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REVIEW

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Dysregulation of histone modifications in bone marrow mesenchymal stem cells during skeletal ageing: roles and therapeutic prospects

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Abstract

Age-associated bone diseases such as osteoporosis (OP) are common in the elderly due to skeletal ageing. The process of skeletal ageing can be accelerated by reduced proliferation and osteogenesis of bone marrow mesenchymal stem cells (BM-MSCs). Senescence of BM-MSCs is a main driver of age-associated bone diseases, and the fate of BM-MSCs is tightly regulated by histone modifications, such as methylation and acetylation. Dysregulation of histone modifications in BM-MSCs may activate the genes related to the pathogenesis of skeletal ageing and age-associated bone diseases. Here we summarize the histone methylation and acetylation marks and their regulatory enzymes that affect BM-MSC self-renewal, differentiation and senescence. This review not only describes the critical roles of histone marks in modulating BM-MSC functions, but also underlines the potential of epigenetic enzymes as targets for treating age-associated bone diseases. In the future, more effective therapeutic approaches based on these epigenetic targets will be developed and will benefit elderly individuals with bone diseases, such as OP.

Keywords BM-MSCs, Methylation, Acetylation, Osteoporosis, Senescence

Introduction

Bone is in a constant dynamic process called bone remodeling, and is involved in a coupling balance between osteoclastic bone resorption and osteoblastic bone formation [1]. Age-associated bone diseases such as osteoporosis (OP) are common in the elderly due to the uncoupling of bone formation and bone resorption [2]. As OP progresses, the bone tissue degenerates and the bone mass decreases, leading to increased susceptibility to fragility fractures [3].Various pathogenic factors, such as ageing [4], alcohol consumption [5], smoking [5], anorexia nervosa [6], concurrent diseases [7, 8], and especially estrogen/androgen deficiency [9], may accelerate the progression of OP. However, estrogen-centric OP pathogenesis has been challenged recently and gradually shifted to ageing-centric OP pathogenesis [10].

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Multipotent bone marrow mesenchymal stem cells (BM-MSCs), a class of non-hematopoietic stem cells with the ability to self-renew and differentiate, are the source of pre-osteoblasts essential for bone formation and bone remodeling [11]. Skeletal ageing is a progressive process that involves the inevitable exhaustion and senescence of BM-MSCs and a subsequent decline in bone homeostasis, accompanied by an elevated propensity for increased bone marrow adipose tissue (BMAT) and decreased bone mass [2, 12]. During the ageing process, the self-renewal potential of BM-MSCs is impaired, which manifests in the downregulation of stemness-associated genes such as *Oct4*, *Sox2* and *Nanog*, and the upregulation of senescence-associated genes such as *Cdkn1a* (also known as *p21*, *Cip1*, and *Waf1*), *Cdkn2a* (encoding $p16^{Ink4a}$ and $p19^{Arf}$ in mice and $p14^{Arf}$ in humans) and *Cdkn2b* (encoding $p14^{Ink4b}$ and $p15^{Ink4b}$) [13–15]. Senescence of BM-MSCs, including the dysregulation of BM-MSC lineage commitment in the senescent bone marrow microenvironment, is critical to the occurrence of OP [16, 17]. Senescent BM-MSCs accumulate in the bone marrow with ageing, characterized by reduced proliferation, enhanced adipogenesis and decreased osteogenesis, and may lead to bone marrow adiposity, bone loss and increased risk of major fractures [2, 4].

Histone modifications are important regulators of the lineage commitment and senescent process of BM-MSCs and control the process of skeletal ageing [15, 18–25]. Here, we summarize the latest findings that histone methylation and acetylation regulate the senescence, self-renewal and differentiation of BM-MSCs during bone ageing, and highlight the potential of regulatory enzymes as therapeutic targets for age-associated diseases, such as OP.

Histone modifications

The impaired function of senescent stem cells is often accompanied by changes in epigenetic modifications, such as DNA methylation, histone alteration, chromatin remodeling, m^6A modulation and ncRNA-mediated regulation of gene expression [26, 27]. Histone modifications and their corresponding regulatory enzymes cause chromatin remodeling without altering the primary DNA sequence, serving as critical modulators in lineage commitment and the senescent process of BM-MSCs [20, 28–30]. Methylation, acetylation, phosphorylation, ubiquitination and sumoylation are well-known covalent histone modifications that take place on active residues in histones that are crucial for chromatin architecture, nucleosome stability and gene transcription [31, 32]. These histone modifications not only alter the histone-DNA binding affinity, but also influence chromatin compaction and accessibility, which results in changes in the folding or exposure state of target gene promoters and affects gene expression [32–34].

Methylation and acetylation are the most widely studied histone modifications (Fig. 1A, B). Histone methylation typically occurs on lysine (*K*) (including mono-, di- and trimethylation) and arginine (*R*) (monomethylation, and symmetric or asymmetric dimethylation) residues mediated by histone methyltransferases (HMTs) and can be removed by demethylases (HDMs) [35, 36]. In general, methylation at H3K4, H3K36, H3K79 and H3R17 promotes transcriptional activation, whereas methylation at H3K9, H3K27 and H4K20 tends to repress transcription [37, 38]. For instance, an increased level of H3K27me3 often indicates a tighter and repressive state of nucleosomes linked to gene silencing [39]. Similarly, lysine acetylation is a dynamic modification that can be added by lysine acetyltransferases (KATs) and removed by lysine deacetylases (KDACs) [40]. KAT-mediated lysine acetylation causes loose chromatin and transcriptional activation. Deacetylation by KDACs causes chromatin condensation leading to gene silencing [41, 42]. These diverse histone modifications constitute a network that regulates the fate of BM-MSCs (Fig. 1C) [43–45].

Regulation and functions of histone modifications in BM-MSCs

Lysine methylation

Lysine methylation is a well-understood epigenetic mechanism in BM-MSC fate regulation mediated by histone lysine methyltransferases (KMTs) and demethylases (KDMs) (Fig. 2 and Table 1) [43]. The KMTs, including DOT1L and SET domain-containing proteins, are responsible for methylation at K4, K9, K27, K36 and K79 of H3, as well as K20 of H4. In contrast, apart from LSD1, all known KDMs have a conserved JmjC domain. Therefore, KDMs are also termed JmjC domain-containing histone demethylases (JHDMs) [36]. KMTs and KDMs reversibly and dynamically regulate methylation at lysine residues of histones, thus modulating the transcription of target genes.

H3K27 methylation

Methylation at H3K27 acts as an important epigenetic switch dictating BM-MSC lineage determination (Fig. 2 and Table 1). Elevated H3K27me3 on pro-osteogenic gene promoters inhibits osteogenesis of BM-MSCs, while H3K27me2 on anti-osteogenic gene promoters impedes adipogenesis of BM-MSCs. EZH2 (also termed KMT6A) catalyzes the methylation of H3K27 on target gene promoters [39]. EZH2 acts as a negative regulator of osteogenesis by increasing H3K27me3 on the promoters of osteoblastic genes like *RUNX2*, *TCF7* and *BGLAP* in vitro [46, 47]. EZH2 is significantly elevated in osteoporotic

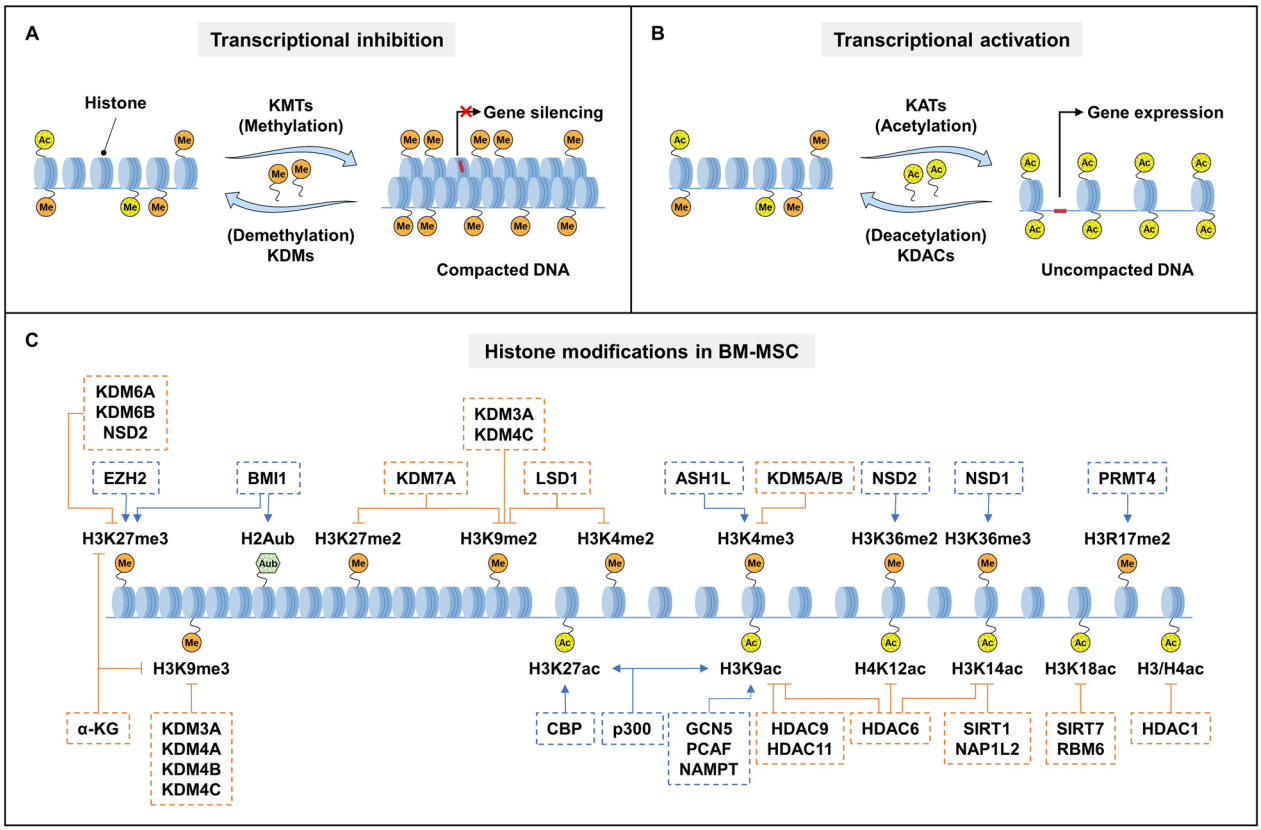

Fig. 1 The landscape of histone modifications in the regulation of BM-MSCs. **A** The schematic diagram of histone lysine methylation. **B** The schematic diagram of histone lysine acetylation. **C** Histone modifications in BM-MSC during skeletal ageing

BM-MSCs and directly upregulates H3K27me3 levels on the promoters of *Wnt1*, *Wnt6*, *Wnt10a* and *Wnt10b* to impede *Wnt* gene transcription [28, 48]. The inhibition of Wnt/β-catenin signaling shifts MSC lineage commitment to adipocyte during OP [28]. *Ezh2* deletion upregulates *Bmp2*, *Runx2* and *Wnt* expression, and accelerates bone remodeling [49, 50]. The methylation state of H3K27 is dynamically regulated by the EZH2 and KDM6 cluster. The KDM6 cluster contains three members, including KDM6A (also termed UTX), KDM6B (also called JMJD3) and inactive UTY [51]. KDM6A and KDM6B are positive regulators of osteogenesis by removing the methyl groups of H3K27 on osteogenic genes. For example, KDM6A demethylates H3K27me3 on osteogenic genes (e.g., *Runx2* and *Bglap*) and activates the expression of these genes in human and mouse BM-MSCs [47, 52, 53]. KDM6B demethylates H3K27me3 to promote the expression of *Bmp2*, *Bmp4*, *Runx2* and *Hoxc6-1* and induce osteogenic commitment of BM-MSCs, thus elevating bone mass in OVX and aged mice [54, 55]. Similar results have also been demonstrated in human dental MSCs [56]. KDM7A (also called KIAA1718 or JHDM1D) has demethylase activity for H3K27me1/me2 and H3K9me1/me2 [57], and can enhance adipogenesis and weaken osteogenesis by demethylating H3K9me2 and H3K27me2 on the promoters of *Sfrp1* and *C/ebpα* in mouse primary BM-MSCs and ST2 cells [58]. Alpha-ketoglutarate (α-KG), an essential endogenous metabolite in the tricarboxylic acid (TCA) cycle, is reported to extend lifespan and compress morbidity in ageing mice [59, 60]. Alpha-KG treatment reduces H3K27me3 at the *Bmp2*, *Bmp4* and *Nanog* promoters, thus restoring the proliferation, migration and osteogenesis abilities of aged BM-MSCs [20]. Collectively, H3K27me3 on pro-osteogenic gene promoters is mainly regulated by EZH2, the KDM6 cluster and α-KG, whereas H3K27me2 on anti-osteogenic genes is partially affected by KDM7A (Fig. 3).

As a regulatory center for lineage determination of BM-MSCs, H3K27 methylation plays an important role in regulating cellular senescence (Fig. 4 and Table 1). EZH2 upregulates the repressive mark H3K27me3 at the promoters of cell cycle inhibitor genes (e.g., $p14^{Arf}$, $p16^{Ink4a}$ and $p21^{Cip1}$), and loss of EZH2 results in transcriptional activation of these genes to promote senescence of BM-MSCs [14, 15, 61]. However, EZH2 enhances H3K27me3 in the promotor of *Foxo1* to inactivate the antioxidative

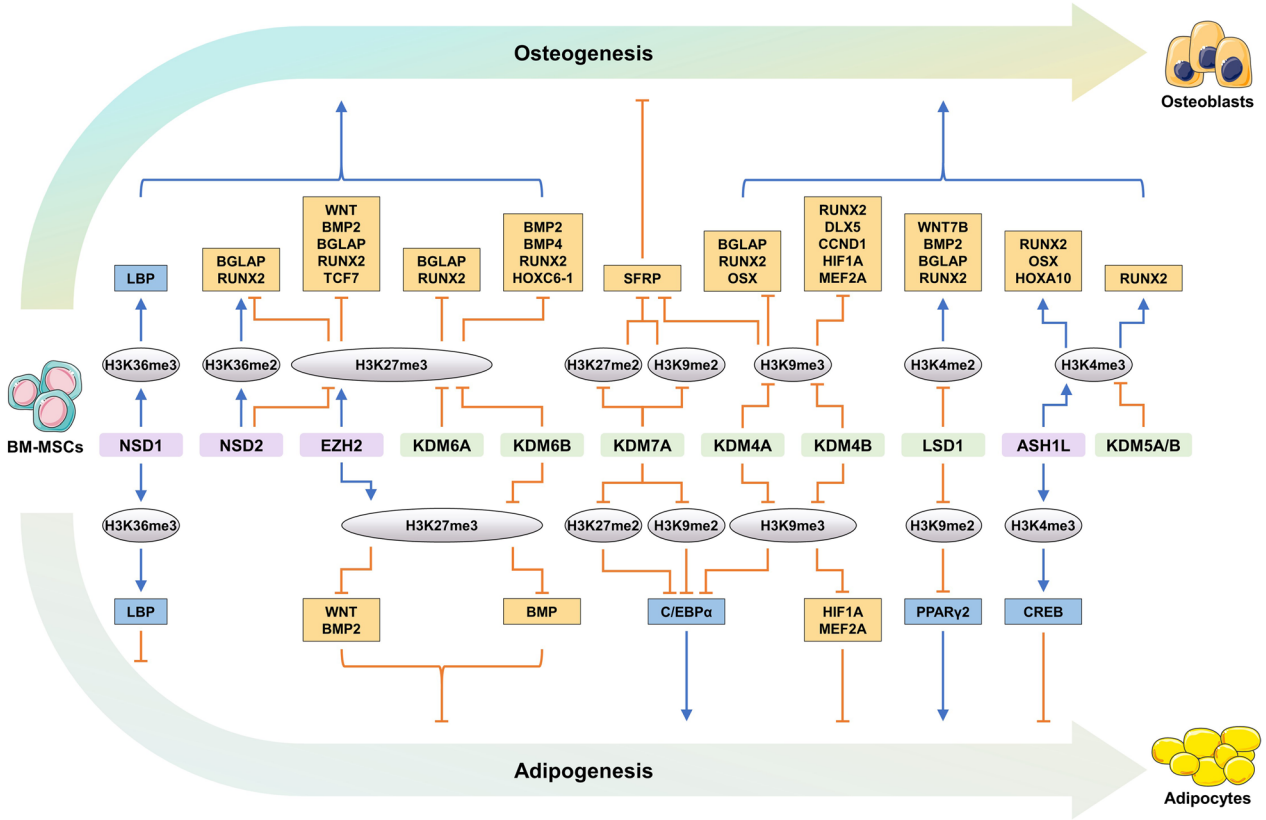

Fig. 2 KMTs and KDMs regulate the osteogenic and adipogenic differentiation of BM-MSCs by histone methylation

defensive system, thus promoting oxidative damage and BM-MSC ageing [19]. Thus, EZH2 shows bifunctional roles in regulating BM-MSC senescence. Notably, BMI1 can prevent senescence and adipogenesis of BM-MSCs by increasing H3K27me3 and H2A ubiquitination (H2Aub) of $p14^{Arf}$, $p16^{Ink4a}$ and *Pax3* [62]. Therefore, EZH2 and BMI1 jointly regulate the ageing process of BM-MSCs.

H3K9 methylation

H3K9 methylation on the promoters of adipogenic *Pparγ2* and *C/ebpα*, as well as anti-osteogenic *Sfrp* inhibits the transcription of these genes, which consequently impedes adipogenesis and promotes osteogenesis of BM-MSCs (Fig. 2 and Table 1). KDMs are key components of potent epigenetic switches that control BM-MSC fates into adipogenic lineages. LSD1 (also termed KDM1A) regulates gene transcription by demethylating H3K9me1/me2 and H3K4me1/me2 [63]. By demethylating H3K9me2, LSD1 induces *Pparγ2* gene expression and promotes adipogenic differentiation of BM-MSCs [64]. The KDM4 cluster is widely expressed in human tissues and can demethylate H3K9me2/me3 and H3K36me2/me3 [43]. KDM4A (also known as JMJD2A, JHDM3A and JMJD2) activates *C/ebpα* and *Sfrp4* transcription by demethylating H3K9me3, thus promoting adipocyte formation and inhibiting bone formation in mouse primary BM-MSCs and ST2 cells [65]. As mentioned above, the removal of H3K9me2 and H3K27me2 by KDM7A also shows similar functions [58]. Taken together, LSD1, KDM4A and KDM7A play a negative role in bone formation through demethylating H3K9me2/me3 at the promoters of adipogenic genes (e.g., *Pparγ2* and *C/ebpα*) and anti-osteogenic genes (e.g., *Sfrp*).

H3K9 methylation can repress the expression of pro-osteogenic genes (e.g., *Bmp2*, *Runx2*, *Osx*, *Bglap*, *Dlx5*, *Ccnd1*, *Hif1α*, *Mef2a* and *Nanog*), thereby inhibiting osteogenic differentiation of BM-MSCs (Fig. 2 and Table 1). The demethylases KDM4A and KDM4B (also termed JMJD2B and JHDM3B) show crucial and positive functions in the osteogenic differentiation of BM-MSCs. KDM4A promotes osteoblast differentiation of rat primary BM-MSCs by removing the silencing epigenetic mark H3K9me3 on osteoblastic genes (*Runx2*, *Osx* and *Bglap*) [66]. Similarly, KDM4B significantly upregulates pro-osteogenic gene expression (e.g., *Runx2*, *Dlx5*, *Ccnd1*, *Hif1α* and *Mef2a*) by demethylating repressive H3K9me3 on the promoters of these

Table 1 Histone methylation and related modifiers regulate the fate of BM-MSC

Modifiers	Histone modification	Targets	Effects on fate of BM-MSC (in vitro)	Effects on bone (in vivo)	References
Methylases					
ASH1L	H3K4me3	*Osx*, *Runx2*, *Hoxa10*, *Sox9*, *Creb*	Promotes osteogenesis and chondrogenesis, while inhibiting adipogenesis	Not evaluated	[70]
EZH2 (KMT6A)	H3K27me3	Osteoblastic genes (*RUNX2*, *TCF7*, *BGLAP*, *Wnt*, *Bmp2*), senescence-associated genes ($p14^{Arf}$, $p16^{Ink4a}$, $p21^{Cip1}$), antioxidant *Foxo1*	Inhibits osteogenesis, while promoting adipogenesis, restraining senescence, accumulating oxidative damage	Inconsistent conclusion	[14, 15, 19, 28, 47, 50, 61]
NSD1 (SETD2, SET2, KMT3A)	H3K36me3	*Lbp*	Promotes osteogenesis while inhibiting adipogenesis	Promotes bone mass increase	[29]
NSD2 (MMSET)	H3K36me2 H3K27me3	*Runx2*, *Bglap*	Promotes osteogenesis while inhibiting senescence	Not evaluated	[21]
SETD7 (SET7, SET9, SET7/9, KMT7)	H3K4me3	Not evaluated	Promotes osteogenesis	Not evaluated	[72]
PRMT3	H4R3me2a	miR-3648	Promotes osteogenesis	Promotes bone regeneration and bone mass increase	[103]
PRMT4 (CARM1)	H3R17me2	*OCT4*, *SOX2*, *NANOG*, *DDR2*	Promotes pluripotency while inhibiting senescence	Not evaluated	[104, 105]
Demethylases					
LSD1 (KDM1A)	H3K9me2	*Pparγ2*	Promotes adipogenesis	Not evaluated	[64]
LSD1	H3K4me2	*Runx2*, *Bglap*, *Wnt7b*, *Bmp2*	Inhibits osteogenesis	Promotes bone loss	[73, 74]
KDM3A (JMJD1A, JHDM2A)	H3K9me2 H3K9me3	*Ncapd2*, *Ncapg2*	Inhibits DNA damage and senescence	Inhibits bone loss	[68]
KDM4A (JMJD2A, JHDM3A, JMJD2)	H3K9me3	*Runx2*, *Osx*, *Bglap*	Promotes osteogenesis	Not evaluated	[66]
KDM4A	H3K9me3	*Sfrp4*, *C/ebpa*	Promotes adipogenesis while inhibiting canonical Wnt signaling	Not evaluated	[65]
KDM4B (JMJD2B, JHDM3B)	H3K9me3	*Runx2*, *Dlx5*, *Ccnd1*, *Hif1a*, *Mef2a*	Promotes osteogenesis while inhibiting adipogenesis	Inhibits age-related bone loss	[18, 54]
KDM4C (GASC1, JMJD2C, JHDM3C)	H3K9me2 H3K9me3	*Ncapd2*, *Ncapg2*	Inhibits DNA damage and senescence	Inhibits bone loss	[68]
KDM5A (JARID1A, RBP2)	H3K4me3	*Runx2*	Inhibits osteogenesis	Promotes bone loss	[75]
KDM5B (JARID1B, PLU1)	H3K4me3	*Runx2*	Inhibits osteogenesis	Not evaluated	[76]
KDM6A (UTX)	H3K27me3	*RUNX2*, *BGLAP*	Promotes osteogenesis	Not evaluated	[47, 52]
KDM6B (JMJD3)	H3K27me3	*Bmp2*, *Bmp4*, *Hoxc6-1*, *Runx2*	Promotes osteogenesis while inhibiting adipogenesis	Not evaluated	[54, 55]
KDM7A (KIA1718, JHDM1D)	H3K9me2 H3K27me2	*C/ebpa* *Sfrp1*	Promotes adipogenesis while inhibiting osteogenesis	Not evaluated	[58]
Other regulators					

Table 1 (continued)

Modifiers	Histone modification	Targets	Effects on fate of BM-MSC (in vitro)	Effects on bone (in vivo)	References
BMI1	H2Aub H3K27me3	*$p14^{Arf}$*, *$p16^{Ink4a}$*, *Pax3*	Promotes hematopoiesis while inhibiting adipogenesis and senescence	Inhibits bone marrow adiposity	[62]
α-KG	H3K9me3 H3K27me3	*Bmp2*, *Bmp4*, *Nanog*	Promotes proliferation, migration and osteogenesis	Inhibits age-related bone loss and promotes bone defect healing	[20]
NO66	H3K4me3 H3K36me3	Not evaluated	Inhibits osteogenesis	Inhibits endochondral and intramembranous bone formation	[81]

Not evaluated: the effects of histone modification enzymes or related modifiers on bone were not verified in vivo

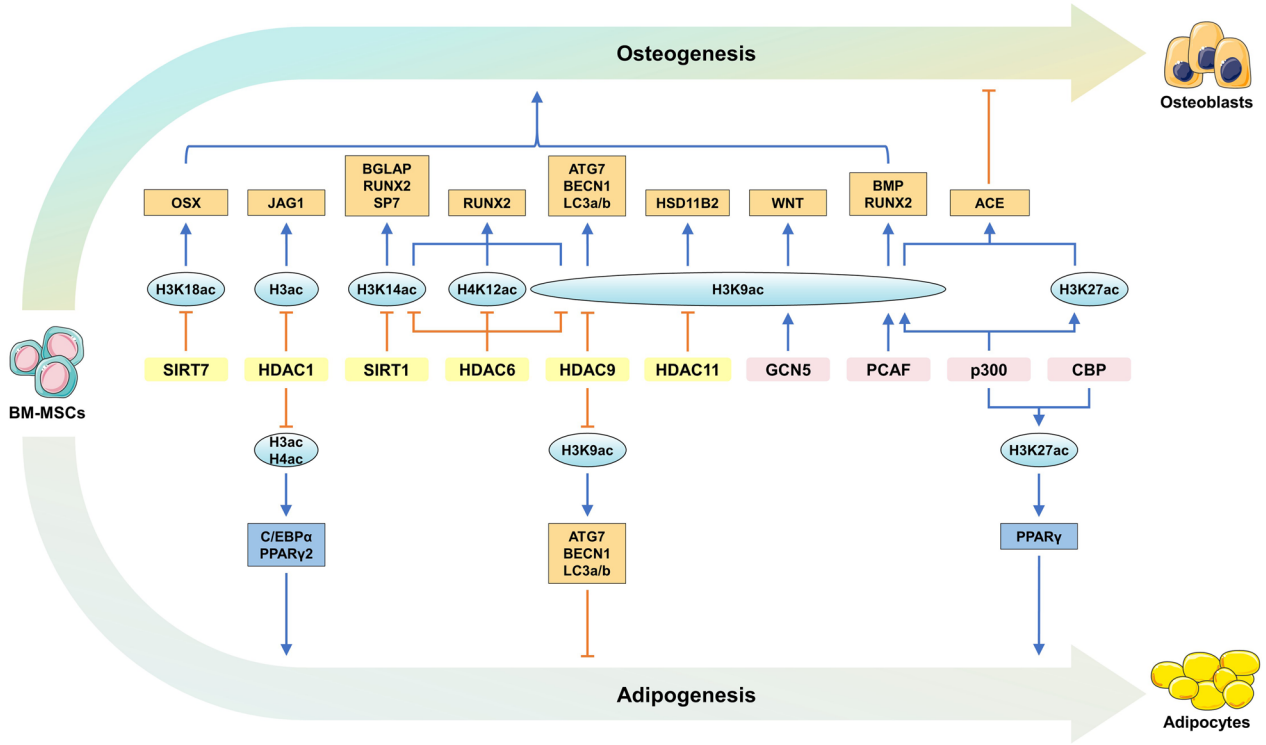

Fig. 3 KATs and KDACs regulate the osteogenic and adipogenic differentiation of BM-MSCs by histone acetylation

genes [18, 54]. Treatment of aged BM-MSCs with α-KG downregulates H3K9me3 occupancy at the *Bmp2* and *Nanog* promoters, ultimately promoting proliferation and osteogenesis of aged BM-MSCs [20]. Therefore, KDM4A, KDM4B and α-KG have positive functions in alleviating skeletal ageing by removing the repressive H3K9me3 on osteoblastic genes to strengthen osteogenesis.

H3K9 demethylases KDM3A (also called JMJD1A and JHDM2A) and KDM4C (also known as GASC1, JMJD2C and JHDM3C) are negatively correlated with BM-MSC senescence [36, 43]. H3K9 methylation along with heterochromatin loss drives human MSC ageing [67]. KDM3A and KDM4C remove the methyl groups of H3K9me2/me3 on the promoters of *NCAPD2* and *NCAPG2* to activate them, which restrains the accumulation of damaged DNA through inducing heterochromatin reorganization, suggesting the protective roles of demethylated H3K9 in BM-MSC senescence and bone ageing (Fig. 4 and Table 1) [68].

Collectively, methylated H3K9 on pro-osteogenic genes is strongly dependent on the levels of KDM3A, the KDM4 cluster and α-KG, whereas H3K9me2/me3 on anti-osteogenic genes is affected by LSD1, KDM4A and KDM7A.

H3K4 methylation

Elevated H3K4 methylation can promote osteogenesis (Fig. 2 and Table 1). ASH1L, a member of the Trx family, activates the expression of multiple genes via its H3K4 and H3K36 methyltransferase activity of the SET domain [36]. ASH1L and H3K4me3 bind to the transcription start site (TSS) of *Hoxa10*, *Osx*, *Runx2*, *Sox9* and *Creb*. Out of them, SOX9 is an important transcription factor that promotes cartilage formation, and CREB may act as a repressive gene of PPARγ [69, 70]. ASH1L interference downregulates H3K4me3 at the TSS of these genes, which inhibits osteogenesis and chondrogenesis and promotes adipogenesis [70]. Another SET domain-containing protein SETD7 (also termed KMT7, SET7, SET9 and SET7/9) is also a methyltransferase of H3K4 [71]. The trace element boron promotes bone regeneration in vivo and stimulates the osteogenic differentiation of human BM-MSCs in vitro by increasing SETD7 and successive H3K4me3, which may further activate the Wnt/β-catenin pathway [72]. Collectively, ASH1L and SETD7 are two methylases associated with the promotion of bone formation by methylating H3K4.

Notably, the LSD1 and KDM5 cluster are demethylases that inhibit osteogenic differentiation by removing the methyl groups of H3K4me2/me3 on osteoblastic gene

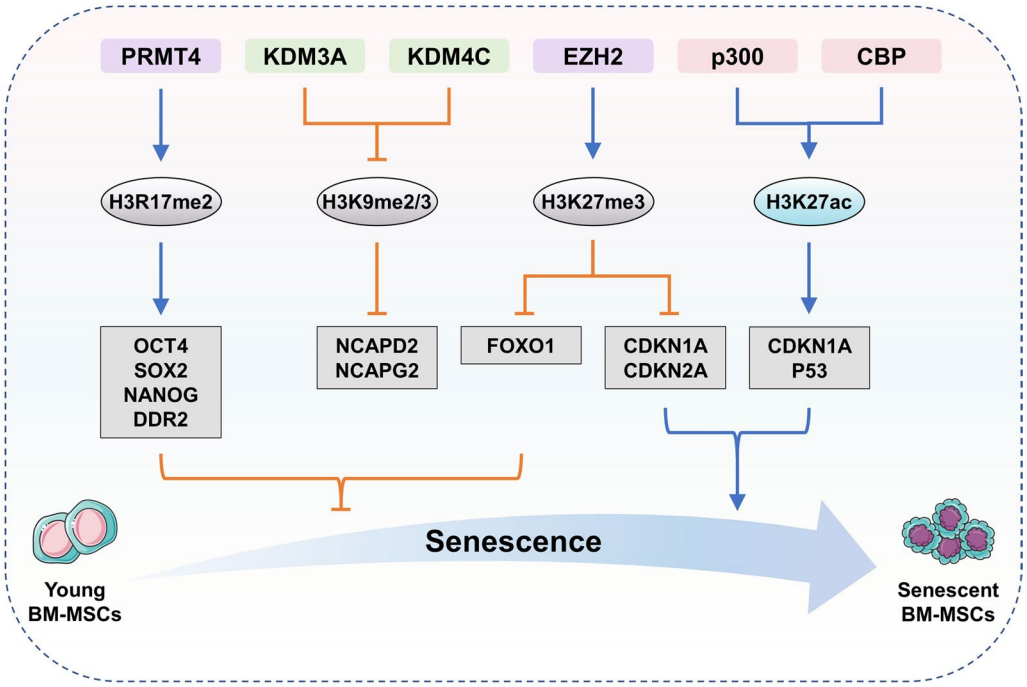

Fig. 4 Histone modifications regulate BM-MSCs senescence

promoters. LSD1 inhibition rescues the osteogenic differentiation ability of BM-MSCs in OVX mice by enhancing H3K4me2 on the promoters of osteogenic genes (e.g., *Runx2* and *Bglap*) [73]. In addition, LSD1 deficiency results in H3K4me2 enrichment on *Wnt7b* and *Bmp2* promoters and enhances bone formation in *Prx1-Cre;Lsd1*$^{fl/fl}$ mice [74]. KDM5A (also termed JARID1A and RBP2) and KDM5B (also called JARID1B and PLU1) can catalyze the removal of mono-, di-, and trimethyl marks on H3K4 to regulate gene expression [36]. KDM5A and KDM5B repress osteogenesis by downregulating H3K4me3 on the promoter of *Runx2* gene [75, 76]. Taken together, the results suggest that the demethylases LSD1 and KDM5 cluster inhibit osteogenesis by demethylating H3K4me2/me3 on the promoters of osteogenic genes, including *Runx2*, *Bglap*, *Wnt7b* and *Bmp2*.

H3K36 methylation

Methylation of H3K36 on *Sox9*, *Lbp*, *Runx2*, and *Bglap* genes promotes chondrogenesis, inhibits adipogenesis, and accelerates osteogenesis (Fig. 2 and Table 1). NSD1 (also termed SETD2, SET2 and KMT3A) and NSD2 (also called MMSET) are well-known H3K36 methyltransferases [36, 77]. Deletion of *Nsd1* decreases *Sox9* expression by reducing H3K36me1/me2 levels, leading to chondrogenic differentiation impairment [78]. The transcription initiation and elongation of the *Lbp* gene is maintained by NSD1-induced H3K36me3 in BM-MSCs [29]. LBP negatively regulates adipocyte differentiation and contributes to a decreased propensity toward adipogenesis and an elevation in bone formation [79]. NSD2-mediated upregulation of H3K36me2 and downregulation of H3K27me3 can increase chromatin accessibility and facilitate osteogenic gene expression (*Runx2* and *Bglap*), consequently ameliorating age-associated bone loss [21]. NO66 has been identified as a JmjC-containing oxygenase, with demethylase activity for methylated H3K4 and H3K36 [36], and can inhibit endochondral and intramembranous bone formation during skeletal development [80, 81]. Therefore, NSD1, NSD2 and NO66 regulate the fate of BM-MSCs by modulating H3K36 methylation.

Lysine acetylation

Reversible protein lysine acetylation is mediated by KATs and KDACs (Fig. 1B) [42]. Mammalian KATs are classified into type A KATs localized in the nucleus and type B KATs present in the cytoplasm. Nuclear histone acetylation events regulated by Type A KATs are usually involved in transcriptional activation [41, 42]. Type A KATs are divided into five families, including GNATs, p300/CBP, MYST (MOZ, YBF2, SAS2 and TIP60), basal transcription factors, and nuclear receptor coactivator (NCoA) subfamilies. In contrast, the number of type B KATs is much smaller. Type B KATs acetylate free histones in the cytoplasm and facilitate

the transport of cytosolic histones into the nucleus [82]. Based on sequence homology and domain organization, KDACs are classified into four groups. Classes I, II and IV belong to Zn^{2+}-dependent histone deacetylases (HDACs), whereas class III KDACs are characterized as NAD^{+}-dependent sirtuins (SIRTs) including SIRT1 to SIRT7 [42, 83].

Histone acetylation is generally associated with the opening of the chromatin structure and enhanced transcriptional activity, which are closely linked to bone homeostasis (Fig. 3 and Table 2). However, KDACs appear to be less selective for histones in regulating BM-MSC fates, as the vast majority of KDACs are 'pan' deacetylases. For example, reduced HDAC1 induces hyperacetylation of H3 and H4 on promoters of adipogenic genes (e.g., *Pparγ2* and *C/ebpα*) in BM-MSCs of GIOP mice [64, 84]. Here we will focus on the effect of H3K9ac, H3K14ac, H3K27ac and H3K18ac on the regulation of BM-MSC functions.

H3K9 acetylation

Upregulated acetylation of H3K9 on the promoters of osteogenic genes, such as *WNT, BMP* and *RUNX2*, has crucial roles in the osteogenic commitment of BM-MSCs (Fig. 3 and Table 2) [85–87]. Downregulated H3K9ac on the *Wnt* gene in BM-MSCs from OVX mice leads to persistent suppression of WNT signaling. Overexpression of GCN5 (also known as KAT2A) promotes osteogenic differentiation of BM-MSCs by increasing H3K9ac on the promoters of *Wnt* genes (*Wnt1*, *Wnt6*, *Wnt10a*, and *Wnt10b*) [85]. GCN5 enhances the proangiogenesis of BM-MSCs by increasing H3K9ac levels on the *Vegf* promoter, consequently contributing to bone formation [88]. In addition, GCN5 can inhibit anti-osteogenic NF-κB signaling by degrading the p65 subunit of NF-κB [89]. PCAF (also known as KAT2B) promotes osteogenic differentiation by catalyzing the acetylation of H3K9 on *BMP2*, *BMP4*, *BMPR1B* and *RUNX2* promoters [86]. In the salvage pathway, NAMPT acts as one of the most critical enzymes controlling NAD^{+} biosynthesis from nicotinamide [90]. The transcription of *Runx2* can be enhanced due to a NAMPT-associated increase in H3K9ac [87]. Collectively, GCN5, PCAF and NAMPT enhance the osteogenic capacity of BM-MSCs mainly by upregulating the level of H3K9ac on osteogenic gene promoters.

HDACs are deacetylases of H3K9ac, by which HDACs inhibit the osteogenic differentiation potential of BM-MSCs (Fig. 3 and Table 2). For example, HDAC6 accumulation and histone hypoacetylation, including H3K9/

Table 2 Histone acetylation and related modifiers regulate the fate of BM-MSC

Modifiers	Histone modification	Targets	Effects on fate of BM-MSC (in vitro)	Effects on bone (in vivo)	References
Acetylases					
GCN5 (KAT2A)	H3K9ac	*Vegf*, *Wnt*	Promotes angiogenesis and osteogenesis	Inhibits bone loss	[85, 88]
PCAF (KAT2B)	H3K9ac	*BMP2*, *BMP4*, *BMPR1B*, *RUNX2*	Promotes osteogenesis	Not evaluated	[86]
p300 (KAT3B)	H3K9ac H3K27ac	*α-KG*	Inhibits osteogenesis	Not evaluated	[98, 99]
p300/CBP	H3K27ac	*Pparγ*, *p53*, *p21*^{Cip1}	Promotes adipogenesis and senescence	Not evaluated	[100]
Deacetylases					
HDAC1	H3/H4ac	*Pparγ2*, *C/ebpa*	Inhibits adipogenesis	Not evaluated	[64, 84]
HDAC1	H3ac	*Jag1*	Inhibits osteogenesis	Promotes bone loss	[109]
HDAC6	H3K9/K14ac H4K12ac	*Runx2*	Inhibits osteogenesis	Promotes age-related bone loss	[91]
HDAC9	H3K9ac	*Atg7* *Becn1* *LC3a/b*	Promotes adipogenesis while inhibiting autophagy and osteogenesis	Promotes age-related bone loss	[92]
HDAC11	H3K9ac	*Hsd11b2*	Inhibits osteogenesis	Not evaluated	[93]
SIRT1	H3K14ac	*Runx2* *Sp7* *Bglap*	Inhibits osteogenesis	Not evaluated	[94]
SIRT7	H3K18ac	*OSX*	Inhibits osteogenesis	Not evaluated	[101]
Other regulators					
NAMPT	H3K9ac	*Runx2*	Promotes osteogenesis	Not evaluated	[87]

Not evaluated: the effects of histone modification enzymes or related modifiers on bone were not verified in vivo

K14ac and H4K12ac, on the *Runx2* promoter contribute to the attenuation of the osteogenic differentiation potential of BM-MSCs in aged mice [91]. HDAC9 directly represses the transcription of genes related to autophagy, such as *Atg7*, *LC3a/b* and *Becn1*, and impairs the autophagy of BM-MSCs by deacetylating H3K9ac, which causes a shift of cell lineages from osteoblasts to adipocytes and leads to skeletal ageing [92]. Prenatal dexamethasone exposure recruits HDAC11 into the nucleus and reduces the expression of *Hsd11b2* by deacetylating H3K9ac, which lasts into adulthood and causes corticosterone accumulation in bone. This condition persisting into adulthood will inhibit the osteogenic function of BM-MSCs [93]. Collectively, HDAC 6, 9, and 11 can be able to inhibit BM-MSCs osteogenesis by deacetylating H3K9ac on the promoters of *Runx2*, *Hsd11b2* and autophagy-related genes.

H3K14 acetylation

Increased H3K14ac on the promoters of genes, including *Runx2, Sp7, Bglap* and *Igf1*, can promote the osteogenesis (Fig. 3 and Table 2) [91, 94, 95]. HDAC6 deacetylates H3K14ac on the *Runx2* promoter and attenuates osteogenic differentiation potential of BM-MSCs in aged mice [91]. Elevated NAP1L2, a histone chaperone, reduces the level of H3K14ac by recruiting SIRT1, thereby preventing osteogenic gene expression (e.g., *Runx2*, *Sp7* and *Bglap*) and inhibiting osteogenic differentiation of MSCs [94]. The enrichment of H3K9ac and H3K14ac at the *Igf1* promoter upregulates the expression of IGF1 in liver and IGF1 signaling in bone, which promotes bone development and bone mass increase [95, 96]. In addition, the increase in H3K9ac and H3K14ac is also correlated with a decreased HDAC1 level [96]. Collectively, HDAC1, HDAC6 and SIRT1 inhibit osteogenesis by deacetylating H3K14ac on pro-osteogenic gene promoters, including *Runx2, Sp7, Bglap* and *Igf1*.

H3K27 acetylation

Elevated H3K27ac, mediated by CBP (also termed KAT3A) and p300 (also known as KAT3B) [97], can inhibit osteogenesis by increasing the levels of ACE, PPARγ, ageing-related p53 and $p21^{Cip1}$ (Figs. 3 and 4, Table 2) [98–100]. Dexamethasone or ethanol exposure during pregnancy upregulates H3K27ac of *Ace* and its expression by recruiting p300, which further induces sustained activation of renin-angiotensin systems (RAS) and suppresses osteogenic differentiation of BM-MSCs, thereby leading to fetal bone development inhibition and osteopenia after birth [98, 99]. P300/CBP activation by maternal obesity results in H3K27ac on the promoters of the *Pparγ*, *p53* and $p21^{Cip1}$ genes in mouse embryonic calvarial osteo-progenitors and in human umbilical cord MSCs, suggesting that obesity during pregnancy may impair osteogenesis in adult offspring [100]. Collectively, p300/CBP inhibits osteogenesis via H3K27ac on the promoters of anti-osteogenic genes, including *Ace*, *Pparγ*, *p53* and $p21^{Cip1}$.

H3K18 acetylation

Acetylation of H3K18 on the osteogenic *OSX* gene can promote osteoblast differentiation of BM-MSCs (Fig. 3 and Table 2). RBM6 recruits SIRT7 to deacetylate H3K18ac and inhibit the expression of isoforms 1 and 2 of the *OSX* gene [101]. In addition, SIRT7 can also repress osteogenesis of human BM-MSCs partially by inactivating the Wnt/β-catenin pathway [102]. Therefore, SIRT7 appears to be a potential therapeutic target for OP.

Arginine methylation

Protein arginine methyltransferases (PRMTs) are divided into 3 subcategories: type I (including PRMT1, 2, 3, 4, 6 and 8), type II (including PRMT5 and 9) as well as type III (only PRMT7) PRMTs [36]. Compared to lysine methylation in BM-MSCs, the regulation and functions of arginine methylation in BM-MSCs are relatively less studied but very important. For example, PRMT3 is an arginine methyltransferase responsible for catalyzing ω-mono- or asymmetric dimethylation on arginine. The expression of miR-3648 is increased by elevating H4 arginine 3 asymmetric dimethylation (H4R3me2a), consequently leading to increased osteogenic differentiation of BM-MSCs [103]. PRMT4 (also termed CARM1) can induce the expression of *OCT4*, *SOX2* and *NANOG* by upregulating H3R17me2 on the promoters of stemness-associated genes, thereby enhancing the adipogenic, osteogenic and myogenic differentiation potentials of human BM-MSCs and adipose-derived MSCs [104]. In addition, PRMT4 is capable of binding to the *DDR2* promoter region and upregulates H3R17me2 in vitro, which can enhance *DDR2* expression and restrain cellular senescence [105]. Collectively, PRMT3 and PRMT4 promote osteogenesis by increasing H4R3me2a on miR-3648 and H3R17me2 on *OCT4*, *SOX2*, *NANOG* and *DDR2* gene promoters (Fig. 4 and Table 1).

Histone modification enzymes are potential targets for OP

Impaired proliferation and biased differentiation of BM-MSCs lead to decreased bone homeostasis, a hallmark of skeletal ageing, with a tendency to increase BMAT and decrease bone mass [2, 12]. Histone modifications are critical for regulating the fate and functions of BM-MSCs, and a large number of preclinical studies suggested that histone modification enzymes could serve as potential targets for enhancing bone formation and treating OP. Small molecule inhibitors of histone modification

enzymes such as EZH2, LSD1, and HDAC have been applied to treat hematological cancers in the clinic [106]. Accumulating findings suggest that the modulation of histone modifications can be used to improve osteogenic differentiation of BM-MSCs, increase bone strength, and prevent skeletal ageing. For example, EZH2 acts as a negative regulator of osteogenesis by increasing H3K27me3 on osteoblastic genes and inhibits the osteogenic lineages of BM-MSCs [28, 46–48]. Therefore, EZH2 inhibitors have osteoprotective potential and offer an opportunity for bone anabolic strategies [107, 108]. Estrogen is an important medication for postmenopausal osteoporosis (PMOP) and can induce the expression of KDM6B. Consequently, KDM6B further activates key osteogenic genes such as *BMP2* and *HOXC6* by removing H3K27me3, thus resulting in MSC osteogenic lineage specification, which may be the partial epigenetic mechanism of estrogen in the treatment of PMOP in the clinic [56]. Calcitriol, namely 1,25-dihydroxyvitamin D_3 ($1,25(OH)_2D_3$), the active form of vitamin D, can be used as an adjuvant for the treatment of OP to promote calcium absorption. Mechanistically, $1,25(OH)_2D_3$ induces the expression of EZH2 to repress the transcription of $p16^{Ink4a}$ by trimethylating H3K27, which inhibits senescence of BM-MSCs and prevents age-related OP [15]. Therefore, EZH2 and KDM6B modulate the fate of BM-MSCs by regulating H3K27 methylation on target gene promoters and are potential therapeutic targets for OP.

In addition, mesoporous bioactive glass scaffolds containing boron (B-MBG) can induce SETD7-catalyzed H3K4 trimethylation and activate the Wnt/β-catenin pathway to promote bone regeneration in OVX rats [72]. However, the underlying mechanisms remain to be explored. Pargyline, an MAO and LSD1 inhibitor, can also rescue the osteogenic differentiation ability of BM-MSCs in aged or OVX mice by enhancing H3K4me2 at the promoters of osteogenic genes (e.g., *Runx2* and *Bglap*) [73]. Collectively, the methylase SETD7 and demethylase LSD1 dynamically modulate H3K4 methylation and regulate the osteogenic differentiation of BM-MSCs, indicating that they may be potential targets for age-related bone loss.

It is well-known that mechanical forces are indispensable for bone homeostasis and that loss of mechanical stimulation can cause disuse OP [1]. Mechanical stimulation induces osteogenic differentiation of BM-MSCs by downregulating HDAC1 expression, increasing H3 acetylation and activating pro-osteogenic JAG1-Notch signaling, and ultimately contributes to fracture healing [109]. MI192, a selective inhibitor of HDAC2 and HDAC3, can enhance the osteogenic capacity of human BM-MSCs in vitro and in mice by regulating epigenetic reprogramming [110]. Notably, nicotinamide mononucleotide (NMN) can also promote osteogenesis via the SIRT1-associated signaling pathway in aged mice [111]. However, the underlying mechanisms remain to be explored. Collectively, some HDACs and SIRT1 are also potential targets for the treatment of bone diseases such as OP by bone anabolic strategies.

Conclusion and future perspectives

In summary, we have introduced the histone modifications and related regulatory enzymes that are implicated in fate determination of BM-MSCs during skeletal ageing. Accumulating evidence indicates that methylation at H3K27, H3K9, H3K4 and H3K36 on the promoters of osteogenic, adipogenic or senescence-associated genes closely regulates the lineage commitment and the senescent process of BM-MSCs [14, 15, 18–21, 28, 29, 47, 50, 52, 54, 55, 58, 61, 62, 64–66, 68, 70, 73–75]. In addition, acetylation of H3K9, H3K14 and H3K18 on pro-osteogenic genes, and H3K27ac on anti-osteogenic genes are tightly regulated by KATs, HDACs and SIRTs [85, 86, 88, 91–93, 98–101]. GCN5 and PCAF, both belong to the GNATs subfamily of KATs, promote osteogenic differentiation of BM-MSCs [85, 86], whereas HDAC6, 9, 11, and SIRT1 inhibit BM-MSC osteogenesis through remodeling histone deacetylation [91–94].

Although tremendous progress has been made, some issues still require further exploration. For example, causes leading to changes in histone modifications and their regulatory enzymes in the early stages of skeletal ageing remain elusive [43, 112–114]. Metabolic, nutritional, and inflammatory balances are important to the health of BM-MSCs and bone [115–118]. The disruption of these balances may affect histone modifications and enzymes, which is still less understood [119–121]. Moreover, there is extensive crosstalk among histone modifications [122]. How these protein modification interactions are involved in the maintenance of bone homeostasis remains unknown [114, 123]. Most importantly, as potential targets for treating bone diseases, the safety and efficacy of targeting histone modification enzymes require further clinical research.

Abbreviations

ACE	Angiotensin-converting enzyme
α-KG	Alpha-ketoglutarate
ASH1L	Absent, small, or homeotic disc1 like
ATG7	Autophagy related protein 7
BECN1	Beclin-1
BGLAP	Osteocalcin
BMAT	Bone marrow adipose tissue
B-MBG	Mesoporous bioactive glass scaffolds containing boron
BMI1	Moloney murine leukemia virus insertion site 1
BM-MSCs	Bone marrow mesenchymal stem cells
BMP	Bone morphogenetic protein
BMPR1B	Bone morphogenetic protein receptor type 1B

CARM1	Coactivator-associated arginine methyltransferase 1
CCND1	G1/S-specific cyclin-D1
CDKN1A	Cyclin-dependent kinase inhibitor 1a
C/EBPα	CCAAT element binding protein alpha
CREB	CAMP-response element binding protein
DDR2	Discoidin domain receptor 2
DLX5	Distal-less homeobox 5
DOT1L	Disruptor of telomeric silencing 1-like
EZH2	Enhancer of zeste homolog 2
FOXO	Forkhead box O
GCN5	General control nonderepressible 5
GIOP	Glucocorticoid-induced osteoporosis
GNATs	General control of amino acid synthesis 5-related N-acetyltransferases
HDACs	Zn^{2+}-dependent histone deacetylases
HDMs	Histone demethylases
HIF1α	Hypoxia-inducible factor 1-alpha
HMTs	Histone methyltransferases
HOXA10	Homeobox protein A10
HOXC6-1	Homeobox domain-containing protein 6 isoform 1
HSD11B2	11-Beta-hydroxysteroid dehydrogenase type 2
IGF1	Insulin-like growth factor-1
JAG1	Jagged 1
JHDMs	JmjC domain-containing histone demethylases
JMJD3	Jumonji domain containing-3
KATs	Lysine acetyltransferases
KDACs	Lysine deacetylases
KDMs	Lysine demethylases
KMTs	Lysine methyltransferases
LBP	Lipopolysaccharide-binding protein
LC3a/b	Light chain 3 alpha/beta
LSD1	Lysine specific demethylase 1
MAO	Monoamine oxidase
MEF2A	Myocyte-specific enhancer factor 2A
MSCs	Mesenchymal stem cells
NAMPT	Nicotinamide phosphoribosyltransferase
NAP1L2	Nucleosome assembly protein 1-like 2
NCAPD2	Chromosome-associated protein D2
NCAPG2	Chromosome-associated protein G2
NMN	Nicotinamide mononucleotide
NO66	Nucleolar protein 66
NSD1	Nuclear receptor binding SET domain protein 1
OCT4	Octamer-binding protein 4
OP	Osteoporosis
OSX/SP7	Osterix/specificity protein 7
OVX	Ovariectomy
PAX3	Paired box 3
PCAF	P300/CBP-associated factor
PMOP	Postmenopausal osteoporosis
PPARγ	Peroxisome proliferator-activated receptor gamma
PRMT	Protein arginine methyltransferase
RBM6	RNA binding motif protein 6
RBP2	Retinol-binding protein 2
RUNX2	Runt-related transcription factor 2
SFRP	Secreted frizzled-related protein
SIRT	Sirtuin
SOX9	SRY-related HMG-box 9
TCA	Tricarboxylic acid
TCF7	Transcription factor 7
TSS	Transcription start site
UTX	Ubiquitously transcribed X-chromosome tetratricopeptide repeat protein
UTY	Y-chromosome homolog of Utx
VEGF	Vascular endothelial growth factor

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YL and MH searched literatures, collected data, and wrote the initial draft of the manuscript. SL and LD are responsible for the outline and figures. JX designed tables and revised the manuscript. All the authors reviewed and approved the final manuscript.

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Declarations

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