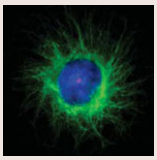
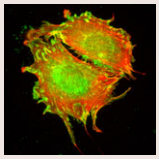
In this issue



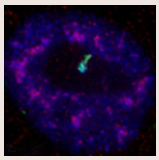
No centre stage for the MTOC

Cell polarity is not only important for the maintenance of epithelial tissues but is also required for the movement of single cells. In migratory cells, polarisation is achieved by repositioning the microtubule-organising centre (MTOC) between the leading edge and the nucleus. Previous studies suggested that these changes result from the nucleus moving to the rear of the cell, while the MTOC remains in a centred position. Here, Denis Wirtz and colleagues (p. 4267) employ a newly developed SMRT (sparse, monolayer, round, triangular) protocol to investigate the factors that affect nuclear and MTOC positioning, and regulate the establishment of cell polarity in mouse embryonic fibroblasts. They find that the MTOC, indeed, becomes positioned between the leading edge and the nucleus when cells are plated on polarisation-inducing micropatterns. However, it becoming off-centred instead of being kept in a central position correlates with polarisation. Actomyosin contractility as well as microtubule dynamics regulate positioning of the MTOC and the nucleus in a manner that depends on cell shape and cell–cell contact. Furthermore, the proteins that are required to establish polarity differ in single and confluent cells. In cells that lack cell–cell contacts, microtubule end-binding protein 1 (EB1) and dynein light intermediate light chain 1 (LIC1) are essential for cell polarisation, whereas LIC2 and the partitioning-defective protein Par3 are not.



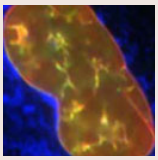
MRTFs stop cells on the move

To achieve directed migration, cells need to precisely coordinate the interplay between the formation and destruction of cell–cell and cell–matrix adhesions and cytoskeletal rearrangements. Depleting cells of serum response factor (SRF) or two of its transcriptional co-activators, myocardin-related transcription factor A (MRTF-A) and MRTF-B (also known as MKL1 and MKL2, respectively), results in impaired cell migration. In addition, changes in actin dynamics affect transcriptional regulation through the MRTF–SRF pathway: monomeric G-actin can repress SRF-mediated transcription by associating with and inhibiting MRTFs. But can changes in SRF-induced gene expression also influence cell motility? On page 4318, Guido Posern and colleagues now find that expression of active MRTF-A impairs the motility of fibroblasts and non-invasive epithelial cells, and results in elongated focal adhesion in these cells. In addition, partial knockdown of MRTF-A and MRTF-B by using siRNAs increases cell migration. The authors identify the genes that encode the cytoskeleton-associated proteins plakophilin 2, integrin α5 and FHL1 as new targets that are regulated by G-actin through the MRTF-A–SRF pathway, and show that knocking down the expression of each of these genes increases cell motility. Cytoskeletal rearrangements can, thus, directly affect the expression of adhesive genes and allow precise regulation of cell motility.



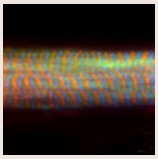
No daughters without Son

Alternative splicing is essential for the generation of protein isoforms that have specific functions. Different splicing factors can be involved in this process, but the roles that individual factors have in the regulation of specific subsets of genes are not always well understood. Son is a member of the serine-arginine-rich (SR) protein family of splicing factors and is essential for maintaining the correct nuclear organisation of pre-mRNA processing factors. On page 4286, Paula Bubulya and co-workers now show that Son is also important for the selection of alternative splicing sites and in maintaining mRNA levels of genes that regulate chromatin organisation and mitotic spindle organisation. By stably expressing a β-tropomyosin minigene in HeLa cells, they demonstrate that the N-terminus of Son is required for its localisation to a transcription site and that depletion of Son results in altered splicing of this gene. Furthermore, Son knockdown leads to defective mitotic spindle organisation during metaphase and to changes in gene expression and splicing of numerous targets. Among the pre-mRNAs that are alternatively spliced are the chromatin-modifying enzymes ADA, HDAC6 and SetD8, and the authors speculate that this, in turn, affects epigenetic regulation of gene expression.



Prelamin A makes nuclei rough

The nuclear lamina – a dense meshwork that contains filamentous lamin proteins lying underneath the nuclear envelope – is required for maintaining nuclear structure, DNA replication and control of gene expression. Changes in its composition affect normal cell function, and mutations in the genes that encode lamins are associated with a variety of diseases. For example, accumulation of an internally truncated form of lamin A, which contains a farnesylation site that is normally removed, results in Hutchinson-Gilford progeria syndrome. Accumulation of farnesylated prelamin A has been shown to result in dysmorphic, highly convoluted nuclei with numerous invaginations. David Vaux and co-workers (p. 4253) now report that a build-up of prelamin A induces the formation of a complex nucleoplasmic reticulum in a CTP:phosphocholine cytidylyltransferase-α-dependent manner. Transmission electron microscopy (TEM) and EM tomography reveal that the nuclear invaginations take on two different shapes. They either result from the inner nuclear membrane folding inwards on its own or from an infolding of both the inner and outer membranes. Furthermore, this nucleoplasmic reticulum harbours numerous nuclear pore complexes, which reduces the number of pores on the nuclear surface. Together, these results provide further understanding of the structure of the nucleoplasmic reticulum and the mechanism behind its assembly.



Growing muscles need no help

During myogenesis, myoblasts must aggregate, differentiate and fuse to form multinucleated muscle fibres. More importantly, they must self-organise over long distances to generate a muscle architecture that is globally aligned with the surrounding tissue. But how do the cells achieve organised myofibre formation without a blueprint over distances that are considerably longer than a single cell? And what role do physical stimuli have in this process? On page 4213, Pak Kin Wong and colleagues now combine micropatterning, microfluidics and cellular automata modelling techniques to show that myoblasts arrange themselves in fibres as a result of an autocatalytic alignment feedback mechanism. The authors find that only differentiating myoblasts that fuse into myotubes can propagate the organised alignment of cells over a long distance and describe a mechanism by which this occurs. Myoblasts initially align and elongate along geometric boundaries as a result of contact guidance. They, in turn, recruit additional cells, which then align in the same direction. During the differentiation process, cells increase in size, which – subsequently – makes them less likely to rotate. This increase in rotational inertia facilitates the following alignment and fusion of nearby cells and, thus, provides a means by which directional information can be self-propagated across long distances.

Development in press

Eph/ephrin signals guide muscle rebuilding

Skeletal muscle regeneration after injury is dependent on satellite cells (skeletal muscle stem cells) that, in response to local myofibre damage, proliferate to build up a supply of adult myoblasts that repair the damage. But do satellite cells relocate within the muscle to respond to distant myofibre damage? If so, how do they find their way? In *Development*, D. D. W. Cornelison and co-workers investigate whether Ephs and ephrins – molecules that are usually associated with axon guidance but that are expressed by activated satellite cells – modulate satellite cell motility and patterning. Using an ephrin 'stripe' assay, they show that multiple ephrins elicit a repulsive migratory response in activated satellite cells and affect the patterning of differentiating satellite cells. Importantly, the same ephrins are present on the surface of healthy myofibres and increase during regeneration, which suggests that muscle regeneration involves ephrin-mediated guidance. Given their results, the researchers propose that Eph/ephrin signalling regulates multiple aspects of satellite cell behaviour during muscle regeneration.

Stark, D. A., Karvas, R. M., Siegel, A. L. and Cornelison, D. D. W. (2011). Eph/ephrin interactions modulate muscle satellite cell motility and patterning. *Development* **138**, 5279-5289.