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PTH Signaling and Epigenetic Control of Bone Remodeling

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Abstract

As our understanding of the mechanisms that govern bone development advance, the role of epigenetic modifications in these processes become increasingly evident. Interestingly, in parathyroid hormone (PTH)-induced bone metabolism and remodeling, recent evidence shows that PTH signaling employs a particular facet of the epigenetic machinery to elicit its desired effects. In this review, we briefly discuss the known epigenetic events occurring in cells of the osteoblast lineage. More specifically, we elaborate on current findings that reveal the utilization of histone deacetylating enzymes (HDACs) in PTH-regulated modulation of gene expression in bone.

Keywords

PTH; HDAC; transcriptional regulation; bone remodeling

Introduction

In the past several years, studies in the field of epigenetics have illuminated a wide array of modifications that occur in the genome. More recently, the discovery of mechanisms such as miRNA binding [1] and nucleosome positioning [2] have yielded surprising new ways in which the genome can be modified. However, the two most prominent modifications, DNA methylation and post-translational modification of histones, have been extensively studied and thus, much information can be gleaned with respect to bone [3,4]. Here, we focus on a specific subset of histone modifying enzymes, histone deacetylases (HDACs), that work in co-repressor complexes to modify chromatin structure and genomic availability and as discussed below, play a crucial role in PTH-regulated gene expression.

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Compliance with Ethics Guidelines

Human and Animal Rights and Informed Consent

This article does not contain studies with human subjects performed by the authors. The article does contain studies with animals for which two of the authors were authors. These studies were performed following protocols approved by NYU Institutional Animal Care and Use Committee (IACUC).

Conflict of Interest

Florante Ricarte and Teruyo Nakatani declare that they have no conflict of interest.

Parathyroid hormone (PTH) is an 84-amino acid peptide hormone which acts as a vital regulator of calcium ion homeostasis and mediator of bone remodeling [5]. It is synthesized as a prepropeptide in the chief cells of the parathyroid glands and undergoes cleavage and transit through the endoplasmic reticulum and lastly, is stored in secretory vesicles [6,7]. The synthesis and release of PTH are governed by the calcium-sensing receptor found on the plasma membrane of gland cells. This mechanism of calcium detection is highly sensitive, as minor changes in Ca^{2+} lead to large changes in PTH [8]. When serum Ca^{2+} levels are low, PTH is quickly exocytosed to restore a strict serum Ca^{2+} concentration of 1.1–1.3mM. Additionally, serum phosphate, $1,25(OH)_2$ vitamin D_3, and FGF23 are also able to modify PTH expression and secretion. Since phosphate is able to bind calcium, its presence in serum can result in a decrease in serum calcium, which promotes PTH secretion. Also, phosphate is able to stabilize PTH mRNA through a stabilizing complex (AUF1/UNR) that binds to the 3'-UTR of PTH [9]. $1,25(OH)_2$ vitamin D_3 and its receptor, VDR, are able to bind regulatory elements in the PTH gene promoter and block transcription of PTH [10,11]. Lastly, FGF23 acts with coreceptors FGFR1c and α-Klotho to directly reduce PTH mRNA levels, as well as PTH secretion [12].

PTH acts through its cognate receptor, PTHR1, a family B G protein-coupled receptor expressed primarily on osteoblasts and kidney cells [13]. PTHR1 mainly signals by coupling with the Gαs/adenylyl cylase/cAMP/protein kinase A (PKA) pathway, but is also able to couple to Gαq/phospholipase C (PLC)/inositol trisphosphate/cytoplasmic Ca2+/protein kinase C (PKC) pathway [14]. The first 34 residues of PTH are able to recapitulate the biological activity of the full length, mature polypeptide. Structurally, the C-terminus of PTH (1–34) interacts with the amino terminal, extracellular domain of PTHR1, while the N-terminus interacts with the transmembrane helices and extracellular loops [15]. Similarly, parathyroid hormone-related protein (PTHrP) binds PTHR1 with the same affinity, but at different conformations of PTHR1 [16, 17]. It bears homology with PTH in the N-terminal 13 amino acids, which are involved in the activation of PTHR1, and due to this, PTHrP is being explored as an alternative to PTH [18].

PTH Signaling in Bone

In order to utilize the calcium-rich bone matrix for maintenance of serum Ca^{2+} levels, the physiological actions of PTH on bone are largely catabolic. Through its actions on osteoblasts and osteocytes, PTH is able to indirectly activate osteoclasts and promote bone resorption. One of the major pathways utilized in PTH-induced resorption is the receptor activator of nuclear factor-kappa B ligand(RANKL)/Rank/osteoprotegerin(OPG) system. RANKL binds its cognate receptor, RANK, which is found on the osteoclast surface, to induce osteoclastogenesis and osteoclast activation, subsequently resulting in bone resorption [19,20]. To counter these effects, osteoblasts are able to express OPG, a soluble decoy receptor, to inhibit RANKL binding to RANK on osteoclasts and in doing so, decreases bone resorption [21]. PTH has been found to modulate this ratio in differentiating osteoblasts by suppressing OPG expression in early osteoblasts and increasing RANKL expression in mature osteoblasts, which ultimately results in an increase in bone resorption [22]. Additionally, previous reports revealed that the expression and enzymatic activity of matrix metalloproteinase-13 (MMP-13), an enzyme responsible for the degradation of bone

extracellular matrix, are induced by PTH [23,24]. MMP-13 is a complex secondary response gene and its activation is dependent upon Runx2 and Jun/Fos, as well as several phosphorylation events executed by PKA. Prior work in our laboratory has found that the PTH regulatory region lies 148bp upstream of the transcriptional start site [25], but more recent studies reveal enhancer regions −10, −20, and even −30kb upstream of the Mmp13 promoter and are utilized by VDR, C/EBPβ, and Runx2, respectively [26].

Conversely, PTH is also able to exert anabolic effects on bone. This was revealed through the study of sclerostin, a glycoprotein secreted mainly by osteocytes. Encoded by the SOST gene, the main function of sclerostin is to inhibit bone formation through inhibition of canonical Wnt/β-catenin osteoanabolic signaling [27–31]. As such, functional mutation of SOST in humans leads to two autosomal recessive disorders, sclerosteosis and Van Buchem disease, both of which are characterized by severe bone overgrowth [32,33]. Remarkably, PTH was found to inhibit Sost, and this action was essential for the osteoanabolic effects of PTH [34–36].

Notably, the periodicity and length of administration of PTH renders the hormone catabolic or anabolic. The continuous administration of PTH leads to an increase in bone resorption and catabolic effects [37]. However, and in contrast to its physiological role, PTH is able to exert anabolic effects on the skeleton upon intermittent administration and is currently the only osteoanabolic therapy available for the treatment of osteoporosis [38]. Nonetheless, PTH achieves either effect through the regulation of key anabolic or catabolic/osteoclastogenic genes. As such, recent evidence suggests that some of these regulatory pathways elicit the use of histone deacetylating enzymes, or HDACs.

HDACs in Bone Development and Remodeling

Histone deacetylases (HDACs) belong to a superfamily of enzymes that play vital roles in several cellular processes, mainly through their repressive effect on transcription [39,40]. They act in converse with a family of enzymes, the histone acetyltransferases (HATs), which enhance transcription by catalyzing the transfer of acetyl groups from acetyl coenzyme A (Acetyl CoA) to epsilon-amino groups of lysine residues within histone tails. This neutralizes their inherently positive charge, which in turn relaxes chromatin structure. In disrupting the structural integrity of the chromatin, transcription factors are free to bind their target genes [41]. In addition, acetylated histones may serve as binding sites for bromodomain proteins, which can serve as transcriptional activators. Thus, removal of acetyl groups by HDACs leads to chromatin compaction and blocks any factors that promote transcription. The intricate balance between HATs and HDACs is a key mechanism in governing gene expression.

The mammalian HDAC superfamily consists of 18 proteins and are classified into the following subfamilies: class I includes HDACs 1–3, 8; class IIa includes HDACs 4, 5, 7, 9; class IIb includes 6,10; class IV includes HDAC11 and lastly, class III includes sirtuins 1–7 [42,43]. The HDACs differ in expression patterns, enzymatic functions, structure, and subcellular location. HDAC Classes I, II, and IV require Zn^{2+}, while the sirtuins require the

cofactor nicotinamide adenine dinucleotide (NAD+), and are intriguingly regarded as a family of genes involved in aging [see 44–45 for reviews].

Interestingly, HDAC activity is not limited to histones. Indeed, they are able to target lysine residues found on non-histone proteins. Because HDACs lack the ability to directly bind chromatin, they rely on proteins that do bind DNA to form complexes to control gene expression, particularly in osteoblast differentiation [46–48]. Specifically, one of the targets in bone is a master transcription factor, Runx2. This action is mediated through deacetylation and/or direct binding of HDACs to Runx2 [49–51]. Runx2 belongs to the Runt related family of transcription factors (RUNX) and these are characterized by a 128-amino-acid domain (runt domain), which binds an RD consensus sequence, PuACCPuCA [52]. The RUNX family are involved in a wide array of functions and systems, but Runx2 has been characterized as an osteoblast-specific transcriptional activator [53,54] and plays a central role in osteoblast differentiation [55,56].

Classes I, IIa, and IIb HDACs are expressed in osteoblasts and bind Runx2 [49,57,58] and these interactions appear to be of great importance during osteoblast maturation. In an effort to identify co-repressors that bind Runx2, Schroeder et al. found that HDAC3 was able to bind the N-terminus of Runx2, but did not associate with the Runt domain itself [49]. Indeed, HDAC3 blocks the activation of the osteocalcin promoter by binding to a region with a Runx2 binding site within it and this repression was blocked with either HDAC inhibitors or shRNAs targeting HDAC3 specifically [49].

By interacting with a Runx2/Smad3 complex, HDAC4 and HDAC5 appear to regulate Tgf-β-dependent signaling and gene expression [59]. Previously, Westendorf et al. showed that in differentiated osteoblasts, HDAC6 localizes to the nucleus and binds Runx2 in a rapid, but transient manner [57]. Also, deficiencies in HDAC6 lead to an increase in trabecular bone density [60]. By stimulating the phosphorylation of HDAC7 by protein kinase D, Bmp2 disrupts the interaction between HDAC7 and Runx2, prompting the association of HDAC7 with 14-3-3 proteins, leading to its exit from the nucleus [61]. This same study also reported that Bmp2 leads to the nuclear exit of HDAC4, but did not affect the subcellular localization of HDAC5 or HDAC6. Studies in our laboratory have shown that HDAC4 controls the activity of matrix metalloproteinase-13 (MMP13) through dissociation from Runx2, and this regulation is governed by PTH in a protein kinase A (PKA) and protein phosphatase 2A (PP2A)-dependent manner [62,63]. Thus, these studies corroborate a defining characteristic of class II HDACs, in which their regulation is governed by subcellular localization.

Of all the class III HDACs, SIRT1 has been the most heavily investigated. Indeed, it appears to play a significant role in bone development, as global deletion of SIRT1 in mice exhibit delayed bone mineralization [64]. Additionally, knockout of Sirt1 in osteoblast-specific or mesenchymal stem cell-specific mice result in a significant loss of bone mass [65,66]. Recent studies suggest that SIRT1 action is also mediated through Runx2 [67,68]. Taken together, the prominent role of HDACs in bone remodeling suggest their likely utilization in PTH-mediated actions on bone.

HDACs in PTH-mediated Bone Remodeling

It is well understood that PTH is able to produce anabolic and catabolic effects on bone, depending on the duration and periodicity of its administration. Continuous treatment creates a catabolic effect, where high bone turnover is stimulated, whereas intermittent treatments increase bone formation [37]. Thus, daily intermittent injections of PTH(1–34) remain the only FDA-approved osteoanabolic therapy [38]. Although the effect of intermittent treatment of PTH(1–34) is well known, the precise mechanisms by which bone formation prevail are poorly understood. Remarkably, studies in PTH signaling in the osteoblast lineage have been shown to regulate class IIa HDACs, HDAC4 and HDAC5 and class III HDAC, Sirtuin 1 and these findings may, in part, aid in furthering understanding the effects of PTH on bone.

As discussed above, studies in our laboratory have shown that PTH, by way of PKA-dependent phosphorylation, utilizes HDAC4 to control Mmp13 expression in the rat osteoblastic cell line, UMR 106-01. Phosphorylation of HDAC4 on Ser-632 (Ser-740 in rats) is a critical event that causes the release of HDAC4 from Runx2 on the Mmp13 promoter. In addition, dephosphorylation of HDAC4 on Ser-246 (Ser-355 in rats) leads to its subsequent translocation out of the nucleus [63]. Together, these events allow for the recruitment of histone acetyltransferases (HATs) such as p300 and P/CAF to promote transcription [69,70]. Conversely, Obri et. al reported that in mouse calvarial cells HDAC4 does not inhibit Runx2 function, but rather, promotes RankL expression through PTH-induced, Smurf2-mediated polyubiquitylation of HDAC4 and its subsequent degradation. Alternatively, the sympathetic tone promotes HDAC4 nuclear accumulation and association with transcription factor, ATF4 [71]. Interestingly, a recent study found that proteasome inhibitor carfilzomib (CFZ) was able to inhibit PTH-induced RANKL expression by preventing HDAC4 degradation in the osteoblast [72], thus inhibiting osteoclastogenesis and suggests the possible combinatorial use of CFZ and PTH in therapy.

Recently, a large transcriptome study was performed to assess the comparative genetic expression elicited by either PTH or 1,25$(OH)_2$ vitamin D_3. This study concluded that PTH and 1,25$(OH)_2$ vitamin D_3 collaborate to simultaneously limit osteocyte differentiation of precursor cells and promote mature osteocyte function [73]. Additionally, they also report the identification of a PKA-activated phospho-Creb (pCREB) cistrome, which revealed that despite many differentiation-related PTH regulated genes were dependent on the PKA-mediated signaling pathway, a number of pCREB binding sites associated with osteocyte-specific PTH targets appeared to involve alternative pathways.

PTH signaling also appears to employ the use of another class IIa HDAC, HDAC5. Baertschi et al. report that PTH induces nuclear translocation of HDAC5, co-localization with MEF2s, and subsequent sclerostin suppression. Conversely, inhibition of class I HDACs by siRNA, HDAC2 and HDAC3, led to a decrease in Sost suppression, which implicates their involvement in Sost expression [74]. It is important to note that the cells used in this study, UMR 106-01, were described as osteocytic in nature, when in fact, they are osteoblastic cells derived from a rat osteosarcoma. Supporting some of this group’s work, a more recent study showed that HDAC5 knockout mice exhibit increased levels of

SOST mRNA, as well as reduced bone formation by osteoblasts. Additionally, chromatin immunoprecipitation studies performed in an osteocytic cell line, Ocy454, reveal an inhibitory relationship between HDAC5 and the binding of MEF2C to a distal intergenic enhancer region within SOST [75].

A recent study in our laboratory has implicated SIRT1 in the PTH-regulated expression of MMP13 [76]. Sirt1 knockout mice exhibited an increase in both MMP13 mRNA expression, as well as protein levels. By using a SIRT1 activator, resveratrol, or SIRT1 inhibitor, EX527, we were able to either block or enhance PTH-stimulated MMP13 expression, respectively. After treating osteoblastic cells with PTH, we observed binding of SIRT1 with c-Jun, which is a component of the transcription factor complex, activator protein 1 (AP-1). This association at the AP-1 site of the Mmp13 promoter inhibits AP-1 activity and thus, downregulates the transcription of Mmp13. Also, Inhibition of SIRT1 led to an increase in PTH-stimulated Mmp13 gene expression. Interestingly, we also found that SIRT1 deacetylates c-Jun in a cAMP dependent manner. These data conclude that SIRT1 is a negative regulator of MMP13 expression, and this regulation is achieved through the direct binding of SIRT1 with c-Jun on the Mmp13 promoter.

Conclusions

Recent studies have shown that the role of HDACs in PTH-induced gene regulation is abundantly clear, particularly with class II HDACs. It is interesting to note that of all the HDACs, these exhibit relatively low expression and are the most spatiotemporally specific. Also, this subfamily possesses the least enzymatic activity and appears to be used more for their ability to bind transcription factors and block recruitment of transcriptional activators. Studies on their ability to occupy promoter sites and the effect this has on blocking histone acetyltransferase access would be insightful. With respect to class III HDACs, Sirt1 plays a significant role in inhibiting a catabolic action of PTH on bone, which may be a potential target in the treatment of osteoporosis. Additional studies on the role of HDACs in PTH signaling would offer a wealth of knowledge, as further understanding of these precise mechanisms would provide novel therapeutic targets in bone disease and treatment.

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