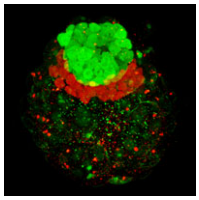
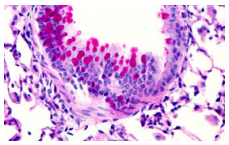


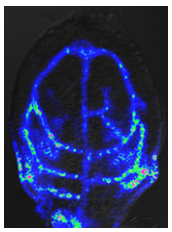
Epiblast and ES cells: same difference?

How similar are mouse embryonic stem (ES) cells to the early embryonic cells they are derived from? On p. 3215, Jennifer Nichols and colleagues now show that both cell types are inherently pluripotent and that signals in the early embryo induce differentiation rather than actively maintain pluripotency. Recent advances in ES cell derivation – involving Gsk3 kinase and Erk kinase pathway inhibition – sparked the idea that epiblast cells from the embryonic inner cell mass (ICM), which normally differentiates into both hypoblast and epiblast, might possess an ES cell-like state that is maintained when inductive signals are inhibited. The authors investigated the effect of such inhibition on early mouse embryonic development and found that it causes the ICM to express the epiblast marker Nanog throughout, indicating that the hypoblast is lost. Like normal epiblast, the Nanog-expressing ICM cells give rise to ES cell clones and can be used to generate chimaeric animals. Thus, the authors propose, embryonic epiblast and cultured ES cells possess essentially the same inherent pluripotency.



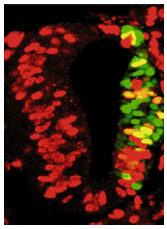
Mig(-6)hty role in lung development and disease

Mitogen-inducible gene 6 (*Mig-6*) encodes a widely expressed adaptor protein that negatively regulates EGF signalling, and about half of all mutant mice that lack *Mig-6* (*Mig-6*$^{-/-}$) die shortly after birth for unknown reasons. Now, Francesco DeMayo and co-workers identify lung defects as a likely cause of these deaths (see p. 3347). The lungs of neonatal *Mig-6*$^{-/-}$ mice display severe morphological defects, such as airway over-branching and abnormal vascularisation, as well as increased EGF signalling and altered cell proliferation and apoptosis. Correspondingly, in a human lung epithelial cell line, *MIG-6* knockdown increases EGF signalling, as well as cell proliferation, whereas it promotes apoptosis in a lung endothelial cell line. Interestingly, surviving adult *Mig-6*$^{-/-}$ mice develop features that resemble obstructive pulmonary disease, which does not occur when *Mig-6* is conditionally inactivated in adult mice. These data support an important, partly EGF-mediated, role for *Mig-6* in lung development, and future studies should address the significance of MIG-6 for human lung disease.



From auxin to leaf veins via ATHB8

In developing *Arabidopsis* leaves, the vein-forming procambial cells arise only from progenitor cells that express the homeodomain-leucine zipper III gene *ATHB8*. By investigating *ATHB8* function, Enrico Scarpella and colleagues now identify a molecular basis for how auxin signalling affects leaf vein development (see p. 3235). By studying mutant leaves that lack *ATHB8*, the authors determined that *ATHB8* restricts preprocambial fate to narrow domains of progenitor cells and coordinates procambium formation within and between veins. In *athb8* mutants, the effects of experimentally perturbing the transport of the plant hormone auxin on both vein development and the distribution of the auxin exporter PIN1 are stronger than in wild-type plants. From their studies, the authors identified an auxin-response element in the *ATHB8* promoter that is required for *ATHB8* preprocambial expression and found that it is targeted by the auxin-response transcription factor MONOPTEROS. Together, these findings provide an important advance towards understanding the mechanisms by which auxin signalling events are translated into developmental patterning processes.

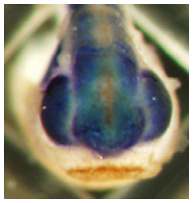


Multitasking Wnts in neural development

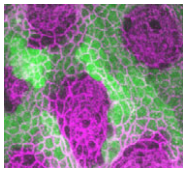
The Wnt/β-catenin pathway promotes neural progenitor proliferation but can also inhibit neuronal differentiation and be required for neurogenesis. In this issue, two studies shed light on some of the mechanisms that allow Wnt/β-catenin signalling to play such multifaceted roles in neural development.

On p. 3301, Elisa Martí and colleagues report that sonic hedgehog (Shh) signalling acts upstream of Wnt/β-catenin signalling to regulate neural progenitor proliferation throughout the chick neural tube (NT). Blocking the Shh pathway is known to result in cell cycle arrest throughout the NT. The authors now show that this is also the case for Wnt/β-catenin signalling because blocking the activity of the Wnt/β-catenin pathway lengthens the G1 phase of the cell cycle in chick embryos. They also demonstrate that Shh activity regulates the Wnt-mediated expression of cyclin D1, an important regulator of cell cycle progression at the G1 stage, by controlling the expression of the Wnt-activated transcription factors Tcf3 and Tcf4. In addition, Shh activity also controls the G2 phase of the cell cycle, independently of Wnt/β-catenin signalling, through the regulation of cyclin E2, cyclin A2 and cyclin B2.These findings indicate that Shh and Wnt/β-catenin signalling co-ordinately regulate cell cycle progression in NT progenitors .

On p. 3289, Vetter, Harris, Moore and co-workers investigate the role of Wnt/β-catenin signalling in the transition of *Xenopus* retinal neural progenitor cells from proliferation to differentiation. These authors have previously reported that Wnt/β-catenin signalling, in addition to promoting retinal progenitor proliferation, activates proneural gene expression in the frog retina by inducing the transcription factor Sox2. They now show that both Wnt/β-catenin signalling and Sox2 block retinal neuron differentiation downstream of proneural gene activity by activating Notch. Moreover, Sox2 inhibits Wnt/β-catenin signalling, and Sox2 protein levels are, in turn, suppressed by the proneural transcription factor Xath5. Thus, the authors conclude, the progenitor-to-neuron transition of retinal neural precursors is driven by a directional modular circuit in which each component inhibits the preceding element while activating the next one.



Taken together, the results of these two papers elucidate how Wnt/β-catenin signalling, through context-dependent regulation, governs neural progenitor fate from proliferation through to neuronal differentiation.



Lowfat recipe for Fat-Dachsous regulation

The large cadherin Fat and its ligand Dachsous (Ds) control the growth and planar polarity of developing tissues. Now, Kenneth Irvine and co-workers shed light on how they are regulated by identifying a conserved cytoplasmic protein, Lowfat (Lft), as a Fat signalling modulator in *Drosophila* (see p. 3223). *lft* mutant flies have shortened wings, a trait typical for Fat pathway defects; when they are crossed with either *fat* or *ds* mutants, these wing defects worsen. Lft binds to the cytoplasmic domains of Ds and Fat, the authors show, and Fat and Ds levels are decreased in *lft* mutants, but increased by *lft* overexpression, indicating that *lft* modulates Fat signalling through post-transcriptional regulation. Furthermore, the human Lft homologues, LIX1 and LIX1-L, bind to the human Fat homologue FAT4. The authors propose, therefore, that Lft is a highly conserved modulator of Fat signalling. Since LIX1 is also linked to spinal muscular atrophy, future studies of Lft might also be important for understanding human disease.