expressed a defective form of Notch, HH effector proteins were aberrantly expressed beyond stage 6. By examining levels of these effector proteins in mosaic *hnt*-mutant egg chambers, Sun and Deng showed that HNT is required for the negative regulation of HH signalling by Notch. Furthermore, examination of the expression of *cubitus interruptus*, a key mediator of the HH signalling output, showed that HNT regulates the transcription of this gene.

This work in the fruitfly has clearly shown how interactions between major developmental signalling pathways, and their influence on the cell cycle, can trigger the switch between proliferation and differentiation. Future studies should clarify whether similar interactions have a role in other developmental contexts.

Louisa Flintoft

ORIGINAL RESEARCH PAPER Sun, J. & Deng, W.-M. Hindsight mediates the role of Notch in suppressing Hedgehog signaling and cell proliferation. *Dev. Cell* **12,** 431–442 (2007)

later demethylation of the Xi at gene bodies.

The authors suggest a model for this differential DNA methylation pattern on the two copies of the X chromosome. They propose that inactive, untranscribed regions, such as the Xi and intergenic regions, are more likely to undergo loss of methylation, resulting in higher methylation levels remaining at gene bodies on the Xa. Whether this is the case or not, this study alters our views of DNA methylation on the X chromosome, revealing marked differences outside the promoter regions that have been the focus of previous studies and setting the scene for other reassessments of DNA methylation patterns.

Louisa Flintoft

ORIGINAL RESEARCH PAPER Hellman, A. & Chess, A. Gene body-specific methylation on the active X chromosome. *Science* **315**, 1141–1143 (2007)
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DEVELOPMENT

Chipping away at developmental networks

Over the years, classical genetic analysis has identified key regulators involved in metazoan development. With the advent of high-throughput approaches, the pathways are beginning to be assembled into networks, the topology of which provides further insights into how development is orchestrated. Two recent studies published in *Genes & Development* used ChIP-on-chip experiments to elucidate transcriptional regulatory networks in the early development of *Drosophila melanogaster*, focusing on a few key transcription factors involved in the specification of mesoderm and the dorsoventral (DV) axis. They revealed unexpected crosstalk between biological processes and hitherto unappreciated modes of regulation.

Sandmann *et al.* focused on the central regulator of mesoderm development in *D. melanogaster* — Twist. To identify Twist-bound *cis*-regulatory motifs, the authors performed ChIP-on-chip analysis at two consecutive time periods in early fly development, combined with expression profiling of *twist* loss- and gain-of-function embryos. The difference in the binding of Twist to *cis* elements at these time points revealed the dynamic nature of Twist-mediated regulation. Furthermore, computational approaches followed by ChIP experiments found evidence for extensive combinatorial binding of Dorsal and Twist at the earlier time point and Tinman and Twist at the later time point.

The analysis unexpectedly revealed that Twist also regulates genes that are essential for proliferation and transcriptional regulation. The authors combined the temporal binding map of Twist with *in vivo* binding data for Myocyte enhancing factor 2 (MEF2), Dorsal and Tinman — three key mesodermal transcription factors. The resulting core network of transcriptional regulation of early mesoderm development reveals extensive combinatorial binding and frequent feed-forward regulation. The topology of this network argues against the hierarchical model of a master regulator function. Instead of regulating only a few factors, each of which has a handful of their own direct targets, Twist directly affects multiple levels in this developmental network.

Zeitlinger *et al.* also used ChIP-on-chip analysis but their focus was on genome-wide discovery of the targets of the DV determinants: Dorsal and its two earliest targets, Twist and Snail. Their ChIP-on-chip analysis was performed on embryos in which Toll receptor has been constitutively activated, which leads to high levels of Dorsal, Twist and Snail, and makes all of the embryo's cells adopt a mesodermal fate. As expected from the genome-wide scale of this work, new DV enhancers were identified. But the discovery that many segmentation genes contain binding sites for Dorsal, Twist and/or Snail uncovered previously unanticipated links between the DV and anterioposterior (AP) networks. Moreover, binding sites for these transcription factors were also found at genes that encode components of signal transduction such as Decapentaplegic (DPP), Epidermal growth factor (EGF) and Notch pathways.

Together, the studies show how ChIP-on-chip analysis can extend the core sets of regulators that are known from genetic studies. In doing so, they reveal previously unanticipated insights into the architecture and the extent of connectivity of early developmental networks.

Magdalena Skipper

ORIGINAL RESEARCH PAPERS Sandmann, T. *et al.* A core transcriptional network for early mesoderm development in *Drosophila melanogaster*. *Genes Dev.* **21**, 436–449 (2007) | Zeitlinger, J. *et al.* Whole-genome ChIP–chip analysis of Dorsal, Twist and Snail suggests integration of diverse patterning processes in the *Drosophila* embryo. *Genes Dev.* **21**, 385–390 (2007)
FURTHER READING Kimelman, D. Mesoderm induction: from caps to chips. *Nature Rev. Genet.* **7**, 360–372 (2006)