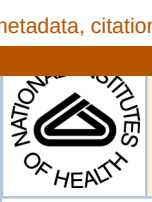

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Repressive Transcription

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Chromatin repression is ironically controlled by the initiation of transcription at specific sites in the genome.

How are active and repressed portions of the genome established and maintained during development? In vertebrates, about 2 m of DNA is packaged into chromatin in a manner that allows for active transcription of some loci and repression of others. Most chromatin regulators do not recognize specific DNA sequences, so how are they recruited to specific sites throughout the genome? For actively transcribed genes, transcription factors or the transcription initiation apparatus recruit regulators associated with active chromatin (1). For genes that are repressed, recent studies suggest a counterintuitive model: Transcription initiates the formation of repressive chromatin (2–9).

The idea that transcription is involved in establishing repressed chromatin is not new. In many eukaryotes, transcription of pericentromeric regions and repetitive elements leads to recruitment of repressive chromatin regulators to these loci (10,11). But the mechanisms by which specific protein-coding genes are silenced by chromatin regulators have been less clear. This issue is important because genes encoding lineage-specific transcription factors must be repressed during early development. Although Polycomb regulators have been implicated in this repression, the means by which they are recruited and maintained at specific genes in vertebrates is not well understood (12).

Genetic and biochemical evidence suggests a competitive balance between the repressive and activating functions of Polycomb group (PcG) and Trithorax group (TrxG) chromatin regulators (13,14). The PcG protein complexes include Polycomb repressive complexes 1 and 2 (PRC1 and PRC2). PRC2 catalyzes the trimethylation of a lysine residue on the chromatin-associated protein histone H3 (H3K27me3). PRC1 and PRC2 can bind to one another and to nucleosomes (the basic packaging unit of DNA and histones) with histone H3K27me3, which provides a mechanism for spreading of these repressive complexes across chromatin domains. In the model fly *Drosophila melanogaster*, transcription factors are thought to recruit PcG complexes to specific sites, but in vertebrates, such recruiting transcription factors have yet to be identified. TrxG protein complexes are recruited to transcriptionally active promoters, most likely by the transcription initiation apparatus, where they catalyze a histone trimethylation modification (H3K4me3) and promote transcription.

How are PcG complexes recruited to specific sites in vertebrate genomes? Recent studies indicate that RNA molecules recruit them to the locus of transcription or to sites located elsewhere in the genome. During mammalian X chromosome inactivation, a noncoding RNA (ncRNA) transcribed from a portion of the *Xist* gene locus forms hairpin structures that recruit the PRC2 complex to the X-inactivation center X(ic) (4). Transcription of full-length *Xist* RNA, which forms the same hairpin structures, leads to further PRC2 recruitment and the spread of PcG-mediated repression across the inactive X chromosome. A ncRNA transcribed from a region adjacent to the *kcnq1* gene recruits PRC2, which

represses genes in the *kcnq1* domain (3). Similarly, a ncRNA transcribed from the *INK4b*/*ARF*/*INK4a* locus mediates repression of that locus by binding PcG complexes (8). The *HOTAIR* ncRNA, which is transcribed from the *HOX C* locus, can target PRC2 and other chromatin regulators to the *HOX D* locus and potentially many other genomic loci (2,6,9). Short ncRNAs are frequently produced by RNA polymerase II in DNA regions that are rich in C and G nucleotides (CpG islands) that are proximal to gene promoters (7); many of these short ncR-NAs can form CG-rich hairpin structures that are similar to those formed by *RepA* and *Xist* RNAs, and some bind to PRC2. Together, these studies suggest that ncRNA molecules contribute to the recruitment of PcG complexes to promoter regions throughout the genome.

Most (70 to 80%) vertebrate promoter regions are transcriptionally active, and many produce short transcripts in sense (coding) and antisense directions (15,16). CpG islands occur in the immediate vicinity of most promoters, and it is within these domains that PcG- and TrxG-catalyzed histone modifications take place. The recent evidence that certain RNA structures can contribute to PRC2 recruitment and that transcripts from promoter regions frequently contain these structures (2–9) suggests a general model for establishing PcG domains (see the figure). An active transcription initiation apparatus can recruit TrxG proteins, whereas transcripts from CpG islands form structures that recruit PcG complexes. PcG complexes can spread across these domains, leading to chromatin repression. At promoters where activating transcription factors continuously recruit the transcription initiation apparatus, demethylation of H3K27me3 can occur (17), and PcG binding is lost. Thus, dynamic competition between PcG and TrxG complexes at promoters is resolved into the steady-state views, produced by genomic analysis, of H3K27me3 and H3K4me3 chromatin domains (1). This model can account for functional antagonism between PcG and TrxG proteins, for the presence of PcG- and TrxG-catalyzed modifications at CpG islands, and for the observation that H3K27me3 and H3K4me3 modifications can occur simultaneously in these promoter-proximal regions.

This model for transcription-linked establishment of PcG/TrxG domains raises many interesting questions. Transcription initiation occurs at most promoters, but what fraction of transcripts recruit PcG complexes and thus, how general is this transcript-mediated process? RNA molecules and transcriptional regulators have been implicated in PcG recruitment, but what exactly are their roles in the dynamics of establishing and maintaining PcG/TrxG domains in vertebrates? Is the conservation of CpG islands a consequence of RNA-mediated PcG recruitment in promoter regions? Answers to these questions should further improve our understanding of the establishment and maintenance of silent and active chromatin during development.

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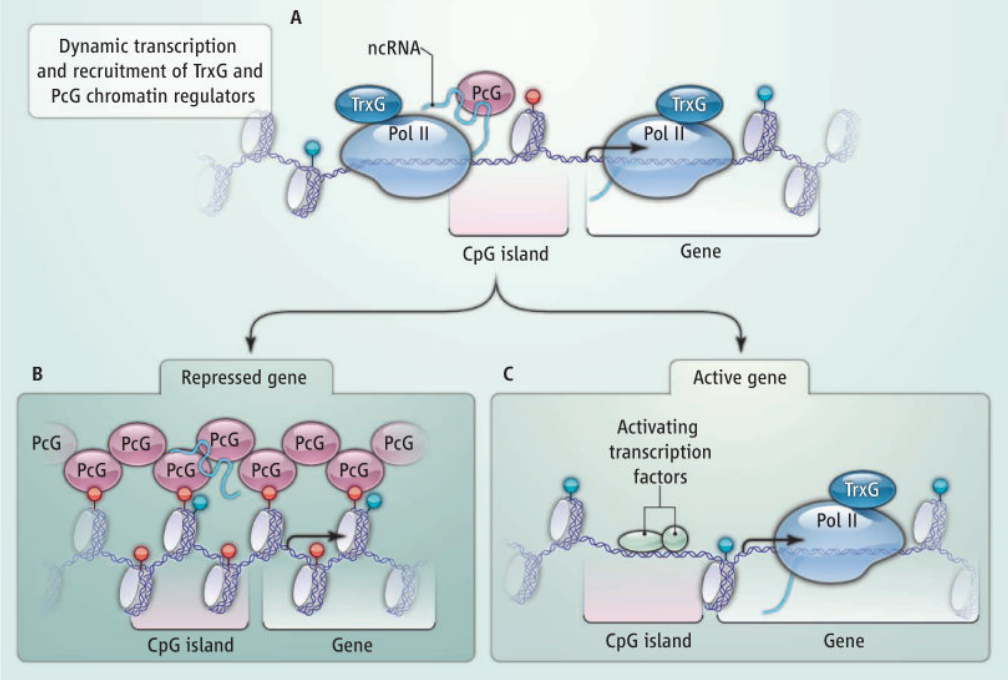

1. . Transcription and chromatin dynamics

(A) Transcription initiation, recruitment of TrxG complexes, which catalyze H3K4me3 (blue dot), and production of CG-rich RNAs occur in the promoter regions of most genes. The CG-rich RNAs often form structures that recruit PcG complexes, which catalyze H3K27me3 (red dot). **(B)** PcG complexes can spread beyond the nucleation site to establish repression. **(C)** At genes where the transcription apparatus is continuously recruited by activating transcription factors, activities associated with TrxG proteins predominate, reducing PcG complexes and their associated histone modifications. Pol II, polymerase II.