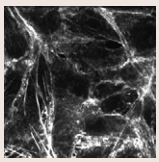
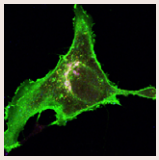
In this issue



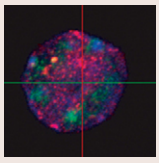
HSCs escape stiffer niche

Hematopoietic stem cells (HSCs) reside in vascular and endosteal niches where they form numerous contacts with the surrounding cells and the extracellular matrix. Remodelling these contacts is crucial for HSC mobilisation from the niche. In addition to chemical signals, the mechanical properties of the microenvironment are crucial for regulating stem cell differentiation and proliferation, but the way in which such mechanical changes could affect HSC mobilisation has remained unclear. On page 3765, Gerd Klein, Joachim Spatz and colleagues now provide evidence that changes in matrix elasticity in the HSC niche in response to specific signals from the nervous system could influence HSC behaviour. By using an in vitro model of the endosteal niche, they show that osteoblasts – which are the major component of the endosteal niche – flatten and remodel their cytoskeleton in response to stimulation with the adrenergic agonist clenbuterol. These changes are accompanied by an increase in stiffness. Furthermore, the authors demonstrate that an increase in matrix stiffness enhances HSC adhesion and migration in a phosphatidylinositol-3-kinase-dependent manner. These findings lead the researchers to speculate that changes in matrix elasticity in the HSC niche lead to increased HSC adhesion and migration, which, in turn, could mediate their mobilisation from the niche.



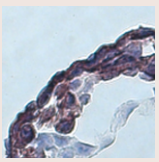
Cells on the go with PRL3

The formation and propagation of malignant cells is often associated with changes in intracellular signalling pathways. Changes in the activity and/or regulation of protein tyrosine phosphatases, for example, are known to contribute to cancer development. Overexpression of phosphatase of regenerating liver 3 (PRL3) enhances motility and invasiveness. But what are the mechanisms by which PRL3 contributes to tumorigenesis and metastasis? On page 3883, Götz von Wichert and colleagues now shed light on the cellular function of PRL3. They find that PRL3 associates with the small GTPase ADP-ribosylation factor 1 (Arf1) and that the two proteins colocalise on membranes of the Golgi complex and early and late endosomes in the perinuclear region. The interaction between PRL3 and Arf1 depends on Arf1 being activated through GTP binding, and the expression of PRL3 increases Arf1 activity. Furthermore, the authors demonstrate that PRL3 expression enhances HeLa cell migration, and that this depends on the presence of Arf1 and Arf3. In addition, PRL3 accelerates the internalization and recycling of α5 integrins, without affecting the total amount of the adhesion receptors at the cell surface. The authors propose that PRL3 facilitates tumour cell metastasis by enhancing Arf1-mediated integrin recycling and thereby altering cell adhesion and migration.



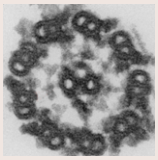
Actin' in the nucleus

Actin and actin-related proteins (Arps) are involved in numerous processes in the cytosol. However, more recently it has become apparent that actin and Arps are also found in the nucleus where they carry out distinct functions. Two papers published in this issue now provide new insight into the role of actin, Arp4 and Arp6 in the nucleus. On page 3739, Masahiko Harata and colleagues describe a role for Arp6 in the spatial organisation of chromatin. Using chicken DT40 cells in which the *ARP6* gene has been conditionally knocked out, they show that Arp6 is required for the radial distribution of macrochromosomes to the periphery of the nucleus and of microchromosomes to the nuclear centre. This effect is mediated by changes in the deposition of H2A.Z and results in transcriptional misregulation. On page 3870, Masatoshi Fujita and co-workers illustrate how β-actin and human Arp4 (BAF53) affect chromatin structure and function. The researchers show that β-actin and Arp4 form a heterocomplex in the nucleus and that depleting human cell lines of Arp4 impairs the integrity of the Brg1 chromatin remodeling complex. Mutations in Arp4 that impair β-actin binding reduce its ability to bind to the Brg1 complex and the Tip60 histone acetyltransferase complex, which indicates that the formation of the heterodimer is important for Arp4 function.



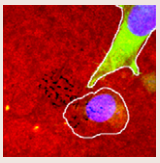
Unc(45b)-oordinated heart development

Cardiac development is a tightly regulated process that requires a network of specific cardiogenic transcription factors and the formation of functional sarcomeres to establish muscle contractility. Unc45b is a molecular chaperone that has been shown to be involved in the organisation of muscle sarcomeres during cardiac development, and this molecular chaperone is involved in the folding and activation of myosins in other eukaryotic cell types. Using mouse lines carrying *Unc45b* loss-of-function mutations, Henry Epstein and colleagues (p. 3893) now demonstrate that Unc45b regulates both sarcomere contractility and gene expression during cardiac development by interacting with myosins and the transcription factor GATA4, respectively. Unc45b is expressed in the heart of E9.5 mice, and *Unc45b* mutant mice display decreased cardiac contraction and fail to correctly develop the right hand side of the heart. Furthermore, loss of Unc45 leads to a reduction in sarcomeric myosin and GATA4 protein levels and decreased mRNA levels of GATA4 target genes. In addition, the authors illustrate that Unc45b can bind to both myosin and GATA4. They conclude that the chaperone helps to prevent the degradation of myosin and GATA4 and thereby contributes to the generation of cardiac contractility, as well as the specific activation of cardiac genes during development.



No beat without FAP46

The microtubules in motile cilia and flagella of eukaryotic cells are arranged in a '9+2' axoneme; two central single microtubules that are surrounded by a ring containing nine microtubule doublets. The central microtubule pair is associated with at least seven individual projections that contain distinct protein complexes. Previous work has indicated that each of these complexes has unique roles in cilia motility, but their precise molecular composition and the mechanisms by which the projections contribute to dynein-driven microtubule sliding have remained unclear. Here, Elizabeth Smith, George Witman and co-workers (p. 3904) isolate and characterise a new *Chlamydomonas* mutant that lacks the C1d projection on the central microtubule pair. They show that *FAP46* encodes a protein that associates with FAP54, FAP74 and FAP221 in the C1d complex and that complex formation depends on FAP46. Furthermore, *FAP46*-null mutants have impaired motility: more than half the cells lacking FAP46 are immobile, whereas the remaining cells are only able to swim with slow and shaky movements. Furthermore, the loss of FAP46 leads to a substantially decreased microtubule-sliding velocity. Together, these results support the hypothesis that the C1d projection on the central microtubule pair has important roles in mediating normal flagellar movement.



Filamins prevent cell invasion

Filamins are actin-binding proteins that not only bundle actin filaments but also connect different membrane-spanning proteins, including adhesion and signalling receptors, to the actin cytoskeleton and serve as a scaffold for intracellular signalling proteins. Deficiency of filamin A (FLNA, the most abundant filamin) is associated with migration defects in melanoma and neuronal cells, but has also been shown to enhance breast cancer invasiveness. Here, David Calderwood and co-workers (p. 3858) now demonstrate that FLNA has a role in extracellular matrix (ECM) remodelling and, consequently, is involved in regulating tumour cell invasion. They show that *FLNA* knockdown in fibrosarcoma cells leads to an increase in matrix metalloproteinase activity compared with that in wild-type cells. As a result, cells lacking FLNA have an enhanced ability to degrade and invade gelatin and fibronectin matrices. *FLNA* knockdown decreases tissue inhibitor of metalloproteinase 2 (TIMP2) secretion, which results in enhanced matrix metalloproteinase 2 (MMP2) activation. By using a trans-well migration assay, the researchers also show that the lack of FLNA does not affect regular cell motility but enhances cell invasion into a three-dimensional matrix. Taken together, these findings illustrate that filamin has an important role in ECM remodelling and cell invasion.