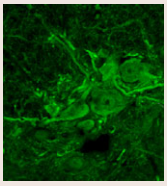
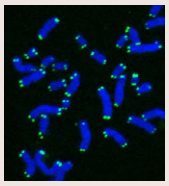
In this issue

By Jane Bradbury



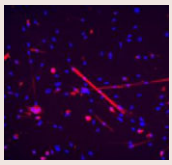
Sync-ing peripherin-filament networks

Intermediate filaments (IFs) are important intracellular cytoskeletal structures that help to provide eukaryotic cells with shape and structure. Consequently, mutations in IF proteins are associated with several human disorders. The motor neuron disease amyotrophic lateral sclerosis (ALS), for example, is associated with specific isoforms of the IF protein peripherin. Here (p. 2543), Kay Davies and colleagues suggest that the atypical type-III IF protein syncoilin is also involved in ALS. The authors show first that syncoilin is expressed in the nervous system and that different syncoilin isoforms are dominant in different regions of the nervous system. They then show that syncoilin colocalises with peripherin and present results that suggest that syncoilin modulates the assembly of the peripherin-filament network in vitro by binding to peripherin isoforms. Finally, the authors report that motor performance is reduced in Sync$^{-/-}$ mice compared with wild-type mice, a phenotype that might be caused by an observed shift from large- to small-calibre motor axons in the ventral root of the knockout mice. Together, these data raise the possibility that syncoilin has a role in ALS and in other neuronal diseases that involve IFs.



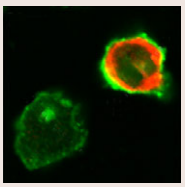
Progerin, damaged telomeres and aging

Hutchinson-Gilford progeria syndrome (HGPS), a rare premature-aging syndrome, is caused by a dominant mutation in the gene encoding the nuclear-envelope protein lamin A. In HGPS, aberrant splicing and processing of lamin A produces a protein called progerin, which induces early cellular senescence that is associated with increased DNA-damage signalling. Ectopic telomerase expression has been shown to increase the lifespan of cells with an HGPS phenotype, but how does it work? Stuart Aaronson and colleagues have been investigating this puzzle and, on page 2605, they report that telomerase extends HGPS cellular lifespan by decreasing progerin-induced DNA-damage signalling, and the activation of the p53 and Rb pathways that mediate the premature senescence of HGPS cells. They also show that progerin-induced DNA-damage signalling is localised to telomeres, and is associated with telomeric aggregates and chromosomal aberrations. Furthermore, the amelioration of DNA-damage signalling by telomerase requires both its catalytic and DNA-binding functions, and occurs concurrently with the acquisition of proliferative ability by fibroblasts obtained from HGPS patients. Together, these findings suggest that progerin-induced telomere dysfunction causes the premature cellular senescence seen in HGPS and might also contribute to normal aging because cells that age normally express increased levels of progerin.



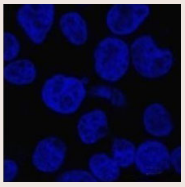
Pax3 muscles in postnatally

The Pax3 transcription factor regulates myogenesis during embryonic and foetal development by controlling the expression of Myf5, myogenin and other canonical myogenic regulatory factors – but what is its role in postnatal myogenesis? On page 2632, Arthur Young and Amy Wagers report that Pax3 induces the differentiation of postnatal, juvenile mouse skeletal-muscle stem cells via an apparently distinct myogenic regulatory pathway. The authors isolate primary myogenic cells from young mice and show that constitutive expression of Pax3 in these cells potently induces myogenic differentiation. By contrast, Pax3 expression in the mouse adult myoblast cell line C2C12 inhibits myogenic differentiation. Surprisingly, the authors show that ectopic Pax3 expression in early postnatal muscle stem cells does not induce expression of any of the canonical myogenic regulatory factors. Indeed, Myf5 or myogenin overexpression fails to induce the differentiation of these cells and Myf5 knockdown promotes their differentiation. Young and Wagers propose, therefore, that distinct sets of myogenic regulators control embryonic, juvenile and adult myogenesis, and that the identification of the relevant postnatal regulators might lead to new approaches for enhancing muscle regeneration after injury.



Lyn-k up with ACSL3 for Golgi export

Lyn – a monopalmitoylated Src-family tyrosine kinase – localises at the cytoplasmic face of the plasma membrane where it is involved in signal transduction. Newly synthesised Lyn, however, accumulates on the Golgi before being trafficked to the plasma membrane by a hitherto elusive mechanism. Here, Naoto Yamaguchi and colleagues (p. 2649) reveal a novel protein-protein interaction between Lyn and long-chain acyl CoA synthetase 3 (ACSL3) that has a crucial role in the export of Lyn from the Golgi. The authors show first that the C-lobe of the Lyn kinase domain associates with ACSL3 on the Golgi. This unexpected interaction only occurs when Lyn is in an open conformation, and is independent of the catalytic activities of both ACSL3 and Lyn. Second, ACSL3 overexpression, they report, accelerates Lyn export from the Golgi, whereas ACSL3 knockdown or formation of a closed Lyn conformation through the action of C-terminal Src kinase block export of Lyn from the Golgi. On the basis of these results, the authors propose a model for the export of Lyn from the Golgi (and possibly of other monopalmitoylated Src-family tyrosine kinases) that involves its conformation-dependent association with ACSL3.



Wnt signalling: p120-catenin joins up

Wnt signalling has diverse roles during embryonic development and is implicated in human cancer. Wnt-ligand binding to the low-density lipoprotein receptor-related proteins 5 and 6 (LRP5/6) and Frizzled receptors activates a signalling pathway that stabilises β-catenin (an E-cadherin-associated protein), thereby stimulating its transcriptional activity. Now, on page 2621, Antonio García de Herreros, Mireia Duñach and colleagues report that a second E-cadherin-associated catenin – p120-catenin – also has a crucial role in Wnt signalling in vitro. The authors show that p120-catenin binds constitutively to casein kinase 1ε (CK1ε, a protein that stabilises β-catenin) and interacts with LRP5/6. Depletion of p120-catenin abolishes CK1ε binding to LRP5/6, they report, and prevents CK1ε activation upon Wnt3a stimulation. Depletion of p120-catenin also inhibits early responses to Wnt, such as LRP5/6 phosphorylation, and later effects, such as β-catenin stabilisation. Furthermore, because CK1ε is needed for phosphorylation of E-cadherin – a modification that releases β-catenin into the cytoplasm in response to Wnt signalling – depletion of p120-catenin prevents Wnt-induced increases in β-catenin transcriptional activity, even in the absence of β-catenin degradation. Together, these results suggest that, through its interaction with CK1ε, p120-catenin is an important regulator of Wnt signalling.

Development in press

TORc1-ing about stem cell differentiation

In adult tissues, the tight regulation of stem cell self-renewal and differentiation maintains tissue homeostasis. In *Drosophila* ovaries, BMP signalling from the local environment maintains germline stem cells (GSCs) by repressing the expression of *bam* (a differentiation-promoting gene). Now, in *Development*, Rongwen Xi and co-workers reveal a role for the tumour suppressor tuberous sclerosis complex proteins (TSC1/2) in GSC maintenance. Human TSC1 and TSC2 proteins form a complex that negatively regulates TOR, a conserved kinase involved in cell growth. TOR functions mainly via the TORC1 complex, which activates the protein translation initiator S6K. Disruption of *Tsc1* or *Tsc2* in *Drosophila* GSCs, the researchers report, leads to precocious GSC differentiation and loss. Elimination of S6K rescues this phenotype, which implicates TORC1 hyperactivation in the precocious differentiation of *Tsc1/2* mutant GSCs. TORC1 hyperactivation also negatively regulates BMP signalling. Thus, suggest the researchers, TSC1/2–TORC1 signalling maintains *Drosophila* GSCs by controlling both BMP–Bam-dependent and -independent differentiation programs, a role that might be conserved in mammals.

Sun, P., Quan, Z., Zhang, B., Wu, T. and Xi, R. (2010). TSC1/2 tumour suppressor complex maintains *Drosophila* germline stem cells by preventing differentiation. *Development* **137**, 2461-2469.