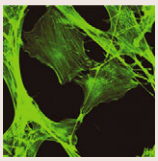
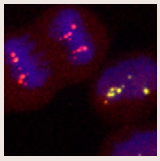
In this issue



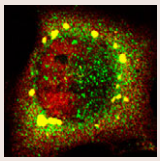
Osteogenesis goes with the flow

There is mounting evidence that the mechanical microenvironment within a tissue can influence stem-cell fate; much remains unknown, however, about how particular mechanical signals are transduced. On page 546, Emily Arnsdorf and colleagues investigate how one such signal – oscillatory fluid flow (which promotes osteogenesis in mature bone) – determines the fate of mesenchymal stem cells. Using C3H10T1/2 progenitor cells as a model, the authors analyse the effect of oscillatory fluid flow on the expression of the transcription factors Runx2, PPARγ and SOX9 (markers of osteogenic, adipogenic and chondrogenic differentiation, respectively). They show that all three proteins are upregulated, as are the GTPase RhoA and its effector ROCKII (which probably enhance tension in the actin cytoskeleton). In addition, chemical activation of RhoA acts additively with flow to upregulate expression of Runx2, whereas disruption of the actin cytoskeleton downregulates flow-induced Runx2 expression. Lastly, they show that – unlike Runx2 – SOX9 and PPARγ are upregulated by actin-cytoskeleton disruption in the absence of flow, and RhoA activation also downregulates PPARγ expression. They conclude, therefore, that oscillatory fluid flow regulates the osteogenic differentiation of progenitor cells via the RhoA-ROCKII pathway.



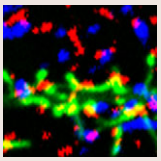
SIRT7 gets rDNA transcription going

Over half of the RNA synthesis in the cell takes place during transcription of ribosomal DNA (rDNA) – a nucleolar process that is tightly regulated in response to cell-cycle stage, ageing, starvation and other factors. For instance, rDNA transcription is repressed during mitosis, but we lack a complete picture of how this is controlled. Now, Valentina Sirri and colleagues (p. 489) investigate the mitotic activity of SIRT7, a nucleolar histone deacetylase that has been reported to help regulate rDNA transcription. The authors show that, in contrast to previous reports, SIRT7 associates with nucleolar organiser regions (NORs; the chromosomal sites at which rDNA genes cluster) even when rDNA transcription is repressed, and that this localisation is mediated by a direct interaction between SIRT7 and the rDNA transcription factor UBF. They next show that SIRT7 is phosphorylated by the CDK1–cyclin-B pathway during mitosis, then dephosphorylated before rDNA transcription resumes after mitosis. Moreover, the resumption of transcription requires SIRT7 activity, and the SIRT7 C-terminus becomes more reactive to cognate antibodies before transcription begins. The authors propose, therefore, that dephosphorylation of SIRT7 promotes a change in its conformation, and that this derepresses transcription. Their data underscore the complexity of rDNA transcriptional regulation.



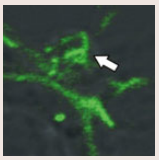
Stressing out with Staufen

In response to stress, mammalian cells halt the translation of mRNA, and instead form stress granules – mRNA-containing cytoplasmic foci that harbour abortive initiation complexes. Stress granules are in dynamic equilibrium with translating polysomes – but how is stress-granule assembly regulated? On page 563, Graciela Boccaccio and colleagues establish a role for Staufen 1 (a polysome-associated RNA-binding protein) in the dissolution of stress granules. Using several cell types, the authors show that Stau1 is recruited to stress granules when cells are subjected to ER stress or oxidative stress. Stau1 is not, however, an essential component of stress granules, which still form in Stau1-depleted cells. The authors note that knocking down Stau1 promotes stress-dependent granule formation, but that this granule formation is impaired when a construct encoding Stau1 is transfected. They show that the N-terminal half of Stau1 is responsible for this inhibitory capacity. Finally, the authors observe that polysomes that remain following stress induction are enriched in Stau1. They propose, therefore, that Stau1 helps to stabilise polysomes, tipping the polysome–stress-granule balance in favour of granule dissolution. These results help to clarify how the cellular stress response can be modulated.



Drebrin A – actin' up at synapses

Most of the excitatory synaptic transmissions in the CNS are received by dendritic spines. These specialised neuronal protrusions change shape through reorganisation of the F-actin cytoskeleton – this appears to modulate synaptic transmission, but the mechanism is not well understood. Now, Lotfi Ferhat and colleagues (p. 524) investigate the role of drebrin A (DA), a neuron-specific F-actin-binding protein, in regulating spine morphology and synaptic transmission. Using high-density cultures of mature hippocampal neurons, the authors first show that overexpression of GFP-tagged DA increases the length and density of dendritic spines, and that this is mediated by the actin-binding domain of DA. Notably, overexpression of DA augments transmission at glutamatergic (excitatory) synapses, probably by increasing their density, but does not affect the efficacy of inhibitory (GABAergic) synaptic transmission. By contrast, downregulation of DA causes a decrease in the activity of both GABAergic and glutamatergic synapses. Thus, modification of the actin cytoskeleton by DA might, the authors suggest, alter synaptic transmission. Their data highlight the intimate relationship between form and function in CNS neurons.



Connexins – taking the scenic route?

Connexins, the transmembrane proteins that make up gap junctions (GJs), form hexameric hemichannels (or connexons) in the Golgi before they are trafficked to the cell membrane. Several mechanistic aspects of connexin trafficking have been well characterised, but their targeting remains controversial – for instance, are connexins targeted exclusively to GJ-rich cell-surface membrane domains, or are they also trafficked to other domains? Using rapid time-lapse imaging of GFP-tagged connexin 43 (Cx43), Dale Laird and colleagues (p. 554) now show that Cx43 is present both in GJ-like clusters and non-GJ membranes (including membrane protrusions and cell surfaces that lack an adjacent cell) on the surface of rat mammary-tumour cells. The authors next use FRAP to analyse lateral mobility of Cx43 within the cell membrane, and show that it is most mobile in non-GJ regions. Within GJ-like clusters, they observe a spectrum of Cx43 mobility, and show that a Cx43 variant that lacks a C-terminus tends to remain more mobile within GJ-like clusters. The authors conclude that Cx43 resides at all cell-surface membrane domains in the cells studied, and propose that Cx43 mobility reflects the assembly state of GJs. Their work contributes to our understanding of the trafficking and assembly dynamics of GJs.

Disease Models & Mechanisms in press

Shedding light on chronic *Listeria* infection

The pathogenic bacterium *Listeria monocytogenes* is the third most common cause of bacterial meningitis in neonates, and causes abortion and stillbirth. Additionally, sporadic outbreaks of listeriosis continue to claim lives, particularly in the very young and the elderly. In a paper published in *Disease Models & Mechanisms*, Christopher Contag and colleagues use in vivo bioluminescent imaging to visualize *L. monocytogenes* in mice. The authors show that the live form of the bacterium, as well as attenuated forms that have defective intracellular replication, reside in the bone marrow and persist for weeks following acute infection. The results draw attention to the bone marrow as a site of residual *Listeria* infection, both during and after treatment. Additionally, this study demonstrates that growth mechanisms that enable *Listeria* to colonise the bone marrow still function in attenuated *Listeria* strains; this is important because these attenuated strains are currently being tested for their ability to induce anti-tumour immune responses in cancer patients.

Hardy, J., Chu, P. and Contag, C. H. (2009). Foci of *Listeria monocytogenes* persist in the bone marrow. *Dis. Model. Mech.* **2**, 39-46.