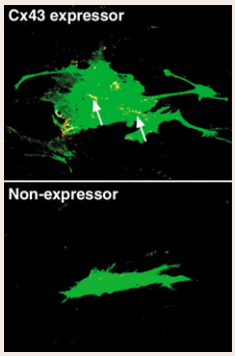
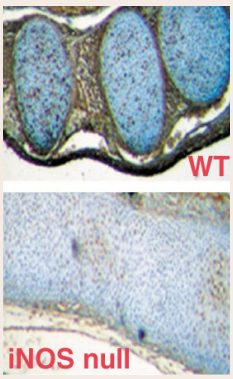
In this issue



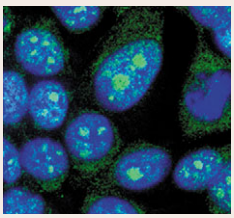
Connexin 43: a labour-saving device

Gap junctions are channels made up of connexin (Cx) proteins that allow direct communication between adjacent cells. The number of Cx43 junctions rises dramatically in the myometrium of the uterus prior to labour, which could help synchronize uterine contractions during delivery by increasing smooth muscle cell coupling. Until now there has been little firm evidence to support this idea. On p. 1715, however, Klaus Willecke and co-workers use a sophisticated conditional-knockout approach to demonstrate the importance of Cx43 for a successful delivery. They have generated mice in which they can abolish expression of Cx43 specifically in smooth muscle by treating them with tamoxifen. The authors find that, under these conditions, parturition still occurs but is often significantly delayed. In addition, they use dye-coupling assays to show that primary myocytes from the animals exhibit decreased cell-cell coupling whereas other features of the cells are unaffected. Their findings thus not only define the critical role of Cx43 in the myometrium in vivo for the first time but also underscore the importance of gap junctions for smooth muscle cell function.



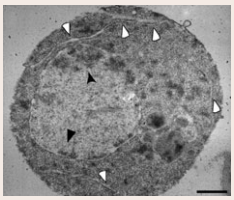
MMP13: make NO bones about it

Nitric oxide (NO) is thought to play an important role in bone formation, but its role in the process is poorly understood. Since remodelling of the extracellular matrix by matrix metalloproteinases (MMPs) is crucial for bone development, Carlos Zaragoza and co-workers have examined whether NO and MMPs are connected (see p. 1896). They find that expression of both MMP-13 and the inducible form of NO synthase (iNOS) increases during differentiation of MC3T3-E1 osteoblast cells, as does production of NO. They also show that NO and activated forms of its downstream signalling molecules cGMP and protein kinase G (PKG) can stimulate the activity of the *MMP-13* promoter in these cells. Moreover, they can block this effect by mutating a site in the *MMP-13* promoter that binds to the transcription factor Cbfa1, a key mediator of bone differentiation. Finally, the authors show that PKG phosphorylates Cbfa1 and that NO-induced expression of MMP-13 is blocked by RNAi directed against Cbfa1. Their results thus indicate that NO regulates bone development by a cGMP-PKG-Cbfa1 pathway that targets *MMP-13* and probably other genes.



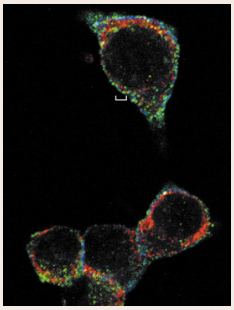
CTCF shuttle puts brakes on growth

CTCF is a transcription factor that is thought to function as a tumor suppressor. It has been implicated in regulation of cell growth, differentiation and apoptosis, but the basis for the growth-suppressing ability that marks it as a potential tumor suppressor has been unclear. On p. 1746, Dolores Delgado and co-workers show that targeting of CTCF to the nucleolus might be crucial. They find that shuttling of CTCF from the nucleoplasm to the nucleolus correlates with growth arrest: in K562 myeloid cells, it is associated with differentiation; in MCF7 breast cancer cells, it is associated with apoptosis. They go on to show that this requires the central Zn-finger domain in CTCF and depends on active transcription by RNA polymerase I. Finally, the authors demonstrate that CTCF inhibits nucleolar transcription and that this is regulated by poly(ADP-ribosyl)ation of the protein. They suggest that translocation of CTCF to the nucleolus is needed to sustain metabolic changes necessary for growth arrest. Since poly(ADP-ribosyl) polymerases (PARPs) are present in nucleoli and regulate numerous nuclear processes, CTCF may function as part of a network of PARP effectors.



'Off' switch for yeast death programme

Whether yeast cells can undergo programmed cell death (PCD) is somewhat controversial. Key to the idea is the identification of yeast proteins related to the death machinery of higher organisms, such as caspase-like proteins and mitochondrial fission factors. On p. 1843, Birthe Fahrenkrog and co-workers provide further support for yeast PCD by describing the first bona fide anti-apoptotic factor in yeast, Bir1p. Bir1p is a relative of the inhibitor of apoptosis proteins (IAPs) that regulate apoptosis in nematode, fly and mammalian cells. The authors now demonstrate that deletion of *BIR1* sensitizes yeast cells to a death stimulus (oxidative stress) and that overexpression of *BIR1* confers resistance to this. They also reveal that Bir1p can be cleaved and inhibited by Nma111p, the yeast orthologue of the pro-apoptotic protease Omi/HtrA2 that antagonizes IAPs in higher organisms. Thus not only do the new findings dispel any lingering doubts that yeast possesses a regulated PCD mechanism; they also indicate that it represents a useful – genetically tractable – model system for examination of evolutionarily conserved apoptotic mechanisms, including those involving IAPs.



Golgi sorting – guilty by association?

Proteins exiting the Golgi can be routed to various destinations, including the cell surface and secretory granules. In cells that exhibit high levels of regulated secretion, an important question is how cells ensure that luminal proteins destined for constitutive secretion do not end up in secretory granules. One possibility is that they lack a sorting signal that directs them to these granules – so-called 'sorting for entry'. However, most studies suggest they enter granules by default and are then removed/excluded during granule maturation – 'sorting by retention'. Peter Arvan and co-workers have examined these possibilities by following the trafficking of two proteins (SEAP and $Cab45_{361}$) that have had their sorting signals removed so that they are constitutively secreted (see p. 1833). SEAP appears to travel via the secretory granules. The $Cab45_{361}$ mutant, by contrast, is excluded from these. Interestingly, the authors show it remains associated with the membrane if the organelles are permeabilized. Their findings thus provide some of the first evidence for constitutive secretion of a protein without passage through immature granules. Perhaps more intriguingly, they also indicate that the luminal face of Golgi/post-Golgi membranes might have a role in capture of constitutively secreted cargo.

Development in press

New dimensions for sonic hedgehog

The mid/hindbrain is an excellent model for studying 3D tissue patterning during development. Although its anteroposterior (AP) patterning is well characterized, however, dorsoventral (DV) patterning is not. In a paper published in *Development*, Blaess et al. examine this. They have used conditional mutagenesis to investigate how the morphogen sonic hedgehog (Shh) directs DV patterning. Shh has two signalling modes involving Gli transcription factors: in Gli2A-mediated Shh signalling, Shh converts Gli2 into a transcriptional activator; and in Gli3R-mediated Shh signalling, Shh opposes the processing of Gli3 into a repressor. The authors conditionally removed all Shh signalling (by mutating its receptor Smo) or just Gli2A-mediated Shh signalling (by mutating Gli2) in the mouse mid/hindbrain. Gli2A-mediated signalling was needed early on for ventral patterning and for the dorsal restriction of Gli3 transcription. Gli3R-mediated signalling was important throughout for the development of dorsal structures and before embryonic day 11 for regulating growth by inhibiting apoptosis. Gli3R-mediated Shh signalling also regulated the expression of the AP organiser Fgf8, leading the authors to conclude that Shh coordinates the AP and DV patterning of the developing mid/hindbrain.

Blaess, S., Corrales, J. D. and Joyner, A. L. (2006). Sonic hedgehog regulates Gli activator and repressor functions with spatial and temporal precision in the mid/hindbrain region. *Development* **133**, 1799-1809.