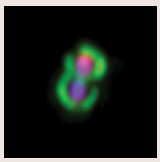
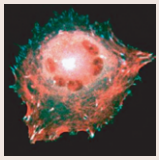
In this issue



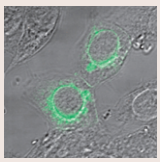
CEP192 and CEP152 bring PLK4 to the centriole

Centrioles serve as platforms for the assembly of centrosomes, the major microtubule-organizing centres of animal cells, and cilia, and are duplicated once during every cell cycle. Polo-like kinase 4 (PLK4) has been shown to be essential for centriole duplication, but it remains unclear how it is recruited to the centriole in mammalian cells or with which proteins it interacts. On page 3223, Katharina Sonnen, Erich Nigg and co-workers aim to answer these questions by focusing on the roles of CEP152, the mammalian homologue of *Drosophila* Asterless, which is known to meditate PLK4 recruitment in flies, and of CEP192, the mammalian homologue of *Caenorhabditis elegans* SPD-2, which targets a PLK4-related kinase in nematodes. They find that CEP192 recruits both CEP152 and PLK4 to the centrosome, and show that CEP192 directly binds to PLK4 through an N-terminal extension that is specific to its largest isoform. The authors also demonstrate that double depletion of CEP192 and CEP152 abolishes the recruitment of PLK4 to centrioles, as well as centriole duplication, suggesting that CEP192 and CEP152 cooperate in PLK4 targeting. Furthermore, they determine the domains of CEP192 and CEP152 that interact with PLK4 as being rich in negatively charged amino acids, which suggests that electrostatic interactions with the positively charged 'polo-box domain' mediate PLK4 recruitment to the centriole. Taken together, these data provide new insights into the spatiotemporal control of centriole duplication during the cell cycle.



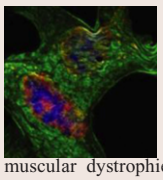
Tension distribution within individual stress fibres

Through actomyosin stress fibres (SFs), cells apply tensile forces on their surroundings – in particular at focal adhesions (FAs). Some FA proteins can act as mechanosensors and undergo conformational changes upon the application of force, but it remains unclear how tensile force in an individual SF is distributed and contributes to tensile homeostasis between the cytoskeleton and the extracellular matrix. On page 3021, Ching-Wei Chang and Sanjay Kumar address these questions by severing single SFs in cells with femtosecond lasers and tracking the tension across the FA protein vinculin with a vinculin tension sensor. They find that severing a single SF leads to an overall decrease in vinculin tension but, surprisingly, tension is not reduced in a uniform manner; vinculin tension is decreased in FAs that are aligned with the severed SFs but can also be increased in many others that are not. In addition, central and peripheral SFs produce different distributions of vinculin tension; severing of peripheral SFs results in a greater overall tension reduction transmitted to FAs in comparatively limited regions, whereas ablation of central SFs transmits tension in a highly dynamic and delocalized fashion. These results suggest that central SFs are structurally interconnected, which helps to dissipate the tension to vinculin mechanosensors when they are severed; however, disruption of peripheral SFs produces a narrower spatial redistribution of tension, accompanied by FA rupture and cell shape change.



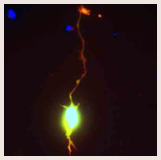
Bridging the gap: insights from connexin mutants

Gap junctions are intercellular channels that allow the direct exchange of ions and small molecules between neighbouring cells and have crucial roles in many biological processes. Mutations in the genes encoding gap junction subunits, connexins (Cxs), have been associated with a number of diseases. Functional gap junction channels are formed through the docking of two compatible hemichannels from adjacent cells, each one consisting of a Cx hexamer, but the underlying molecular mechanisms are not fully understood. Donglin Bai and colleagues now (p. 3113) develop homology models for homotypic and heterotypic channels of Cx32 and/or Cx26, which predict that there are six hydrogen bonds at the docking-interface of each pair of the second extracellular domain (E2). Their model also predicts that Cx32 mutant N175H and the human-disease-linked mutant N175D would lose the majority of the hydrogen bonds at the E2 docking-interface, which they confirm experimentally, as both mutant proteins failed to form morphological and functional gap junctions. To further validate their docking model, the authors designed mutants that they predict would restore hydrogen bonds, and these proteins indeed formed functional gap junctions. By testing additional mutants, they show that a minimum of four hydrogen bonds are required at the E2 interface to allow functional gap junctions to form. Taken together, these results provide insights into the docking mechanism of gap junctions formed by Cx32 and Cx26 that might be extended to other compatible connexins and exploited for therapeutic targeting of gap junction channelopathies.



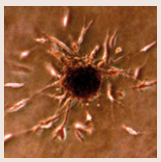
Lamin aggregates in liver injury

Intermediate filaments (IFs) are important components of the cytoskeleton and include the cytoplasmic keratins and vimentin, as well as the nuclear lamin filaments that provide structural integrity to the nucleus among other functions. Mutations in lamins result in laminopathies, including muscular dystrophies, lipodystrophy, cardiomyopathies and premature aging. IFs can also form protein inclusions or aggregates, for instance the keratin aggregates in the Mallory–Denk body (MDB) inclusions are commonly seen in some types of liver disease. As lamins belong to the same IF family as keratins, in this study (p. 3105), M. Bishr Omary and colleagues hypothesized that lamins also aggregate during liver injury and tested this idea in two MDB mouse models, one induced with a porphyrinogenic drug and the other a genetic porphyria model. They indeed found lamin aggregates in both MDB models (these were associated with changes in the lamin organization and shape of the nucleus) and also in liver samples from patients with alcoholic cirrhosis. These lamin aggregates sequestered nuclear proteins, such as transcription factors and ribosomal and nuclear pore components, as demonstrated by mass spectroscopy and biochemical analysis. Furthermore, the authors observe that the formation of lamin aggregates is rapid and precedes keratin aggregation in the livers of mice, suggesting that it is an early sensor of porphyria-associated liver injury and might serve to buffer oxidative stress.



A direct link between netrin signalling and microtubule dynamics

The coordination of actin filament and microtubule (MT) dynamics is important for axon pathfinding in the developing nervous system. A number of axon guidance cues are known, including netrins and their receptors, but it is unclear whether they regulate MT dynamics directly or indirectly. Guofa Liu and colleagues now (p. 3070) investigate netrin signalling in cultured primary neuron cells isolated from embryonic mice. They show that TUBB3, a neuronal β-tubulin isotype III and the most dynamic tubulin type, directly interacts with the netrin receptor DCC (deleted in colorectal cancer) and that this interaction is induced by netrin-1. DCC and TUBB3 also colocalize to the growth cones of primary neurons. The authors furthermore demonstrate that the interaction between DCC and TUBB3 is dependent on MT dynamics, because treatment with either the MT-stabilizing drug taxol or the MT-destabilizer nocodazole inhibited this association. Importantly, knockdown of TUBB3 resulted in inhibition of netrin-1-induced neurite and commissural axon outgrowth *in vitro*, and in defects in commissural axon growth projection *in vivo* in the developing spinal cord of chick embryos. Taken together, these data suggest that TUBB3 interacts directly with DCC and is required for netrin-1-induced axon outgrowth and tuning in the developing nervous system, thus providing a direct link between axon guidance cues and MT dynamics.



Angiogenesis: balance between BMPER and Tsg is key

Angiogenesis is important during development and in adult diseases, such as cancer, ischaemic heart disease and stroke. The generation of a complex vasculature is regulated by a number of signalling cascades and growth factors, including the bone morphogenetic protein (BMP) family. BMPs themselves are regulated by the modulators BMP endothelial cell precursor derived regulator (BMPER), chordin, noggin, gremlin/Drm and twisted gastrulation (Tsg). Jennifer Heinke and colleagues have previously shown that BMPER has a proangiogenic effect on endothelial cells, and in this work (p. 3082) they now analyse the functions of the other BMP modulators. Using a human umbilical vein endothelial cell (HUVEC) sprouting assay, they show that chordin and noggin have no stimulatory effect, whereas Tsg and gremlin enhance sprouting. Surprisingly, they found that both stimulation with Tsg and depletion of Tsg enhance the sprouting, migration and proliferation of HUVECs in a concentration-dependent manner, which results in activation of the AKT, ERK and SMAD signalling pathways that are known to be crucial for angiogenesis. Interestingly, when they stimulated HUVECs with BMPER and Tsg, endothelial sprouting was inhibited, suggesting that a tight balance between these factors *in vivo* results in their overall proangiogenic function. This notion is supported by their finding that, in zebrafish, both BMPER and Tsg are required for the normal development of the vasculature.