mainly to lysosomes. A dileucine motif and a tyrosine-based endocytic motif control lysosomal targeting, the authors report, and N-linked glycans protect the receptors from degradation once they arrive in lysosomes. The authors also show that, during phagocytosis, $P2X_4$ receptors accumulate in the phagosome membrane, which suggests a function for them in intracellular membranes. By contrast, after stimulation of lysosomal exocytosis, the receptors (and the lysosomal marker LAMP-1) return to the cell surface and stimulate $P2X_4$-mediated currents across the plasma membrane. Thus, the authors conclude, lysosome-resident $P2X_4$ receptors provide a pool of functional receptors that can be mobilized to upregulate cellular responsiveness to extracellular ATP.



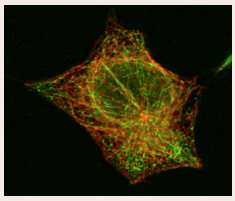
Repeated role for RPTPα in rigidity

A cell's behaviour is profoundly influenced by the rigidity of the matrix on which it grows, but the effects can be quite different from one cell type to another. For example, fibronectin-coated rigid surfaces stimulate fibroblasts to spread but inhibit neurite extension (a related response) and differentiation of neurons. In fibroblasts, the rigidity response involves receptor-like protein tyrosine phosphatase α (RPTPα). Now, on p. 3895, Michael Sheetz and co-workers report that the same is true in hippocampal neurons. Rigid fibronectin-coated polyacrylamide surfaces normally inhibit neurite extension and differentiation more than soft surfaces, they report, but in neurons lacking RPTPα neither substrate inhibits these processes. They demonstrate that the RPTPα-dependent rigidity response is fibronectin-specific and involves clustering of integrins (fibronectin receptors) at the leading edge of the growth cone. Furthermore, as in fibroblasts, integrin-dependent activation of RPTPα recruits and activates the Src family kinase Fyn. Thus, the authors suggest, although neurons and fibroblasts respond in opposite ways to matrix rigidity, they sense it using the same molecular mechanism.



More than one way to grow a pollen tube

During plant fertilization, male genetic material moves from the pollen grain into the ovule along a pollen tube. This slender tube is formed by polarized tip growth, which involves targeting and fusion of secretory vesicles with the apical plasma membrane (PM). But the amount of vesicle fusion greatly exceeds the amount by which the PM is extended; so how is excess membrane retrieved? On p. 3804, Alessandra Moscatelli and colleagues report that several distinct endocytic pathways – including a clathrin-independent one – do this in tobacco pollen tubes. The authors use positively and negatively charged nanogold (which labels subapical and apical PM domains, respectively) and electron microscopy to show that the subapical PM is mostly recycled by the secretory pathway after internalization but the apical PM mostly follows a degradative pathway to vacuoles. The authors then use ikarugamycin (an inhibitor of clathrin-dependent endocytosis) to show that PM recycling and at least one degradative pathway involve clathrin-dependent endocytosis. Importantly, however, their experiments also demonstrate that, as in animal cells, clathrin-independent endocytosis occurs in plants.



Microtubules STIM-ulate Ca^{2+} influx

Many important cellular processes are regulated by Ca^{2+} signalling. Ca^{2+} can enter certain cells by the store-operated Ca^{2+} entry (SOCE) pathway, which is activated when depleted intracellular stores send messages to plasma membrane (PM) channels. On p. 3762, James Putney and colleagues report that microtubules facilitate SOCE by optimizing the localization of the Ca^{2+} sensor stromal interaction molecule 1 (STIM1). The ER is the primary Ca^{2+} store in mammalian cells. When this is depleted, STIM1 moves within the ER to regions near the PM and activates SOCE channels. In HEK 293 cells, the authors report, fluorescently tagged STIM1 (EYFP-STIM1) colocalizes with α-tubulin in fibrillar structures; this localization is lost after treatment with nocodazole, which depolymerizes microtubules. Nocodazole, they show, inhibits SOCE, but overexpression of EYFP-STIM1 rescues this inhibition. Indeed, nocodazole treatment alone induces SOCE in EYFP-STIM1-expressing cells and relocalization of EYFP-STIM1 towards the PM. The authors conclude that microtubules are not essential for the movement of STIM1 after store depletion but instead facilitate SOCE by optimizing its localization.

Development in press

More to separase than sister separation

Fertilization triggers several events in oocytes. These include resumption of the cell cycle and, frequently, exocytosis of cortical granules that modify the surface of the zygote. In a paper appearing in *Development*, Bembenek and co-workers now identify cortical granules in nematodes for the first time and show that their exocytosis after fertilization is regulated by several cell-cycle components – most notably separase, which is required for chromosome segregation during anaphase. The exocytosis of cortical granules in fertilized *C. elegans* oocytes, the researchers report, leads to the formation of an impermeable three-layered eggshell. Using RNAi, they show that separase is required for granule exocytosis and chromosome segregation. Then, using immunofluorescence and live-cell imaging, they show that, after fertilization, separase moves from filamentous structures into cortical granules. These, they report, are exocytosed during anaphase I. Together, these results lead the researchers to propose that separase helps to coordinate the cell cycle with the other events that occur during egg activation.

Bembenek, J. N., Richie, C. T., Squirrell, J. M., Campbell, J. M., Eliceiri, K. W., Poteryaev, D., Spang, A., Golden, A. and White, J. G. (2007). Cortical granule exocytosis in *C. elegans* is regulated by cell cycle components including separase. *Development* **134**, 3837-3848.