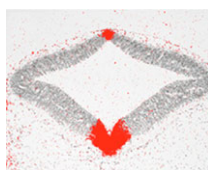


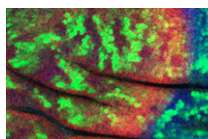
Delta endocytosis: Mind bomb minds Notch

Notch signalling is essential for many aspects of development, including the mechanism of lateral inhibition, where cells that adopt a particular fate prevent adjacent cells from doing likewise. The endocytosis of the Notch ligand Delta is important for lateral inhibition and is regulated in zebrafish by the ubiquitin ligase Mind bomb 1 (Mib1). Now, Matsuda and Chitnis reveal that the endocytosis of certain zebrafish Delta homologues, such as DeltaD, crucially depends on their interaction with Notch itself and leads to their subsequent degradation (see p. 197). The authors report that DeltaD, which normally predominantly localises to the cytoplasm, instead localises to the plasma membrane in *mib1* mutants and *notch* morphants. This is because DeltaD endocytosis depends on Notch-DeltaD interactions, regardless of whether Notch is expressed in the same (in cis) or in adjacent cells (in trans). Interactions in cis, however, are probably inhibitory, whereas interactions in trans activate Notch signalling in the adjacent cells, suggesting a mechanism whereby this process might contribute to lateral inhibition.



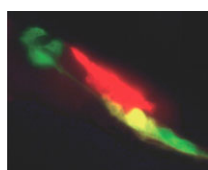
Midbrain neuron selection: gift of the GAB(A)

Midbrain GABAergic neurons control several aspects of behaviour, including mood and motivation, but what controls their development? On p. 253, Kala and colleagues identify the transcription factor *Gata2* as a tissue-specific post-mitotic selector gene for these neurons in developing mouse brains. During neurogenesis, selector gene activation in post-mitotic neural precursors drives the selection of particular neuronal phenotypes from among distinct alternatives. The researchers show that *Gata2* is expressed in developing midbrain GABAergic neurons as they exit the cell cycle and differentiate. Tissue-specific inactivation of *Gata2*, they report, switches all the inhibitory GABAergic neural precursors in the embryonic midbrain to an excitatory glutamatergic phenotype without affecting neural progenitor proliferation or early neurogenic processes. The inactivation of *Gata2* also switches all the GABAergic neurons in neonatal brains to a glutamatergic fate, except for those associated with the ventral dopaminergic nuclei. These results identify *Gata2* as an essential post-mitotic selector gene for midbrain GABAergic neurons and provide insights into the generation of regional identities in distinct GABAergic neuron subpopulations.



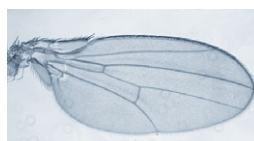
Phosphorylation balancing act in Hh signalling

Hedgehog (Hh) signalling, which mediates many important developmental processes, is regulated by the phosphorylation state of both the seven-transmembrane protein Smoothened (Smo) and the Zn-finger transcription factor Ci/Gli. In *Drosophila*, multiple kinases are involved in Smo and Ci phosphorylation. Now, Jia and co-workers report that the serine/threonine protein phosphatases PP4 and PP2A also regulate Hh signalling by controlling Smo and Ci dephosphorylation, respectively (see p. 307). By examining wing development, they show that RNAi knockdown of PP4 increases Smo phosphorylation and accumulation, which leads to increased Hh signalling activity. Other experiments suggest that Hh normally promotes Smo phosphorylation, at least in part, by downregulating the Smo-PP4 interaction, which is mediated by the kinesin-related protein Costal 2. The researchers also provide evidence that PP2A is a Ci phosphatase and that it upregulates the signalling activity of full-length Ci, the form of Ci that activates Hh target genes. Thus, they conclude, multiple phosphatases – as well as multiple kinases – regulate the Hh signalling cascade.



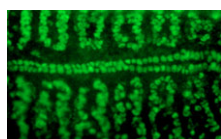
Ciona brain patterning pushes back boundaries

The elaboration of the complex vertebrate brain is thought to depend partly on a unique signalling centre known as the midbrain-hindbrain boundary (MHB) organiser. But now (on p. 285), Kaoru Imai and colleagues report that an MHB-like organising structure patterns the central nervous system (CNS) of the invertebrate sea squirt, *Ciona intestinalis*. *Ciona* is a tunicate, which, like vertebrates, belong to the chordate phylum. Its larvae closely resemble frog tadpoles and possess a simplified CNS with at least four morphologically distinct compartments. By characterising gene expression and function in the *Ciona* larvae CNS, the researchers assemble a provisional gene regulatory network (GRN) for CNS development in *Ciona*. This GRN reveals that an FGF, called FGF8/17/18, has a central role in *Ciona* CNS compartmentalisation, similar to that of FGF8 in patterning the vertebrate MHB. Based on these findings, the researchers propose that FGF8-mediated CNS patterning was present in the last common ancestor of tunicates and vertebrates, and served to delineate two regions of the chordate brain.



Armadillo positively stabilised by Hip(k)s

The conserved Wnt/wingless (Wg) signalling pathway controls many essential developmental processes. Consequently, it must be tightly regulated to ensure that development proceeds smoothly. On p. 241, Lee and colleagues reveal for the first time that homeodomain-interacting protein kinases (Hipks) positively regulate Wnt/Wg signalling. They report that the expression of *hipk* in developing *Drosophila* wings rescues the effects of Wg signal loss, while its overexpression in *Drosophila* cells promotes Wg signalling by stabilizing Armadillo, the *Drosophila* β -catenin homolog, which interacts with the transcription factor Tcf to promote target gene expression (in vertebrate cells, β -catenin interacts with Lef1 to achieve the same outcome). Furthermore, in Wg transcriptional assays, Hipk enhances Tcf/Armadillo-mediated gene expression in a kinase-dependent manner. Finally, the researchers show that, in vertebrate cells, Hipk2 promotes both β -catenin stabilization and Lef1/ β -catenin-mediated gene expression. Together, these results suggest that the Hipks have a conserved role in promoting Wnt signalling that, somewhat surprisingly, involves Hipks acting in both the cytosol and the nucleus.



A fly's tup-thumping heart

The transcription factor (TF) *Isl1* (*Isl1*) is important for the development of a cardiac cell lineage in mouse called the second heart field, which contributes to certain heart structures. However, the precise role of *Isl1* in the early regulatory network that specifies cardiac progenitors from mesoderm remains unresolved. Now, Petra Pandur and co-workers report that *tailup* (*tup*), the *Drosophila* homolog of *Isl1*, is required for early cardiogenesis in flies (see p. 317). They show that *Tup* protein is expressed during cardiogenesis, and that *tup* is required for cardiac progenitor specification. In *tup* mutants, the expression of three conserved TFs (*tinman/Nkx2.5*, *pannier/Gata4* and *Dorsocross/Tbx5/6*) that are part of the early cardiac regulatory network is downregulated. Conversely, *Tup* expression depends on each of these TFs. All four TFs interact genetically, and *tup* functions in both the ectoderm and mesoderm to regulate heart development. From their findings, the authors propose that *tup* is a crucial component of the early cardiac specification network, a role that might be conserved in vertebrates.