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Review

Understanding the chromatin remodeling code

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ABSTRACT

Remodeling a chromatin structure enables the genetic elements stored in a genome to function in a condition-specific manner and predisposes the interactions between *cis*-regulatory elements and *trans*-acting factors. A chromatin signature can be an indicator of the activity of the underlying genetic elements. This paper reviews recent studies showing that the combination and arrangements of chromatin remodeling marks play roles as chromatin code affecting the activity of genetic elements. This paper also reviews recent studies inferring the primary DNA sequence contexts associated with chromatin remodeling that suggest interactions between genetic and epigenetic factors. We conclude that chromatin remodeling, which provides accurate models of gene expression and morphological variations, may help to find the biological marks that cannot be detected by genome-wide association study or genetic study.

Contents

1. Introduction

A genome stores all of the genetic information of an organism. Eukaryotic genome is packaged in a nucleus as a chromatin structure, which is a complex of DNA with proteins and RNAs. Chromatin structure can tightly pack genomes and restricts the interaction of DNA segments with protein factors. On the other hand, remodeling chromatin structure can allow proteins to interact with specific genomic DNA segments. Recent studies show that chromatin structure is dynamically remodeled. Specific chromatin structures are recognized by protein factors involved in transcription and DNA replication. In this way, remodeling chromatin structure controls DNA replication and transcription in a condition-specific manner. Therefore, understanding the specific

Abbreviations: H3K4me3, tri-methylations at histone H3 Lysine 4; ChIP-seq, chromatin immunoprecipitation and sequencing; siRNA, small interference RNA.

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pattern of chromatin remodeling affecting the activity of genetic elements may enable us to predict cellular status.

Chromatin's basic structural unit is a nucleosome consisting of a ~147 bp DNA segment and histone octamers which consist of pairs of H2A, H2B, H3 and H4. The eukaryotic chromatin structure can be remodeled by at least five mechanisms (reviewed in [1]): (1) the nucleosome formation, entailing tendency of nucleosome formation, nuclesome occupation levels, and arrangement of nucleosomes; (2) adding covalent modifications to histones; (3) replacing histones with histone variants [2,3]; (4) methylations at DNA cytosine; and (5) small and long non-coding RNAs. All of these chromatin remodeling processes change constituent, condensation, accessibility, and interacting proteins of the chromatin structures. Therefore, chromatin remodeling marks reflecting chromatin structural modification status include DNA methylations, nucleosome formation, proportion of nucleosomes containing histone variants, and histone modifications such as histone methylations, acetylations, ubiquitylations, and phosphorylations. By the action of ATP-dependent chromatin remodelers, the combination of specific chromatin modification marks are arranged and interact with specific proteins involved in transcription, DNA replications, and DNA repair [4,5]. Therefore, distinct arrangement of chromatin remodeling marks may play roles as chromatin remodeling code.

This paper focuses on the data analytics for understanding features of chromatin remodeling processes at the primary organization level–nucleosome, histone variants, histone modifications, DNA methylation and RNA generations–and their coordination. We first review the significance of chromatin remodeling in epigenetics and gene regulation in response to development and environmental cues. We extend the ideas to the chromatin remodeling code hypothesis; arrangement of chromatin remodeling marks can partly regulate the function of genetic code. We then discuss several strategies to decipher chromatin signatures for prediction and controlling the gene expression and plant traits. Our objective is to apply chromatin codes to the field of genome engineering for crop improvement and human health. There are excellent reviews on chromatin remodeling and epigenetics [1,2,6,7]. Rather than reviewing detailed molecular mechanisms of chromatin remodeling, we focus on the general methods for analyses of genome-wide chromatin remodeling measurements in eukaryotes including plants. We then focus on the current literature inferring the primary DNA sequence contexts associated with chromatin remodeling that suggest interactions between genetic and epigenetic factors.

2. Chromatin remodeling mechanisms

2.1. Chromatin remodeling as a main epigenetic mechanism

Various definitions of epigenetics originated from "study how genes interact with environment and result in development and phenotypes" by Waddington in 1942 [8]. Currently, epigenetics generally refers to the study of reversible and heritable morphological variations not caused by DNA sequence changes. Chromatin remodeling may be a major molecular mechanism of epigenetics. Sometimes, epigenetic trait is defined as "a stably heritable phenotype resulting from changes in a chromosome without alterations in the DNA sequence [9]." First, chromatin remodeling does not change the underlying genome sequence, although it is reversible due to the activity of chromatin modifiers and environmental changes. Second, chromatin remodeling is a reversible process by the action of chromatin modifiers. Eukaryotic genomes contain multiple copies of chromatin modifiers. Three families of histone acetyltransferases and 3 families of histone deacetylases are conserved in *Arabidopsis thaliana*, *Saccharomyces cerevisiae*, *Schizosaccharomyces pombe*, *Caenorhabditis elegans*, and *Drosophila melanogaster* [10,11]. Third, the cell-type specific chromatin remodeling pattern is maintained during development and involved in gene expression regulation in developmental processes [12]. Chromatin remodeling processes are reversible and therefore play an important role in the transcriptional regulation associated with developmental programs and environmental conditions. In conclusion, chromatin remodeling may be a fundamental principle of epigenetics.

Gene expression is highly regulated by the interactions among *cis*-regulatory elements and *trans*-acting factors. Debate is ongoing whether *cis*- or *trans*-regulation is the primary source of morphological variations within and between species in genetics [13,14]. In *cis*-regulation, the *cis*-regulatory elements encoded in the same DNA strand direct the specific expression of the target genes. Sequence variations in *cis*-regulatory elements change the affinity of the genetic elements with protein factors and differentiate the regulation of target gene expression. In *trans*-regulation, proteins or RNAs encoded in other DNA strands interact with the target loci and regulate the expression of the target genes. Sequence variation in *trans*-regulatory loci can change target specificities or expression levels of trans-acting factors which then changes the expression levels of the target loci. Remodeling the chromatin structure on top of the genes and genetic elements in part can affect the interactions among *cis*- and *trans*-regulatory factors without changing the DNA.

2.2. Dynamics of chromatin remodeling in response to environmental stimuli

Chromatin is remarkably dynamically modulated in response to pathogen infection and environmental changes. The signaling networks induce chromatin modifiers that facilitate the fast gene expression changes involved in defensive systems. For example, virus-derived double-strand RNAs in plants will activate small RNA generation and RNA-dependent DNA methylations, and eventually silence the virus-derived RNA transcription [6]. In *Arabidopsis* and rice, pathogen infection and salicylic acid (SA) hormone can induce DNA methylation changes around genes involved in biotic stress responses [15]. These examples show that DNA methylation can change as fast as gene expression changes in response to pathogen infection. However, the kinetics of chromatin remodeling has not been well investigated.

In *Arabidopsis*, the regulation of flowering in response to environmental and developmental cues is accompanied by chromatin remodeling (reviewed in [16]). In *Arabidopsis*, cold temperature in winter induces expression of VIN3, a histone methyltransferase resulting in tri-methylations at Lysine 27 of H3 histone (H3K27me3) and methylations at Lysine 9 of H3 histone (H3K9me). VIN3 induction by cold increases H3K27me3 levels at the 5′ end of the FLC gene, a repressor of flowering [17]. FLC is repressed by H3K27me3, and this accelerates flowering after cold treatment [18]. Even after the plants are removed from the cold state, the chromatin remodeling states repressing FLC expression are stably maintained.

2.3. Encryption of parental environmental signals in descendant's genomic DNA

Parental environmental factors can affect the embryo chromatin structure and the morphology of progeny during development. In mice, high exposure to the mother's xenobiotic chemical bisphenol A (BPA) leads to the fetus's hypo-methylation of the cytosines at Agouti gene [19]. This hypo-methylation increases the risk of chronic adult diseases during development of the progeny [20]. In *Arabidopsis* seeds, embryo-nourishing endosperm genome is demethylated by DEMETER (DME) but embryo genome is hyper methylated [21,22]. This leads to silencing of transposable elements