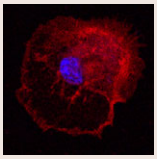
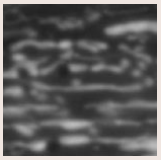
In this issue



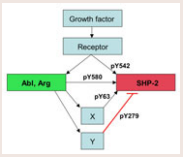
Getting defensive with nonaspanins

The phagocytosis of invading bacteria is an important facet of the cellular immune response in multicellular organisms. The nonaspanin TM9SF4 (the homologue for which, *PHG1A*, mediates phagocytosis in the unicellular slime mould *Dictyostelium*) has been proposed to be important in cellular immunity – but does it have a phagocytic role? Marie-Odile Fauvarque and colleagues (p. 3325) have previously shown that TM9SF4 is required for resistance of *Drosophila* to infection by Gram-negative (but not Gram-positive) bacteria. They now report that haemocytes (macrophages) in TM9SF4 mutant flies have decreased phagocytic activity against Gram-negative bacteria in vitro. In addition, the mutant fly larvae have a diminished cellular immune response in response to parasitisation by wasp eggs. Notably, macrophages from mutant flies have disorganised lamellipodia and atypical intracellular actin organisation – thus, cytoskeletal defects might underpin the phagocytic deficiency of TM9SF4$^{-/-}$ cells. In phagocytic *Drosophila* cells in culture (S2 cells), the authors show, TM9SF4 and the related nonaspanin TM9SF2 both contribute to bacterial internalisation. These data indicate that TM9SF4 has a key role in phagocytosis during cellular immunity.



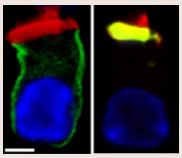
CED-9: moulding mitochondria?

The morphology of mitochondria impacts on their function and is highly dynamic – mitochondria can undergo fission (to become fragmented) and fusion (to form an interconnected network). The proteins of the BCL2 family, which regulate apoptosis, have been proposed to modulate mitochondrial morphology by interacting with large GTPases such as DRP-1 and mitofusin (which control fission and fusion, respectively) – but how important is their role? To address this question, R. Blake Hill and colleagues (p. 3373) investigate the effect of CED-9 (the sole BCL2 homologue in *C. elegans*) on mitochondrial homeostasis. The authors show that in worms carrying *ced-9* loss-of-function mutations, mitochondrial morphology in muscle cells is grossly normal, but worms that lack CED-9 are more prone to DRP-1-induced mitochondrial fragmentation than those expressing the wild-type protein. By contrast, increasing CED-9 expression leads to highly interconnected mitochondria; this phenotype is partially suppressed by the increased expression of DRP-1, and is dependent on the BH3-binding domain of CED-9. Thus, although CED-9 is not essential for either fission or fusion, it can regulate both processes. This increases our understanding of the interplay between BCL2 proteins and mitochondrial morphology.



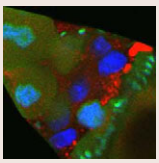
Abl and SHP-2: proliferative partners

The Abl-family tyrosine kinases (Abl and Arg) promote growth-factor-dependent cell proliferation by accelerating the G1-S transition and, in several forms of leukaemia, Abl (as the constitutively active BCR-Abl fusion protein) drives cell transformation. The tyrosine phosphatase SHP-2 is phosphorylated in BCR-Abl-transformed cells – but is it also a target of Abl and Arg during growth-factor-controlled proliferation? On page 3335, Rina Plattner and colleagues show that it is. By treating cells with a pharmacological Abl-family inhibitor or with siRNAs targeting Abl and Arg, the authors show that growth-factor-induced SHP-2 phosphorylation requires Abl kinases. SHP-2 is directly phosphorylated by Abl kinases at Y580 in growth-factor-stimulated cells, they show, which leads to sustained activation of ERK kinases; moreover, a constitutively active mutant of SHP-2 rescues the G1-S transition in Abl-Arg-null fibroblasts. The authors identify two further SHP-2 tyrosine residues (Y63 and Y279) that are indirectly phosphorylated by Abl kinases – notably, phosphorylation at Y63 potentiates ERK activation and cell proliferation, but phosphorylation at Y279 has the opposite effect. SHP-2, therefore, is an important mediator of Abl-kinase-dependent cell proliferation in response to growth factors.



Spectrin defies convention in OHCs

Within the mammalian cochlea, outer hair cells (OHCs) amplify sounds by electromotility – the voltage-dependent contraction and elongation of the lateral plasma membrane (LPM). Electromotility is driven by the OHC transmembrane protein prestin, and the actin- and spectrin-based cortical lattice that underlies the LPM is also important in this process; however, the precise composition of the cortical lattice, and the way in which it interacts with prestin, have so far been unknown. Now, Aziz El-Amraoui and colleagues (p. 3347) characterise the composition of spectrin (which exists as an α-β heterodimer) within the cortical lattice. On the basis of previous studies in red blood cells, it had been thought that the lattice included conventional spectrins – surprisingly, though, the only β-spectrin subunit that is concentrated at the cortical lattice is the unconventional βV-spectrin, which is almost twice the length of conventional β-spectrins. βV-spectrin interacts directly with other lattice components, the authors show, and its progressive postnatal recruitment to the lattice in mouse parallels that of prestin. Moreover, the pleckstrin homology domain of βV-spectrin interacts indirectly with the C-terminal cytoplasmic domain of prestin. These results shed light on the molecular basis of sound amplification in the mammalian ear.



Widerborst springs into Akt-ion

Akt (protein kinase B) is a key intermediate in the insulin-IGF signalling (IIS) pathway, and its misregulation is associated with diabetes, obesity and cancer. Recently, several studies have indicated that the activity of Akt (which is upregulated by PI3K and downregulated by PTEN) can be modulated independently in individual subcellular compartments – but what are the mechanisms involved? On page 3383, Clive Wilson and colleagues shed light on this question by identifying Widerborst (Wdb), a regulatory subunit of protein phosphatase 2A (PP2A) in *Drosophila*, as a key player in the cytoplasm-specific regulation of Akt1. Using a genetic screen for novel phosphatase regulators of IIS, the authors show that Wdb negatively regulates the PI3K-PTEN-Akt signalling cassette, and that it does this by regulating the activity of the PP2A catalytic subunit Microtubule star. In the nurse cells of the ovary, they show, Wdb physically interacts with Akt1 and controls cytoplasmic (but not nuclear) levels of activated Akt1 (pAkt1). In addition, lipid-droplet size is markedly increased in *wdb* mutants, consistent with the known upregulation of lipid storage by pAkt1. The authors conclude that PP2A regulatory subunits can act as subcellular-compartment-specific regulators of Akt, and might provide new therapeutic targets in insulin-linked disease.

Development in press

Semaphorin applies brakes to branching

Semaphorins are secreted signals that function during diverse developmental events, from axon guidance to angiogenesis. Although the plexin A family of semaphorin receptors has been well characterised, less is known about the B-type plexins, particularly their roles in organogenesis. In a paper published in *Development*, Rohini Kuner and colleagues have discovered that the semaphorin-4d–plexin-B1 ligand-receptor pair negatively regulates branching morphogenesis during kidney development by activating the RhoA-ROCK pathway. By analysing the expression of this pair of proteins in developing organs, the authors show that plexin B1 and semaphorin 4d are expressed in epithelial and mesenchymal compartments, respectively, which implicates them in the epithelial-mesenchymal interactions that occur during organogenesis. In cultured mouse embryonic kidneys, the authors show, exogenously applied semaphorin 4d reduces ureteric branching and activates RhoA; when the RhoA-ROCK pathway is blocked, however, semaphorin 4d stimulates ureteric branching. From these findings, the authors conclude that RhoA-ROCK signalling acts as an endogenous brake on plexin-B1-triggered, branch-promoting signalling.

Korostylev, A., Worzfeld, T., Deng, S., Friedel, R. H., Swiercz, J. M., Vodrazka, P., Maier, V., Hirschberg, A., Ohoka, Y., Inagaki, S., Offermanns, S. and Kuner, R. (2008). A functional role for semaphorin 4D/plexin B1 interactions in epithelial branching morphogenesis during organogenesis. *Development* **135**, 3333-3343.