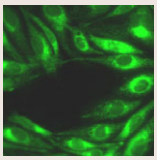
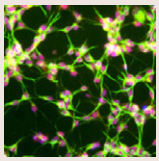
In this issue



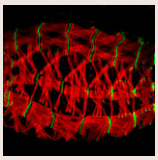
Electric shock makes cells soft

Blood flow and blood pressure subject the vascular endothelium lining the blood vessels to various physical forces. The stiffness of endothelial cells helps them to withstand these forces, and also has an important role in regulating deformation-dependent nitric oxide release from the vascular endothelium. But although the importance of mechanical stiffness for vascular endothelial cells is well known, how this property is regulated is poorly understood. On page 1936, Chiara Callies, Hans Oberleithner and colleagues now show that changes in the electrical plasma membrane potential directly affect cell stiffness. Using a new experimental set-up that combines fluorescence-based membrane potential measurements and atomic-force microscopy to assess changes in cell rigidity, the authors illustrate that depolarisation of the plasma membrane results in an ~20% decrease in cell stiffness. It is well known that this rigidity is largely determined by the actin cytoskeleton, and the authors show that, in endothelial cells, depolarisation alters the cortical actin network. On the basis of these results, the authors propose that a change in the electrical field across the plasma membrane of vascular endothelial cells is sensed directly by the submembranous actin network, thereby leading to changes in the actin polymerisation: depolymerisation ratio, which in turn changes cell stiffness.



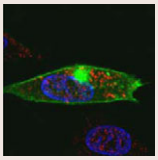
FGF2 keeps rat NSCs going

Advances in stem cell biology have steadily increased the possibilities for studying diseases and developing treatments. Cultured mouse and human neural stem cells (NSCs) have been invaluable for the investigation of neurodegenerative diseases and the screening of pharmacological compounds. Rats have been used extensively for cognitive, pharmaceutical and surgical research, so cultured rat NSCs would, therefore, be beneficial for complementary in vitro studies. Unfortunately, culturing rat NSCs has proven difficult so far, because they arrest proliferation and differentiate. In search for conditions that allow long-term maintenance of rat NSCs in vitro, Austin Smith and colleagues (page 1867) identify an extrinsic stimulatory network comprising bone morphogenetic protein (BMP) and fibroblast growth factor (FGF) 2 that regulates rat NSC proliferation and differentiation. They show that autocrine BMP stimulation induces growth arrest through members of the Smad family of transcription factors – an effect that can be overcome by conditioned medium from proliferating cells or the BMP antagonist Noggin. Importantly, FGF2 is necessary to block terminal differentiation in the presence of BMP and maintain potency in quiescent NSCs. It is thus the careful balance of these two factors that is required to regulate rat NSC cell fate; manipulating this balance in vitro provides a new way to achieve their long-term expansion.



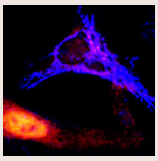
Talin: deciphering domain function

Integrins are essential components of focal adhesions that link cells to the extracellular matrix (ECM). Intracellularly, these adhesion receptors associate with a dynamic network of proteins – the integrin adhesion complex (IAC). The cytosolic adaptor protein talin not only links integrins and the IAC, but also directly connects integrins with actin and regulates their affinity for the ECM. But how does talin carry out all of these roles? On page 1844, Guy Tanentzapf and colleagues now provide an answer. They find that the two integrin-binding sites (IBS-1 and IBS-2) on talin act redundantly to recruit the adaptor to the cytoplasmic integrin tail, and also carry out specific, differential roles that provide a regulatory mechanism for integrin-mediated adhesion. Whereas the IBS-2 domain is required to maintain the link between integrins and the IAC, the IBS-1 domain regulates integrin binding to ECM ligands through an inside-out activation mechanism. By replacing wild-type talin with proteins mutated in the IBS-1 or IBS-2 domains, Tanentzapf and co-workers also show that the two domains confer individual functions during *Drosophila melanogaster* development. These observations highlight a mechanism through which diversity in integrin-mediated adhesion can be achieved and suggest a regulatory switch in the talin–integrin interaction, with important roles during development.



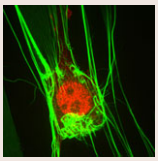
No IPOD for prion proteins

The aggregation of misfolded proteins in cellular deposition sites can lead to a number of 'conformational disorders', including Alzheimer's, Parkinson's, Huntington's and prion diseases. Misfolded prion proteins (PrPs) have been shown to accumulate in deposition sites termed 'aggresomes'. Two distinct subsets of such sites have been characterised: the dynamic 'juxta nuclear quality control department' (JUNQ), which attracts chaperones and proteasomes to refold or degrade misfolded proteins, and the 'insoluble protein deposit' (IPOD), which, by contrast, does not exchange proteins with the cytosol and acts as an assembly site for terminally aggregated proteins. Disease-linked amyloidogenic proteins, such as PrPs, are thought to primarily aggregate in the IPOD but, on page 1891, Ehud Cohen and colleagues now provide evidence that misfolded PrPs instead aggregate in a JUNQ-like compartment. These PrP aggresomes are dynamic structures that contain highly mobile proteins and, similar to the JUNQ, recruit chaperone proteins. In addition, proteins from these aggresomes are rapidly exchanged with the cytosol, where they are degraded by proteasomes. Therefore, the authors propose that the PrP aggresomes act as dynamic quality-control compartments that protect cells from proteotoxic stress by directing misfolded proteins to appropriate refolding or degradation pathways.



Romo1: taking the Myc

The Myc protein is a key regulator of cellular proliferation and its dysregulation is associated with tumour formation. Myc expression levels are therefore tightly controlled. Myc degradation occurs primarily through ubiquitin-mediated proteolysis, which depends on E3 ubiquitin ligases, such as S-phase kinase-associated protein (Skp2). The precise mechanism of Skp2-mediated Myc degradation is, however, unknown. On page 1911, Young Do Yoo and colleagues demonstrate a new role for reactive oxygen species modulator 1 (Romo1) in stimulating Skp2-mediated Myc degradation. The authors demonstrate that Myc induces Romo1 expression during mitosis, which subsequently triggers the translocation of Skp2 into the cytoplasm, where it ubiquitylates Myc, thereby promoting Myc degradation. In addition, Romo1 enhances the Skp2–Myc interaction that drives Myc ubiquitylation. Furthermore, the authors show that a negative-feedback mechanism involving these proteins is important during mitosis: endogenous levels of Romo1 produce reactive oxygen species (ROS) that induce Myc expression, causing quiescent cells to enter the cell cycle. Moreover, Myc-induced Romo1 expression during G1 phase stimulates Skp-mediated Myc degradation. The authors therefore conclude that ROS derived from Romo1 has an important role in Myc turnover.



Interdependencies in matrix remodelling

Membrane type 1 matrix metalloproteinase (MT1-MMP) – one of a family of membrane-tethered proteases – drives tissue remodelling during events ranging from embryogenesis to cancer cell invasion. Thomas Ludwig and co-workers (page 1857) use a new in vitro model system to determine whether MT1-MMP-mediated proteolysis of the extracellular matrix is interdependent on cell adhesion, force generation and rigidity sensing by the cell. In this system, the human melanoma MV3 cell line is stably transfected with MT1-MMP and seeded onto a matrix that consists of a single layer of parallel, fluorescently labelled collagen I fibres. Using atomic-force microscopy and fluorescence imaging, the authors visualise the impact of MT1-MMP on collagen matrix remodelling under varying conditions. They reveal that expression of MT1-MMP results in structural matrix defects that are characterised by gaps in the collagen lattice and loose fibre bundles. Furthermore, the authors show that the functionality of integrins, the actin network and myosin motor activity are all necessary for matrix remodelling, as drug inhibitors that interfere with the function of $\alpha 2\beta 1$ integrins (cell adhesion), actin and myosin II (force generation and rigidity sensing) interfere with matrix remodelling. The authors conclude that key features of matrix remodelling depend on the synergy of cellular traction, adhesion and proteolysis.