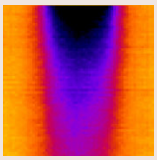
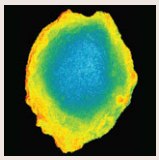
In this issue



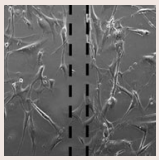
Mature adhesions lock Arm(s)

Apical–basal polarity in epithelial cells is essential for tissue morphology and function. The polarised formation of cell junctions, such as adherens junctions (AJs), and the dynamic turnover of adhesion complexes are required for the generation and maintenance of cell polarity. But how do AJ dynamics change during the establishment of polarity? Here, Yang Hong and co-workers (p. 4001) use fluorescence recovery after photobleaching (FRAP) assays in *Drosophila* embryonic epithelial cells to assess the turnover of the two main components of AJs – *Drosophila* E-cadherin (DE-Cad) and β-catenin (Armadillo, Arm) – in polarising and polarised cells. They find that the biosynthetic delivery of DE-Cad and Arm is much faster in early-stage embryos – where polarity is being established – than in established epithelia. By analysing the diffusion of membrane pools of these proteins into AJs, they also show that the membrane redistribution dynamics of DE-Cad are not affected by AJ maturation. By contrast, Arm diffusion into AJs is slower in mature epithelial cells. This suggests that Arm binds dynamically to DE-Cad during polarisation, and that these proteins only become tightly associated in polarised cells to form mature AJs. Modulating the molecular interaction between these two proteins might, therefore, be crucial for the correct establishment of apical–basal polarity during development.



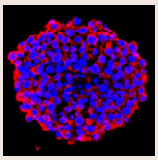
Ruffles keep signals in place

Macropinocytosis is characterised by the initial extension of actin-rich, cup-shaped circular ruffles that eventually close to form endocytic vesicles. In macrophages, macropinosome formation occurs in response to stimulation with macrophage-colony-stimulating factor (M-CSF). The signalling components that activate this process, such as Rac1 and PtdIns(3,4,5)P_3, are restricted to these cup-shaped membrane domains, and the disruption of the actin cytoskeleton prevents both Rac1 activation and membrane ruffling. On page 4106, Joel Swanson and colleagues now investigate whether an actin-based diffusion barrier creates an enclosed space within circular ruffles that allows amplification of the signals required for Rac1 activation and subsequent macropinosome formation. To achieve this, they employ a plasma-membrane-localised, photoactivatable green fluorescent protein (PAGFP-MEM). Following activation of PAGFP-MEM in specific membrane regions and by analysing its diffusion pattern they find that, compared with flat membranes, circular ruffles limit diffusion. They also observe that proteins within these specific membrane domains do not mix freely with those outside this area. This retention is the result of a barrier in the ruffles at the rim of the cup. Thus, circular ruffles provide a way to concentrate and amplify the signals that are required for macropinosome formation in discrete membrane regions.



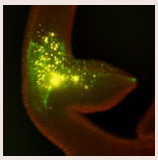
microRNA meets atherosclerosis

The development of atherosclerosis is marked by accumulation of oxidised low-density lipoprotein (oxLDL). This form of LDL, which has been modified by reactive oxygen species, binds to the scavenger receptor lectin-like oxidised-low-density lipoprotein receptor 1 (LOX-1, also known as OLR1). LOX-1 is expressed in endothelial cells, macrophages and smooth muscle cells, which are known to be involved in the pathogenesis of atherosclerosis. Its activation by oxLDL results in the expression of inflammatory genes and the formation of superoxide radicals, which contribute to atherogenesis. On page 4115, Suh-Hang Hank Juo and co-workers now provide evidence for a new negative-feedback regulatory loop involving LOX-1 and the microRNA let-7g. They report that let-7g inhibits the protein synthesis of LOX-1 through a let-7g-binding site in the 3′-untranslated region of *LOX1*. In return, activation of LOX-1 by oxLDL activates a signalling cascade that involves Ca^{2+}-activated protein kinase C and leads to the binding of the transcriptional repressor OCT-1 (also known as POU2F1) to the let-7g promotor, thereby inhibiting let-7g expression. These results not only identify a role for this microRNA in the oxLDL-induced pathogenesis of atherosclerosis but, importantly, also highlight a potential new therapeutic target for treating cardiovascular disease.



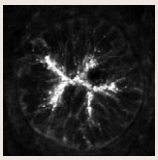
No sulfate is the same for NSCs

Glycosaminoglycans (GAGs) are important components of the extracellular matrix. They are involved in the regulation of cell–cell and cell–matrix interactions, and can influence cellular signals through interaction with growth factors and cytokines. The GAGs chondroitin sulfate (CS) and dermatan sulfate (DS) are enriched in the neural stem cell (NSC) niche and have been shown to be involved in the regulation of NSC proliferation and differentiation. Melitta Schachner and colleagues (p. 4051) now unravel the specific functions of these two GAGs in NSC biology by using transgenic mice that are deficient in the sulfotransferase enzymes that synthesise CS or DS. Deficiency in dermatan 4-*O*-sulfotransferase-1 (Chst14), which is required for DS synthesis, results in impaired NSC proliferation and neurosphere formation, as well as reduced neurogenesis. By contrast, the ablation of chondroitin 4-*O*-sulfotransferase-1 (Chst11) does not have these effects. In addition, the expression of epidermal growth factor receptor and fibroblast growth factor receptor 1 is upregulated in *Chst14*$^{-/-}$, but not *Chst11*$^{-/-}$, neurospheres. Thus, CS and DS have specific roles in the regulation of NSC biology. The authors suggest that DS generated by Chst14, but not CS, affects proliferation and differentiation of NSCs by modifying cell–cell and cell–matrix contacts, as well as the interaction between growth factor receptors with their respective ligands.



Hydra showcase dynamic ECM

Remodelling of the extracellular matrix (ECM) occurs during embryonic development, asexual reproduction and tissue regeneration. However, the processes by which ECM dynamics contribute to the establishment of tissue shape and function are poorly understood. Roland Aufschnaiter, Xiaoming Zhang and colleagues (p. 4027) now show that, instead of simply providing a static substrate for cell movement, the ECM acts as a dynamic tissue component that influences growth and morphogenesis in epithelial tissues. They employ the freshwater polyp *Hydra* – a simple metazoan that consists of an epithelial double layer separated by an intervening ECM, the mesoglea – to track the fate of the ECM throughout the organism. By labelling collagen-1 and laminin with fluorescently tagged antibodies they show that the mesoglea is stable in the head region. By contrast, it is continuously displaced along the body column and towards the tips of tentacles in a movement that largely overlaps with that of epithelial cells. At the sites of bud evagination, however, the mesoglea is stretched and remodelled, which involves the site-specific degradation of laminin. In addition, during bud formation the cells move at different rates than the mesoglea. Taken together, these data highlight that the ECM carries out more dynamic functions than previously thought and can have different biological functions depending on its location.



Spectrin scaffold lets cells spread

The scaffold protein spectrin α2 (αII-spectrin), together with any of the five β-spectrins, has roles in various cellular processes ranging from the formation of membrane domains to providing a scaffold for signalling pathways. In *Drosophila* and *C. elegans*, deletion of αII-spectrin is embryonic lethal but, so far, little is known about its roles in vertebrate development. On page 3956, Jon Morrow and colleagues now provide insight into the functions of αII-spectrin in vertebrates by generating αII-spectrin knockout mice. Embryos with a homozygous deletion of the *Spna2* gene display prominent cardiac, craniofacial and neural tube abnormalities and die between E12.5 and E16.5. On the cellular level, the loss of αII-spectrin results in a substantial reduction in βII- and βIII-spectrin and ankyrins B and G, and the redistribution of these proteins to the apical membranes of epithelial cells. Epithelial cell morphology, however, is unaffected by the loss of αII-spectrin. In vitro, *Spna*$^{-/-}$ mouse embryonic fibroblasts (MEFs) spread and grow more slowly than wildtype MEFs, and display a spiky morphology and sparse lamellipodia. Thus, αII-spectrin is not only required for the stability and organisation of related proteins but, by being a key component of the spectrin–ankyrin scaffold, is also required for cell spreading, tissue patterning and organ development in vertebrates.