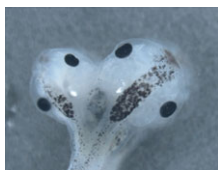


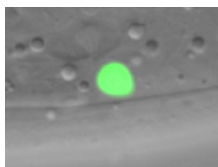
PHOX2A single-handedly builds a brain nucleus

In vertebrate brains, neuronal cell bodies that share functional properties form clusters called nuclei. Although nuclei organize much of the brain's circuitry, little is known about their development. Now, Cliff Ragsdale and colleagues report that a single homeodomain transcription factor – PHOX2A – regulates the nucleogenesis of the chick oculomotor complex (OMC; see p. 1205). The chick midbrain OMC contains two subnuclei – a dorsal Edinger-Westphal nucleus of visceral oculomotor neurons that control pupil dilation and a ventral nucleus of somatic oculomotor neurons that innervate the eye's external muscles. The researchers show that exogenous delivery of *Phox2a* to the embryonic chick midbrain drives the development of a complete, spatially organized midbrain OMC. *Phox2a* overexpression, they report, is also able to generate ectopic motoneurons that innervate extraocular muscles directly. Combined with previous findings in mouse and human, these results show that a single transcription factor can both specify motoneuron cell fates and orchestrate the construction of a spatially organized brain nucleus.



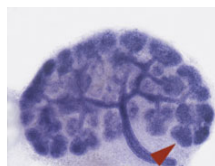
Organizing early for left-right asymmetry

Although the overall vertebrate body plan is bilaterally symmetrical, internal organs show consistent left-right (LR) asymmetry. One model proposes that the motion of nodal cilia during gastrulation sets LR asymmetry. However, on p. 1095, Laura Vandenberg and Michael Levin show that in *Xenopus* embryos the crucial LR asymmetry events occur shortly after fertilization, well before ciliogenesis. The researchers ablate the primary dorsal organizer by UV irradiation, induce a new organizer either early (before cleavage) or late (after the 32-cell stage), and then examine the position of the heart, stomach and gall bladder. The LR axis is usually properly oriented when the new organizer is induced early, they report, but not when it is induced late. Intriguingly, late-induced organizers can correctly orient asymmetry if instructed by a conjoined twin arising from an organizer that was present during the first cleavages. Together, these results suggest that very early symmetry-breaking events, rather than events happening at the node during gastrulation, are of prime importance in establishing LR asymmetry in *Xenopus* embryos.



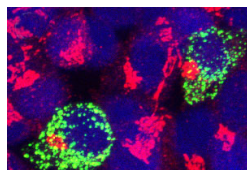
BETs and HATs on for cell-fate maintenance

During development, the progeny of stem cells adopt increasingly restricted fates that must then be maintained, probably through epigenetic mechanisms, to ensure normal development and tissue homeostasis. Hitoshi Sawa and colleagues now reveal the role that the double bromodomain protein BET-1 and the MYST histone acetyltransferases (HATs) play in cell-fate maintenance in *C. elegans* (see p. 1045). The researchers show that cells in most *bet-1* mutants adopt their correct fate initially but transform later into lineally related cells. By expressing BET-1 at various times during the development of *bet-1* mutants, the researchers show that BET-1 functions both when the cell fate of various lineages is acquired to establish a stable fate and at later stages to maintain that fate. Finally, they show that disruption of MYST HATs causes *bet-1*-like phenotypes, which suggests that BET-1 is recruited to its targets by binding to acetylated histones through its bromodomains. These new insights into cell-fate maintenance might have implications for the treatment of cancer and for the development of cell therapies.



Kidney development: WT1 hits its targets

The Wilms' tumour suppressor 1 (*WT1*) gene encodes a DNA- and RNA-binding protein that regulates nephron progenitor differentiation during renal development and that is often inactivated in Wilms' tumour, a childhood kidney malignancy. Now, on p. 1189, Jordan Kreidberg and co-workers provide a comprehensive description of *WT1* target genes that are expressed in nephron progenitors in embryonic mouse kidneys. Using chromatin immunoprecipitation coupled to mouse promoter microarray (ChIP-chip) to analyse chromatin prepared from embryonic mouse kidneys, the researchers identify more than 1600 genes to which *WT1* binds. These genes include essential kidney development genes, such as *Bmp7*, and numerous genes not previously studied in developing kidneys. To validate these genes as *WT1* targets, the researchers use a *WT1* morpholino loss-of-function approach in kidney explants. Low doses of *WT1* morpholino reduce *WT1* target gene expression in nephron progenitors, they report, whereas high doses arrest kidney development. Collectively, these data provide novel insights into the signalling networks and biological processes that *WT1* regulates during kidney development.



Polycystin regulation and function in PKD

Polycystic kidney diseases (PKDs) are characterised by the presence of numerous fluid-filled cysts in the kidney that are produced by the unregulated expansion of renal epithelial cells. A leading cause of end-stage renal failure, autosomal dominant PKD is caused by mutations in *PKD1* and *PKD2*, which encode polycystin 1 and 2. These large transmembrane proteins form a cation channel complex that is involved in mechanosensation-triggered Ca^{2+} influx into cells. In this issue, two papers investigate the regulation and function of the polycystins.

On p. 1107, Oliver Wessely and colleagues report that the RNA-binding protein bicaudal C (*Bicc1*) is a post-transcriptional regulator of polycystin 2. *Bicc1*-null mice develop severe PKD, they report, and *Bicc1* is normally expressed in the mouse meso- and metanephric kidney. The authors also demonstrate that *Bicc1* regulates the stability of *Pkd2* mRNA and its translation efficiency by antagonising the repressive activity of the microRNA *miR-17* on the 3'UTR of *Pkd2* mRNA. To confirm this result, they show that the kidney defects caused by *bicc1* knockdown in *Xenopus* are rescued by *miR-17* knockdown. Finally, they report that *Bicc1* is localised to cytoplasmic foci that contain proteins involved in post-transcriptional regulation of mRNAs. Together, these results reveal the important role played by a microRNA-based translational control mechanism in PKD and in normal kidney development.

On p. 1075, Rong Li and colleagues describe how the mechanosensory function of polycystins prevents the development of renal cysts. Using expression microarray analysis, they show that myocyte enhancer factor 2 (*MEF2C*) and histone deacetylase 5 (*HDAC5*) are targets of polycystin-dependent stress sensing in polarised mouse renal epithelial cells. Fluid flow stimulation of polarised epithelial monolayers, they report, induces the phosphorylation and nuclear export of *HDAC5*. This, in turn, leads to the activation of *MEF2C* target genes, including *missing in metastasis* (*MIM*), which encodes a regulator of the actin cytoskeleton. Finally, the researchers show that kidney-specific knockout of *Mef2C* or the inactivation of *MIM* in mice causes renal tubule dilation. By contrast, treatment with an HDAC inhibitor reduces cyst formation in *Pkd2*^{-/-} mouse embryos. They suggest, therefore, that HDAC inhibition might be a potential treatment for autosomal dominant PKD.

