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Epigenetic histone modifications and master regulators as determinants of context dependent nuclear receptor activity in bone cells ☆

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ABSTRACT

Genomic annotation of unique and combinatorial epigenetic modifications along with transcription factor occupancy is having a profound impact on our understanding of the genome. These studies have led to a better appreciation of the dynamic nature of the epigenetic and transcription factor binding components that reveal overarching principles of the genome as well as tissue specificity. In this minireview, we discuss the presence and potential functions of several of these features across the genome in osteoblast lineage cells. We examine how these features are modulated during cellular maturation, affect transcriptional output and phenotype, and how they alter the ability of cells to respond to systemic signals directed by calcemic hormones such as 1,25-dihydroxyvitamin D_3 and PTH. In particular, we describe recent experiments which indicate that progressive stages of bone cell differentiation affect RUNX2 binding to the genome, modify and restrict patterns of gene expression, and dramatically alter cellular response to the vitamin D hormone. These studies expand our understanding of mechanisms that govern steroid hormone regulation of gene expression, while highlighting the increasing complexity that is evident relative to these basic cellular processes. The results also have profound implications with respect to the impact of skeletal diseases on transcriptional outcomes as well.
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Contents

Introduction

Chromatin immunoprecipitation (ChIP), coupled initially to tiled oligonucleotide microarrays (ChIP-chip) and subsequently to massively parallel deep sequencing methods (ChIP-seq), together with numerous additional genome-scale techniques, has enabled investigators to annotate cellular genomes in ways fully unappreciated less than a decade

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earlier [1]. While it has long been known that histones represent a particular focus of post translational modification, efforts by numerous groups including those of the ENCODE (Encyclopedia of DNA Elements) Consortium have focused upon both the identification of such modifications (marks) and elucidation of their structural and functional significance relative to the control of gene expression and other processes [2]. These and additional efforts have led to an appreciation of the cell-type specific nature of histone modifications, the dynamic nature of their appearance during cellular development and differentiation, and the realization that their presence frequently denote specific functional attributes. Perhaps most importantly, the presence of many of these histone modifications or combinations thereof have been found to be enriched at sites of specific regulatory significance, whether as indicators of nucleosome presence, the location of promoters or of active enhancers [3–5]. In addition, many of these marks provide insight into the functional state of transcription at specific genes, indicating whether genes are silenced, poised for activation or are actively being transcribed. Aside from the importance of these marks as predictors of the unique activities at genes of interest, their presence has accelerated an already emerging field of transcriptional and genomic enzymology associated with the exploration of chromatin active regulators and their capacity to dynamically impose or erase these marks, or to recognize and interpret these marks, presumably to affect downstream functions associated with the genome [6,7]. Perhaps most importantly, the presence of many of these marks can now be overlaid across regions with small nucleotide polymorphisms (SNPs) associated with human disease, further supporting the idea that small changes in sequence, often times highly remote relative to neighboring target genes, can be associated with altered transcriptional output [8,9]. The evidence for these functional linkages to minor changes in DNA sequence is rapidly accumulating.

In this brief review, we explore the ability of certain histone modifications to identify site-specific structural and functional features of genes expressed within the osteoblast lineage and to efficiently highlight regions that either contain pre-bound transcription factors or contain binding sites to which conditional transcription factors can be recruited. We also explore the dynamic nature by which these marks are not only altered during osteoblast differentiation, but influence the binding of key factors such as the master regulator RUNX2 and the inducible receptor for vitamin D (VDR) thus altering the transcriptome of cells as they become differentiated. The dynamic nature of these modifications suggests that the primary determinants of cellular response are not limited to changes in the expression of transcription factors and their interaction with the genome, but also include changes to the target genome as well. The importance of this issue is highlighted by the fact that dynamic changes similarly occur to cellular genomes as a function of progression of diseases such as in cancer as well as throughout differentiation in the skeleton [10,11].

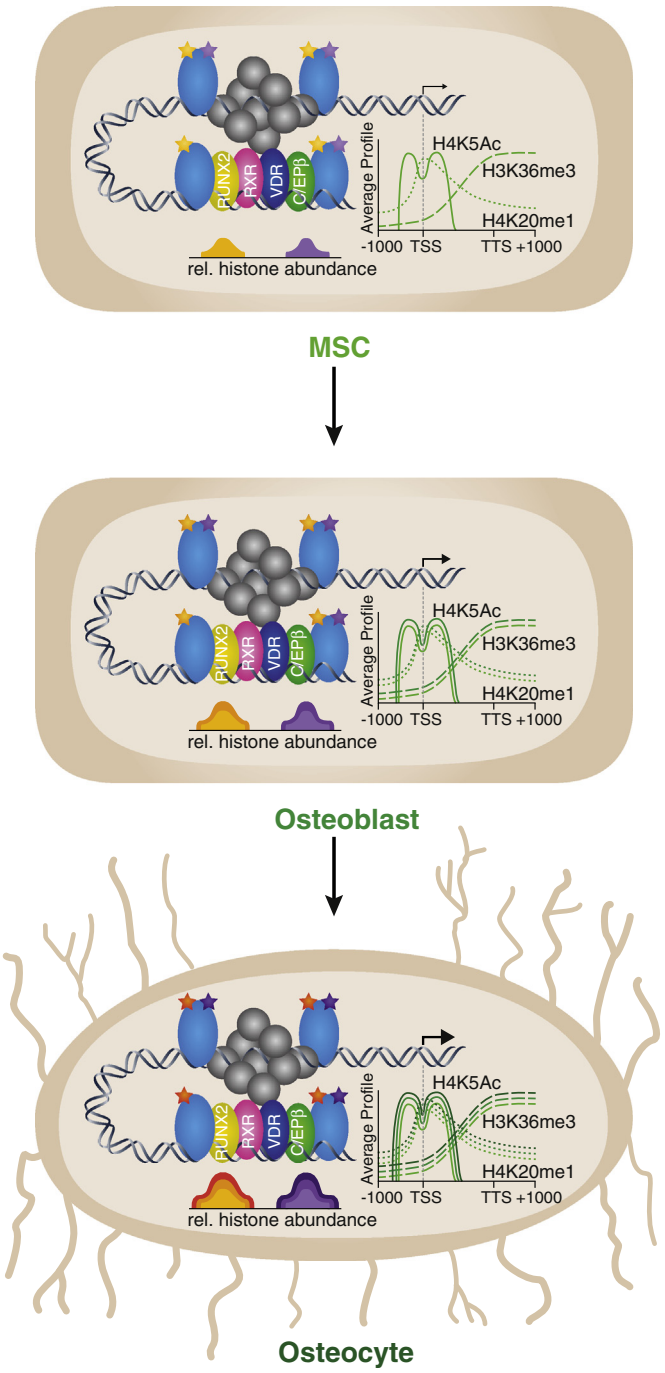

Fig. 1. Modulation of transcriptional output during the MSC to osteocyte transition is correlated with epigenetic abundance at enhancers and across the gene body. A model of gene up-regulation is shown schematically with associated changes in several representative histone (light blue) modifications (yellow and purple stars) and their quantitated abundance (bottom peaks) at osteoblast lineage enhancers marked by RUNX2 (yellow), RXR (pink), VDR (blue), and C/EBPβ (green). CEAS (Cis-regulatory element annotation system) analyzed histone modifications (right side) for H3K36me3 (dashed line), H4K20me1 (dotted line), and H4K5ac (solid line) across the gene body are also associated, and increased, with gene expression changes during this transition. The transcriptional start site is depicted by a black arrow (arrow size represents transcriptional output). (See references [15,17,31]).

Histone marks and differentiation

The structural/functional significance of known histone marks

A considerable effort over the past few years has led to the observation that epigenetic marks, whether at histones or on DNA, are dynamic and highly cell-specific, indicating that they impose strong functional consequences on gene expression profiles and are thus linked directly to differences in cellular phenotype [12]. These can be seen, for example, in the unique transcriptomes of cells of the osteoblast lineage relative to those of many other lineages. However, these marks also identify common structural/functional features of genes in all cell types, highlighting their utility in defining domains at individual gene loci that represent regulatory regions (enhancers and repressors), transcriptional start sites, promoters, transcription and elongation functions, and marks that are indicators of overall chromatin condensation and activity [12]. In many cases, the assignation of a particular common feature such as an enhancer at a gene requires the integration of more than one mark (or the absence of a mark), particularly as it relates to regions of regulatory significance [13,14]. Using ChIP-seq analysis, we and others have shown that the presence of individual histone marks is particularly evident across genes that are expressed uniquely in the osteoblast lineage

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