Bone xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Bone

journal homepage: www.elsevier.com/locate/bone

Review

Multiple levels of epigenetic control for bone biology and pathology

Martin Montecino [a,*], Gary Stein [b,*], Janet Stein [b], Kaleem Zaidi [b], Rodrigo Aguilar [a]

[a] Center for Biomedical Research and FONDAP Center for Genome Regulation, Faculty of Biological Sciences and Faculty of Medicine, Universidad Andres Bello, Avenida Republica 239, Santiago, Chile

[b] Department of Biochemistry and Vermont Cancer Center, University of Vermont College of Medicine, 89 Beaumont Avenue, Burlington, VT, USA

ARTICLE INFO

Article history:
Received 13 March 2015
Accepted 13 March 2015
Available online xxxx

Keywords:
Histone modifications
DNA methylation
Intanuclear domains
RUNX2 epigenetics
Mitotic bookmarking

ABSTRACT

Multiple dimensions of epigenetic control contribute to regulation of gene expression that governs bone biology and pathology. Once confined to DNA methylation and a limited number of post-translational modifications of histone proteins, the definition of epigenetic mechanisms is expanding to include contributions of non-coding RNAs and mitotic bookmarking, a mechanism for retaining phenotype identity during cell proliferation. Together these different levels of epigenetic control of physiological processes and their perturbations that are associated with compromised gene expression during the onset and progression of disease, have contributed to an unprecedented understanding of the activities (operation) of the genomic landscape. Here, we address general concepts that explain the contribution of epigenetic control to the dynamic regulation of gene expression during eukaryotic transcription.

This article is part of a Special Issue entitled Epigenetics and Bone.

Contents

Introduction

There is increasing appreciation for the contributions of genetic and epigenetic regulation to skeletal biology and evidence is accruing for perturbed epigenetic mechanisms in skeletal disease. Once principally restricted to DNA methylation and a limited series of post-translational histone modifications, the repertoire of epigenetic mechanisms is rapidly expanding with growing insight into both molecular and biochemical parameters of biological processes that are epigenetically mediated. With comprehensive understanding for the scope of epigenetic impact on skeletal gene expression and compromised epigenetic mechanisms in congenital and acquired skeletal disorders, the potential for epigenetic-based therapeutic targets is precipitously emerging.

* Corresponding authors.
E-mail addresses: mmontecino@unab.cl (M. Montecino), gary.stein@uvm.edu (G. Stein).

http://dx.doi.org/10.1016/j.bone.2015.03.013
8756-3282/

There are a number of authoritative reviews on specific dimensions of epigenetic control that collectively provide a comprehensive treatment of epigenetic biochemistry and regulatory biology [1–7]. These reviews effectively consider the challenges and opportunities encountered when interrogating epigenetic mechanisms within the context of normal cells, skeletal genesis, bone remodeling and bone metabolic disorders that are directly linked to genetic or acquired perturbations or are consequential to a spectrum of diseases and/or treatments that are standards of care. Here, we will illustrate options for the power of epigenetic mechanisms to support transformative insight into skeletal biology and pathology. We will emphasize the convergence of skeletal epigenetic mechanisms that can provide insight into regulatory networks that are pivotal for regulation of gene expression. Epigenetic control will also be explained in relation to the dynamic architectural organization of regulatory machinery from the perspective of nuclear structure-gene expression relationships. Similarly, we will consider extrapolations from the biology of skeletal epigenetic control to paradigm shifting options with the diagnosis and treatment of bone disease.

Multiple dimensions to epigenetic control

Histone modifications

From a historical perspective, epigenetic control was initially confined to DNA methylation (reviewed in [8,9]) and three post translational histone modifications designated acetylation (reviewed in [10,11]), methylation (reviewed in [12,13]) and phosphorylation (reviewed in [14]) with the assumptions that acetylation and phosphorylation are reversible while methylation is not under biological conditions. In the past several years, there has been a significant expansion in understanding the scope of complexity to histone acetylation, methylation and phosphorylation, with compelling evidence for the reversibility of these three classes of histone modifications. Table 1 summarizes the various enzymatic modifications that occur on specific histone protein residues and their functional implications in regulating transcription of a gene. Beyond expanded insight into the histone subtypes that are post-translationally modified and specific amino acid residues that undergo post-translational modifications, there has been significant progress in identification and characterization of the enzymology for histone modifications, both the addition and removal of acetate, methyl and phosphate groups [15,16].

In addition to expanding the understanding of the enzymology of the histone modifications, compelling evidence is emerging for association of particular histone modifications and specific histone modifying enzymes with specific biological circumstances, including developmental stages, cell cycle progression and disease-related changes [17–24]. The sequence of recruitment and engagement of the regulatory components remains to be determined and identification of the rate limiting factors for fidelity of histone modification is open ended. Stochastic relationships between components of the histone modification machinery can be mechanistically informative. Addressing these parameters of control will provide insight into the metabolism of histone modifications.

The recent observation of epigenetically bivalent genes in stem cells, that is, genes including both activation and suppression histone "marks" (H3K4me3 and H3K27me3, respectively), provide an additional dimension to histone-mediated epigenetic regulation (for a recent review, see [25]). The restriction of bivalency to pluripotency is rapidly evolving to recognition of a broader presence. While the functional significance for bivalency needs to be further established, a viable possibility is that the simultaneous representation of activating and suppressing histone modifications at a particular promoter poises the downstream gene to subsequently acquire an epigenetic landscape. In response to developmental, phenotypic or physiological regulatory queues, conditions are established leading to either gene transcription or silencing and resulting in a committed cell phenotype. Recent evidence supports cell cycle-stage specific bivalency that can reinforce regulatory competency for responsiveness to regulatory signals required for establishing, sustaining and/or modifying phenotype ([26,27], and Grandy R et al., submitted manuscript).

Mechanistic contributions of histone modifications to biological control are emerging from developments in technologies able to analyze whole genomes. These approaches include chromatin immunoprecipitation using well characterized antibodies to most histone modification, followed by massive parallel sequencing (ChIP-Seq) or a ChIP-on-chip procedure to identify interacting proteins with the enzyme that mediates the histone modification. The RNA-seq identifying the cell's gene expression profile allows determining histone modifications profiles on genes or for genome-wide screens to comprehensively establish

Table 1
Transcription-associated covalent histone modifications.

Residue	Modification	Relation with gene expression	Localization
Histone H3			
K4	me1	Inactive or active [74]	Widespread [75]; Enhancers [74,76]
	me2	Active [77,78]	TSS [75]
	me3	Active [75–80]; inactive (poised) [81,82]	TSS [75,76,80]
R8	Me	Inactive [83,84]	
K9	Ac	Active [75,77,79,80,85–87]	TSS [75,80,85]
	me3	Inactive [79,82,88,89]	Heterochromatin [90]
S10	P	Active [91,92]	TSS [92]
K14	Ac	Active [75,77,85–87]	TSS [75,85]
K16	Ac	Active [79]	
R17	me1/me2-asym	Active [93]	
K18	Ac	Active [87,93]	
K20	me1	Inactive [88]	
K23	Ac	Active [87,93]	
K27	Ac	Active [74]	Enhancer [74]
	me3	Inactive [79,81,82,88,89]	
K36	me3	Active [80,82,85]; hallmark of elongation [79,85]	Coding [80]
K79	me1	Inactive [94]	TSS or Intergenic [94]
	me2	Active [94]	Coding [80]; TSS [94]
	me3	Active [94]	TSS [94]
Histone H4			
R3	me2 (sym)	Inactive [83,95,96]	TSS [95]
K5/K8/K12/K16	Ac	Active [78]	Widespread [75]
K20	me3	Inactive [82]	

Abbreviations: *ac*: acetylation; *K*: lysine residues; *me*: methylation, where me1, 2, 3 denotes mono-, di-, or trimethylation; *P*: phosphorylation; *R*: arginine residue; (*a*)*sym*: (a)symmetrical; *TSS*: transcription start site.

Please cite this article as: Montecino M, et al, Multiple levels of epigenetic control for bone biology and pathology, Bone (2015), http://dx.doi.org/10.1016/j.bone.2015.03.013