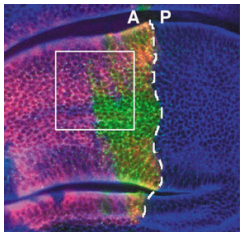
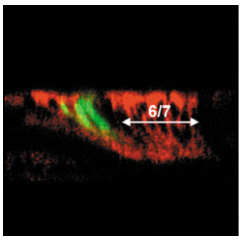
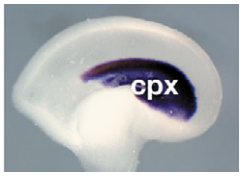


Hedgehog: a low cholesterol spread?

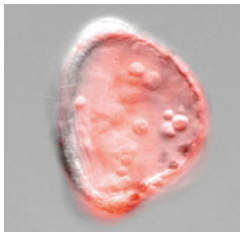
Hedgehog (Hh) is a crucial regulator of development that acts over short and long ranges to control cell fate decisions. How Hh spreads to form a signalling gradient is particularly intriguing because active Hh is lipid modified (it carries cholesterol and palmitoyl adducts), and lipid-modified proteins are usually membrane tethered. Previous findings about the role of lipid modification in Hh signalling have been contradictory, with results differing in particular between vertebrates and *Drosophila*. Now two papers shed light on these events but also raise more questions. On p. 471, Callejo and colleagues report that lipid modification is required for Hh to interact with heparan sulphate proteoglycans (HSPGs). This interaction, they report, restricts the spread of lipid-modified Hh in the fly wing disc and leads to the activation of high Hh threshold response genes, perhaps with HSPGs acting as a co-receptor. Unlipidated Hh forms more extensive gradients, spreading for many more cell diameters than lipidated Hh and inducing the same low threshold-response genes as lipidated Hh, independently of HSPGs. The two Hh forms are also internalised differently – lipidated Hh laterally and unlipdated Hh through the apical membrane. Together, these results indicate that lipid modification plays a conserved role in Hh signalling by affecting multimerisation, Hh spreading and signalling activity. On p. 407, Gallet et al. also conclude that Hh lipid modification serves this conserved role but from quite different results. These authors compared the behaviour of lipidated Hh with that of a truncated, cholesterol-free (Hh-N) form in *Drosophila* embryonic ectoderm and imaginal disc tissue. The absence of cholesterol, they report, affects the secretion of Hh, its multimerisation and also, intriguingly, its long-range signalling activity. For example, distant cell types in the dorsal ectoderm, which require low Hh levels, are absent in Hh-N-expressing embryos, indicating that the range of activity of Hh-N is limited. From these and other results, the authors propose that cholesterol modification is required for the controlled planar movement of Hh to prevent its unrestricted spreading. Future experiments should resolve how lipid modification affects the precise range and activity of Hh in different fly tissues and the degree to which such events are conserved.





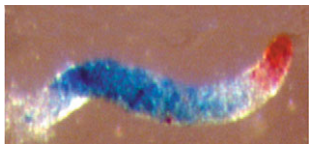
Reelin-in neocortical layers

The neocortex – the outer region of the mammalian brain – contains distinct layers of cells that develop in a specific spatiotemporal order. Reelin, which is mainly made by Cajal-Retzius (CR) cells in the developing neocortex, is essential for this process, but it is unclear whether this secreted glycoprotein provides positional information or is permissive for cell migration. On p. 537, Yoshida and colleagues provide strong evidence for the latter role. CR cells arise from the cortical hem of the developing mouse brain. Unexpectedly, when the researchers genetically ablated the hem, neocortical layers formed in the normal order in mutant embryos, even though most CR cells were lost; in *reeler* mice, which lack functional reelin but have CR cells, the layers are inverted. The researchers suggest that reelin diffusing in from elsewhere in the brain can compensate for CR cell loss and that, therefore, layer order is not driven by positional information from a localised source of reelin.



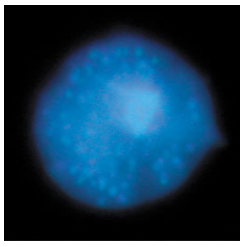
A new conserved role for Wnts in gastrulation?

During gastrulation, morphogenetic movements establish the three embryonic cell layers. In sea urchins, secondary mesenchyme cells (SMC) at the vegetal pole trigger the formation of the archenteron, the central cavity of the gastrula that later develops into the primitive gut. On p. 547, Croce and co-workers report that a newly identified sea urchin Wnt receptor – Frizzled (Fz) 5/8 – is required in SMCs to control archenteron invagination. They show that Fz5/8 is expressed only in the animal domain and in the SMCs during sea urchin embryogenesis. Loss-of-function analyses indicate that Fz5/8 is not involved in the early specification of embryonic cell types but is required to control the primary invagination of the archenteron, which it does through the non-canonical planar cell polarity pathway of Wnt signalling. The researchers suggest that Fz5/8 modulates the morphogenetic movements that initiate gastrulation by controlling SMC adhesion, shape and polarity, a mechanism that is likely to be conserved in vertebrates.



DimB light illuminates *Dicty* development

Dictyostelium is a powerful model system in which to study developmental decision making, as illustrated by two new papers that report that DimB, a bZIP transcription factor, directly regulates the responses of *Dictyostelium* amoebae to the differentiation factor DIF-1. On starvation, *Dictyostelium* amoebae aggregate and form a migrating slug. During this process, they differentiate into prestalk (pst) or prespore cells. pstA cells occupy the tip of the slug, while pstO cells lie behind the tip and prespore cells occupy the rear four-fifths. DIF-1, which is made by prespore cells, is required for the differentiation of pstO cells, but its signal transduction pathway is largely unknown. Now, two groups report that DimB, a bZIP transcription factor, directly regulates DIF-1 responses in *Dictyostelium*. Zhukovskaya et al. identified DimB by purifying molecules that interact with two promoter elements in *ecmA*, a gene expressed in prestalk cells (see p. 439). They show that DimB establishes a gradient of *ecmA* expression in the slug tip by repressing its expression in cells at the rear and centre of the prestalk zone, and suggest that competition between DimB and an unknown activator controls *ecmA* expression. They also show that DimB accumulates in the nucleus when cells are exposed to DIF-1 and becomes associated with the *ecmA* promoter. Huang et al. used bioinformatics to identify DimB (see p. 449). Their search of the *Dictyostelium* genome for factors that could heterodimerize with DimA – another bZIP transcription factor that regulates *Dictyostelium* responses to DIF-1 – identified DimB. They show that DimB interacts with DimA in vitro and that DIF-1 stimulation of cells causes the rapid nuclear accumulation of both DimA and DimB. Together, these papers provide new insights into how DIF-1 controls *Dictyostelium* differentiation and draw parallels with mammalian systems, where interactions between transcription factors increase their regulatory potential.



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