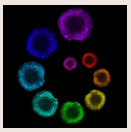
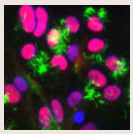
In this issue



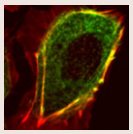
MINIFOCUS: Invadopodia and podosomes

In this issue, JCS is pleased to present a collection of articles that focus on invadopodia and podosomes. These actin-rich cellular structures (which are also known collectively as invadosomes) establish close contact with the extracellular matrix (ECM) and can degrade ECM components. Invadopodia (which have been visualised in cancer cells) are thought to have a role in metastatic invasion, whereas podosomes (which are found in osteoclasts and other monocytic cells) contribute to bone degradation, among other processes. This issue's Minifocus highlights several important areas of invadosome biology. A schematic overview of invadosome structure and function is presented by Stefan Linder (p. 3009). Next, Philippe Chavrier and colleagues (p. 3015) highlight the role of invadopodia in cancer progression by describing how matrix metalloproteases traffic to, and are secreted at, these sites. On page 3025, Chris Carman explores the evidence that leukocytes employ invadosome-like structures when crossing the endothelial barrier. Finally, Corinne Albiges-Rizo and colleagues (p. 3037) evaluate recent insights into invadosomal actin dynamics and discuss how invadosomes respond to mechanical force. Together, these articles showcase key recent findings on the structure and function of invadosomes, and highlight the diversity of biological settings in which they are important.



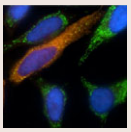
RFX3: the X factor for motile cilia

Regulatory factor X (RFX)-family proteins are transcription factors involved in ciliogenesis in worms, flies and mice. In mice, it has been shown that RFX3 regulates the growth of primary cilia. However, further investigation of the biological role of RFX3 has been a challenge because *Rfx3*$^{-/-}$ mouse embryos die at birth, and ciliogenesis is completed only postnatally. Bénédicte Durand and colleagues (p. 3180) now provide new evidence that RFX3 also has a crucial role in the biogenesis of motile cilia. Here, they describe a novel primary-cell culture system that allows multiciliated ependymal cells to be differentiated from E18.5 neural stem cells in vitro. Using this system, they show that *Rfx3*$^{-/-}$ cultures exhibit a marked decrease in the number of multiciliated cells compared with wild-type cultures, and that cilia in *Rfx3*$^{-/-}$ cultures are significantly shorter. Furthermore, ciliary beating efficiency is defective in *Rfx3*$^{-/-}$ cultures, indicating that RFX3 is required for both ciliary biogenesis and motility. The authors then use PCR and ChIP experiments to show that RFX3 is required for the optimal expression of genes involved in ciliary assembly and motility. As *Rfx3*$^{-/-}$ cultures also show a modest decrease in the expression of FOXJ1, another transcription factor thought to be central for ciliogenesis, the authors propose that RFX3 and FOXJ1 might work together to regulate the expression of other ciliary genes.



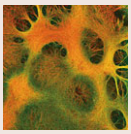
Coronin 2A breaks it down

Focal adhesion (FA) dynamics influence cell motility in morphogenesis, cancer progression and immune responses. The factors that regulate FA dynamics are numerous and complex, and include members of the F-actin-binding coronin family of proteins. On page 3061, James Bear and colleagues now investigate the role of coronin 2A, a type-II coronin that was functionally uncharacterised, in regulating FA dynamics. They first show that, unlike type-I coronins (which localise to the leading edge of cells), coronin 2A localises to internal FAs and is not present in lamellipodia. Furthermore, coronin-2A-depleted cells migrate more slowly than control cells owing to a 50% decrease in the disassembly rate of internal FAs. But how is this effect mediated at the molecular level? The authors go on to show that coronin 2A affects FA dynamics through cofilin, which – despite its well-known role in regulating actin dynamics – has not previously been shown to directly regulate FA turnover. On the basis of these findings, the authors propose a new role for coronin 2A in enhancing the disassembly of a subset of FAs by activating the actin-severing activity of cofilin. As coronin 2A is also shown to physically interact with the cofilin-activating phosphatase Slingshot-1L, they suggest that coronin 2A might regulate cofilin activity via Slingshot-1L.



Redefining NLRX1 in mitochondria

Innate immunity relies on the detection of conserved microbial structures by pattern recognition molecules (PRMs). NLRX1 is a PRM that was initially shown to localise to the mitochondrial outer membrane (MOM) and to modulate the function of mitochondrial antiviral signalling protein (MAVS), which is anchored in the MOM through its transmembrane (TM) domain. However, Stephen Girardin and colleagues (p. 3161) now report new findings that refute these previous data. They use in silico analyses to show that NLRX1 contains an N-terminal mitochondrial targeting sequence but not a TM domain, which are characteristics typical of proteins that localise to the mitochondrial matrix but not to the MOM. Biochemical analyses support these predictions and show that NLRX1 strongly associates with the matrix side of the mitochondrial inner membrane (MIM). Similar to other MIM proteins, NLRX1 is targeted to the mitochondrial matrix only in the presence of an intact MIM potential ($\Delta\Psi_m$) and is proteolytically processed at this site by mitochondrial processing peptidases. But how does NLRX1 mediate innate immune function if it is located in the mitochondrial matrix? NLRX1 is also shown to associate with UQCRC2, a MIM component of the respiratory chain complex III required for the generation of reactive oxygen species; the authors propose that this association may underlie the innate immune activity of NLRX1.



A cleaner route to retinal cells?

Methods to induce the in vitro differentiation of embryonic stem (ES) cells into retinal progenitors, retinal pigment epithelium (RPE) cells and photoreceptors (PRCs) have recently been established. However, the need for recombinant proteins or other biological molecules to differentiate these cells has limited their therapeutic potential. On page 3169, Fumitaka Osakada, Masayo Takahashi and colleagues report a new method for differentiating retinal cells from ES cells. Previous findings showed that disrupting the Wnt and Nodal signalling pathways promotes the differentiation of ES cells into retinal progenitors; here, the authors use the small-molecule inhibitors CKI-7 and SB-431542, respectively, to block these two pathways. They show that human ES cells treated with these inhibitors differentiate into retinal progenitors; retinal specification is indicated by the loss of the ES-cell markers Nanog and Oct3/4 and an increase in retinal progenitor markers. Importantly, retinal progenitors can also be differentiated from human induced pluripotent stem (iPS) cells with combined CKI-7 and SB-431542 treatment. Finally, they show that both ES-cell- and iPS-cell-derived retinal progenitors can differentiate into RPE cells, and into PRCs that can respond to light. These data represent a step forward in cellular therapy approaches to treat currently incurable retinal degenerative diseases.

Development in press

Thinking BicC about cilium orientation

Defects in cilia are often linked to disturbed left-right asymmetry and to kidney cysts, which are seen in mice and frogs that lack the conserved RNA-binding protein Bicaudal C (BicC). In a paper published in *Development*, Daniel Constam and colleagues now identify a role for BicC in ciliary biology. These authors find that disrupting BicC function in either mouse or *Xenopus* embryos randomises left-right asymmetry by disturbing the regular planar orientation of motile cilia and, hence, cilia-driven fluid flow. Furthermore, they show that, in kidney cell lines, the BicC sterile α-motif (SAM) domain guides the localisation of BicC to cytoplasmic structures that contain the canonical Wnt signalling component Dishevelled2 (Dvl2), and to RNA-processing bodies known as P-bodies. BicC interferes with Dvl2-mediated canonical Wnt signalling; such interference has been suggested to promote planar cell polarity (PCP) signalling. Therefore, the authors propose that BicC might link cilium orientation with PCP signalling by modulating P-body-mediated RNA silencing or by regulating Dvl2 function.

Maisonneuve, C., Guilleret, I., Vick, P., Weber, T., Andre, P., Beyer, T., Blum, M. and Constam, D. B. (2009). Bicaudal C, a novel regulator of Dvl signaling abutting RNA-processing bodies, controls cilia orientation and leftward flow. *Development* **136**, 3019-3030.