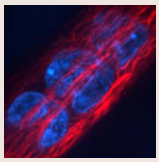
In this issue

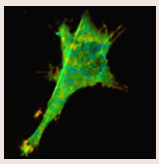
NEW ARTICLE SERIES: Cell Biology and Disease

In this issue, *JCS* is pleased to announce the launch of a new Article Series on Cell Biology and Disease, which aims to highlight how cell biology can shed light on mechanisms that drive the development of disease and open up new avenues for treatment of human disease. As argued in the Editorial by our Deputy Editor-in-Chief Kathleen Green, the time for such a series is ripe; the confluence of technical advances in biochemistry, engineering, genetics and imaging now provide unprecedented opportunities for defining how chemical signaling pathways interact with structural elements in the cell to control cell behaviour and influence pathogenesis. The series is kicked off with a poster article by Lane and Haines (p. 3923) on the role of keratins in disease that discusses the molecular basis underlying the many known keratinopathies, including the skin-blistering condition epidermolysis bullosa simplex. In the second inaugural article, Maria Antsiferova and Sabine Werner (p. 3929) discuss the ambivalent roles of activin. This factor is involved in normal wound healing, but as the authors argue, it can be involved in skin carcinogenesis and also enhances tumour formation in other organs. Future articles in the series will cover a diverse range of human diseases and pinpoint possible therapeutic interventions.



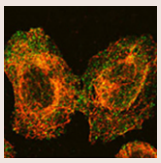
Rotating to locate: nuclear positioning in myotubes

Proper nuclear positioning is crucial in large multi-nucleated skeletal muscle fibers. Positioning is controlled by connections between the nuclear envelope and the cytosketelon, and driven by microtubule-dependent nuclear movement. The nuclei are normally evenly spaced along the long axis of the fiber, whereas abnormally clustered nuclei have been found in patients with Emery–Dreifuss muscular dystrophy. On page 4158, Meredith Wilson and Erika Holzbaur investigate the mechanisms of nuclear translocation in developing myotubes, which, apart from the requirement for microtubules, is not well understood. The authors find that as a nucleus is actively translocated through the cell, it rotates in three-dimensions as a unit that contains the nuclear envelope, nucleoli and chromocenters. Importantly, they show that the plus- and minus-end-directed microtubule motors kinesin-1 and dynein localise to the nuclear envelope and are required for nuclear rotation and its translocation along the microtubule cytoskeleton. Taken together, their data suggest that oppositely directed motors, which act from the surface of the nucleus, drive nuclear motility in myotubes by exerting force on the local microtubule network to allow the nuclei to navigate the complex and crowded cellular environment.



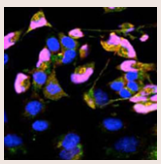
Cells under stress: cofilin to the rescue

Cofilin is one of the best-known actin-binding proteins and has a multitude of roles in diverse cellular processes. Under conditions of stress, cofilin–actin rods form in either the nucleus or cytoplasm as a potential means to stop actin tread-milling and make free ATP available. These cofilin–actin rods have been implicated in neurodegeneration, such as in Huntington's disease (HD) and Alzheimer's disease (AD), suggesting that the dynamics of the actin cytoskeleton is crucial for maintaining neuronal health. On page 3977, Ray Truant and colleagues further characterise the dynamics of the actin–cofilin interaction by analysing the nuclear import and export of cofilin in detail. They identify a previously uncharacterised nuclear export signal (NES) in cofilin, and also show that its known nuclear localisation signal (NLS) is of a bipartite type. Using advanced imaging microscopy approaches and automated image analysis in live cells, the authors show that subtle mutations in the NLS still allow cofilin to bind to actin in vivo, yet affect cofilin dynamics during stress. On the basis of their results, they propose that the nuclear shuttling of cofilin is dynamically regulated during stress and is crucial for cofilin–actin rod formation in response to stress, suggesting that targeting cofilin nuclear shuttling might be a feasible therapeutic approach for HD and AD.



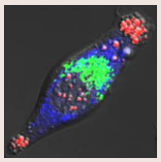
New role for Rab11 in exocytosis

Rab11 is one of best-studied Rab GTPases; it associates primarily with recycling endosomes (REs), which are often found in a perinuclear region, and regulates the recycling of endocytosed proteins. However, it remains poorly understood which step in the recycling process Rab11 is involved in. On page 4049, Kazuhisa Nakayama and colleagues aim to shed light on this question by closely analysing the Rab11 distribution in the cell. They find that some of the Rab11, together with the recycling protein transferring receptor (TfnR), also localises to the peripheral tip regions of the cell. Importantly, the authors show that Rab11 acts with the exocyst complex in the docking and fusion of REs at the plasma membrane (PM), as depletion of Rab11, or of exocyst components, abolishes the fusion of the vesicles with the PM and leads to their accumulation beneath it. On the basis of these observations, the authors propose that Rab11 participates in one of the final steps in exocytosis, the exit of recycling vesicles from perinuclear REs, which are transported along microtubules towards the cell periphery without any involvement of Rab11, by regulating the tethering of recycling vesicles to the PM in concert with the exocyst complex. Further experiments will help to elucidate how exactly Rab11 mediates the fusion of REs before their exocytosis and the other factors involved.



How semaphorin 3A increases vascular permeability

Endothelial cells at the inner side of blood vessels tightly regulate vascular integrity and homeostasis. The weakening of endothelial cell–cell junctions is mediated by VE-cadherin and initiates the paracellular pathway, which allows plasma molecules and cells to pass between endothelial cells. Vascular permeability is strictly controlled; it is enhanced during neovascularisation or in response to inflammation, whereas aberrant leakiness has been associated with tumour angiogenesis. Semaphorin 3A (S3A) is one of few known anti-angiogenic factors that exhibit pro-permeability activity, but the mechanism by which it triggers vascular leakage is unknown. On page 4137, Julie Gavard and colleagues investigate whether S3A has any effects on VE-cadherin-mediated cell–cell junctions in a co-culture of endothelial cells with brain-tumour-derived cells expressing S3A. Indeed, they find that S3A mediates endothelial cell–cell junction destabilisation and elevates endothelial permeability, which is caused by VE-cadherin serine phosphorylation and internalisation. Specifically, the authors show that S3A disrupts the complex between VE-cadherin and the phosphatase PP2A, thus allowing VE-cadherin phosphorylation to take place. Taken together, this suggests that perturbation of the finely tuned PP2A and VE-cadherin balance might promote tumour vessel abnormalities.



Different roles for different Plins

Intracellular lipid storage droplets (LSDs) are unique organelles that store metabolic precursors; they contain different lipids [e.g. triacylglyceride (TAG) or cholesteryl ester (CE)] at their core, and their surface is coated with members of the perilipin family of proteins (Plins). Plins regulate lipid storage metabolism through the recruitment of lipases, and other regulatory proteins, to lipid droplet surfaces, and the loss of Plin activity can significantly reduce the intracellular lipid levels in adipocytes and hepatocytes. In mammals, there are five Plin genes as well as several splice variants, but it is not known whether they exert distinct functions. On page 4067, Alan Kimmel and colleagues address this question and show that, within individual cells of various cell types, distinct Plins preferentially sequester to LPS pools that contain either TAGs or CEs, and can alter the relative intracellular TAG or CE levels towards the targeted lipid. For example, adipose and heart muscle, which predominantly accumulate TAGs, also express the Plins that favour TAG-containing lipopolysaccharides, whereas steroidogenic cells, which accumulate CE, express other distinct Plins. These results point to separate Plin functions that might have important implications for the pathogenesis associated with abnormal lipid storage.