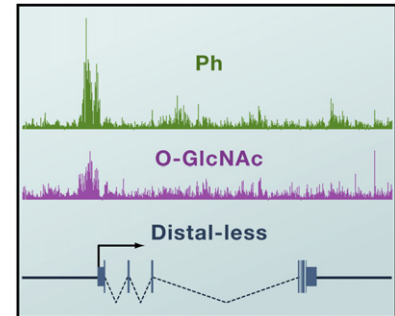


The role of chromatin regulation in development is the subject of this issue's Developmental Biology Select. Recent discoveries link glycosylation to the repression mediated by Polycomb group proteins and provide insight into a developmental disorder that stems from the loss of a histone methyltransferase. Other work sheds light on particular developmental transitions, including loss of plasticity during embryogenesis, the temporal control of *Hox* gene expression, and the impact of long-range chromatin interactions on T cell maturation.

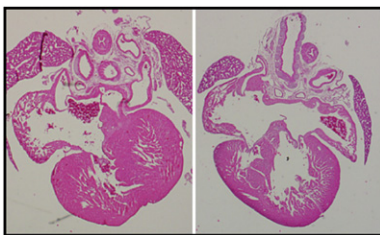
Sugar Is Needed for Polycomb Recipe

Polycomb group (PcG) proteins keep key developmental regulators, such as *Hox* genes, turned off in cells where they must remain inactive. Gambetta et al. (2009) now make the surprising discovery that the PcG gene *super sex combs* (*sxc*) in the fruit fly *Drosophila* encodes a glycosyltransferase. They show that *Sxc* is the fruit fly homolog of the O-linked N-acetylglucosamine transferase (*Ogt*) found in vertebrates, which modifies serine and threonine residues with N-acetylglucosamine (GlcNAc). GlcNAc-modified proteins have in prior work been reported to colocalize with chromatin. Building on this observation, the authors conduct a chromatin immunoprecipitation (ChIP) assay using an antibody that recognizes O-GlcNAc. Of the 1138 sites in the genome that they identify as being occupied by GlcNAc-modified proteins, 490 are at Polycomb response elements bound by the PcG protein Polyhomeotic or the PcG complex PhoRC. The authors further show that Polyhomeotic is a target of GlcNAc modification in vivo. Whether this particular substrate accounts for the effects of loss of *Sxc* is not yet clear. If it does, future work may determine the mechanism by which GlcNAc modification of Polyhomeotic (or other targets) supports PcG-mediated transcriptional repression. Another interesting angle of PcG-mediated repression that might be explored is the potential impact of glucose availability, which in other settings has been shown to regulate the activity of OGT.

M.C. Gambetta et al. (2009). *Science*. Published online May 29, 2009. 10.1126/science.1169727.



Colocalization of O-linked N-acetylglucosamine (O-GlcNAc) and Polyhomeotic (Ph) at *Distal-less*, a PcG target gene. Image courtesy of J. Müller.



The atrial septal defects observed in the hearts of *Whsc1*^{+/-} *Nkx2-5*^{+/-} mice (right; E18.5) are not seen in either *Nkx2-5*^{+/-} or *Whsc1*^{+/-} single heterozygous mutant mice (left). Image courtesy of K. Ura.

WHSC1 Blends Transcriptional Regulation and Histone Modification

Wolf-Hirschhorn syndrome is a developmental disorder characterized by mental retardation, midline defects, heart malformation, and craniofacial abnormalities. Among the genes potentially involved is Wolf-Hirschhorn syndrome candidate 1 (WHSC1), which is found in a region of the human genome exhibiting hemizygous loss in affected individuals. Nimura et al. (2009) now link the function of mouse *Whsc1* to features of the human disease. *Whsc1* is a histone H3 lysine 36 (H3K36) trimethyltransferase, and the authors show that loss of *Whsc1* decreases the level of H3K36 trimethylation in embryonic stem (ES) cells. In addition, mice deficient in *Whsc1* exhibit abnormalities similar to the human syndrome, including heart and midline defects. They provide evidence that *Whsc1* physically interacts in ES cells with transcription factors with important roles in development (such as *Sall1*, *Sall4*, and *Nanog*) and a handful of other proteins with interesting

potential functions, such as the O-linked N-acetylglucosamine transferase (OGT), discussed above. The interaction of *Whsc1* with these transcription factors appears to suppress the transcription of their targets. In heart, *Whsc1* interacts with the transcription factor *Nkx2-5*, a critical regulator of cardiac development, and the authors provide evidence that altered transcription of *Nkx2-5* target genes contributes to the heart defects observed with *Whsc1* deficiency. These findings reveal that *Whsc1* collaborates with key transcription factors in development to carefully tune gene expression.

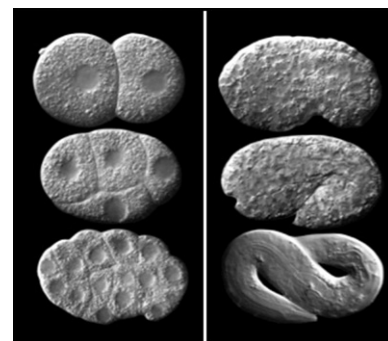
K. Nimura et al. (2009). *Nature*. Published online May 31, 2009. 10.1038/nature08086.

Mes-2 Brings Plasticity to an End

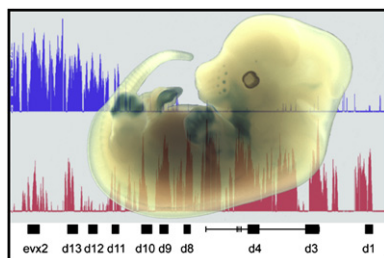
As embryos mature, most cells become restricted to particular cell fates. Yuzyuk et al. (2009) now show that the window of developmental plasticity that characterizes early embryogenesis can be extended in the nematode *Caenorhabditis elegans* when the Polycomb Repressive Complex 2 (PRC2) is disrupted. The authors examine gene expression and use in vivo imaging to track developmental transitions in early embryos after loss of the PRC2 component MES-2/E(z). For example, ectopic expression of the muscle fate determinant *MyoD* reveals that embryos lacking MES-2 retain a greater

capacity to differentiate into muscle than do wild-type embryos at equivalent developmental stages. Collectively, the findings of Yuzyuk et al. suggest that cell-fate specification and developmental plasticity are not inextricably linked and may be under independent control. The authors also provide evidence that PRC2 may contribute to the loss of developmental plasticity through its effects on chromatin structure. During the period of embryogenesis when developmental plasticity markedly decreases, chromatin becomes more compacted and this transition is impaired by the loss of MES-2. This reorganization occurs at individual loci important for differentiation, such as *myo-2* and *pax-1*, in a MES-2-dependent manner. Future efforts may uncover the mechanisms by which PRC2 directs this large-scale reorganization of the genome and may determine what factors control its timing.

T. Yuzyuk et al. (2009). *Dev. Cell* **16**, 699–710.



Developmental plasticity decreases during embryogenesis of the nematode *C. elegans*. Image courtesy of S. Mango.



Pattern of chromatin marks at a *Hox* gene cluster in a mammalian embryo. Image courtesy of N. Soshnikova.

Chromatin Modifications Take Part in the *Hox* Gene Relay

Hox genes are expressed according to a temporal sequence that matches their linear order in genomic clusters. Although this feature of *Hox* gene expression controls many aspects of body patterning and provides a compelling link between linear gene order and the timing of gene expression during development, the underlying mechanisms of this phenomenon remain unclear. New findings by Soshnikova and Duboule (2009) establish that specific patterns of chromatin modifications spread across the *HoxD* gene cluster during development of the mouse tail bud. This pattern of activating and repressive marks, controlled by Trithorax group proteins and Polycomb group proteins, respectively, correlates with which of the genes are expressed at a given embryonic stage. Remarkably, the steady march of this pattern

of histone modifications appears to require that the genes are arranged as an unbroken chain. If the middle of the *HoxD* gene cluster is disrupted by a 3 Mb inversion, the temporal sequence of *Hox* gene expression is abnormal past the breakpoint, which corresponds with an altered pattern of histone marks. Does this pattern of histone marks move like a wave along the locus, and, if so, how is the speed of its advance so carefully controlled? Future work may also explore whether this type of epigenetic spreading occurs at other loci besides *Hox* genes, which could reveal unexpected connections between gene neighbors.

N. Soshnikova and D. Duboule (2009). *Science* **324**, 1320–1323.

Cohesin Maintains a Long-Distance Chromosomal Relationship

Cohesin, well-known for its role in sister chromatid cohesion in mitosis, may have important roles in regulating gene expression in development, according to new work by Hadjur et al. (2009). They provide evidence that cohesin stabilizes a long-range chromosomal interaction at the *IFNG* locus, which encodes the cytokine interferon γ (IFN- γ). IFN- γ is expressed by T helper 1 (T_H1) cells, but not by their progenitors, nonpolarized $CD4^+$ T cells. The authors use the technique known as chromosome conformation capture (3C) to analyze the topology of the *IFNG* locus during this step of T cell differentiation. They show that in T_H1 cells, the *IFNG* locus has long-range interactions in *cis* with both upstream and downstream regions of chromatin that are enriched for CTCF and cohesin binding. Prior work has shown that cohesin associates with CTCF, a multifunctional DNA-binding protein thought to establish chromatin loops. These long-range interactions at the *IFNG* locus are markedly less prevalent in nonpolarized $CD4^+$ T cells and in T_H2 cells, which do not express IFN- γ . In addition, these interactions are lost and there is a reduction in the expression of IFN- γ when T_H1 cells are treated with a short interfering RNA targeting the cohesin subunit RAD21. This finding suggests that cohesin helps to maintain a cell type-specific chromosome conformation at the *IFNG* locus that fosters IFN- γ expression. The larger implication is that the cohesin may have a widespread role in constraining chromosome topology to regulate gene expression at loci important for cell differentiation or other aspects of development.

S. Hadjur et al. (2009). *Nature*. Published online May 20, 2009. 10.1038/nature08079.

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