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Introduction to the Thematic Minireview Series: Chromatin and transcription

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Regulation of transcription in eukaryotic cells is a dynamic interplay between chromatin structure and recruitment of a plethora of transcription factors to enhancers, upstream activator sequences, and proximal promoter elements. These factors serve to recruit RNA polymerase to the core promoter for productive transcription. In this Thematic Minireview Series on chromatin and transcription, five reviews summarize current knowledge of diverse aspects of transcriptional regulation and the role of chromatin structure in transcription and development.

RNA polymerase II (pol II)² is the enzyme responsible for synthesis of protein-coding mRNAs and various noncoding RNAs in eukaryotic cells. The key step in transcription is the formation of the pre-initiation complex (or PIC), composed of the Mediator co-activator complex, the general transcription factors (GTFs), and RNA pol II, at core promoters (Fig. 1). RNA pol II core promoters contain diverse DNA sequence elements, such as the TATA box, B-response element (BRE), the downstream promoter element (DPE), and initiator element (INR), which serve as binding sites for various GTFs (1). The “classical” pol II promoter contains a TATA element ~30 bp upstream of the transcription start site, which is the binding site for the TBP subunit of the GTF TFIID; however, many genes (perhaps most) are TATA-less, but nonetheless utilize TFIID (or the related SAGA complex (2)) and associated TBP-associated factors (TAFs) at an equivalent site upstream of the transcription start site (reviewed in Refs. 1 and 3). Other components of the PIC include TFIIA, TFIIB, TFIIE, TFIIIF, and TFIIH, and pol II itself. Recent reviews have summarized structural studies that have provided valuable insights into the mechanisms of assembly of the PIC and the roles of each of the GTF in transcription initiation and elongation by RNA pol II (4–7).

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² The abbreviations used are: pol II, polymerase II; PIC, pre-initiation complex; TF, transcription factor; GTF, general transcription factor; TBP, TATA-binding protein; CDK, cyclin-dependent kinase; eRNA, enhancer RNA.

In addition to the GTFs, another protein complex involved in transcription of virtually all genes by RNA pol II is the Mediator complex. Mediator, as the name implies, communicates signals from activating transcription factors to the GTFs of the PIC and RNA pol II. Mediator was first discovered by Kornberg and colleagues (8) and shown to be essential for activated transcription *in vitro*. Subsequently, Mediator was purified from yeast and shown to be a multisubunit complex that directly interacts with RNA pol II (9). Recent insights into the structural complexity of Mediator are reviewed in this series by Harper and Taatjes in their Minireview entitled “The complex structure and function of Mediator” (10). Mediator complexes differ in composition across species, and even in different cell types of a single mammalian species. For example, yeast Mediator contains 21 subunits (exclusive of a cyclin-dependent kinase (CDK) module), whereas mammals have up to 26 subunits. Mediator interacts with various activator proteins bound at enhancers and proximal promoters and with the core transcription GTFs and RNA pol II. Mediator is thought to be involved in chromatin looping between enhancers and promoters (Fig. 1). Structural studies reviewed by Harper and Taatjes (10) show that Mediator is composed of four main protein modules, the head, middle, tail, and CDK module. Each of these modules in turn is composed of various polypeptides. The CDK module is believed to transiently interact with the core domains of Mediator but dissociates to allow recruitment of RNA pol II to the PIC. Both crystallographic and cryo-EM studies have been carried out to elucidate the structures of each of these modules, as well as the interactions of Mediator with GTFs, such as TFIIB and TFIID, and RNA pol II. These studies and cross-linking experiments show that polypeptides in the head and middle modules, interact directly with RNA pol II, particularly the C-terminal domain (CTD), whereas the tail module interacts with upstream activators. Just how Mediator communicates information from activators to the PIC and RNA pol II is a subject of intense investigation (reviewed by Harper and Taatjes (10)).

While Fig. 1 illustrates the “classical” view of an RNA pol II promoter element and other regulatory sequences, more recent studies have revealed striking complexity and diversity in transcription in eukaryotic cells. Although there are only ~20,000 protein-coding genes in the human genome, most of the genome (~60%) is transcribed, and much of this transcription comes from bidirectional transcription at gene promoters and enhancer elements caused by distinct PICs. As part of this

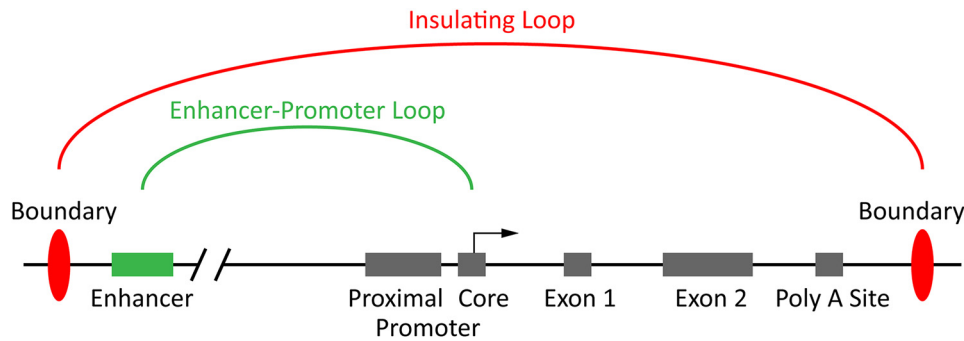


Figure 1. A typical regulated gene. A typical protein coding mammalian gene bears multiple regulatory regions including one or more enhancers and a promoter driving expression of a gene composed of multiple exons, introns, and a signal for polyadenylation. Enhancers are located usually 2–100 kb upstream or downstream from the promoter, sometimes within introns but occasionally downstream of the poly(A) site. Promoters are subdivided into proximal and core promoters. The proximal promoter is located within 2 kb upstream of the transcription start site (*arrow*). The core promoter is ~80–200 bp in length and encompasses the transcription start site (*arrow*). Proximal promoters and enhancers contain specific DNA sequence motifs, which bind combinatorial arrays of sequence-specific transcriptional activators that, in turn, recruit co-activators such as Mediator or EP300. The core promoter is composed of different combinations of a series of DNA elements including the TATA box, the INR, the DPE, and others (1). These DNA elements collectively bind to TBP and the TAFs, which tether the other general transcription factors, Mediator and pol II, at the start site. This complex of GTFs, pol II, and Mediator is commonly termed the pol II PIC. Chromatin loops form between the proteins bound at the enhancer and promoter during gene activation. The gene and its regulatory elements are often flanked by boundary elements or insulators, which in mammals typically bind to the sequence-specific factor CTCF-binding factor (CTCF). CTCF recruits the Cohesin complex, which catalyzes the formation of a chromatin loop encompassing the gene, the promoter, and its enhancers. This loop spatially sequesters or insulates the gene and its regulatory elements, preventing its enhancers from acting on the promoters of flanking genes and vice versa.

series, Meng and Bartholomew (11) review this complexity and provide insights into the possible regulatory roles of noncoding RNAs in their Minireview entitled “Emerging roles of transcriptional enhancers in chromatin looping and promoter-proximal pausing of RNA polymerase II.” Enhancer elements can be located at distant sites (Fig. 1), both upstream and downstream, from core promoters. Enhancers bind a variety of master transcription factors (see below) and recruit chromatin-modifying enzymes as well as the GTFs and RNA pol II to core promoters. Enhancers are characterized by hypersensitivity to digestion by DNase I, reflecting nucleosome-depleted DNA (just as at promoters), and by association of the adjacent nucleosomes with particular histone variants (*e.g.* H2AZ and H3.3) and particular histone post-synthetic modifications (*e.g.* H3K4me1 and H3K27ac). Bidirectional transcription of short-lived, noncoding enhancer RNA (eRNA) is a common feature of active enhancers. Meng and Bartholomew (11) review current models for how enhancers communicate with promoters of mRNA-coding genes, including tracking, scanning, and looping mechanisms. These different mechanisms appear to depend upon the distance between an enhancer and its regulated promoter. The proteins responsible for communication between enhancers and promoters include Mediator, Cohesin, and lineage-specific TFs. Meng and Bartholomew also review the evidence for a gene-regulatory role for eRNAs, including mediating chromatin modifications at promoters, and whether eRNAs control pausing of RNA pol II after initiation and the transition to productive elongation.

The “pioneer” transcription factors, one class of TFs that bind enhancers, are the subject of Mayran and Drouin’s Minireview entitled “Pioneer transcription factors shape the epigenetic landscape” (12). Pioneer TFs have the property of being able to bind to their cognate sites in the context of the nucleosome (13), whereas most transcription factors are unable to do so. The first described pioneer factor HNF3 (also known as FoxA), a winged-helix TF, was proposed to access the nucleosome by mimicking the binding of the linker histone H1 (14).

After binding, pioneer factors have been shown to recruit chromatin-modifying enzymes and ATP-dependent chromatin-remodeling factors, causing opening of enhancers and promoters for binding of additional transcription factors. Remarkably, pioneer factors can also influence DNA methylation, which is an epigenetic mark largely associated with gene silencing at promoters. Pioneer TFs are essential for patterns of cellular differentiation and activation of lineage-specific genes. Mayran and Drouin review the current understanding of how pioneering factors access condensed chromatin and mediate chromatin opening and DNA methylation, as well as how these factors are important for cell lineage determination (12). One recent example of the power of pioneer TFs is the reprogramming of fibroblasts to induced pluripotent stem cells, where the epigenetic landscape of somatic cells (fibroblasts) is changed by the pioneer TFs to the induced pluripotent stem cells, with concomitant changes in gene expression. Although pluripotency TFs may not share the same mechanism of chromatin binding as HNF4, a common theme among the pioneering TFs is that weak binding to nucleosomal sites is accompanied by a transition to stable binding and chromatin remodeling, allowing the binding of other TFs and enhancer activation (12).

Chromatin modification states are also associated with gene silencing, and one important histone mark associated with repression is methylation of lysine 27 of histone H3, which is mediated by a multisubunit complex called polycomb repressive complex 2 or PRC2. Important roles for PRC2 have been documented in X chromosome inactivation, imprinting, and cell fate maintenance, especially stem cell fate. The evolutionary conserved PRC2 complex comprises four subunits: SUZ12, EED, EZH1 or EZH2, and a histone-binding subunit. EZH2 harbors the histone methyltransferase activity of PRC2. PRC2 can both methylate H3K27 (mono-, di-, and trimethylation) and also bind to trimethylated H3K27, leading to spreading of this modification and hence repression along regions of chromatin. In their Minireview, entitled “Structure, mechanism, and regulation of polycomb repressive complex 2,” Moritz and

Triebel discuss the importance of the PRC2 complex in cellular differentiation and development, as well as the high-resolution structural studies that have been performed on this complex and its subunits (15). The results of these studies have yielded valuable insights into the catalytic mechanism of the histone methyltransferase subunit EZH2, its allosteric regulation, and development of novel classes of methyltransferase inhibitors. Structural studies reveal that these pyridone inhibitors bind to the SET domain of EZH2 and compete with binding of *S*-adenosylmethionine, the methyl donor in the methyltransferase reaction. These compounds and other EZH2 inhibitors may have benefit as cancer therapeutics because PRC2 overexpression and mutations are associated with a variety of human cancers. Also, mutation of H3K27 to methionine has been associated with pediatric brain cancers and shown to widely inhibit PRC2 activity (16), demonstrating the critical importance of the PRC2 complex in human health and disease.

The genome of mammalian male germ cells (sperm) is packaged in a manner that is substantially different from that of somatic cells and even oocytes. Early studies found that essentially all of the histone proteins in the developing spermatocyte are replaced by smaller basic proteins called protamines, and hence the epigenetic information contained in histone post-translational modifications was thought to be lost in male gametes. Contrary to early work, more recent studies suggest that up to ~8% of sperm chromatin is packaged in nucleosomes. Using current genome-wide mapping techniques, a number of labs have probed histone and transcription factor occupancy and DNA methylation in mammalian sperm. For example, one study showed that many promoters in mouse sperm are flanked by well-positioned nucleosomes marked by active histone modifications and that some transcription factors are also retained (17). In their Minireview entitled “Not just heads and tails: The complexity of the sperm epigenome” (18), Gold, Jung, and Corces provide an up-to-date overview of the epigenetic landscape in developing sperm, suggesting that sperm do carry regulatory information for gene expression during the early stages of zygote development. This information resides not only in histone post-synthetic modifications but also in three-dimensional chromatin architecture. The phenomena of transgenerational inheritance may be explained, at least in part, by the preservation of chromatin marks in male germ cells (reviewed in Refs. 17 and 19). The Editors of the *Journal* hope that this Thematic Minireview Series will spark new directions in research in chromatin and transcription, and lead to important new publications in the *Journal*.

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