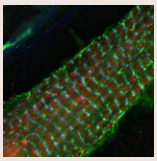
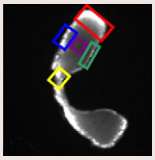
In this issue



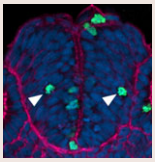
Muscling in with nebulin knockouts

Nebulin is a large protein that determines the level of force developed by the skeletal-muscle sarcomere, the basic contractile unit of muscle, by specifying thin-filament length and regulating crossbridge cycling kinetics. On page 384, Henk Granzier and colleagues now find that nebulin has additional roles in skeletal muscle in their study of nebulin-knockout (KO) mice. They show that Z-disks – the lattices that connect the sarcomere longitudinally and enable force transmission along myofibrils – are wider and misaligned in muscle from nebulin-KO mice compared with the uniform size and regular alignment of Z-disks in muscle from wild-type mice. Such structural disorganisation in the muscle of nebulin-KO mice is in agreement with reports that nebulin mutations cause a muscle disorder known as nemaline myopathy in humans. Previous work has shown that nebulin interacts with the intermediate-filament protein desmin, which has a role in maintaining the lateral organisation of myofibrils. Here, the authors show that nebulin has an additional function in laterally connecting myofibrils by regulating the assembly of desmin at the Z-disk region; accordingly, desmin assembly at Z-disks is perturbed in nebulin-KO mice and when nebulin expression is inhibited in wild-type cells. Together, these data indicate that, in addition to its role in contraction, nebulin modulates Z-disk width and myofibrillar connectivity.



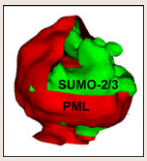
Live! from the pituitary

Studies of cultured pituitary cells have demonstrated dynamic, large-scale fluctuations in the expression of hormones by the many endocrine cell types that make up this tissue. However, whether such fluctuations occur in intact pituitary tissue, and how tissue architecture influences the function of individual cells, was previously unknown. On page 424, Claire Harper, Julian Davis, Michael White and colleagues make use of recently developed live-imaging techniques to quantify the spatiotemporal organisation of prolactin expression in intact pituitary tissue from transgenic rats. By quantifying activity of the prolactin gene promoter for up to 72 hours, the authors find that the absolute signal intensity and amplitude of the change varies in different regions of the tissue; however, the overall temporal pattern of expression is similar in each region, suggesting long-range synchronised regulation of cellular behaviour. By contrast, such synchronisation is lost when tissue cells are dispersed in culture. Furthermore, several distinct short-range patterns can be detected among neighbouring cells in intact tissues over shorter time periods (15 hours). Therefore, the authors conclude, pituitary tissue exhibits short-term stochastic gene expression by discrete cell 'ensembles' that are synchronised by region-specific signals to achieve long-range and long-term coordinated cellular behaviour.



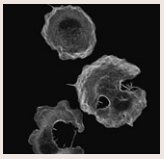
Extracellular cues for neurogenesis

Planar cell division (PCD) and interkinetic nuclear migration (INM; cell-cycle-dependent local oscillation of nuclei within the developing neuroepithelium) are important for maintaining a neural progenitor pool during neurogenesis. Although the involvement of intracellular components (such as the cytoskeleton and polarity proteins) has been investigated, little was known about the contribution of extracellular cues to these processes. In their study of the medaka fish *tacobo* (*tab*) mutant (p. 484), Hiroyuki Takeda and colleagues now reveal that extracellular signals mediated by focal adhesion kinase (FAK) are essential for both PCD and INM during development of the vertebrate nervous system. They identify that the *tab* locus encodes laminin γ1, and that mutation of this locus causes abnormal PCD and INM in the developing neuroepithelium. Downstream signals of laminin-integrin interactions include FAK; here, the authors find that FAK-mediated signals have a pivitol role in *laminin-γ1*-dependent morphogenesis by acting in a cell-autonomous manner to regulate localised mitosis, spindle orientation and neurogenesis. Finally, they provide evidence that FAK-mediated signalling cooperates with the dynein motor complex to coordinate these processes in the neural tube.



PML nuclear bodies in 3D

Promyelocytic leukAemia nuclear bodies (PML-NBs) are functionally heterogeneous structures involved in diverse nuclear functions. These functions are enabled by dynamic association of several different proteins with the PML-NB subcompartment – but how does PML-NB structure enable them to act as assembly platforms for the various factors? On page 392, Johann Engelhardt, Karsten Rippe and colleagues investigate this issue by combining high-resolution techniques of 4Pi and correlative electron microscopy. On the basis of imaging PML and Sp100 proteins (both integral to PML-NB structure) and their relative localisation to small ubiquitin-related modifier 1 (SUMO-1), SUMO2/3, heterochromatin protein 1 (HP1) and telomeres, they derive a model to explain how various activities can be concentrated in PML-NBs in a dynamic manner. First, conjugation of PML and Sp100 proteins to SUMO-1 results in their self-assembly into a spherical shell of 50-100 nm thickness and variable diameter. By contrast, SUMO2/3 is found mainly in the interior of a subset of PML-NBs, where it might control the protein composition and therefore function of these PML-NBs. For example, HP1 might be recruited to the interior of PML-NBs through sumoylation of an HP1 interaction partner. Finally, the authors also show that PML-NBs are accessible to diffusing nuclear factors. These data on the dynamic three-dimensional structure of PML-NBs help to explain their biological functions.



Myosin-IIA in cytoplasmic coherence

The maintenance of a continuous mechanical network across the cytoplasm is important for cellular processes such as matrix force generation, cell shape and motility. Actin stress fibres are involved in this network, but how forces are transmitted across the cytoplasm, and whether other cellular components also contribute, has been unclear. On page 413, Michael Sheetz and colleagues now uncover a role for nonmuscle myosin-II (NMII) contractility in maintaining a coherent cytoplasmic actin network in spreading cells. They show that, when NMII activity is inhibited, a loss of 'cytoplasmic coherence' is observed during later stages of spreading and cells become fragmented; in addition, circumferential actin bundles and stress fibres are disrupted. By assessing the capacity of cells to pull on force-sensing pillars, the authors also show that NMII inhibition reduces both the level and symmetry of traction forces, which – together with the loss of cytoplasmic coherence – results in increased spreading of fragmented cells. siRNA experiments show that these activities are mediated by the A isoform of NMII (NMIIA), rather than by NMIIB or C. Finally, the authors provide evidence that microtubules and intermediate filaments are dispensable for cytoplasmic coherence and force transmission. These data expand our understanding of the cellular components that maintain a coherent cytoskeletal network in spreading cells.

Development in press

Focus on induction and morphogenesis

Morphogenesis is important throughout embryogenesis, but the mechanisms that underpin it are poorly understood. In an article published in *Development*, Richard Lang and colleagues shed light on this issue by reporting that the expression of the actin-binding protein Shroom3 regulates apical constriction (a cellular shape change from cylindrical to conical) during lens placode invagination in mice. Several types of epithelial cells undergo apical constriction during embryonic development, and Shroom3 has previously been associated with apical constriction during neural-plate morphogenesis in mouse and frog embryos. Lang and colleagues now show that, during lens placode invagination, Shroom3 is required for the apical localisation of F-actin and myosin-II, both of which are required for apical constriction, and for the apical localisation of Vasp, another protein involved in actin dynamics. They also show that Shroom3 expression depends on Pax6, a transcription factor that is required for lens placode induction. Together, these results provide new insights into the mechanisms of epithelial morphogenesis and reveal a link between lens induction and lens morphogenesis.

Plageman, T. F., Jr, Chung, M.-I., Lou, M., Smith, A. N., Hildebrand, J. D., Wallingford, J. B. and Lang, R. A. (2010). Pax6-dependent Shroom3 expression regulates apical constriction during lens placode invagination. *Development* **137**, 405-415.