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Review

Decoding transcriptional enhancers: Evolving from annotation to functional interpretation

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ABSTRACT

Deciphering the intricate molecular processes that orchestrate the spatial and temporal regulation of genes has become an increasingly major focus of biological research. The differential expression of genes by diverse cell types with a common genome is a hallmark of complex cellular functions, as well as the basis for multicellular life. Importantly, a more coherent understanding of gene regulation is critical for defining developmental processes, evolutionary principles and disease etiologies. Here we present our current understanding of gene regulation by focusing on the role of enhancer elements in these complex processes. Although functional genomic methods have provided considerable advances to our understanding of gene regulation, these assays, which are usually performed on a genome-wide scale, typically provide correlative observations that lack functional interpretation. Recent innovations in genome editing technologies have placed gene regulatory studies at an exciting crossroads, as systematic, functional evaluation of enhancers and other transcriptional regulatory elements can now be performed in a coordinated, high-throughput manner across the entire genome. This review provides insights on transcriptional enhancer function, their role in development and disease, and catalogues experimental tools commonly used to study these elements. Additionally, we discuss the crucial role of novel techniques in deciphering the complex gene regulatory landscape and how these studies will shape future research.
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1. Introduction

Easily accessible, inexpensive DNA sequencing technologies have led to fundamental changes in our understanding of gene regulation and genome function. Although closer attention has traditionally been paid to protein-coding sequences, recognition of the importance of non-coding DNA segments has shifted our focus to the remaining ~98% of the genome. Numerous large, multi-center efforts such as the Encyclopedia of DNA Elements consortium (ENCODE) [1] and the Roadmap Epigenomics Project [2] have helped to make significant progress towards assigning function to the non-coding genome. The further discovery of diverse, functional, non-coding elements in genomes has gained increased attention as we have begun to more fully appreciate the roles of these distinct regulatory features (i.e. insulators, silencers, enhancers, etc.) and associated non-coding RNAs (i.e., siRNA, lncRNA, eRNAs, etc.; reviewed in Refs. [3–5]) in transcriptional control and higher-order genome architecture. These non-coding elements confer an added level of genetic control by regulating the spatial and temporal expression of genes, as well as the degree of transcriptional activation.

Enhancers are an important class of regulatory elements that up-regulate or "enhance" the expression levels of target genes. A hallmark of enhancers is their ability to communicate across long distances, as many as hundreds of kilobases, to direct gene expression [6,7]. Despite the identification of the first eukaryotic enhancers decades ago [8–10], the ubiquitous use of these regulatory elements is becoming more appreciated [11]. This focused look at regulatory elements has been greatly facilitated by the advent of next generation sequencing (NGS) platforms and associated functional genomic approaches for large-scale, genome-wide annotation. However, we are currently reaching the horizon of another revolution as new, highly efficient genome editing technologies have become available. These innovative methodologies will enable the first large-scale, functional interpretation of genome function and structure, and will allow for the elucidation of the underlying molecular mechanisms governing coordinated, genome-wide enhancer activity across diverse biological contexts. In this review, we describe the current understanding of enhancer function, including a brief discussion of the role of these elements during development and in disease susceptibility. We further delineate diverse, genome-wide experimental approaches that are available to researchers and conclude with how these new technologies will drive future advances in the field.

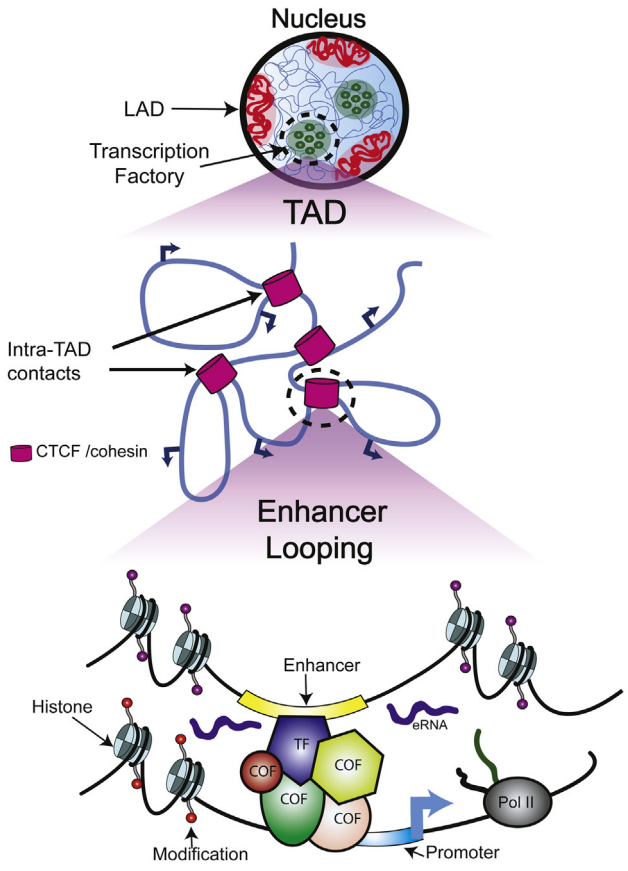

Fig. 1. Multiple levels of genome architecture and gene regulation. A schematic of distinct levels of gene regulatory control and nuclear architecture is given. Structural features of the nucleus including lamina associated domains (LADs) and transcription factories are shown. A topologically associated domain (TAD) within a transcription factory is given below. Intra-TAD enhancer-promoter contacts are displayed. A closer look at enhancer looping between intra-TAD enhancer-promoter interactions is given in the last panel. Chromatin state near active regulatory elements and promoter sequences are altered through histone modifications and correlate with enhancer state as well as gene expression levels. Enhancer elements expressing eRNAs and bound by transcription factors (TF) and associated transcriptional cofactors and chromatin remodeling enzymes (COF) associate with distal promoter sequences through long-range looping interactions, leading to increased expression of target genes.

2. brief view of enhancer function

2.1. Enhancer sequence structure directs its function

The specific DNA sequence composition of an enhancer contains the information necessary for imparting its composite functional effect [8]. Notably, although enhancers maintain gene regulatory functions, the evolutionary constraints placed on their sequences are less stringent than those observed in protein coding loci and gene promoters [12–14]. In fact, alteration of enhancer sequences is thought to occur rapidly and drive much of the phenotypic divergence observed between species (reviewed in Ref. [15]). The nucleotide changes that occur within enhancers during evolution are thought to alter the binding affinities of specific transcription factor (TF) proteins [16], and may even generate or ablate entire binding sites or enhancer elements. Multiple studies have provided examples in which alteration of enhancers at the sequence level lead to phenotype differences during evolution [12,13,17–20]. For instance, a set of alterations in enhancer sequences is thought to explain the differences in human and chimpanzee forebrain structure [20]. Single nucleotide changes in enhancers are also sufficient to alter phenotypes in *Drosophila* [21–23]. Despite the pervasive use of enhancers to regulate gene expression, a large knowledge gap concerning the complexities of enhancer mechanisms exist. This knowledge gap renders prediction of functional enhancers and their mechanisms difficult. Additionally, predicting the functional effects of different sequence variants within enhancers is further complicated by the recently described phenomenon that pairs of factors cooperatively binding to a DNA segment influence motif preference and binding kinetics [24]. Furthermore, although enhancer function is traditionally believed to be independent of DNA strand orientation, recent studies have challenged this notion [23,25].

The occupancy of specific TF proteins and associated cofactor proteins generate macromolecular complexes involved in transcriptional regulation (Fig. 1; reviewed in Ref. [26]). These proteins also serve as a molecular bridge by physically tethering enhancers to target gene promoters through long-range contacts (referred to as the "looping model"). However, additional models have been proposed, including tracking and variations of tracking [27,28]. Long-range looping contacts are believed to activate target gene transcription by increasing the local concentration of the RNA

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