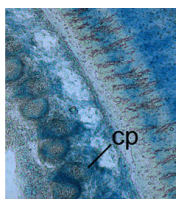
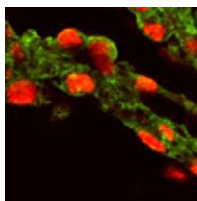


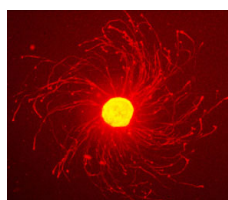
An outflow of cardiac FGF signalling

Nearly 1% of newborn babies have heart defects, often caused by abnormal cardiac outflow tract (OFT) development. The OFT is initially a myocardial tube that forms from a mesodermal cell population called the second heart field (SHF). During OFT remodelling, the myocardial cells secrete extracellular matrix (ECM) to form the OFT cushions, which are invaded by neural crest cells and by endothelial cells that line the OFT myocardium. The endothelial cells undergo an endothelial-to-mesenchymal transition (EMT) and, finally, the OFT septates into the aorta and the pulmonary artery and realigns/rotates into its final position. Two papers in this issue of *Development* provide new information about how FGF signalling controls these complex morphogenetic events in mice. On p. 3599, Anne Moon and colleagues report that an FGF signal produced in the SHF mesoderm establishes an autocrine loop that regulates OFT development *in vivo*. The researchers inactivate two FGF receptors (*Fgfr1* and *Fgfr2*) and overexpress the FGF antagonist sprouty 2 in various embryonic cell types to dissect FGF's role during OFT development. Unexpectedly, given the paradigm of FGF paracrine signalling established in other tissues, the neural crest cells and endothelial cells are not the direct targets of the SHF-derived FGF. Instead, interrupting FGF signalling in SHF mesodermal cells prevents the secretion of signalling and ECM factors by their progeny, which secondarily perturbs endothelial and neural crest cell invasion into the OFT cushions, and also the EMT and OFT septation. On p. 3611, Fen Wang and colleagues use ablation of *Frs2α*, which encodes an adaptor protein that links FGF receptor kinases to multiple signalling pathways, to investigate the downstream pathways that mediate FGF signalling in cardiac progenitors. They report that ablation of *Frs2α* in SHF mesodermal cells affects their expansion into the OFT myocardium and results in OFT misalignment and hypoplasia. In addition, EMT and neural crest recruitment into the OFT cushions are defective in *Frs2α* mutants, resulting in OFT septation defects. Taken together, the results of these two papers provide new molecular insights into the regulation of OFT morphogenesis by FGF signalling.



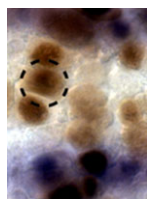
Evolution not just by degeneration

Gene duplication is a major source of evolutionary novelty because paralogous (duplicated) genes can acquire new functions. Paralogous genes are preserved in the genome mainly through subfunctionalization (the division of an ancestral function). The duplication-degeneration-complementation (DCC) model proposes that subfunctionalization occurs when duplicated genes retain different subsets of regulatory elements (so-called complementary degeneration). But, on p. 3543, Jarinova and colleagues claim that the DCC model does not totally explain the evolution of duplicated *hoxb5* genes in teleosts. In zebrafish, the expression patterns of *hoxb5a* and *hoxb5b* suggest that the ancestral *hoxb5* gene underwent subfunctionalization. By comparing the *Hoxb5* loci of human, mouse, zebrafish and *Takifugu*, the researchers identify conserved non-coding elements (CNEs) near the zebrafish *hoxb5* genes. Analysis of the regulatory activities of these CNEs individually and collectively in transgenic assays shows that multiple CNEs are needed to target reporter gene expression to specific *hoxb5a* and *hoxb5b* expression domains. Thus, complementary degeneration of regulatory elements might not be the only route to subfunctionalization.



Shh... autonomous axon guidance in progress

The motility of many cell types is controlled during development by Shh secreted by adjacent tissues (non-autonomous signalling). Now, unexpectedly, Cristina Sánchez-Camacho and Paola Bovolenta uncover a role for autonomous Shh signalling in the growth and guidance of mouse retinal ganglion cell (RGC) axons (see p. 3531). In mammals, the axons of contralateral RGCs (C-RGCs) cross the developing brain's midline (a source of Shh signals), whereas ipsilateral RGC (I-RGC) axons do not. The researchers first show that mouse C-RGCs but not I-RGCs express Shh. Then, by blocking Shh activity *in vivo* with antibodies, they show that midline-derived Shh funnels C-RGC axons to the contralateral side of the brain. Finally, by blocking Shh signal transduction in the RGCs themselves, they show that the outgrowth of C-RGCs is impaired well before they reach the midline, which indicates that the axons of these neurons require autonomously produced Shh for proper extension. Thus, the researchers conclude, Shh signalling influences growth cone behaviour both autonomously and non-autonomously.



A window on neuronal specification

Even the simplest animal nervous system contains numerous cell types. In *Drosophila*, such diversity arises through neural precursors (called neuroblasts, NBs) dividing asymmetrically and generating a stereotyped sequence of neuronal and glial progeny. This process is controlled by a set of sequentially expressed regulators, the temporal identity factors, which specify a neuron's fate, depending on when it was 'born' during neurogenesis. In addition, timing factors, such as Seven up, define how long each temporal identity factor is expressed and thus the number of each type of neuron produced. Now, Tran and Doe use a newly characterized NB lineage to show that two late temporal identity factors, Pdm and Castor, also function as timing factors, while Hunchback and Kruppel act as early temporal identity factors, as in other previously studied lineages (see p. 3491). These findings highlight the importance of lineage-specific cues in modulating the function of temporal identity and timing genes. For more on the temporal control of neuronal diversity, see the Hypothesis by Gould and colleagues on p. 3481.

Jane Bradbury

IN JOURNAL OF CELL SCIENCE Widerborst springs into Akt-ion

Akt (protein kinase B) is a key intermediate in the insulin-IGF signalling (IIS) pathway, and its misregulation is associated with diabetes, obesity and cancer. Recently, it has been shown that Akt activity (which is upregulated by PI3K and downregulated by PTEN) can be modulated independently in individual subcellular compartments. In *J. Cell Sci.*, Vereshchagina et al. shed light on the mechanisms involved by identifying Widerborst (Wdb), a *Drosophila* phosphatase 2A (PP2A) regulatory subunit protein, as a key player in the cytoplasm-specific regulation of Akt1. In a genetic screen for novel phosphatase regulators of IIS, the authors show that Wdb negatively regulates the PI3K-PTEN-Akt signalling cassette by regulating the activity of the PP2A catalytic subunit Microtubule star. In nurse cells, Wdb physically interacts with Akt1 and controls cytoplasmic (but not nuclear) levels of activated Akt1 (pAkt1). From these and other findings, they conclude that PP2A regulatory subunits can act as subcellular-compartment-specific regulators of Akt, providing new therapeutic targets for insulin-linked disease.

Vereshchagina, N. et al. (2008). The protein phosphatase PP2A-B' subunit Widerborst is a negative regulator of cytoplasmic activated Akt and lipid metabolism in *Drosophila*. *J. Cell Sci.* 121, 3383-3392.