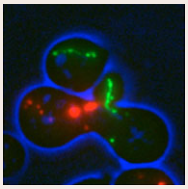
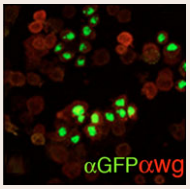
In this issue



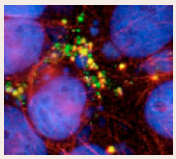
Peroxisomal fission goes both ways

Like mitochondria, peroxisomes proliferate by fission. The number of peroxisomes in the cell varies in response to environmental conditions, but what is the molecular machinery that controls their proliferation? The dynamin-related proteins Dnm1p (which has a role in mitochondrial fission) and Vps1p are thought to be involved in the duplication of peroxisomes, but their roles have been unclear. Now, Ewald Hettema and colleagues (p. 1633) demonstrate that the yeast *Saccharomyces cerevisiae* harbours two redundant machineries for peroxisomal division. The authors show that Vps1p and Dnm1p act independently to promote the fission of peroxisomes, and that Dnm1p acts in concert with the proteins Fis1p, Mdv1p and Caf4p, just as it does in mitochondrial fission. Moreover, the relative contributions of the two systems can be manipulated – for instance, Dnm1p-dependent fission dominates in yeast that have impaired mitochondrial function. The authors go on to show that mitochondria and peroxisomes compete for Dnm1p, and that Fis1p helps to distribute Dnm1p between the two organelles. These results draw parallels between peroxisomal and mitochondrial fission, and hint at the interdependence of the two systems.



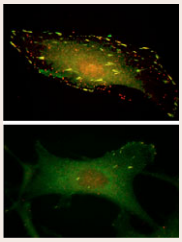
Lipids latch on to Wingless

Several signalling proteins, including members of the Wnt and Hedgehog families, are lipid-modified, which can affect both their secretion and their signalling activity. Wnt proteins are modified at two sites, an N-terminal cysteine and a centrally located serine. Both residues are conserved in the *Drosophila* Wnt protein Wingless, which is expected to undergo the same modifications. On page 1587, Jean-Paul Vincent and colleagues use imaginal wing discs to analyse the effect of lipidation on Wingless function in vivo. Using transgenic flies that express either [C93A]Wingless (no palmitoylation site) or [S239A]Wingless (no site for the addition of palmitoleic acid), the authors show that the C93A mutant is not detectable at the cell surface, whereas the S239A mutant is present there; however, unlike wild-type Wingless, neither mutant protein spreads to nearby non-expressing cells. The authors use immunogold EM to demonstrate that the C93A mutant accumulates in the ER at a ten times higher concentration than wild-type Wingless, and is absent from multivesicular bodies (where the wild-type protein is present). Thus, the palmitoylation of Wingless is necessary for its secretion, and palmitate and palmitoleic acid are both required for its signalling activity.



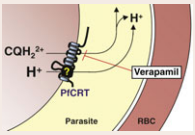
An autophagic role for Rab5

In macroautophagy, proteins are cleared from the cytoplasm by engulfment in a double-membraned structure (the autophagosome). In Huntington disease, for example, macroautophagy mediates the clearance of the aggregation-prone mutant of the protein huntingtin, which contains an abnormally long polyglutamine tract. David Rubinsztein and colleagues (p. 1649) now describe a new modulator of the degradation of huntingtin by macroautophagy – the small GTPase Rab5, previously better known as a regulator of early endocytosis. The authors show that, in mammalian cells that express a mutant huntingtin exon 1 fragment, Rab5 activity significantly decreases toxicity. Moreover, Rab5 overexpression decreases the characteristic photoreceptor degeneration that is seen in flies that express mutant huntingtin. The authors show that Rab5 is a member of a complex that also contains the proteins beclin 1 and Vps34, and that associates with autophagosomal precursors. When Rab5 is inhibited, autophagosomal precursors accumulate in cells, whereas the number of autophagic vacuoles decreases. By contrast, autophagic vacuoles accumulate when endocytosis is inhibited. The authors conclude that Rab5 is important in the early stages of macroautophagy, and that this role is distinct from its endocytic function.



Constructing the matrix with PAI1

For cells to migrate and invade, the surrounding extracellular matrix (ECM) must be remodelled, a process that involves both the assembly and proteolysis of ECM components. Plasminogen activator inhibitor 1 (PAI1) is known to slow ECM proteolysis by inhibiting uPA, a protein that (when bound to its cell-surface receptor uPAR) promotes the formation of the protease plasmin. Daniel Vial and Paula McKeown-Longo (p. 1661) now show that PAI1 has another role in matrix assembly. The authors previously demonstrated that PAI1 could stimulate the assembly of the fibronectin matrix, and they now show that this activity is independent of uPA and uPAR but requires the binding of PAI1 to vitronectin. They also show that PAI1 causes the disassembly of β5-integrin-containing focal adhesions, and that the polymerisation of fibronectin can also be stimulated by disrupting the binding of vitronectin to αvβ5 integrin. Moreover, β5-integrin-blocking agents increase the number of activated α5β1 integrins at the cell surface. The authors conclude that PAI1 acts by displacing αvβ5 integrin from vitronectin, and that this process involves crosstalk between αvβ5 and α5β1 integrins. PAI1 has therefore been identified as a novel regulator of the fibronectin matrix.



Springing a chloroquine leak

Chloroquine is used extensively as an antimalarial treatment, but its efficacy has been limited by the emergence of chloroquine-resistant strains of *Plasmodium falciparum*, the parasite that causes malaria. Chloroquine is thought to kill the parasite by accumulating within its acidic digestive vacuole, and the intravacuolar accumulation of chloroquine is diminished in chloroquine-resistant (CQR) strains; however, the molecular basis of this decrease remains unclear. On page 1624, Kiaran Kirk and colleagues identify a possible pathway of chloroquine efflux from the vacuole of CQR parasites. The authors show that the leak of vacuolar H^+ into the cytoplasm occurs at a faster rate in CQR than in chloroquine-sensitive (CQS) parasites. Moreover, in the presence of chloroquine the rate of H^+ leakage increases dramatically in CQR parasites but not in CQS parasites. This chloroquine-induced H^+ leak is inhibited by verapamil, which is known to increase chloroquine accumulation by CQR parasites. The authors propose, therefore, that chloroquine efflux from the vacuole occurs in tandem with H^+ efflux in CQR – but not in CQS – parasite strains. These data shed light on the mechanism of chloroquine resistance in *Plasmodium*.

Development in press

Syn4: directed protrusion

Directed cell migration is crucially important for development, and is a feature of neural crest (NC) cells, which have remarkable migratory abilities. In a paper published in *Development*, Roberto Mayor and colleagues investigate how the NC keeps to the correct path in zebrafish and *Xenopus* embryos, by studying the effects of the proteoglycan Syndecan-4 (Syn4) on NC migration. Syn4, they report, is essential for directional NC migration, and directs NC cell movement by regulating the polarised formation of membrane protrusions in a manner similar to that of non-canonical Wnt/planar cell polarity (PCP) signalling. To investigate how Syn4 orients cell protrusions, the authors use in vivo FRET analysis to measure the localised activity of several small GTPases involved in cell migration. Syn4, they discover, inhibits activity of Rac, a small GTPase that controls cytoskeletal dynamics and cell adhesion, whereas PCP signalling activates RhoA, which also inhibits Rac in NC cells. Thus Syn4 and PCP signalling seemingly control directional NC migration by regulating membrane protrusions through the localised inhibition of Rac.

Matthews, H. K., Marchant, L., Carmona-Fontaine, C., Kuriyama, S., Larraín, J., Holt, M. R. Parsons, M. and Mayor, R. (2008). Directional migration of neural crest cells in vivo is regulated by Syndecan-4/Rac1 and non-canonical Wnt signaling/RhoA. *Development* **135**, 1771-1780.