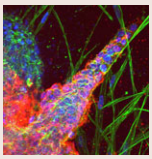
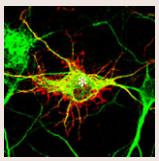
In this issue



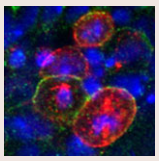
MINIFOCUS: Collective cell migration

The migration of individual cells has been closely studied for many years, but more recently it has become clear that cells can also migrate as a group in many physiological contexts, such as during development and wound repair. Importantly, it has been shown that collective cell migration can also occur when tumour cells invade surrounding tissues during metastasis – thus, the study of collective cell migration is likely to yield important therapeutic insights. This issue's Minifocus highlights three important aspects of collective cell migration. In a Cell Science at a Glance poster article (p. 3203), Olga Ilina and Peter Friedl dissect the different mechanisms that underpin this phenomenon, exploring how migrating cells interact with one other, with resident tissue cells and with the extracellular matrix. In an accompanying poster article, Tanya Shaw and Paul Martin (p. 3209) provide a comprehensive overview of wound repair at the cellular level, including the role of collective cell migration in this process. On page 3215, Cornelis Weijer explores the diverse forms of collective cell movement that occur during development and morphogenesis in several model organisms. Together, these articles showcase recent key findings on the nature of collective cell migration, and highlight the diversity in the biological settings in which it is important.



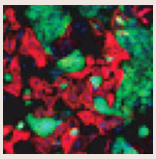
Selective sorting of Caspr2

In neurons, the distribution of proteins within the plasma membrane (PM) is highly polarised. For instance, the cell-adhesion protein Caspr2 is enriched at juxtaparanodes of Ranvier in the axonal compartment, where it is necessary for the clustering of potassium channels such as Kv1.2. It is known that Kv1.2 is sorted selectively into axonal vesicles – but is Caspr2 targeted in tandem with Kv1.2? On page 3403, Catherine Faivre-Sarrailh and colleagues show that it is not. The authors first transfect hippocampal neurons with labelled Caspr2, and show that Caspr2 is present in the PM in axons, but that it colocalizes with early endosomes in the remainder of the cell (the somatodendritic compartment). Moreover, Caspr2 is eliminated from the PM at the somatodendritic compartment through dynamin-dependent endocytosis. The authors identify a short amino acid sequence (which contains a PKC substrate motif) within the cytoplasmic region of Caspr2 that is required for its endocytosis, and show that mutation of this motif, or chemical inhibition of PKC, disrupts the internalisation of Caspr2. Therefore, the authors conclude that PKC-regulated endocytosis of Caspr2 underlies its selective cell-surface expression, and that Caspr2 and Kv1.2 are targeted through distinct mechanisms. Their results underscore the diversity of mechanisms that maintain PM polarisation in neurons.



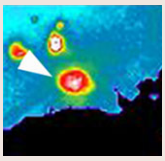
PP2A: balancing neuroblast polarity

Drosophila neuroblasts are an ideal model for studying asymmetric cell division, in which cell polarity is coupled to mitosis. Atypical protein kinase C (aPKC), which forms a complex with Bazooka and Par-6, is essential for establishing neuroblast polarity and for proper asymmetric cell division. Previous work has shown that, upon entry into mitosis, phosphorylation of Par-6 by Aurora-A kinase prevents a Par-6–aPKC interaction, thereby activating aPKC. Although the tumour suppressor Lgl is known to inhibit aPKC at the substrate level, the putative dephosphorylation event that negatively regulates aPKC activity in this pathway was unknown. On p. 3242, Fumio Matsuzaki and colleagues now provide new evidence on how aPKC activity is balanced to maintain polarity in neuroblasts. Using a genetic screen, the authors show that Mts – the catalytic subunit of protein phosphatase 2A (PP2A) – is an antagonist of aPKC signalling, and that cell division of Mts-deficient neuroblasts is defective. Biochemical evidence shows that Mts physically interacts with and directly dephosphorylates Par-6, permitting Par-6 to inhibit aPKC activity. The authors conclude that PP2A, together with Lgl, antagonises the positive action of Aurora-A kinase on aPKC in neuroblasts, thereby modulating the balance of aPKC activity required for asymmetric cell division.



Directing differentiation via VEGFR2

Vascular endothelial growth factor receptor 2 (VEGFR2) is essential for blood vessel formation, but the mechanisms linking VEGFR2 activation to endothelial cell (EC) differentiation have not been characterised in detail. On page 3303, Keiji Miyazawa and colleagues now dissect these signalling pathways in vitro using embryonic stem cell-derived VEGFR2$^+$ vascular progenitor cells. The authors express a chimeric receptor containing the intracellular kinase-active domain of VEGFR2, and show that this domain is sufficient to direct the differentiation of ECs from VEGFR2$^+$ vascular progenitor cells. Within this domain are several key tyrosine residues that become phosphorylated upon receptor activation; mutation analysis shows that, of these, only Y1175 is essential for EC differentiation. Importantly, Y1175 is required for both the specification of ECs and their subsequent survival. Furthermore, the authors show that intact VEGFR2-PLCγ1 signalling is essential for the specification of ECs, but not their survival. By contrast, closely related VEGFR3 supports EC survival but not specification, owing to its inability to activate PLCγ1. These results increase our understanding of the diverse roles of VEGFR2 and VEGFR3 in EC differentiation and underscore the importance of PLCγ1 in this process.



Macropinosomes up close

Macropinosomes form in ruffling regions of the plasma membrane following growth-factor stimulation of macrophages or epithelial cells. Variability in the size of these large endocytic vesicles, and in the kinetics of their formation, has made quantification of macropinocytosis a challenge. On page 3250, Joel Swanson and colleagues examine this process in detail in macrophages stimulated with M-CSF. They first define four stages of macropinocytosis: the irregular ruffle stage, curved ruffle stage (when the ruffle adopts a C-shape), circular ruffle stage (when it adopts an O-shape) and motile stage (when the closed macropinosome moves into the cell interior). Importantly, distinct signalling events occur at forming macropinosomes during each stage. Using quantitative fluoresence microscopy to image stimulated macrophages, the authors show that the small GTPase Rac1 is activated at the beginning of the circular ruffle stage; this coincides with a spike in the levels of the phosphoinositide PtdIns(3,4,5)P_3, which is concentrated in forming macropinosomes. Finally, an accumulation of PtdIns(3)*P* and the small GTPase Rab5 is observed during the late circular ruffle and motile stages, suggesting that these factors might have a role in vesicle closure. This work clarifies the kinetics and molecular mechanisms of macropinocytosis.

Development in press

To acetylate or trimethylate: that is the question

Transcriptional silencing by Polycomb group (PcG) proteins, which is crucial during development, requires histone H3 lysine 27 trimethylation (H3K27me3). The trithorax protein (TRX) counteracts PcG silencing, but what underpins this antagonism? In a paper published in *Development*, Feng Tie, Peter Harte and co-workers now propose that, in *Drosophila*, H3K27 acetylation (H3K27ac) by the TRX-associated histone acetyltransferase CBP might be involved. They show that CBP acetylates H3K27 (which requires TRX), and that CBP or TRX overexpression increases H3K27ac levels while decreasing H3K27me3 levels and causing defects in PcG-mediated silencing. Similarly, RNAi-mediated knockdown of the PcG protein E(Z) decreases H3K27me3 and increases H3K27ac. These data suggest that H3K27 acetylation and trimethylation are alternative modifications of the same site. Accordingly, the high H3K27ac levels found in early embryos decline as H3K27me3 levels increase, and genome-wide ChIP-chip analysis reveals that H3K27me3 and H3K27ac are mutually exclusive at PcG target genes. Therefore, the authors propose that TRX-dependent H3K27 acetylation by CBP prevents H3K27 trimethylation, thereby antagonising PcG silencing.

Tie, F., Furuyama, T., Prasad-Sinha, J., Jane, E. and Harte, P. J. (2009). The *Drosophila* Polycomb Group proteins ESC and E(Z) are present in a complex containing the histone-binding protein p55 and the histone deacetylase RPD3. *Development* **128**, 275-286.