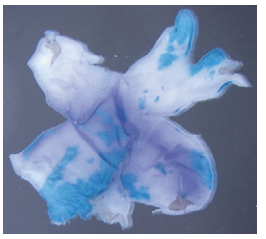
In this issue

By Jane Bradbury

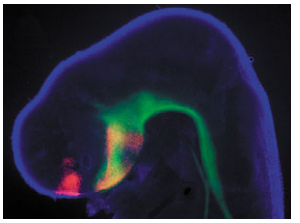
A guiding role for retinoic acid

During the development of the neural retina, neighbouring neurons in the retina send projections to adjacent regions in higher brain centres. Retinal gradients of axonal guidance molecules underlie the formation of this topographic map, but what establishes these gradients? On p. 5147, Sen et al. report that in the chick retina, retinoic acid (RA) regulates the expression of the dorsoventral (DV) topographic guidance molecules EphB2, EphB3 and ephrin B2. They show that expression of a dominant-negative RA receptor reduces expression of EphB2 and EphB3 in the ventral retina and of ephrin B2 in the dorsal retina, and that the transcription factor Vax, which regulates the expression of these guidance molecules, functions upstream or parallel to RA. The researchers conclude that RA signalling is important for the establishment of the topographic map in the retina through its regulation of axon guidance.



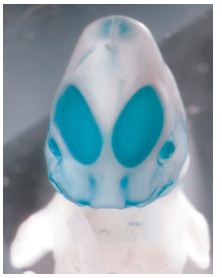
When signalling sequence matters

The hypothalamus controls temperature, hunger and many other physiological functions in animals, but the signals that control the development of hypothalamic neurons are poorly understood. Ohyama and colleagues remedy this by reporting that the sequential action of sonic hedgehog (Shh) and bone morphogenetic protein 7 (Bmp7) directs the differentiation of hypothalamic dopaminergic neurons in chick embryos (see p. 5185). By examining the expression of hypothalamic regional markers in embryo explants exposed to Shh and Bmp7, and to inhibitors of these molecules, the researchers show that the induction of dopaminergic neuron identity is initiated by Shh signalling. Bmp7 then acts on cells that have been ventralised by Shh, including unexpectedly postmitotic cells, to generate hypothalamic neurons. Finally, the researchers report that Shh and Bmp7 in combination are sufficient to direct neural progenitors derived from mouse embryonic stem cells to a hypothalamic dopaminergic fate.



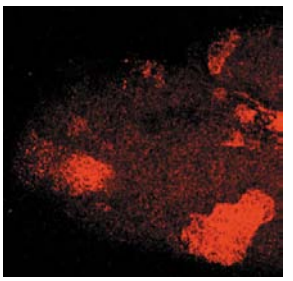
Fgf8 noses into olfactory development

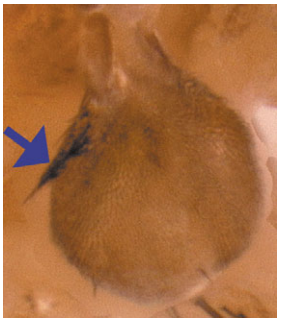
Fibroblast growth factors (FGFs) promote the proliferation, differentiation and survival of most neural cell types during development. Kawauchi et al. now report that *Fgf8* expression is essential for neurogenesis in mouse olfactory epithelium (see p. 5211). Around mid-gestation, the olfactory placodes (epithelial patches on the head of developing embryos) invaginate to form nasal pits in which neurogenesis occurs. The researchers show that *Fgf8* is expressed in the rim of invaginating nasal pits – they call this region the morphogenetic centre. They then demonstrate that early inactivation of the *Fgf8* gene in the olfactory epithelium leads to the apoptosis of cells in the morphogenetic centre. Consequently, nasal invagination ceases and olfactory neurogenesis fails. The researchers conclude that *Fgf8* expression is crucial for the morphogenesis of the nasal cavity, and for the survival and subsequent expansion of the stem cell population that generates olfactory neurons.



Ubx: a case study for selector protein evolution

The misregulation or misexpression of selector proteins – transcription factors that regulate batteries of target genes during development – can change the identities of cells and tissues, and the shape of whole organisms. Consequently, the functional domains of selector proteins are highly conserved. Researchers now provide new insights into how conserved peptide motifs in the *Drosophila* Hox protein Ultrabithorax (Ubx) mediate different aspects of its function. By both activating and repressing transcription, Ubx controls many morphogenetic decisions in fly embryos, including limb formation, which it prevents by repressing *Distal-less* transcription. On p. 5271, Tour and co-workers investigate several conserved motifs within Ubx that are required for its activation and repression functions. They find that the activation function of Ubx is mediated by an N-terminal motif that is conserved between fly and human Hox proteins, and show that its repressive functions are concentration dependent and involve multiple domains, including the conserved YPWM motif. On p. 5261, Hittinger and colleagues report that the conserved QA peptide in Ubx – originally identified as a motif required for limb repression – has different effects in different tissues. In addition, they show that the requirement for QA in limb repression is dose dependent and partly redundant with Abd-A, another Hox protein. Overall, the researchers suggest that the additive and redundant effects of protein motifs in Ubx, and more generally in other selector proteins, might be important in modulating the effects of their evolution.





Intracellular traffic disruption: red light to bile flow

Reduced bile flow – cholestasis – is usually the result of liver injury but is also seen in some inherited syndromes. In arthrogryposis-renal dysfunction-cholestasis syndrome (ARC), which is caused by mutations in the vacuolar sorting protein *VPS33B*, improper bile duct development in the liver contributes to the cholestasis part of the syndrome. Now, Matthews and co-workers describe a zebrafish model of ARC. They report that *vps33b*-deficient zebrafish larvae have poorly developed bile ducts and impaired lipid absorption, as do people with ARC, but that they lack the characteristic motor axon or renal defects (see p. 5295). In addition, they identify *vps33b* as a downstream target gene of the transcription factor *hnf6*, which regulates bile duct development in zebrafish. Further elucidation of the role of VPS33B in biliary development will require the identification of the proteins whose intracellular trafficking is disrupted by its loss.