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Epigenetics and Bone Remodeling

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Abstract

Bone remodeling is a diverse field of study with many direct clinical applications; past studies have implicated epigenetic alterations as key factors of both normal bone tissue development and function and diseases of pathologic bone remodeling.

Purpose of Review—The purpose of this article is to review the most important recent advances that link epigenetic changes to the bone remodeling field.

Recent Findings—Epigenetics describes three major phenomena: DNA modification via methylation, histone sidechain modifications, and short non-coding RNA sequences which work in concert to regulate gene transcription in a heritable fashion. Recent findings include the role of DNA methylation changes of Wnt, RANK/RANKL, and other key signaling pathways, epigenetic regulation of osteoblast and osteoclast differentiation, and others.

Summary—Although much work has been done, much is still unknown. Future epigenome-wide studies should focus on extending the tissue coverage, integrating multiple epigenetic analyses with transcriptome data, and working to uncover epigenetic changes linked with early events in aberrant bone remodeling.

Keywords

Bone remodeling; epigenetics; DNA methylation; histone modification; miRNA; review

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Compliance with Ethical Guidelines

Conflict of Interest

Matlock Jeffries and Ali Husain declare no conflicts of interest.

Human and Animal Rights and Informed Consent

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Introduction

Human bone is a remarkably dynamic organ, capable of simultaneously providing multiple supporting roles for the greater human organism. A highly metabolically active tissue, it must carefully balance anabolic and catabolic activities throughout life to properly maintain its structural strength while providing a variety of endocrinological, immunological, and structural roles [1,2]. Bone remodeling, a general description of the paired, continuous restructuring process that bone undergoes in order to repair mechanical aberrations, is an important basic and translational research topic with direct clinical consequences. Perhaps the most clinically and epidemiologically relevant consequence of dysfunctional bone remodeling are osteoporotic fractures. In Western countries, the lifetime risk of any osteoporotic fracture approaches 50% in women and 22% in men [3]. In 2010 in the US, there were more than 99 million adults with osteoporosis or low bone mass over the age of 50 [4]. Of particular concern, post-fracture hospitalization and recovery is associated with a substantial reduction in quality of life, increase in disability, and reduction in lifespan [5–9].

Bone remodeling occurs through the coordinated efforts of three general cell lineages: osteoclasts, which break down old bone, osteoblasts, which lay down new bone, and osteocytes, cells residing within clefts in the bone matrix itself which play important roles in paracrine signaling. Interestingly, osteoblasts and osteoclasts arise from different embryonic cell lineages: the former are mesenchymal in origin whereas the latter are hematopoietic. This dichotomy has important ramifications in a variety of diseases associated with a bone dysregulation phenotype. In rheumatoid arthritis (RA) for example, autoreactive cells drive increased bone catabolism through cytokines like TNF alpha which induce RANK/RANKL interactions on both osteoblasts and osteoclasts [10].

Several large genome-wide association studies have been undertaken to examine genetic contributions to low bone mineral density (BMD) [11]. Although many genes have been associated with BMD (estimates are around 500), the strength of these associations are all relatively low. As with many complex polygenic disorders, the etiology of bone dysregulation diseases is more likely to be an interaction of the environment and underlying genetic code. Epigenetics is a common mechanism whereby organisms alter gene expression in response to both external and internal environmental cues such as diet, mechanical stressors, obesity-related adipokines, inflammatory cytokines, and aging. It is defined as heritable changes in gene expression and/or function that occur in the absence of mutations of underlying genomic DNA. Epigenetic dysregulation that leads to inappropriate gene expression or silencing has been shown to play an important role in several musculoskeletal and rheumatic diseases, including systemic lupus erythematosus, rheumatoid arthritis, and osteoarthritis [12–15]. There are three fundamental mechanisms which fall under the heading of epigenetic control as we understand it today: DNA methylation, post-translational modification of histone proteins via the addition or removal of various chemical sidechains, and noncoding RNA modulation of gene expression. In this review article, we will first introduce each of these mechanisms then explore how changes in each of these have been implicated in both normal and pathologic bone remodeling.

DNA Methylation

Methylation of genomic DNA occurs on the 5' carbon position of the pyrimidine ring of cytosine residues. Although classically described in the context of CpG dinucleotides, it is now understood that other motifs (e.g. C-H-G or C-H-H) are present in embryonic tissue and induced pluripotent stem cells [16]. Interestingly, CpG dinucleotides represent approximately 4% of the genome, much less than one would expect at random (6%), due mainly to CpG "drift" caused by the instability of methylated cytosines and spontaneous deamination of unmethylated cytosine to uracil [17]. Although CpG pairs are found throughout the genome, their transcriptionally relevant activity is generally ascribed to two regions. The first are within 5' promoters upstream of a particular gene: as our group and others have shown, the most important regions are between 1000bp and 800bp upstream of the transcription start site [18]. The second is at distantly upstream enhancer regions.

The addition of methyl groups to cytosine residues is provided by a set of evolutionarily divergent set of DNA methyltransferases (DNMTs). Demethylation of DNA occurs via both active and passive demethylation [23]. Passive demethylation occurs by an inhibition of maintenance DNA methylation during replication, whereas active DNA demethylation occurs via a methylcytosine-to-hydroxymethylcytosine conversion and subsequent base excision repair by ten eleven ten gene family members (TET) [24].

Histone modification

Histones are highly conserved proteins that function stabilize, organize, and condense DNA within the limited confines of the cell nucleus and wrap genomic DNA around their outer surface. They alter the local chromatin geography to either facilitate transcription or repress it by interacting with DNA packaging proteins controlled by post-transcriptional modifications including acetylation and methylation of the amino acid sidechains [25]. Acetylation of histones is associated with an increase in transcription, and deacetylation with repression; thus, various histone deacetylase inhibitors have been widely studied as a means to increase transcription of a variety of genes with impacts on bone remodeling, as will be discussed later.

Noncoding RNA

The field of noncoding RNA research, particularly in musculoskeletal disease, is still young with new categories being described regularly. The first and most widely-studied of these RNA subtypes are microRNAs (miRNA). Composed of small, non-protein-coding nuclear-DNA-encoded RNAs of around 22 nucleotides in length, miRNAs modulate gene expression by three principal mechanisms. First, certain types bind to complementary sites on the 3' tails of messenger RNA transcripts and target them for degradation by the RNA-induced silencing complex (RISC), composed of microRNAs bound to target mRNA and various cleavage proteins, notably including members of the Argonaut family [27]. A second mechanism involves the binding and destabilization of mRNAs without cleavage; a third reduces the efficiency of ribosomal translation [27]. Several novel functions of miRNAs have been proposed, and several new classes of larger noncoding RNA with important

transcriptional significance have been recently described, including long non-coding RNAs (lncRNA), Piwi-interacting RNAs (piRNAs), small nucleolar RNAs (snoRNAs), and others [28,29].

Epigenetics in bone remodeling

DNA methylation, candidate gene studies

Studies of DNA methylation are the most established in the bone remodeling field. There are two basic approaches: studying individual (or small groups) of key genes in detail, or performing genome-wide surveys. We will discuss each individually, starting with individual candidate gene studies.

Arguably the most important signaling molecules in the development and regulation of osteoblasts are the bone morphogenic proteins (BMPs) and the wntless/int class (Wnt) pathways, based on findings of at least three early seminal articles. The first, by Gong et. al., identified a dominant negative homozygous mutation in the *LRP5* gene as causative of the rare human disease osteoporosis pseudoglioma, demonstrating that Wnt signaling through LRP5 (now known as 'canonical' Wnt signaling) is intimately linked to bone formation [30]. Two subsequent studies demonstrated that mutations in *LRP5* (which render it unable to bind to the WNT inhibitors dickkopf-related protein 1 [DKK1] and sclerostin, among others) are associated with genetically inherited high bone mass in humans [31–34]. Multiple subsequent studies have substantiated this association, implicating other Wnt pathway genes in human genetic diseases of bone mineral density [35].

It follows, then, that epigenetic changes in Wnt pathway genes are associated with alterations of bone mineral density and osteoblast function. The Wnt inhibitor sclerostin is primarily expressed in osteocytes with paracrine effects on osteoblast function, causing activation and acceleration of bone formation in both humans and animal models [36–38]. It binds to and inhibits the Wnt cell surface receptors LRP5 and LRP6 in osteoblasts and osteocytes [39–41]. The epigenetic state of *SOST*, the gene encoding sclerostin, has been extensively studied not only in candidate epigenetic studies but in epigenome-wide arrays where it reached multiple-test-correction statistical significance [42]. In osteocytes, hypermethylation of the proximal promoter and first exon of *SOST* is associated with decreased sclerostin expression, whereas hypomethylation has the opposite effect [43]. Researchers have demonstrated that *SOST* is generally hypomethylated in osteocytes but hypermethylated in basal osteoblasts, and that significant increases in gene expression can be produced by forcibly demethylating this region in osteoblasts *in vitro* with the DNA methylation (DNMT1)-inhibiting drug 5-azacytidine. A recent study by Reppe et. al. of iliac crest bone biopsies in osteoporosis patients compared to age- and BMI-matched healthy controls confirmed this *in vivo*, demonstrating hypermethylation of *SOST* (albeit in a mixed cell population) and describing a reduction in serum sclerostin concentration in these patients [44]. The authors hypothesize that this hypermethylation and reduction in sclerostin is a compensatory mechanism in osteoporotic patients to prevent further bone formation by “inhibiting the inhibitor”. A recent study by Lhaneche et. al. further linked DNA methylation of the *SOST* promoter and expression in human tibial plateau samples [45]. Interestingly, they were able to narrow down the most transcriptionally relevant methylation

sites by principal component analysis to three groups, but described a counter-intuitive association of DNA hypermethylation with increased *SOST* mRNA expression.

DNA methylation has been shown to be an important regulator of other Wnt pathway genes as well. For example, the Wnt pathway coreceptor *ROR2* demonstrates a progressive reduction in DNA methylation of its promoter during the transition from mesenchymal stem cell to fully differentiated osteoblasts [46]. Hypomethylation of *ROR2* and *WNT5a* has also been found in mesenchymal stem cells isolated from spinal ligaments of patients with diffuse idiopathic skeletal hyperostosis (DISH), a disease characterized by progressive ossification of the longitudinal spinal ligaments in older individuals leading to limitations in spine mobility [47]. This hypomethylation was associated with increased gene expression of both *ROR2* and *WNT5a*. A recent article by Cho et. al. demonstrated that the vital Wnt downstream factor *Bmp2* is epigenetically “locked” in non-osteogenic cells against expression by a repressive epigenetic pattern consisting of DNA methylation of its promoter region and repressive surrounding histone marks, including decreased acetylation and increased methylation of histone 3 lysine 9 (H3K9) [48]. Furthermore, treatment of mouse adipocytes and mouse fibroblast cell lines with the DNA methylation inhibitor 5'-aza-2'-deoxycytidine rendered these cells responsive to Wnt3a signaling. They encountered a similar pattern in the classical osteoblast gene alkaline phosphatase gene (*Alp*). Complementary findings were also identified by Zhou et. al., who demonstrated that pretreatment of mesenchymal stem cells with the similar demethylation agent 5-azacytidine facilitated subsequent osteogenic differentiation, with demethylation of the *Dlx5* promoter in particular [49]. Others have demonstrated that several additional genes involved in differentiation of osteogenic cells from mesenchymal stem cells are controlled by DNA methylation, including the key osteogenic transcription factors runt-related factor 2 (*Runx2*) and osteocalcin [50].

DNA methylation also figures prominently in the control of genes related to osteoclast differentiation and function. For example, the expression of receptor activator of nuclear factor-kappa B ligand (RANKL) is tightly correlated with methylation of its promoter [51], and treatment of mouse cells with demethylating agents greatly increases the expression of RANKL. This finding has been confirmed in multiple human cell lines [51]. Interestingly, a previously described lab artifact, the loss of osteoclastogenic potential of the mouse stromal cell line ST2 with progressive *in vitro* passages, has been shown to be related to methylation of the *Rankl* promoter [52,53]. In contrast with sclerostin and despite differences in RANKL expression in osteoporosis patients compared to osteoarthritic controls, differential methylation of *RANKL* has not been found in human samples [51].

Genome-wide DNA methylation studies

In 2013, Delgado-Calle and colleagues reported the first genome-wide DNA methylation analysis of trabecular bone biopsies taken from femur fracture patients compared to control osteoarthritis patients. Utilizing the Illumina 27k microarray platform, which covered around 27,000 individual CpG sites throughout the genome, they identified 241 CpG sites in 228 genes which were significantly differentially methylated between these two groups [42], the vast majority being hypomethylated. The genes associated with these CpG sites were

enriched in glycoprotein metabolism, cell differentiation, and homeobox superfamily transcription factor pathways. Reppe et. al. subsequently completed a genome-wide DNA methylation study of bone biopsies from postmenopausal women using the expanded Illumina Infinium 450k platform, which covers around 480,000 CpG sites spread throughout the genome [54]. They focused initially on 100 genes found to be differentially expressed in these samples by microarray analysis, and found four genes whose transcription level was highly correlated with methylation state (*MEPE*, *SOST*, *WIF1*, and *DKK1*). They identified 63 additional CpG sites that demonstrated differential methylation between osteoporotic patients and healthy controls. One site, located in a gene involved in nucleotide excision repair, was found by covariate analysis to explain a remarkable 19% of the observed variation in bone mineral density [55].

Recently, del Real et. al. performed an epigenome-wide association study in mesenchymal stem cells isolated from femoral heads of osteoporotic women undergoing hip replacement surgery for fracture to age-, sex-, and BMI-matched osteoarthritis patients. They combined the Illumina 450k platform with RNA-seq profiling to determine gene transcription effects [56], and found differentially methylated genes in pathways related to osteoblast differentiation and mesenchymal stem cell differentiation. Our group further examined the methylation patterns in subchondral bone from hip osteoarthritis (OA) patients who underwent hip replacement for primary OA. OA is a degenerative form of arthritis associated with low-level intraarticular and systemic inflammation, characterized by progressive shifts from an anabolic to catabolic chondrocyte phenotype associated with subchondral bone sclerosis and cartilage destruction, reduction in autophagy, and increases in measures of cellular senescence [13,57,58]. Several studies have suggested that subchondral bone plays a critical role in the early stages of OA [59,60]. Utilizing the same Illumina 450k platform mentioned above, we found a number (7,316) of differentially methylated loci from subchondral bone regions underlying eroded cartilage compared to regions underlying intact cartilage from within the same joint. Of particular interest was *NFATC1*, a key regulator of bone mass homeostasis, which, along with calcineurin in osteoblasts, controls the expression of chemokines which attract osteoclast precursors to ensure coupled bone formation and resorption [61]. Our findings were later confirmed and expanded upon by Zhang and colleagues [62], who used a unique three-region sampling system that allowed them to compare genome-wide DNA methylation patterns from intermediate, transitional, and late-stage OA subchondral bone from patients undergoing total knee arthroplasty for primary OA. Their data also implicated differential methylation of key osteoblast transcription factors including SOX9, ALP, and FOS. They identified differential methylation of several HOX genes which clustered in the Oct4 pathway, a factor linked with pluri/multipotency in a variety of tissue types, including mesenchymal stem cells [63].

In 2013, de la Rica et. al. performed an intriguing genome-wide DNA methylation study focused on the opposite end of the bone remodeling spectrum: osteoclasts. They compared differentiated osteoclasts from human patients (following a 14-day *in vitro* M-CSF and RANKL culture) to the CD14+ macrophage precursors in these same subjects [64]. This differentiation was associated with both hypo- and hypermethylation of many genes (1,895 and 2,054, respectively) which were conserved across samples from different donors. They found that promoters of genes including *ACP5*, *CTSK*, *TM7SF7*, and *TM4SF19*

demonstrated rapid demethylation following RANKL and M-CSF stimulation between baseline and 4 days, in the absence of cell division, highlighting the importance of active demethylation mechanisms in osteoclast differentiation. The differentially methylated CpG sites they identified were highly enriched for PU.1 binding sites (a widely conserved myeloid-cell transcription factor), and they went on to demonstrate that PU.1 recruited both the maintenance DNA methyltransferase DNMT3b to hypermethylated loci and the DNA glycosylase TET2 (which catalyzes the first step in active DNA demethylation) to hypomethylated loci. Inhibition of PU.1 via transfection with PU.1-specific short interfering RNA (siRNA) restricted the recruitment of DNMT3b and TET2 and impaired the activation or repression of PU.1-enriched, osteoclast-related genes.

Histone modification studies

Few studies have sought to determine specific histone sidechain patterns in particular genomic regions associated with bone remodeling. The most extensive to date was published by Zhang et. al. in 2015 [65]. They examined the dynamic changes of histone acetylation and methylation in osteogenic genes *Runx2*, *osterix* (*Osx*), *Alp*, and others during osteogenesis in a mouse *in vitro* bone model (C3H10T1/2 cell line) as well as in a glucocorticoid-induced osteoporosis mouse model.

There have been, however, many studies examining the effects on bone remodeling of more general methods of altering histone sidechains. The best studied epigenetic histone mark is acetylation; the addition and removal of acetyl groups occurs via the action of histone acetyltransferases and histone deacetylases. This is of particular clinical relevance, as histone deacetylases are the target of a number of drugs, mostly used as cancer therapy [66]. There are 18 human histone deacetylases (HDACs), falling into four broad classes, and several studies have examined the impacts of HDAC inhibitors on bone formation and maturation.

HDAC1-selective inhibitors (MS-275, for example) suppress osteoclast formation, and prevent differentiated osteoclasts from resorbing osteoid matrix via prevention of c-fos and NFATc1-induced RANKL signaling [67], as well as stimulating osteoblast proliferation and maturation in mouse cell lines and primary osteoblast cell cultures [68]. The HDAC1 inhibitor butyrate was found by Lee et. al. to accelerate osteogenesis [69] in cultured mouse cells. They went on to show that knockdown of HDAC1 by siRNA stimulated osteoblast maturation. HDAC3 interacts directly with Runx2, one of the key osteoblast-regulating transcription factor, and inhibition of HDAC3 increases expression of Runx2-associated genes in mouse MC3T3 cells [70] and accelerates bone mineralization. Conversely, another group generated HDAC3 osteoblast-specific conditional knockout mice and demonstrated reduce bone mass globally with aging [71], highlighting the complexity and context specificity of epigenetic changes and epigenetic modifiers in osteoblastic function. Fewer studies have been conducted utilizing Class II-specific HDACi in osteoblasts. Genetic polymorphisms within HDAC5 are risk loci for femoral neck and lumbar spine bone mineral density in humans [72]. HDAC5 knockout mice have impaired osteoblastogenesis and low bone density [73], a phenotype driven by overexpression of the anti-osteoblastic paracrine factor sclerostin. This is in stark contrast with findings in human adolescents suffering from

primary osteoporosis, whose osteocytes demonstrate increased HDAC5 and low RUNX2 expression [74]. HDAC5 induces chromatin changes that reduce NFATc1 expression and, in bone marrow macrophages, overexpression of HDAC5 reduces RANKL-induced osteoclast differentiation [75], but no studies have yet elucidated the effects of HDAC5-specific inhibition on osteoclastogenesis or osteoclast function.

Like type I HDACs, HDAC6 inhibition can suppress the activity of human osteoclasts *in vitro* and can prevent osteoclast differentiation in human and murine cells [67,76]. HDAC7, a type II HDAC, has opposite effects on osteoclastogenesis. Overexpression of HDAC7 in murine cells inhibits both the size and number of tartrate-resistant acid phosphatase (TRAP) multinucleated cells, whereas knockdown of HDAC7 enhances osteoclast differentiation [77,78]. Although its effects are discordant, it appears that HDAC7 accomplishes its osteoclast modulation via a similar pathway as other HDACs; in this case, by attenuation of NFATC1 signaling [78]. Similar to HDAC7, HDAC9 knockout mice have increased numbers of osteoclasts and lower bone mass [79].

Broad-spectrum HDAC inhibitors (HDACi) including trichostatin A inhibit osteoclast formation and activity in rat bone marrow derivatives [80]. This finding was later confirmed in both murine cell lines and primary human osteoclasts [67,81,82]. This suppression of osteoclastogenesis has been linked to increased proteasomal activation and degradation of the key osteoclast transcription factors NF-kappa B and nuclear factor of activated T cells (NFATC1) induced by histone deacetylase inhibitors [67,81], as well as the induction of osteoclast inhibitory factors by HDACi [81].

MicroRNAs

RUNX2 is a core transcription factor in the regulation of osteogenesis, particularly in osteoblast differentiation, as mentioned previously. Its genomic target is osteoblast specific cis-acting element 2 (OSE2), a roughly 18-bp, highly conserved DNA sequence present in the promoter region of a variety of osteogenic genes, including collagen 1 alpha 1 (COL1A1), secreted phosphoprotein 1 (SPP1), alkaline phosphatase (ALP), and others [83,84]. In addition to the aforementioned DNA methylation and histone sidechain epigenetic controls of *RUNX2* transcription, a number of miRNAs have been identified as activators or attenuators of its expression. In 2011, Zhang et. al. identified eleven miRNAs which are expressed in mesenchymal stem cells in a lineage-related pattern, including miR-23a, miR-30c, miR-34c, miR-133a, miR-135a, miR-137, miR-204, miR-205, miR-217, miR-218, and miR-338). All eleven of these microRNAs bind directly to the 3' untranslated region of murine *Runx2* and contribute to downregulation of the gene. Overexpression of any of these (excluding miR-218) in *in vitro* cell cultures were able to impede the generation of osteoblasts, a phenotype that could be rescued with a corresponding anti-miRNA [85]. The same group have also shown that removal of the miRNA regulation framework completely, in this case by conditional deletion of the *Dicer* gene of osteoprogenitor cells via a *Col1a1*-Cre system, resulted in fetal demise. Interestingly, *in vivo* removal of the *Dicer* gene via an *Osteocalcin*-Cre system in mature osteoblasts generated live births, but with delayed bone mineralization. This strongly suggests that miRNAs are indispensable during skeletal development, and play a maintenance role in bone remodeling as mice age [86].

Members of the miR-30 family have been confirmed as key regulators in osteogenic differentiation. For example, miR-135b is consistently downregulated during osteogenesis *in vitro*, and overexpression of this miRNA leads to reductions in bone mineralization and markedly decreased expression of integrin-binding sialoprotein (IBSP, a major bone matrix structural protein) and Osterix genes [87]. miR-125b expression is inversely correlated in a time-dependent fashion with osteoblast differentiation, and overexpression in mouse mesenchymal cells leads to an arrest in both proliferation and differentiation [88]. Both miR-141 and miR-200a modulate pre-osteoblast differentiation by targeting and repressing *Dlx5* in a mouse cell line [89]. Both miR-204 and the homologous miR-211 attenuate Runx2, again by binding to the 3'UTR, in human mesenchymal progenitor cells, and shunt the fate of these cells away from osteogenesis and towards adipogenesis [90].

A few miRNAs have been identified as promoters of osteogenesis. One is miR-218, which upregulates the Wnt signaling pathway by inhibition of the Wnt inhibitors Dickkopf family 2 (DKK2), secreted frizzled-related family 2 (SFRP2), and sclerostin [91]. miR-218 expression is induced by the expression of the Wnt pathway gene Wnt3a, forming an amplification circuit [92]. miRNAs can also control other epigenetic circuits and affect osteogenesis; for example, miR-449a targets HDAC1, which prevents HDAC1 from altering the chromatin structure around RUNX2, thereby facilitating osteogenesis [93].

Osteoclasts are also targets of miRNA-directed regulation. miR-503, for example, targets RANK. Its expression is dramatically reduced in circulating CD14+ macrophages of human osteoporosis patients compared to controls, and silencing miR-503 with an antagomir increases RANK expression and osteoclast differentiation, increases bone resorption and reduces bone mass in ovariectomized mice. Conversely, overexpression of miR-503 with an agomir limits ovariectomy-associated bone loss [94]. Another clinical example is rheumatoid arthritis (RA), characterized in part by cytokine-driven osteoclast resorption of periarticular bone, where miR-233 is elevated in synovial cells of RA patients [95]. In a mouse osteoclast precursor cell line, Sugatani and colleagues showed that overexpression of miR-233 blocks the formation of TRAP-positive multinucleated giant cells. Furthermore, Li et. al. have more recently confirmed the overexpression of miR-233 in the synovium of both RA patients and the RA mouse model collagen-induced arthritis (CIA), and demonstrated that knockdown of miR-233 by lentiviral-mediated silencing reduced the severity of bone erosion, osteoclastogenesis, and clinical symptoms in this same mouse model [96].

Several miRNAs have drawn attention in the bone field as potential clinical biomarkers. A recent article by Seeliger and colleagues identified a panel of 9 miRNAs from patient serum were strongly upregulated and correlated with the presence of osteoporosis, and five of these were found to be overexpressed in femoral tissues from these same patients [97], offering hope for future blood-based diagnostics.

Conclusion

Bone remodeling is a complex process involving multiple cell types receiving and integrating environmental information and coordinating the expression of catabolic and anabolic disease to maintain several critical roles for the human organism as a whole.

Epigenetics, defined as heritable alterations in gene expression that are not related to underlying alterations of the gene code, has emerged as an important and fruitful area of research within the wider field of bone remodeling. Epigenetic changes in key genes, particularly related to osteoblast and osteoclast cellular differentiation and cellular signaling, have been described as intimately involved in the process of bone remodeling, both in healthy tissues and associated with diseases of dysregulated remodeling including osteoporosis and osteoarthritis. Further research in this area will no doubt reveal additional insights into the basic mechanisms underlying bone biology and the delicate balance of anabolism and catabolism within bone tissue, as well as offer the potential for novel diagnostic and therapeutic agents for common disorders of bone remodeling.

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