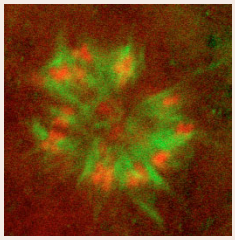
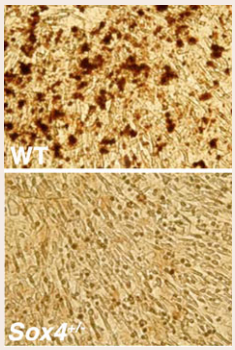
In this issue

by Jenny Bangham



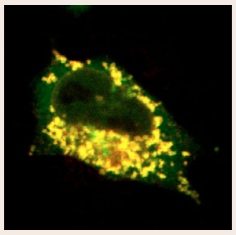
Motoring through plant mitosis

The molecular mechanisms that build and power the mitotic spindle in vascular plants are not well understood. In animals and fungi, the balance of forces provided by motor proteins is crucially important, and kinesin-5 motors (motors that move towards microtubule plus ends) provide outwardly directed forces that are essential for spindle integrity. On p. 2819, Tobias Baskin and colleagues turn their attention to the roles of a kinesin-5 motor protein – AtKRP125c – in vascular plants. Using GFP-labelled AtKRP125c, they find that the protein localises to all microtubule arrays throughout the cell cycle, and analysis of a conditional mutant shows that AtKRP125c has an important role stabilising the mitotic spindle. Unusually for a kinesin-5, AtKRP125c also appears to function in interphase – the researchers observed AtKRP125c localising to interphase microtubules and found that these microtubules are disorganized in the mutant. The spindle architecture of kinesin-5-defective cells is similar in plants, animals and fungi. The motor's mitotic function therefore appears to be widely conserved, but plants take advantage of its activity in interphase as well.



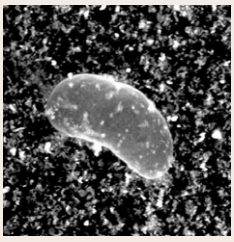
Sox4 rattles some bones

Which genes are responsible for controlling bone density? This is a question that Kaare Gautvik and colleagues address on p. 2785, where they shed new light on the mechanisms of osteoporosis. The researchers suspected that the transcription factor Sox4 might have a role in bone formation – they knew that other *Sox* genes regulate chrondrocyte and osteoblast differentiation and they had previously shown that *Sox4* is expressed in skeletal tissue. To test the possibility, they made *Sox4*$^{-/+}$ heterozygous mice (homozygous *Sox4*$^{-}$ mice die as embryos) and measured aspects of their bone density and strength. These heterozygotes have osteopenia – reduced bone density – and reduced bone strength compared with their wild-type counterparts. Probing the molecular mechanisms underlying these phenotypes in osteoblast cell cultures, Gautvik and colleagues found that, without Sox4, proliferation, differentiation and mineralization are all inhibited. Furthermore, cells lacking Sox4 display reduced expression of Osterix (a protein crucial for osteogenesis), although, curiously, expression of Runx2 (which has been shown to function upstream of Osterix) is not affected. The researchers conclude that Sox4 is crucial for osteoblast proliferation and differentiation and that it functions upstream of Osterix but independently of Runx2.



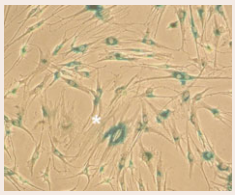
Lethal sting in a Bcl2 tail

Bcl2-family proteins can have pro- or anti-apoptotic functions in different subcellular contexts. Jianjie Ma and colleagues are interested in how distinct tail-anchor domains of Bcl2 proteins relate to these pro- and anti-apoptotic effects and to localisation to specific organelles. On p. 2912 they investigate BFL1, a Bcl2 family member that is both pro- and anti-apoptotic and contains an unusual amphipathic tail domain. The researchers show that it is this tail – called ATAP (amphipathic tail-anchoring peptide) – that targets the protein to the mitochondrial membrane and, by inducing mutations in nucleotides flanking the ATAP sequence, they have defined the residues required for its localisation. They also show that ATAP is responsible for caspase-dependent apoptosis induced by BFL2 and identify the specific hydrophilic charged residues required for pro-apoptotic function. The researchers suggest that these residues compromise mitochondrial membrane permeability by forming a pore or interacting with mitochondrial proteins. Other peptides that cause mitochondria-mediated apoptosis are being tried as anti-cancer molecules; and the authors raise the possibility that ATAP peptides might also represent potential cancer therapies.



EnSNAREd in the nuclear envelope

The nuclear envelope (NE) is constantly having to remodel itself – before cell division the envelope breaks down and at the end of cell division it is reformed. Hemmo Meyer and colleagues are interested in the way that reformation of the NE by membrane fusion is mediated and coordinated with assembly of nuclear pore complexes (NPCs) – the complexes that allow molecules to move in and out of the nucleus. On p. 2895, they turn their attention to crucial mediators of membrane fusion: the SNAREs (interacting membrane proteins present on the two membranes that fuse) and NSF (a protein that dissociates the SNARE complex after membrane fusion). Analysing extracts of *Xenopus* eggs by fluorescence microscopy, they find that, without NSF, reformation of the NE membrane cannot occur. Blocking SNARE function causes a similar fusion defect, and, although certain NPC proteins are recruited, without NSF and SNAREs these 'nucleoporins' do not assemble into NPCs. Looking more closely at the timing of events, the researchers see that NSF is required right up until the chromatin is completely surrounded by the NE. They go on to discuss the possibility that NSF works closely with the ATPase p97, a protein also required at late stages of NE formation.



Stem cells: Brg1 tips the balance

Combinations of chromatin-remodelling factors are important for the correct balance between stem cell renewal and differentiation. On p. 2904, Umberto Galderisi and colleagues describe the influence of Brg1 (the ATPase subunit of the SWI/SNF ATP-dependent chromatin-remodelling enzymes) on proliferation and differentiation of mesenchymal stem cells (MSCs). SWI/SNFs are known to regulate the cell cycle, apoptosis and cell differentiation. Now, the researchers show that forced expression of Brg1 causes cell cycle arrest, apoptosis and senescence in MSCs. The researchers show that ectopic expression of Brg1 upregulates both Rb- and p53-related pathways. Dissecting the molecular mechanisms behind these observations, they find that the apoptosis that occurs is mediated by p53, and both Rb- and p53-related pathways are required for the observed cell cycle arrest and senescence. Intriguingly, ectopic expression of Brg1 is also associated with the differentiation of adipocytes, although the authors note that – unlike other ATP-dependent chromatin-remodelling factors – Brg1 does not appear to directly regulate access to promoters of genes that encode transcription factors. Instead, it promotes differentiation when other, extrinsic factors that promote adipogenesis are added to the culture medium.

Development in press

About face

Ellis-van Creveld (EvC) syndrome is characterized by severe skeletal and craniofacial abnormalities. Victor Ruiz-Perez, Judith Goodship and colleagues previously cloned two genes – *EVC* and *EVC2* – that underlie this disorder. Now, in a paper published in *Development*, the researchers have knocked out *Evc* in mice and used these to pick apart the developmental roles of *Evc*. They show that *Evc* is expressed in developing bones and in the orofacial region (the mouth and face). Within chondrocytes, the protein appears to localise to the primary cilium – an organelle that is central to hedgehog (Hh) signalling – which piqued the researchers' interest in Evc's relationship with Indian hedgehog (Ihh), a 'master regulator' of bone development. *Ihh* itself is unaffected in *Evc*$^{-/-}$ mice, but downstream elements in the signalling pathway, such as *Ptch1* and *Gli1*, display reduced expression. The researchers therefore conclude that Evc is required for transduction of the Ihh signal. They now plan to use the model to find out whether other cell lineages rely on Evc for Hh signal transduction.

Ruiz-Perez, V. L., Blair, H. J., Rodriguez-Andres, M. E., Blanco, M. J., Wilson, A., Liu, Y.-N., Miles, C., Peters, H. and Goodship, J. A. (2007). Evc is a positive mediator of Ihh-regulated bone growth that localises at the base of chondrocyte cilia. *Development* **134**, 2903-2912.