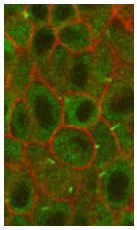
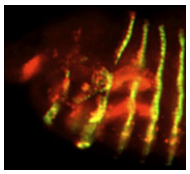


Hooked: a conserved role for cilia in Hh signalling

It is well known that cilia are important for hedgehog (Hh) signalling in mice, but their role in zebrafish has been somewhat contentious. On p. 3089, Huang and Schier now unambiguously demonstrate that zebrafish that lack cilia have normal Wnt, but disrupted Hh, signalling. The authors overcame the experimental problems posed by the maternal contribution of ciliary components by generating maternal-zygotic (MZ) mutants for *oval*, which encodes an intraflagellar transport protein that is essential for cilia formation. MZ *oval* mutants lack all cilia and have normal Wnt signalling; Hh signalling, however, is spatially expanded, but its levels are reduced. By comparison, mice with defective cilia have reduced Hh signalling levels due to the loss of *gli1*, a Hh signalling component that is entirely dependent on Hh signalling for its expression in mice, but not in zebrafish. Together, these findings reveal a conserved requirement for cilia in vertebrate Hh signalling, with distinct effects in mice and zebrafish owing to divergent *gli1* regulation.

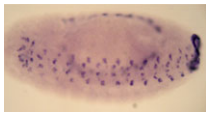


Homing in on enhancer-promoter interactions

Enhancers can be many tens of kilobases away from the promoters they bind to, but what regulates these interactions? In this issue, two papers shed light on the mechanisms that control enhancer-promoter (E-P) communication.

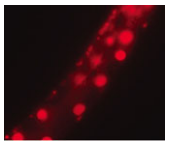
On p. 3067, Judith Kassis and co-workers reveal that at the *Drosophila engrailed* (*en*) locus, which is regulated by multiple enhancers, at least three different mechanisms enable context-specific E-P interactions. Using transposable elements that contain *en* promoter sequences and that preferentially insert near the *en* gene (a phenomenon known as homing), the authors show that, for one set of enhancers involved in early embryogenesis, the *en* promoter sequence itself is necessary for E-P interactions. By contrast, the interaction of the later-acting imaginal disc enhancers with the *en* promoter depends on sequences – termed tethering elements – that lie near the promoter. Finally, long-range *en* E-P interactions require the combined presence of the *en* promoter and neighbouring Polycomb-group response elements (PREs). The authors speculate that other genes with extensive regulatory regions might also employ multiple, context-dependent mechanisms to achieve E-P interaction specificity.

On p. 3077, James Jaynes and colleagues report that the region between the *Drosophila* genes *even skipped* (*eve*) and *TER94* blocks enhancers (displaying so-called insulator activity) and also mediates the homing of *eve* promoter-containing transgenes to the *eve-TER94* genomic region. Even when localised to a 600 bp sequence, these two activities cannot be separated, indicating that they are functionally linked. Interestingly, homed *eve* promoter-containing transgenes respond to endogenous *eve* enhancers from distances as far away as 3300 kb.



This extremely long-range E-P communication depends on both the insulator/homing sequence and the *eve* promoter, similar to the combinatorial effect of *en* promoters and PREs on *en* E-P interaction specificity reported by Judith Kassis and co-workers. These data have far-reaching implications for how insulators might regulate E-P communication.

An additional study, by Michael Levine and co-workers (see p. 3153), indicates that naturally occurring variations in the interaction of conserved enhancers with different target genes might contribute to the evolutionary diversification of insect species. Together, these findings highlight the importance and complexity of E-P communications in the tightly controlled process of development.

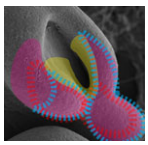


miRNAs target developmental signals

MicroRNAs (miRNAs) regulate many developmental processes, but despite the numerous miRNA-mRNA interactions that have been bioinformatically predicted, few miRNA targets have been experimentally confirmed. Now, on p. 3043, Min Han and colleagues present a systematic analysis of these interactions during *C. elegans* development. Using a previously established immunoprecipitation approach, they have found that distinct sets of miRNAs and their target mRNAs are present at five different developmental stages. Although most mRNAs targeted by miRNAs are continuously and stably regulated throughout development, ~28% of them, the authors report, display complex temporal changes. Interestingly, developmental miRNA regulation predominantly affects genes involved in cell signalling, whereas housekeeping genes are largely unaffected, and at least some of the miRNA regulation preferences are stage dependent. Thus, the authors propose, subsets of miRNAs might orchestrate developmental events by coordinately targeting or avoiding genes involved in specific biological processes. This study also yields important insights into the rules of physiological target recognition by miRNAs, which should benefit future studies in this field.

To acetylate or trimethylate: that is the question

Transcriptional silencing by Polycomb group (PcG) proteins, which is crucial during development, requires histone H3 lysine 27 trimethylation (H3K27me3). The Trithorax protein (TRX) counteracts PcG silencing, but what underpins this antagonism? Tie, Harte and co-workers now propose that, in *Drosophila*, H3K27 acetylation (H3K27ac) by the TRX-associated histone acetyltransferase CBP might be involved (see p. 3131). They show that CBP acetylates H3K27 (which requires TRX), and that CBP or TRX overexpression increases H3K27ac levels while decreasing H3K27me3 levels and causing PcG silencing defects. Similarly, RNAi-mediated knockdown of the PcG protein E(Z) decreases H3K27me3 and increases H3K27ac. These data suggest that H3K27 acetylation and trimethylation are alternative modifications at the same site. In support of this, the high H3K27ac levels found in early embryos decline as H3K27me3 levels increase, and genome-wide ChIP-chip analysis reveals that H3K27me3 and H3K27ac are mutually exclusive at PcG target genes. From their results, the authors propose that TRX-dependent H3K27 acetylation by CBP prevents H3K27 trimethylation, thereby antagonising PcG silencing.



Lrp6 fuses lips

Cleft lip, with or without cleft palate, occurs in around 1 in 700 human newborns, but little is known about the mechanisms involved. Now, on p. 3161, Chengji Zhou and colleagues identify the Wnt co-receptor Lrp6 as being crucial for normal lip morphogenesis in mice. All mice in which Lrp6 is deleted develop a cleft lip with cleft palate. These defects correlate with blocked Wnt/β-catenin signalling and with reduced cell proliferation in the primordia of the lip and palate (known as the orofacial primordia) earlier in development. Concomitantly with reduced Wnt/β-catenin signalling, the expression of the homeobox genes *Msx1* and *Msx2*, which are important for mesenchyme proliferation, is decreased in the orofacial primordia. Conversely, the expression of *Raldh3*, which encodes a retinoic acid-synthesising enzyme that counteracts tissue fusion, expands. The authors demonstrate that *Msx1* and *Msx2* are direct targets of Wnt/β-catenin signalling and conclude that Lrp6-mediated Wnt/β-catenin signalling regulates lip formation and fusion by balancing the activities of Msx1 and Msx2 with the opposing activity of Raldh3.