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 remodeling 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 Cbfα1, a key mediator of bone differentiation. Finally, the authors show that PKG phosphorylates Cbfα1 and that NO-induced expression of MMP-13 is blocked by RNAi directed against Cbfα1. Their results thus indicate that NO regulates bone development by a cGMP-PKG-Cbfα1 pathway that targets MMP-13 and probably other genes.

**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. Together, these results demonstrate that deletion of Biri1 sensitizes yeast cells to a death stimulus (oxidative stress) and that overexpression of Biri1 confers resistance to this. They also reveal that Bir1p can be cleared and inhibited by Nna11p, 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.


**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 shutting 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 nuclear 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 Biri1 sensitizes yeast cells to a death stimulus (oxidative stress) and that overexpression of Biri1 confers resistance to this. They also reveal that Bir1p can be cleared and inhibited by Nna11p, 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’. On p. 1833, Peter Arvan and co-workers have examined these possibilities by following the trafficking of two proteins (SEAP and Cab45) that have had their sorting signals removed so that they are constitutively secreted. SEAP appears to travel via the secretory granules. The Cab45 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.

**Gap junctions and their role in myometrial contractility**
Gap junctions are channels that allow direct communication between adjacent cells, and are thought to be important for the contractility of the myometrium during labor. The expression and function of gap junctions, particularly those involving connexin 43 (Cx43), have been studied extensively in the context of myometrial contractility. In a recent study published in the Journal of Cell Science, Karlie Malek and colleagues examined the role of Cx43 in myometrial contractility during labor.

They utilized a conditional-knockout approach to generate mice in which expression of Cx43 could be suppressed specifically in smooth muscle cells. The resulting mice exhibited delayed parturition, suggesting a critical role for Cx43 in myometrial contractility. Furthermore, experiments utilizing dye-coupling assays confirmed the reduced cell-cell coupling in these mice, further supporting the importance of Cx43 in myometrial contractility.

In addition, the authors investigated the role of NO in myometrial contractility, as NO production increases during labor and is known to modulate contractility. They found that inhibition of NO production in these mice resulted in a further delay in parturition, indicating a possible synergistic interaction between Cx43 and NO in regulating myometrial contractility.

Overall, these findings underscore the importance of gap junctions, particularly Cx43, for the coordination of myometrial contractility during labor. Understanding the molecular mechanisms underlying this process is crucial for developing strategies to enhance or inhibit labor, which could have significant clinical implications.

**Mechanisms of Cx43 regulation during myometrial contractility**
The regulation of gap junction protein expression and function is complex and involves multiple layers of control. In the context of myometrial contractility, the expression and activity of connexin 43 (Cx43) are particularly relevant.

The expression of Cx43 in myometrial cells is controlled by a variety of factors, including extracellular stimuli such as cycling and hormonal signals. Previous studies have shown that the Cx43 promoter is regulated by estrogen and progesterone, hormones that play a key role in the physiological processes of labor.

In addition to hormonal control, Cx43 expression can be regulated at the translational level through mechanisms involving microRNAs (miRNAs). miRNAs are small non-coding RNAs that can target specific mRNAs, leading to their degradation or translational repression. In the context of myometrial contractility, miRNAs have been shown to regulate the expression of Cx43 and other gap junction proteins, potentially modulating their function in the myometrium.

Furthermore, the activity of gap junction channels can be modulated by post-translational modifications such as phosphorylation. The connexins, including Cx43, are subject to phosphorylation by various kinases, which can alter their channel properties and thereby influence gap junction function.

Understanding the interplay between these regulatory mechanisms is crucial for elucidating the complex regulation of gap junctions in the myometrium during labor. Further research is needed to fully unravel the regulatory networks that control Cx43 expression and activity in the context of myometrial contractility.