Epigenetic roles of chromatin remodeling complexes in bone biology and the pathogenesis of bone-related disease (Review)

WENXIAO WU[1*], YINXING CUI[1,2*], YUQI WU[1], YAN NI[1], CHUNLING ZHAO[1], WEICHAO SUN[2] and QIAN YI[1]

[1]Department of Physiology, School of Basic Medical Sciences, Southwest Medical University, Luzhou, Sichuan 646000, P.R. China; [2]Department of Orthopedics, Shenzhen Second People's Hospital/First Affiliated Hospital of Shenzhen University Health Science Center, Shenzhen, Guangdong 518035, P.R. China

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Abstract. Chromatin remodeling complexes are essential regulators of chromatin architecture, facilitating critical processes such as nucleosome sliding, eviction, histone exchange and post-translational modifications. By providing an additional layer of epigenetic regulation beyond the canonical genetic code, these complexes significantly influence bone biology and health. Epigenetic regulation through chromatin remodeling complexes is crucial in modulating gene expression and cellular behavior in bone cells. However, alterations in the activity of chromatin remodeling complexes can also contribute to the progression of various bone diseases. Emerging evidence suggests that specific chromatin remodeling factors may serve as potential biomarkers for diagnosing bone-related conditions and as therapeutic targets for intervention. The present review aims to elucidate the intricate relationship between chromatin remodeling complexes and bone-related diseases, including osteoporosis, osteoarthritis and osteosarcoma. The present review discusses the diverse subunits of these complexes and their multifaceted roles in regulating key cellular processes such as stemness, differentiation, proliferation, senescence and apoptosis in bone cells. Notably, the present review provides a comprehensive overview of the roles of various chromatin remodeling subunits, such as BRG1, BAF47 and chromodomain-helicase-DNA binding 7 (CHD7), in bone metabolism, highlighting their disease-specific mechanisms, including bromodomain-containing protein (BRD)9-mediated pyroptosis in intervertebral disc degeneration and CHD7-driven bone-fat imbalance. Furthermore, the present review highlights the therapeutic potential of targeting dysfunctional subunits (such as BRD7 in osteosarcoma and SS18 in synovial sarcoma) and propose AI-driven structural biology approaches to design chemical modulators. The understudied impact of aging on chromatin remodeling activity in bone homeostasis is also underscored, advocating for longitudinal studies to address this gap. Finally, the distinct functions of each chromatin remodeling complex and its specific subunits in the context of bone-related diseases were also explored, providing a comprehensive understanding of their contributions to both normal bone physiology and pathological conditions.

Correspondence to: Dr Qian Yi, Department of Physiology, School of Basic Medical Sciences, Southwest Medical University, 1 Section 1, Xianglin Road, Luzhou, Sichuan 646000, P.R. China
E-mail: yiqian2010@yeah.net

Dr Weichao Sun, Department of Orthopedics, Shenzhen Second People's Hospital/First Affiliated Hospital of Shenzhen University Health Science Center, 3002 Sungang West Road, Futian, Shenzhen, Guangdong 518035, P.R. China
E-mail: weichaosunshine@163.com

*Contributed equally

Abbreviations: lncRNAs, long non-coding RNAs; SWI/SNF, switch/sucrose-non-fermenting; ISWI, imitation switch; CHD, chromodomain-helicase-DNA binding; INO80/SWR, inositol requiring 80/SWi2/snf2-related 1; EWS-FLI1, Ewing sarcoma-friend leukemia integration 1; EWSR1, Ewing sarcoma RNA binding protein 1; hESCs, human embryonic stem cells; FGFR3, fibroblast growth factor receptor 3; BMP, bone morphogenic protein; MSCs, mesenchymal stem cells; PBAF, polybromo BAF; TSS, transcriptional start site; PPAR, peroxisome proliferator-activated receptor; IDD, intervertebral disc degeneration; NP, nucleus pulposus; OA, osteoarthritis; AIS, adolescent idiopathic scoliosis; PMOP, postmenopausal osteoporosis

Key words: chromatin remodeling complexes, epigenetic regulation, bone biology, bone development, bone-related diseases

Contents

1. Introduction

Bone is a highly dynamic tissue that undergoes continuous remodeling to maintain skeletal integrity and support various physiological functions (1,2). This remodeling process, known as bone turnover, involves a delicate balance between bone formation and resorption (3). Through this ongoing process, bone homeostasis is achieved, which is critical for maintaining overall skeletal health. Specifically, bone homeostasis is maintained through the coordinated activities of osteoblasts, osteoclasts, osteocytes and chondrocytes, which work together to ensure that bone density and structure remain stable (4). Disruptions in this balance can lead to various bone-related diseases. Bone-related diseases encompass a variety of conditions such as osteoporosis, osteopetrosis, osteonecrosis, osteoarthritis (OA), osteosarcoma and chondrosarcoma, characterized by abnormalities in bone density, structure and integrity (5). These conditions can lead to grave corresponding clinical symptoms. For instance, osteoporosis is characterized by increased bone loss and low peak bone mass, which give rise to low bone density (bone brittleness); with a propensity to fall and poor bone quality, fractures are inexorable in this disease (6). Additionally, osteopetrosis manifests with higher bone mass resulting in phenotypic features such as macrocephaly and altered craniofacial morphology, especially influencing other organs and tissues, notably the bone marrow and nervous system (7). While OA is a complex condition involving mechanical cartilage degradation and matrix protease activities, resulting in pain and loss of joint function, osteonecrosis occurs when there is a lasting inflammatory environment due to distinguished detrimental factors such as glucocorticoids or alcohol, triggering bone tissue death (8,9). As for bone tumors, they are rare and heterogeneous groups of neoplasms that occur in the bones (10). Epigenetic research has greatly enhanced our understanding of these diseases by focusing on gene expression regulation rather than changes in the DNA sequence itself (11). Key epigenetic mechanisms involve DNA methylation, histone modifications, non-coding RNAs (ncRNAs) and chromatin remodeling complexes (12). For instance, ncRNAs, including microRNAs (miRNAs) and long ncRNAs (lncRNAs), play crucial roles in regulating bone formation, resorption processes and tumorigenesis in bone cancer (13). These epigenetic factors collectively impact the differentiation, proliferation and apoptosis of bone cells, contributing to the development and progression of bone-related diseases (14-19).

Chromatin is a densely packed and highly regulated structure that packages DNA, facilitating numerous cellular processes in eukaryotes, particularly in the context of gene expression regulation, DNA replication and repair. The fundamental unit of chromatin is the nucleosome, a highly stable structure that wraps 145-147 bp of DNA around an octamer of histone proteins (20). The 2-meter-long DNA is compressed into chromatin within the nucleus of each cell, creating a notable barrier to cellular processes such as transcription (21). Chromatin remodeling complexes are sophisticated multiprotein assemblies that serve as pivotal regulators of chromatin architecture, mediating dynamic changes that profoundly influence gene expression, DNA repair, replication and a wide range of other critical cellular processes (22). To date, four families of chromatin remodeling complexes have been identified: Switch/sucrose-non-fermenting (SWI/SNF), imitation switch (ISWI), chromodomain-helicase-DNA binding (CHD) and inositol requiring 80/SWi2/snf2-related 1 (INO80/SWR) (23). Each of these families perform unique, non-redundant roles within the cell. Chromatin remodeling complexes are typically composed of three parts: Nucleosome, module [ATPase module, actin-related protein (ARP) module or body module] and proteins. However, different chromatin remodeling complexes have notably different components, including diversities in the nucleosomes and configurations. For example, the SWI/SWF family is composed of the nucleosome, ATPase module, ARP module, body module and diverse proteins (including snf2, RT102, Arp7 and Arp9) (24). The ISWI family does not entail an ARP module and contains dissimilar proteins, such as Isw1, Ioc2, Ioc3 and Ioc4 (25). For the CHD family, the ATPase module exclusively contains distinct proteins. SWR1 contains three main modules and differing proteins (26). Therefore, with such a framework, chromatin remodeling complexes comprise crucial enzymes or cooperate with other chromatin-related factors to play a key role in dynamically regulating various cellular processes, including transcription and DNA repair, by controlling access to genomic DNA (26). Additionally, these gene-mediated chromatin remodeling complexes are crucial contributors to the molecular pathology of bone-related diseases by engaging in bone epigenetic mechanisms such as differentiation, proliferation and senescence. For instance, disturbances in bromodomain-containing protein (BRD)9 within the SWI/SWF family can lead to debilitating bone-related diseases such as osteoporosis, osteopetrosis and osteonecrosis (14).

Therefore, chromatin remodeling complexes play a pivotal role in bone-related diseases. The present review aims to provide an overview of the mechanisms and functions of gene-mediated chromatin remodeling complexes in bone-related diseases. Through literature mining and investigation (Data S1), the present review will examine the relationship between chromatin remodeling complexes and bone-related diseases, and the potential clinical relevance of this relationship, such as pathological mechanisms and disease targets, ultimately aiming to generate further effective clinical therapeutic applications, such as BRM inhibitors for osteoporosis treatment and BRD9 inhibitors for advanced synovial sarcoma treatment. The primary strength of the present review lies in its thorough examination of the role of chromatin remodeling complexes specifically in bone-related diseases. Additionally, the present review emphasizes the potential therapeutic applications of chromatin remodeling complexes, which has been a relatively underexplored area in bone research. Unlike earlier reviews (27-30), which tend to focus on a narrow subset of chromatin remodeling complexes or bone diseases, the present review covers a broader range of chromatin remodeling complexes and bone-related diseases, including bone tumors, OA, bone-fat disorder, adolescent idiopathic scoliosis (AIS) and osteoporosis. A detailed review of the role and mechanisms of chromatin remodeling complexes in bone metabolic processes, such as stemness maintenance, chondrogenesis, osteogenesis, osteoclastogenesis and angiogenesis, are also provided. Additionally, the impact of chromatin remodeling complexes on key bone biological functions, including

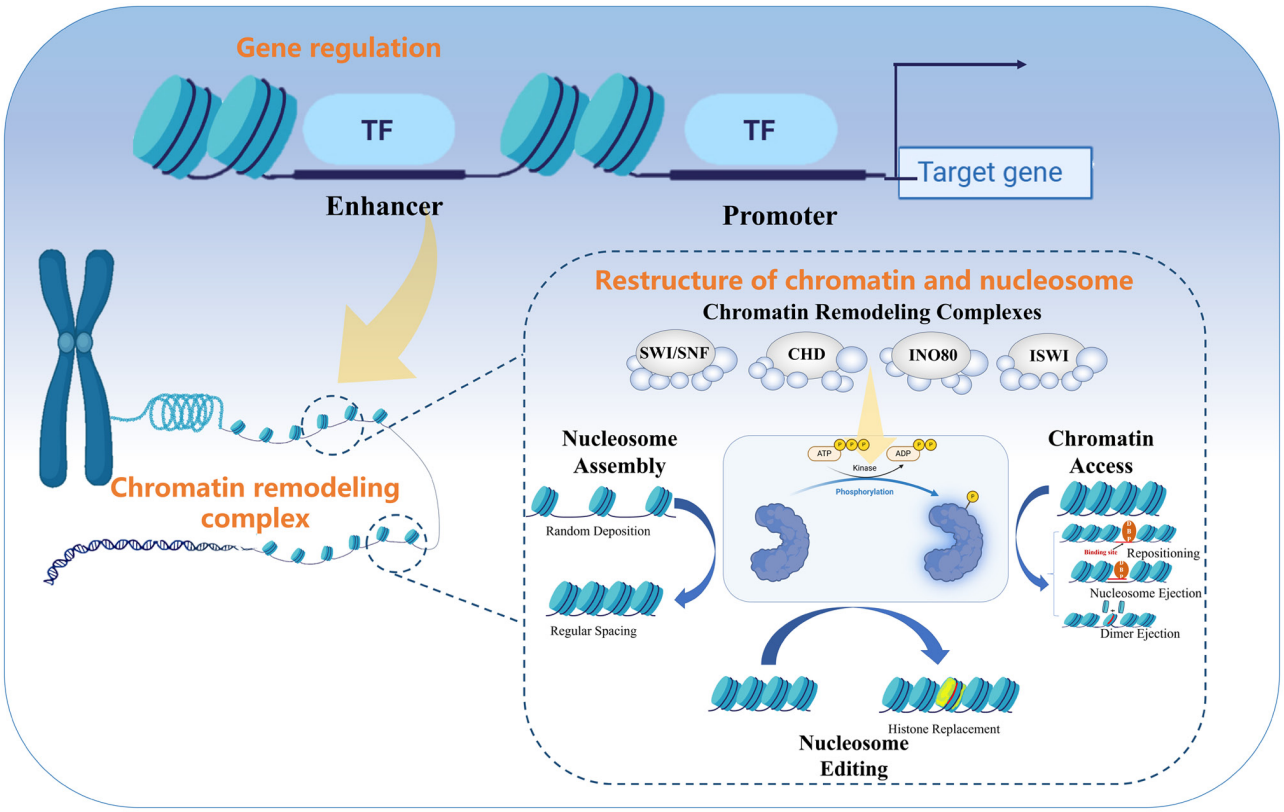

Figure 1. During gene transcription, chromatin remodeling complexes restructure the chromatin and nucleosomes in mainly three aspects: Chromatin access, nucleosome assembly and nucleosome editing. TF, transcription factor; SWI/SNF, switch/sucrose non-fermentable complex; CHD, chromodomain-helicase-DNA binding protein; INO80, inositol requiring 80 complex; ISWI, imitation switch complex. This figure was created with BioRender.com.

proliferation, senescence and programmed cell death are explored in the present review. Another strength of this review is its focus on therapeutic implications, such as how chromatin remodeling complexes could be targeted for intervention in bone-related diseases.

2. Classification, mechanisms and regulations of chromatin remodeling complexes

Chromatin remodeling complexes primarily operate through three fundamental mechanisms (Fig. 1). First, these complexes can edit assembled nucleosomes by replacing, moving or removing specific nucleosomes, thus altering chromatin structure and function. Second, chromatin remodeling complexes are involved in the assembly and reorganization of nucleosomes from random deposition to regular space. Third, chromatin remodeling complexes alter the structure of chromatin to make specific regions of DNA more accessible to transcription factors and other regulatory proteins (22,31,32). This is achieved through various mechanisms, including repositioning nucleosomes, nucleosome ejection and dimer ejection, which all contribute to the dynamic remodeling of chromatin (22,31,32). Collectively, these mechanisms serve as the driving force behind chromatin activation and represent a key component of the hereditary code governing diverse epigenetic regulations.

Based on the sequence homology of the catalytic ATPase and the accessory subunits, chromatin remodeling complexes are classified into four distinct families (Fig. 2): SWI/SNF, ISWI, CHD and INO80/SWR (33,34). The SWI/SNF complex in human cells is characterized by a notable diversity of assemblies. There are several variants of this complex, including canonical BAF (cBAF), polybromo BAF (PBAF) and non-canonical BAF (ncBAF/gBAF), each distinguished by the presence of unique subunits (26). However, the ISWI and CHD family have only one assembly (22). Although INO80 and SWR belong to the same family of chromatin remodelers, they are classified into different subfamilies with distinct components (22,35,36). To this point, each family of chromatin remodeling complexes performs specialized functions within the cell (26). The SWI/SNF family, for instance, includes the BRG1 ATPase subunit, which can independently remodel nucleosome positioning on nucleosomal templates. A minimal four-subunit complex composed of BRG1, BAF155, BAF170 and BAF47 efficiently achieves chromatin remodeling *in vitro* (37). ISWI complexes facilitate the maturation of initial histone-DNA complexes (pre-nucleosomes) into canonical octameric nucleosomes and help space nucleosomes at relatively fixed distances (38,39). CHD family members contain a conserved ATPase domain, comprising SNF2_N and Helicase_C PFAM domains, which act as a motor to drive dynamic interactions with chromatin and nucleosome substrates (40,41). However, INO80, features multiple ATPases that provide catalytic activity and enable ATP-dependent nucleosome sliding within the cell (42,43). Additionally, Ino80p serves as a docking site for several core subunits, including actin, ARPs and the Rvb AAA+ ATPases (44). While these chromatin remodeling complex families implement diverse

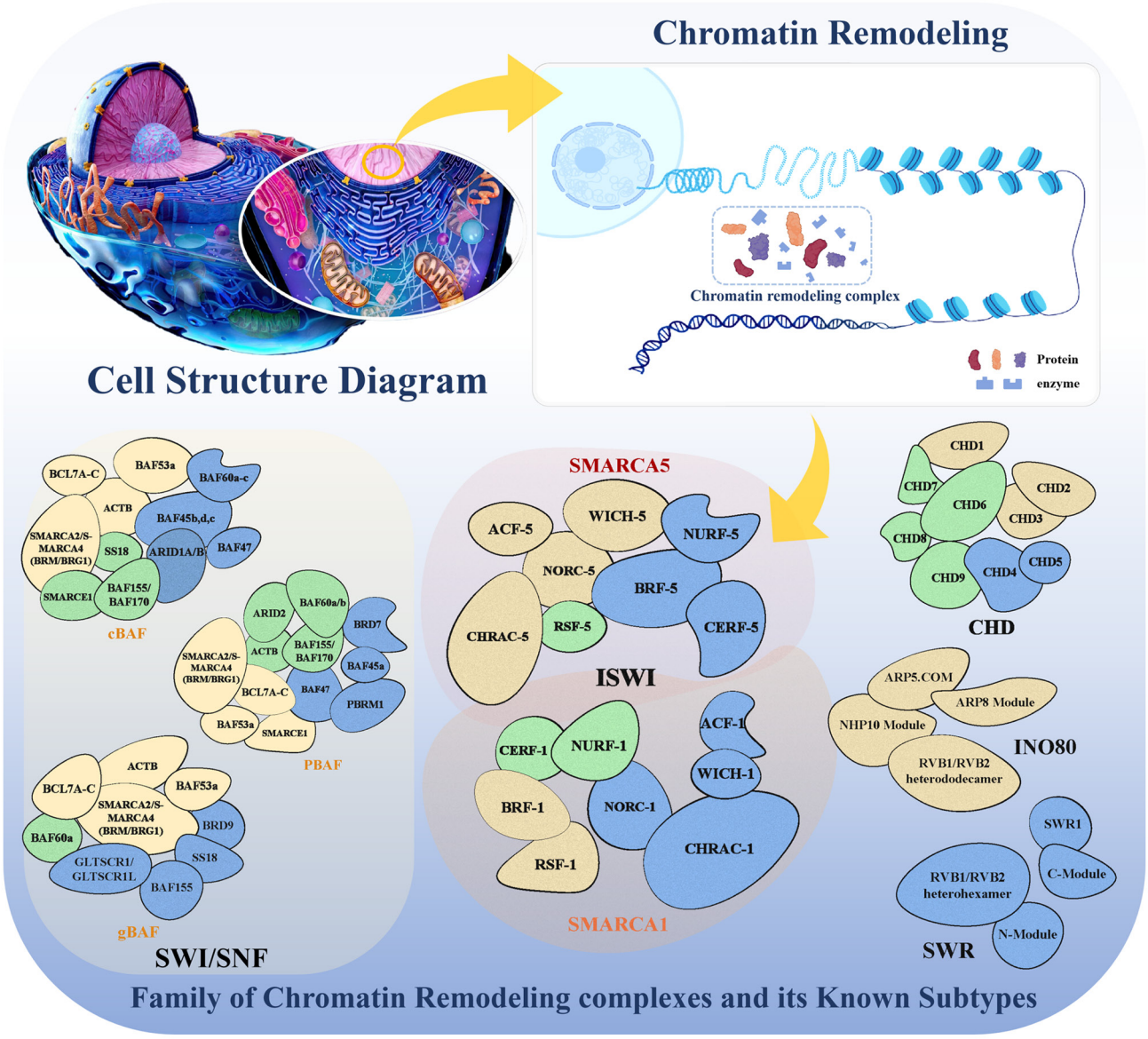

Figure 2. Chromatin remodeling complexes have diverse subtypes to implement their indispensable functions. Chromatin remodeling complexes are categorized into four distinct families: SWI/SNF, ISWI, CHD and INO80/SWR. The SWI/SNF family complexes in human cells are characterized by a marked diversity of assemblies. There are several variants of this complex, including the cBAF, PBAF and ncBAF/gBAF subtypes, which are large assemblies with core subunits such as BRG1/BRM (ATPase), BAF155/BAF170 (scaffold proteins), BAF47 (tumor suppressor) and BAF60 (linking proteins to transcription factors). The ISWI family complexes, including NURF, CHRAC and ACF, feature key subunits such as the ATPase ISWI (SMARCA1/SMARCA5), the large chromatin-binding NURF301 (BPTF), the accessory proteins CHRAC15/CHRAC17 and the scaffold protein ACF1 (BAZ1A). The CHD family complexes, ranging from CHD1 to CHD9, include subunits such as CHD1/CHD2 (chromodomains for histone binding) and CHD3/CHD4 (NuRD complex) with ATPase activity. In INO80/SWR family complexes, INO80 and SWR are presented separately since, although they belong to the same family of chromatin remodelers, they are classified into different subfamilies with distinct components. Crucial for histone exchange, these complexes include subunits such as the INO80 ATPase, RVB1/RVB2 for structural integrity and, within the SWR1 complex, the SWR1 ATPase, Swc2 for binding H2A.Z and Swc5/Swc6 for histone variant incorporation. cBAF, canonical BAF; ncBAF, non-canonical BAF; BCL7A-C, B-cell lymphoma 7A-C; BAF, brahma-associated factor; ACTB, β actin; SS18, synovial sarcoma translocation protein 18; ARID1A/B, AT-rich interactive domain 1A/B; BRD, bromodomain-containing protein; PBRM1, polybromo-1; PBAF, polybromo-associated BAF; GLTSCR1/GLTSCR1L, glioma tumor suppressor candidate region gene 1/glioma tumor suppressor candidate region gene 1-like; gBAF, germinal center B-cell-specific BAF; SWI/SNF, switching defective/sucrose non-fermenting; ACF-5, ATP-dependent chromatin assembly and remodeling factor-5; WICH, WSTF-ISWI chromatin-remodeling complex; NURF, nucleosome remodeling factor; NORC, nucleolar remodeling complex; RSF, remodeling and spacing factor; CERF-5, chromatin-associated Ets-related factor-5; ISWI, imitation SWI; ACE, activating chromatin element; CERF-1, chromatin-associated Ets-related factor-1; CHRAC-1, chromatin accessibility complex-1; CHD, Chromodomain-helicase-DNA-binding; ARP5. COM, actin-related protein 5 complex; ARP8 module, actin-related protein 8 module; NHP10 module, non-histone protein 10 module; INO80, inositol-requiring 80; SWR1, Swi2/Snf2-related 1; C-Module, C-terminal module; N-Module, N-terminal module. This figure was created with BioRender.com.

functions *in vivo*, they share a common mission: Facilitating genome utilization, which includes processes such as transcription factor binding, DNA replication and repair (45,46). It is important to note that ATP-dependent chromatin remodeling complexes can be distinguished not only by the composition of their subunits but also by the domain organization of their catalytic subunits (32). Overall, chromatin remodeling complexes play a crucial role in epigenetic regulation.

Chromatin remodeling complexes are regulated by several factors that govern their own ultimate epigenetic

functions (Fig. 3). First, ncRNAs, miRNAs and lncRNAs exert a pivotal influence on chromatin remodeling complexes. miRNAs can target the mRNA of chromatin remodeling complex subunits pre-transcriptionally, leading to their degradation, and can also inhibit the translation of these subunits. lncRNAs can interact with chromatin remodeling subunits post-transcriptionally in several ways including binding to these subunits to inhibit the assembly of the complex, acting as guiding lncRNAs to recruit chromatin remodeling complexes and as decoy lncRNAs, limiting the chromatin localization of the complexes (47-51). Second, actin and ARPs are integral components of chromatin remodeling complexes and regulate ATPase activity, facilitate complex assembly and enhance DNA binding and nucleosome repositioning through direct interaction with ATPase subunits. Additionally, ARPs interact with histones and serve as molecular bridges between chromatin-modifying complexes, coordinating higher-order chromatin regulation (22,52). Lastly, chromatin remodeling complexes are under the strict regulation of posttranslational modifications, namely, they are modulated by phosphorylation, acetylation and PARylation (22,53,54). For example, during mitosis, human SWI/SNF is phosphorylated and this modification inhibits its remodeling activity, which may contribute to the widespread inhibition of chromatin remodeling during cell division (54). What's more, the human nucleosome acetyltransferase of the histone H4 (NuA4)/Tat-interactive protein 60 kDa coactivator complex, a homologous fusion of the yeast SWR1 and NuA4 complexes, facilitates the incorporation of the histone variant H2A.Z into nucleosomes while acetylating histones H4, H2A and H2A.Z. This dual function plays a crucial role in gene regulation and genome stability maintenance (52). Additionally, Sala *et al* (55) found that PARylated ISWI displays a reduced nucleosome-binding affinity, as well as lower DNA- and nucleosome-stimulated ATPase activity. Therefore, chromatin remodeling complexes must first be regulated by upstream modulators before exerting their functions. Under normal conditions, chromatin remodeling complexes serve as facilitators and protectors of cellular molecular activities, but aberrations in their functions can lead to various diseases, such as cancer, Coffin-Siris syndrome and fibromuscular dysplasia (56). Chromatin remodeling complexes play a pivotal role in bone pathology (11,28). Numerous studies have identified a variety of relevant chromatin remodeling complexes and their subunits as well as elucidated their specific functions (26,37). For instance, the SWI/SWF complex includes subunits such as BRG1, BRM, BAF45, BAF47, BAF155, BAF170, BAF180, BAF200, BAF250a, BRD7, BRD9 and SS18. The ISWI complex is characterized by the presence of the bromodomain adjacent to zinc finger domain 1A (BAZ1A) subunit. The CHD family comprises subunits such as CHD1, CHD4, CHD7 and CHD9, and the INO80/SWR complex is composed of multiple subunits, such as INO80, SWR1, ARP4, ARP5, RvB1 and RvB2 that participate in chromatin remodeling. Each subunit is involved in distinct functions, with some overlapping roles and others being unique (28). The relationship between chromatin remodeling complexes and bone biology and bone-related diseases is dissected further below.

3. Role of chromatin remodeling complexes in bone metabolic processes

Chromatin remodeling complexes are intimately linked to bone metabolic processes, performing various regulatory mechanisms and functions in the modulation of gene expression (Figs. 4 and 5). For instance, their expression at specific stages of bone biology directs progenitor cells to differentiate and proliferate into osteoblasts. Conversely, these complexes can also contribute to bone-related diseases when their functions become aberrant (28,29,57). Therefore, in this section, the specific functional properties of these chromatin remodeling complexes in normal bone metabolic processes as well as aberrant settings are discussed (Table I).

Chromatin remodeling complexes and stemness maintenance. Stemness maintenance is crucial for bone development and the prevention of bone-related diseases, as it ensures the continuous supply of progenitor cells capable of differentiating into osteoblasts and other bone-forming cells (58,59). In the following sections, the specific mechanisms through which chromatin remodeling complexes influence stemness maintenance, and their implications for bone biology and disease, will be discussed.

BRG1 (also known as SMARCA4) and BRM (also known as SMARCA2). Well-established interactions between esBAF (BRG1 or BRM) and polycomb complexes have been documented, highlighting that both esBAF and polycomb group proteins play roles in maintaining pluripotency through both antagonistic and synergistic acts in polycomb group proteins (60,61). In osteoblast precursors, BRG1-containing SWI/SNF typically induces the expression of osteogenic genes, while BRM-specific complexes act in conjunction with p130 and repressor E2Fs to primarily restrain differentiation. This action helps sustain the committed precursor state until pre-osteoblasts receive the appropriate differentiation signals (60). Moreover, BRG1 and BRM can function as either oncogenes or tumor suppressors. In chondrosarcoma, both subunits in the esBAF complex exhibit oncogenic properties when inhibited (62). Conversely, loss of BRG1 leads to a loss of both self-renewal capacity and pluripotency (62,63), while the loss of BRM results in enhanced osteoblast differentiation and impaired adipocyte differentiation (64). Additionally, a previous study found that BRG1 interacts with Ewing sarcoma-friend leukemia integration 1 (EWS-FLI1) fusion protein or Ewing sarcoma RNA binding protein 1 (EWSR1), with the EWS-FLI1 fusion protein being detected in >85% of Ewing sarcoma cases. This interaction is a key regulator in the cell growth of Ewing sarcoma (65).

BAF47 (also known as SMARCB1/INI1). BAF47 plays a crucial role in ensuring the stability and functionality of the BAF complex. Specifically, the presence of BAF47 is essential for the SWI/SNF complex to effectively resolve bivalency in the genome, highlighting its critical role in regulating gene expression at bivalent promoters and enhancers (66,67). Therefore, the loss of BAF47 decreases the chromatin affinity of the intact BAF complex, leading to dysfunctional BAF complex activity, which is vital for every step of bone development (67). A study demonstrated that knockdown of BAF47 impedes differentiation in human

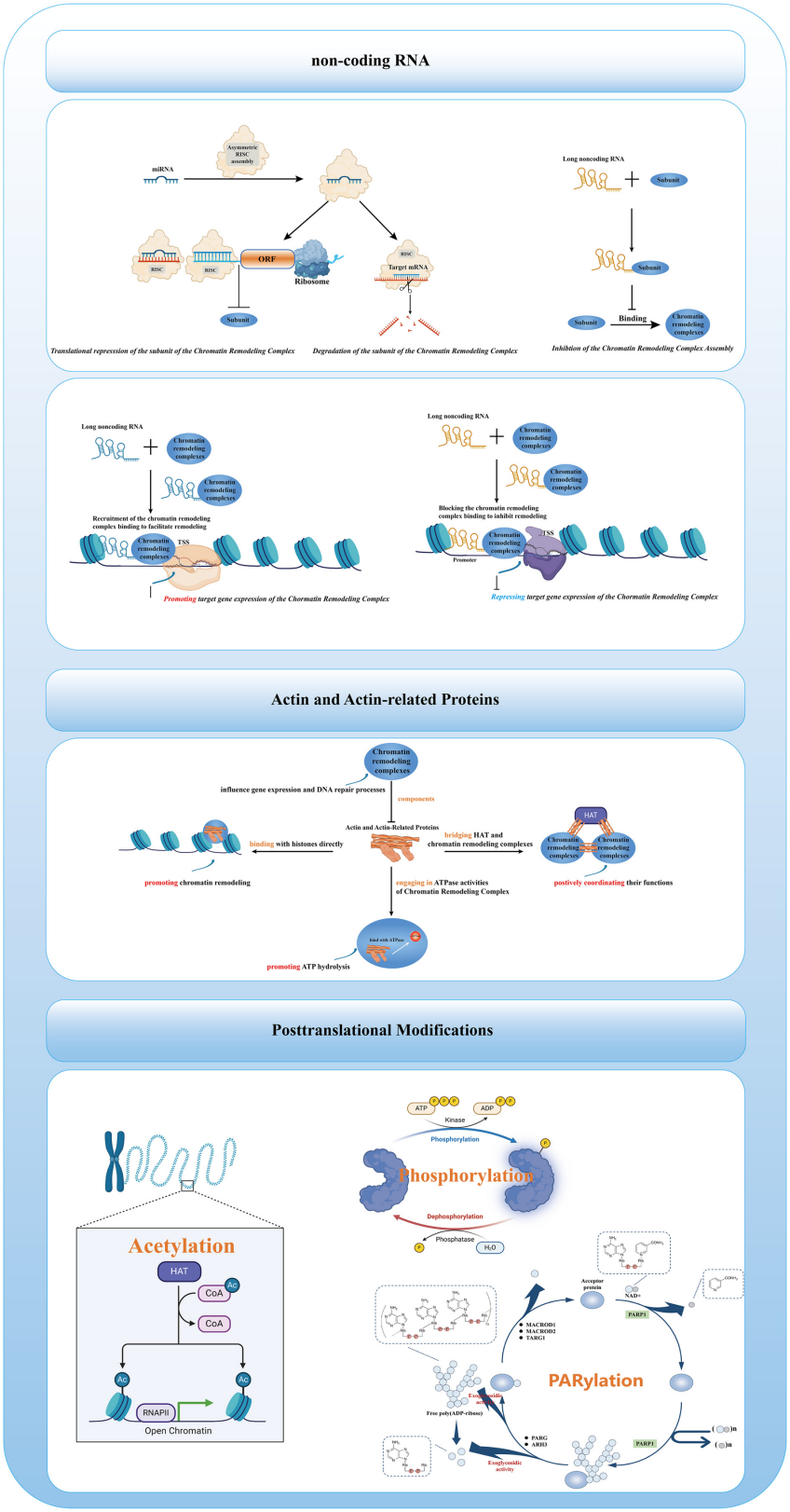

Figure 3. Chromatin remodeling complexes are under three main regulation factors: Non-coding RNA, actin and actin-related proteins, post-translational modifications. Non-coding RNA: i) miRNAs mediate translational repression or target mRNA degradation by assembling the RISC, thereby inhibiting the expression of subunits of the chromatin remodeling complex; ii) lncRNA inhibits the assembly of the chromatin remodeling complex by binding to its subunits; iii) lncRNA facilitates the recruitment of chromatin remodeling complexes to target gene promoter regions, thereby promoting gene expression; and iv) lncRNA represses gene expression by preventing the binding of chromatin remodeling complexes, thereby inhibiting chromatin remodeling. Actin and actin-related proteins: These proteins serve as components of chromatin remodeling complexes, influencing gene expression and DNA repair processes. They facilitate chromatin remodeling by directly binding to histones and promoting ATP hydrolysis through interaction with ATPase. Additionally, actin-related proteins bridge HAT and chromatin remodeling complexes, thereby positively coordinating their functions. Posttranslational modifications: Chromatin remodeling complexes are regulated by the histone post-translational modifications including phosphorylation, acetylation and PARylation. RISC, RNA-induced silencing complex; ORF, open reading frame; TSS, transcription start site; HAT, histone acetyltransferase; Ac, acetyl; MACROD1, macrodomain-containing protein 1; TARG1, tankyrase-associated RING-containing protein 1; PARG, poly (ADP-ribose) glycohydrolase; ARH3, ADP-ribosylhydrolase 3; PARP1, poly (ADP-ribose) polymerase 1. This figure was created with BioRender.com.

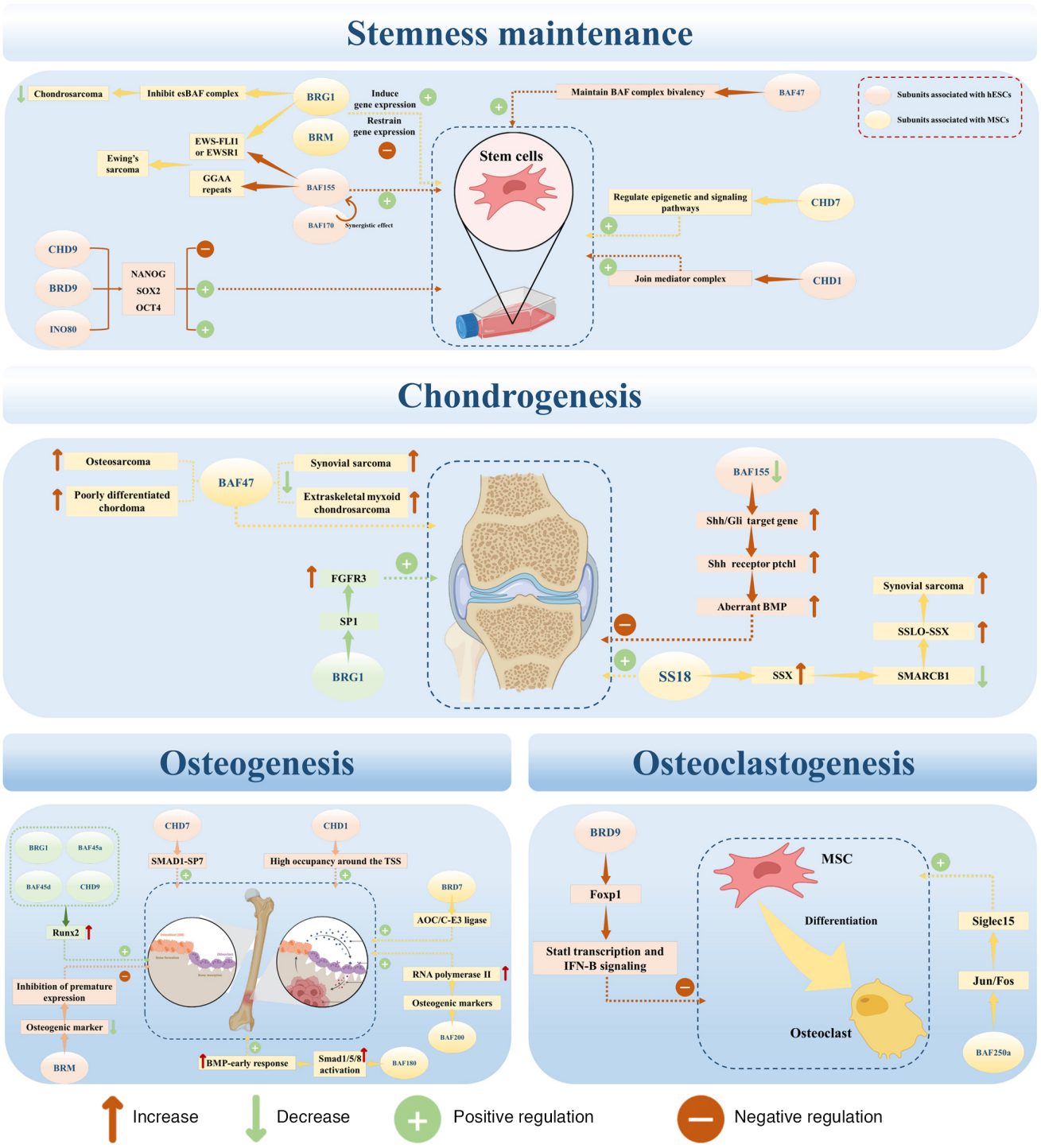

Figure 4. Epigenetic roles of chromatin remodeling complexes in bone metabolic processes, including stemness maintenance, chondrogenesis, osteogenesis and osteoclastgenesis. This figure shows how each relevant subunit, through its unique molecular mechanism, performs epigenetic changes including in normal and pathological conditions. AOC/C-E3 ligase, activator of c-Jun/C-E3 ligase; BAF, brahma-associated factor; BMP, bone morphogenetic protein; BRD, bromodomain-containing protein; BRG1, breast cancer susceptibility gene 1-associated protein; BRM, bromodomain-containing protein BRM; CHD, chromodomain-helicase-DNA-binding protein; EWS-FLI1, Ewing sarcoma breakpoint region 1-Friend leukemia virus integration 1 transcription factor; EWSR1, Ewing sarcoma breakpoint region 1; FGFR3, fibroblast growth factor receptor 3; Foxp1, forkhead Box Protein P1; INO80, inositol-requiring 80; IFN-B, interferon-β; MSC, mesenchymal stem cell; OCT4, octamer-binding transcription factor 4; Ptch1, Patched-1; Runx2, Runt-related transcription factor 2; Shh/Gli, Sonic hedgehog/glioma-associated oncogene family zinc-finger protein; Siglec15, sialic acid-binding immunoglobulin-like lectin 15; SMAD1-SP7, SMAD family protein 1-specificity protein 7; SOX2, Sex-determining region Y-box 2; SP1, specificity protein 1; SS18, synovial sarcoma translocation protein 18; SSLO-SSX, synovial sarcoma X-breakpoint gene; TSS, transcription start site. This figure was created with BioRender.com.

embryonic stem cells (hESCs), while upregulation of BAF47 enhances differentiation (68,69). Therefore, BAF47 plays a notable role in maintaining the balance of stemness in the human body.

BAF155 (also known as SMARCC1) and BAF170 (also known as SMARCC2). Together with BRG1, BAF155 and BAF170 play pivotal roles in maintaining pluripotency and self-renewal in hESCs. The depletion of these three subunits

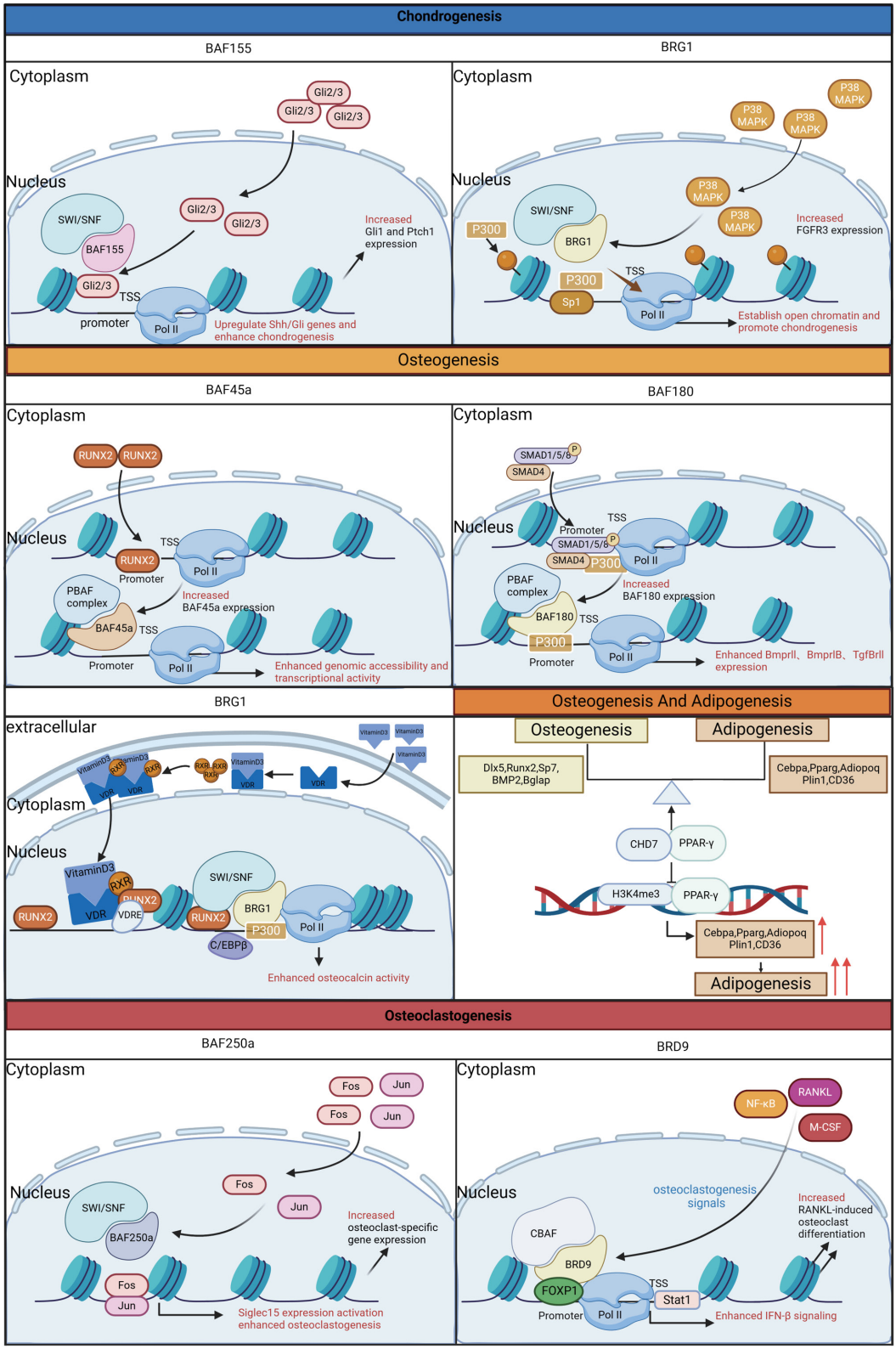

Figure 5. Chromatin remodeling complexes employ various biological regulatory mechanisms that contribute to the balance of bone development. This figure illustrates eight well-established mechanisms involved in chondrogenesis, osteogenesis, osteoclastogenesis and adipogenesis, each characterized by its unique features. Gli2/3, glioma-associated oncogene family zinc-finger protein 2/3; SWI/SNF, switch/sucrose non-fermentable; BAF, brahma-associated factor; Ptch1, Patched-1; Pol II, RNA polymerase II; RISC, RNA-induced silencing complex; ORF, open reading frame; TSS, transcription start site; HAT, histone acetyltransferase; Ac, acetyl group; MACROD, macrodomain-containing protein; TARG1, tumor necrosis factor α receptor-associated protein 1; PARG, Poly (ADP-ribose) glycohydrolase; ARH3, ADP-ribosylhydrolase 3; PARP1, Poly (ADP-ribose) polymerase 1; P38 MAPK, p38 mitogen-activated protein kinase; BRG1, brahma-related gene 1; Sp1, specificity protein 1; FGFR3, fibroblast growth factor receptor 3; RUNX2, Runt-related transcription factor 2; PBAF, polybromo-associated BAF; RXR, retinoid X receptor; VDR, vitamin D receptor; VDRE, vitamin D response element; Dlx5, Distal-less homeobox 5; BMP2, bone morphogenetic protein 2; Bglap, Bone γ-carboxyglutamate-containing protein; CHD7, chromodomain-helicase-DNA-binding protein 7; H3K4me3, Histone H3 lysine 4 trimethylation; PPAR-γ, peroxisome proliferator-activated receptor γ; Cebpa, CCAAT-enhancer-binding protein α; Adiopoq, adiponectin; Plin1, perilipin 1; CD36, NF-κB, nuclear factor-κB; RANKL, receptor activator of NF-κB ligand; M-CSF, macrophage colony-stimulating Factor; CBAF, chromatin assembly factor; BRD9, bromodomain-containing protein 9; FOXP1, forkhead box protein P1. This figure was created with BioRender.com.

Table I. Diverse role of chromatin remodeling complexes in the bone metabolic process and the biological functions of bone.

Chromatin remodeling complex	Subunits	Key features	Functions in the bone metabolic processes	Roles in the bone biological functions
SWI/SNF complex	BRG1	ATPase activity, essential for remodeling.	Regulates gene expression during chondrogenesis and osteogenesis, while also playing a role in the maintenance of stemness.	Sustains hESC proliferation, activates autophagy, induces cell cycle arrest and apoptosis in MSCs and prevents cellular senescence.
SWI/SNF complex	BRM	A core SWI2/SNF2-type ATPase, functions as a gene suppressor.	BRM-deficient preosteoblasts show early expression of osteoblast markers, indicating enhanced osteogenesis.	Regulates cell proliferation.
SWI/SNF complex	BAF250a/ BAF250b	Bromodomain-containing, transcriptional regulator, involved in targeting transcription factors and recruitment.	Promotes osteoclast differentiation by facilitating the cooperation between chromatin and thetranscription factor Jun/Fos.	Loss of BAF250b impairs MSC quiescence and proliferation through the pERK pathway.
SWI/SNF complex	BAF47	Enhancer activation and rescues BAF complex-mediated resolution of bivalency.	Regulates gene expression during chondrogenesis while also playing a role in stemness maintenance.	-
SWI/SNF complex	BAF155	Increase DNA accessibility by remodeling nucleosomes.	Regulates target genes during chondrogenesis and a crucial factor in stemness maintenance.	Depletion of BAF155 in ESCs decreases proliferation and increases cell death.
SWI/SNF complex	BAF170	A subunit of the BAF chromatin remodeling complex, working with BAF155 and BRG1 in gene regulation and development.	Maintains pluripotency and self-renewal in hESCs.	-
SWI/SNF complex	BRD9	A bromodomain-containing protein, essential for SWI/SNF complex stability.	Loss of BRD9 reduces NANOG and SOX2 levels, while its high expression suppresses osteoclastogenesis by interacting with FOXP1 to enhance STAT1 transcription and activate IFN-β signaling.	Promotes pyroptosis.
SWI/SNF complex	SS18	Involved in SS18-SSX fusion from t(X;18) chromosomal translocation, inactivates SMARCB1.	Regulates gene expression during chondrogenesis and has a notable role in synovial sarcoma.	-
SWI/SNF complex	BAF45a and BAF45d	Regulate chromatin accessibility and gene expression through interactions with various transcription factors, including PBAF-RUNX2 crosstalk.	Regulates gene expression during osteogenesis	-
SWI/SNF complex	BAF180	A subunit of the PBAF complex, crucial for chromatin remodeling and gene regulation.	Facilitates the progression of osteogenesis.	-
SWI/SNF complex	BRD7	A bromodomain-containing protein, involved in chromatin remodeling.	Regulates gene expression in osteogenesis and osteosarcoma.	Upregulation of BRD7 reduces apoptosis via the PI3K and YAP1 pathways.
CHD complex	CHD1	Chromodomain-containing, ATP- dependent, engages in the transcriptional start site.	Facilitates chromatin accessibility in hESCs, pre-initiates gene transcription and induces pluripotent stem cells and osteogenesis	-

Table I. Continued.

Chromatin remodeling complex	Subunits	Key features	Functions in the bone metabolic processes	Roles in the bone biological functions
CHD complex	CHD7	Interacts with important osteogenesis and stem cell signaling pathways.	Regulates gene expression in osteogenesis and stemness.	-
CHD complex	CHD9	Binds to related genomic domains, interacts with the transcriptional regulation of Pol II and works synergistically with BRG1.	Regulates gene expression in osteogenesis and the stemness of MSCs.	-
INO80/ SWR complex	INO80	Maintains an open chromatin environment and facilitates the recruitment of transcription factors and coactivators.	Maintains the pluripotency of hESCs and stabilize the osteogenesis.	Regulates the proliferation of ESCs.

SWI/SNF complex, switch/sucrose non-fermentable complex; BRG1, brahma-related gene 1; BAF, BRG1-associated factor; BRD, Bromodomain-containing protein; SS18, synovial sarcoma translocation protein 18; CHD, chromodomain-helicase-DNA-binding protein complex; INO80, inositol-requiring 80; SOX2, sex-determining region Y-box 2; FOXP1, forkhead box protein P1; IFN-β, interferon-β; SSX, synovial sarcoma X-breakpoint gene; PBAF, polybromo-associated BAF; RUNX2, Runt-related transcription factor 2; APC/C, anaphase-promoting complex/cyclosome; YAP1, Yes-associated protein 1; hESC, human embryonic stem cell; MSC, mesenchymal stem cell; Pol II, RNA polymerase II.

leads to pluripotency dysfunction in hESCs, significantly reducing the potential for future bone development (62,70). Additionally, BAF155 interacts with EWS-FLI1, which acts as an aberrant transcription factor that drives the cellular transformation of Ewing sarcoma. Moreover, this chimeric protein directly binds to GGAA repeats, thereby modifying the transcriptional profile of Ewing sarcoma, eventually promoting the progression of this disease (65).

BRD9. BRD9 is recruited by BRD4 to regions linked to naive pluripotency genes in a bromodomain-dependent manner, playing a crucial role in regulating and maintaining the naive pluripotent state of ESCs (71). Inhibition of BRD9 expression leads to decreased levels of NANOG and SOX2, impairing self-renewal and altering differentiation, particularly inhibiting mesoderm differentiation while promoting neural ectoderm differentiation. Since the mesoderm is essential for the development of various tissues, including cartilage and bone, its disruption can affect skeletal formation (72). BRD9 also regulates pluripotency gene expression and TGF-β/Nodal/Activin and Wnt signaling pathways by forming a complex with BRD4, SMAD2/3, β-CATENIN and p300, and modulating H3K27 acetylation to sustain hESC differentiation (72). Furthermore, inhibition of BRD9 enhances somatic cell reprogramming by downregulating fibroblast genes, limiting chromatin accessibility at enhancers and reducing reprogramming inhibitors such as MN1 and ZBTB38, thereby facilitating reprogramming (73).

CHD1. CHD1 is an ATPase-dependent chromatin remodeling protein that plays a crucial role in maintaining pluripotency and stemness in ESCs and mesenchymal stem cells (MSCs) by facilitating chromatin accessibility and regulating key gene expression. hESCs possess chromatin accessibility that enables them to differentiate into various daughter cell types, including hematopoietic, neural stem, mesenchymal stem and other lineage cells (74-76). Notably, MSCs serve as progenitor cells of osteoblasts, and osteoprogenitors originating from mesenchymal stromal cells are also committed to their differentiation into osteoblasts, the cells responsible for bone formation and maintenance (77,78). In this context, CHD1 plays a critical role in the mediator complex, facilitating chromatin accessibility in hESCs, pre-initiating gene transcription and inducing pluripotent stem cells by maintaining a heterochromatin-poor pluripotent stem cell state (75). Specifically, CHD1 is crucial for maintaining open chromatin and pluripotency in mouse ESCs; its downregulation leads to heterochromatin accumulation, loss of pluripotency and the impaired reprogramming of somatic cells to the pluripotent state (74). Moreover, CHD1 is essential for early mouse embryogenesis and pluripotency, as its loss results in embryonic lethality after implantation by significantly downregulating key regulators of cell fate specification, such as Pou5f1 and Nanog, and impairing the activation of Hmgpi during zygotic gene activation, which can be rescued by Hmgpi mRNA microinjection (79). Furthermore, CHD1 is vital for maintaining the integrity of the genome in ESCs by preventing the accumulation of DNA double-stranded breaks, thereby further supporting their pluripotency and overall stemness during hypertranscription (76). Additionally, a previous study demonstrated that CHD1 regulates the stemness of MSCs, with higher levels promoting their tissue regeneration and hematopoietic stem cell-supporting activity, while lower levels are associated with a loss of clonogenic potential in pathological conditions (2). Ultimately, the loss of CHD1 leads to the

transformation of heterochromatin and a significant loss of pluripotency (28,80).

CHD7. CHD7 is a crucial gene for stemness maintenance as it regulates epigenetic and signaling pathways and is highly expressed in active gene expression signals within stem cells (80). Research has shown that CHD7 is also vital for maintaining open chromatin in ESCs, regulated by the trithorax protein Ash2l, and the knockdown of Ash2l reduces H3K4 methylation and promotes a silenced chromatin state (81) Additionally, the co-localization of BRG1 and CHD7 at distal regions in ESCs influences the expression of key transcription factors such as NANOG, SOX2 and OCT4, further affecting ESC pluripotency (82). Furthermore, it has been reported that CHD7 interacts with lysine-specific histone demethylase 1 (LSD1) in mouse ESCs and is crucial for maintaining stemness and proper differentiation. The increased co-occupancy of methylated H3K4 and CHD7 on chromatin following LSD1 deletion underscores the essential role of LSD1 in facilitating the binding of CHD7 to chromatin and regulating differentiation (83). Finally, CHD7 knockout ESCs exhibit defective expression of ectodermal markers that affect pluripotency, which is vital for the stemness associated with subsequent differentiation into bone, cartilage and skeletal muscle (83). Notably, the depletion of CHD7 in MSCs leads to the repression of osteogenic transcription factors and impairs the osteogenesis ability of these cells (84).

CHD9. CHD9 is dispensable for pluripotent marker expression, including OCT4, SOX2, NANOG and SSEA-1 (85). The knockout of CHD9 promotes hESC proliferation through binding to genomic domains that overlap with DNA motifs recognized by cell cycle-related transcription factors and interacting with the transcriptional regulation of Pol I-controlled genes and nuclear receptors (85,86). Additionally, a study found that CHD9 is transiently expressed during mesenchymal cell differentiation both *in vivo* and *in vitro*, with expression observed in osteoprogenitors and downregulation in mature osteoblasts (78).

INO80. The INO80 is crucial for the self-renewal of hESCs, as well as for reprogramming and embryonic development. INO80 specifically binds to the promoters of key pluripotency genes in conjunction with transcription factors such as OCT4, NANOG, SOX2 and Krüppel-like factor 4, with its binding reliant on WD repeat domain 5 (WDR5). INO80 helps maintain an open chromatin structure, enabling the recruitment of the mediator complex and RNA polymerase II, which enhances the expression of these pluripotency genes (87). Furthermore, silencing INO80 leads to the abnormal morphology of hESCs (87). While in mouse ESCs, INO80 deficiency causes a notable increase in the duration of the G1-phase in ESCs cultured under primed conditions. Additionally, INO80 directly associates with the transcription start site to modulate the expression of genes involved in the cell cycle, including Ccne1, Cdc25b and Cdkn1b (78).

Chromatin remodeling complexes and chondrogenesis. Chondrogenesis is the process by which MSCs differentiate into chondrocytes, ultimately forming cartilage models (anlagen) that serve as precursors to future bones through endochondral ossification while also secreting cartilage matrix to form cartilage (88,89). In the following section, the impact of chromatin remodeling complexes on chondrogenesis under both normal and pathological conditions of cartilage will be discussed.

BRG1. BRG1 is an indispensable chromatin regulator that engages in numerous cellular activities and plays a core role in DNA replication, repair, recombination and transcriptional regulation (90,91). The expression of fibroblast growth factor receptor 3 (FGFR3) is essential for cartilage development and can be induced by bone morphogenic protein (BMP) 2. This induction is mediated by the downstream factor Sp1, which is influenced by BRG1. BRG1 promotes FGFR3 expression by remodeling chromatin regions that have Sp1-binding sites at the FGFR3 transcriptional initiation sites. This alteration enhances Sp1's binding to the proximal promoter, which facilitates p300 recruitment and leads to modifications in the 'histone code', including phosphorylation and methylation changes (92). The natural small molecule spermidine has been reported to protect against and restore cartilage damage in OA (93-95), and BRG1 mediates its protective effects by enhancing osteoarthritic cartilage through the Nrf2/KEAP1 and STAT3 signaling pathways (96).

BAF47. Studies have shown that BAF47 serves as a genetic hallmark in malignant tumors, and its loss is associated with extraskeletal myxoid chondrosarcoma (EMC) featuring rhabdoid cytological characteristics. However, in one case of EMC exhibiting high-grade features such as increased cellularity and prominent nucleoli, with no rhabdoid features present, the expression of nuclear BAF47 remained intact (97,98). Additionally, BAF47 levels are reduced in synovial sarcoma, and this reduction can be assessed using immunohistochemical staining for diagnostic purposes (29,99). In addition, compared with other atypical teratoid tumors where BAF47 is absent or lost, in mesenchymal chondrosarcoma, the level of BAF47 is retained (100). Therefore, BAF47 is an excellent marker to diagnose different tumor types but the mechanisms remain unclarified (101).

SS18. Mutations in the BAF subunit across human cancer types display a notable tissue-specific pattern, with BAF subunits mutated in >20% of all human cancers (102). Notably, almost all cases of synovial sarcoma are attributed to the SS18-SSX fusion due to the t(X;18) translocation, whereas mutations in the SS18 BAF subunit are infrequently observed in other types of cancer (103,104). The underlying mechanism involves the SS18-SSX gene fusion, which indirectly inactivates the function of SMARCB1 by binding to the chromatin remodeling complex, thereby promoting the transcription of the oncoprotein, SS10-SSX, and contributing to the development of synovial sarcoma (104,105).

BAF155. BAF155 is a component of SWI/SNF chromatin remodeling complexes, which help make DNA more accessible by altering the arrangement of nucleosomes during gene transcription (106). The targeted deletion of BAF155 leads to a failure in the transcriptional activation of Sonic hedgehog (Shh)/Gli target genes within limb buds that are undergoing development, such as the Ptch1 receptor for Shh and its downstream effector Gli1 in the posterior region of the limb bud. This disruption of the Hh pathway is associated with aberrant BMP activity and the initiation of chondrogenesis (107).

Chromatin remodeling complexes and osteogenesis. Osteogenesis is the biological process through which new

bone is formed, involving the differentiation of MSCs into osteoblasts (108). This complex process is regulated by various signaling pathways and factors, including hormones, growth factors, transcription factors and ncRNAs, ensuring proper bone development and homeostasis (109,110). Regulating MSC osteogenic differentiation is essential for advancing bone tissue engineering (111). Several subunits of chromatin remodeling complexes play a pivotal role in osteogenesis, making them valuable for applications in bone tissue engineering (84,112). For example, overexpression of CHD7 can interact with downstream factors of BMP signaling, such as SMAD1, thereby enhancing the osteogenic potential of MSCs (84). Additionally, BAF180 influences MSC osteogenic differentiation by modulating BMP/Smad signaling, improving chromatin accessibility, and increasing binding at key osteogenic genes, including Alpl, BmprIb, TgfbrII and Runx2, in BMP2-treated MSCs (112). Overall, a deeper understanding of how chromatin remodeling complexes regulate MSC osteogenic differentiation can optimize the ability of MSCs to differentiate into osteoblasts, thereby facilitating their application in bone tissue engineering and the treatment of bone-related diseases (84).

BRG1. BRG1, a core component of the SWI/SNF chromatin remodeling complex that functions as an ATPase, has been identified in developing skeletal structures of the mouse embryo and in *ex vivo* osteoblast cultures (113). A study has demonstrated that BRG1 expression is consistently present throughout skeletal components and is positively correlated with the key osteogenic regulatory protein, runt related transcription factor 2 (RUNX2) (57). These observations suggest that SWI/SNF chromatin remodeling activity is essential for supporting RUNX2-dependent skeletal gene expression. RUNX2 is crucial for initiating osteogenesis upstream of SP7 in the regulatory hierarchy of osteoblast development, ensuring independent and autonomous regulation in cartilage and bone development (57,114). In the context of BRG1 depletion, the induction of alkaline phosphatase, an osteogenic marker, is impaired in pre-osteoblasts (115). Additionally, another study found that the knockout of BRG1 severely damages the ability of bone cells to mineralize and to express key markers of osteoblast differentiation, such as osteocalcin and alkaline phosphatase (60). Osteocalcin itself plays an important role in determining bone size, shape and strength (116,117). Furthermore, BRG1-containing SWI/SNF complexes stimulate basal tissue and vitamin D3-enhanced osteocalcin promoter activity via the transcription factor, CCAAT/enhancer-binding protein β. This factor, together with RUNX2, forms a stable complex that facilitates RNA polymerase II binding and the activation of osteocalcin gene transcription in osteoblastic cells (118). Moreover, p107, alongside retinoblastoma protein (pRB), plays a distinct role in the induction of the osteogenic gene, Alpl, during osteoblast differentiation, with p107 being crucial for the efficient recruitment of the BRG1-SWI/SNF chromatin-remodeling complex, necessary for Alpl activation (119).

BRM. Notably, unlike other subunits of the chromatin remodeling complex, BRM-deficient preosteoblasts exhibit premature expression of osteoblast differentiation markers suggesting an enhancement of osteogenesis and subsequent bone formation (64,120).

BAF45a and BAF45d. In the BAF45 family, there are four homologs, including BAF45a, BAF45b, BAF45c and BAF45d (68,121). Among these homologs, BAF45a and BAF45d are more accessible during the induction of bone MSC differentiation into osteoblasts compared with BAF45b and BAF45c, as BAF45a and BAF45d are preferentially expressed in osteoblasts. Notably, BAF45a serves as a vital subunit of the chromatin regulatory complex and, through the bone tissue-specific RUNX2-BAF45A-EZH2 molecular epigenetic axis, determines chromatin accessibility during the early stage of commitment and differentiation of mineralized cells (122). The deletion of BAF45a results in decreased promoter accessibility for vital transcription factors required for the induction and maturation of osteoblasts (15,122).

BAF180 (also known as PBRM1). Mechanistically, BMP and osteogenic signaling pathways induce the expression of BAF180 and PBAF in MSCs, promoting ossification *in vivo* by affecting the activation of SMAD1/5/8 through locus-specific epigenomic remodeling. This involves PBRM1 bromodomains and the transcriptional regulation of BMPR/TGFβRII, which together lead to the expression of BMP-early-responsive genes and facilitate the progression of osteogenesis (57,112).

BAF200 (also known as ARID2). A study has suggested that BAF200 is crucial for promoting osteoblast commitment and differentiation (123). BAF200 targets key osteogenic markers, such as the Alpl promoter and Bglap, and in some cases, significantly contributes to the recruitment of RNA polymerase II, ultimately facilitating the commitment and differentiation of osteoblasts. Conversely, the depletion of BAF200 expression during the osteoblast differentiation process results in a failure to mineralize into a calcified bone matrix (124,125).

BRD7. In addition to functioning alongside BAF180 and BAF200 as components of the PBAF complex to promote osteogenesis (112), BRD7 has also been identified as a novel substrate of the APC/C-E3 ligase during the cell cycle. This role may provide a therapeutic target for treating osteosarcoma and serves as a crucial regulator for stabilizing and suppressing tumor progression in osteosarcoma (126).

CHD1. As a member of the CHD family, CHD1 is required for the induction of osteoblast-specific gene expression, extracellular matrix (ECM) mineralization and ectopic bone formation *in vivo*. CHD1 is closely associated with transcription and nucleosome turnover downstream of the transcriptional start site (TSS); it exhibits high occupancy around the TSS of differentiation-activated genes, thereby supporting the differentiation of MSCs into osteoblasts (2,75).

CHD7. SMAD1 and SP7 are core components of the canonical BMP signaling pathway. Previous studies have elucidated that CHD7 is required for the osteogenic differentiation of human bone MSCs by interacting with SMAD1 and binding to the enhancer region of SP7 to promote differentiation. By contrast, the absence of CHD7 impairs bone formation *in vivo* (80,84). Additionally, other studies have demonstrated that depletion of CHD7 in MSCs and preosteoblasts results in a phenotype characterized by low bone mass and significantly increased marrow adiposity. This occurs through the enhancement of the peroxisome proliferator-activated receptor (PPAR) signaling associated with methylated H3K4 patterns, which subsequently activates the transcription of downstream

lipogenic genes. This disruption of the balance between osteogenesis and lipogenesis ultimately results in bone and fat disorder (127-129).

CHD9. CHD9, a master regulator of ribosomal gene transcription in MSCs and osteogenesis, works synergistically with BRG1 to upregulate the expression of RUNX2 (86,130). Additionally, CHD9 binds to skeletal tissue-specific promoters associated with key genes involved in osteoblast differentiation, including glycan, core-binding factor subunit α1, collagen II, osteocalcin and myosin (85).

INO80. The only subunit in the INO80/SWR family that contributes to osteogenesis is INO80. INO80 interacts with WDR5 in MSCs, regulates canonical Wnt activity and stabilizes the expression of key osteogenic markers, including RUNX2, SP7, collagen type I α1 chain and osteopontin, all of which promote osteogenesis (131).

Chromatin remodeling complexes and osteoclastogenesis. Osteoclastogenesis plays a crucial role in bone development and bone diseases by regulating the resorption of bone tissue, thereby maintaining the balance between bone formation and degradation (132). On the other side of the bone remodeling balance, osteoclastogenesis requires chromatin remodeling complexes to exert their influence and contribute to the overall process.

BAF250a (also known as ARID1a/OSA1). The expression of BAF250a facilitates the cooperation between chromatin and the transcription factor, Jun/Fos, leading to the upregulation of sialic acid-binding Ig-like lectin 15 in osteoclast precursors, thereby triggering the differentiation of osteoclasts (16). Moreover, BAF250a plays a critical role in safeguarding osteoclast fate canalization during the proliferation-differentiation switch by facilitating the formation of transcriptional condensates with coactivator BRD4 and lineage-specifying transcription factor PU.1 at the Nfatc1 super-enhancer (133). Additionally, the antagonistic interactions between the ARID1A-cBAF and BRD9-ncBAF complexes, along with the dependency on coactivator BRD4, highlight the intricate balance required for proper cell fate canalization during osteoclastogenesis (133). Furthermore, a recent study has shown that the expression of BAF250a is downregulated in osteosarcoma compared with non-tumor tissues, suggesting its potential as a novel prognostic and therapeutic marker (134,135).

BRD9. BRD9 is upregulated during receptor activator of NF-κB ligand-induced osteoclast differentiation and suppresses osteoclastogenesis by interacting with the transcription factor, FOXP1. This interaction enhances STAT1 transcription by increasing chromatin accessibility at the STAT1 promoter and enhancer regions, subsequently activating IFN-β signaling, which serves as a negative feedback mechanism for osteoclastogenesis. Conversely, the absence of BRD9 expression can lead to debilitating bone diseases such as osteoporosis, osteopetrosis, osteonecrosis and Paget's disease (14).

Chromatin remodeling complexes and angiogenesis. Angiogenesis is crucial for bone formation and resorption, as blood vessels play a vital role in bone regeneration and are influenced by aging and pathological conditions (136,137). Vascular endothelial growth factor (VEGF), which is expressed by osteoprogenitors, hypertrophic chondrocytes and osteoblast precursors, regulates angiogenesis within the skeletal system (138). In addition, the hypoxia-inducible factor (HIF)-1α pathway is essential for maintaining bone homeostasis and angiogenesis, significantly impacting the development of bone metabolic diseases (138). Sena *et al* (139) demonstrated that BRM and BRG1 enhance the hypoxic induction of HIF1α and HIF2α genes, along with their target genes, by recruiting BRG1 complexes to gene promoters. Additionally, the SWI/SNF subunits, BRM and BRG1, enhance HIF-1-mediated target gene activation in an ATPase-dependent manner and are recruited to the VEGF gene promoter under hypoxia (140). CHD4 also acts as a crucial coactivator of HIF1 and HIF2, amplifying HIF-driven transcriptional programs (141). Although there is currently no direct research exploring the role of chromatin remodeling complexes in angiogenesis during bone development and related diseases, their influence on angiogenesis-related genes suggests that they may also play a significant role in these processes.

During the embryonic stage, angiogenesis serves a crucial role in bone development by providing essential signaling molecules, such as VEGF, and supporting osteoblasts and bone marrow stromal cells. This process not only promotes bone formation but also contributes to bone function, making it a key regulatory factor in bone development (142). It has been reported that BRG1-deficient mutants die by embryonic day 11.5 and show abnormal angiogenesis in the yolk sac (143). BRG1 deletion also reduces COUP-TFII expression in venous endothelial cells and causes improper arterial marker expression in veins during embryonic vascular development (144). CHD4 also plays a key role in embryonic vasculature development by suppressing plasmin activation, with its loss leading to increased urokinase-type plasminogen activator receptor expression and decreased thrombospondin-1, both critical for plasmin activation (145). While chromatin remodeling complexes play a crucial role in embryonic vascular development, their influence on angiogenesis during bone formation and its overall impact on bone development remain largely unexplored. Further research is needed to deepen the understanding of these mechanisms and their relevance to bone-related diseases.

4. Role of chromatin remodeling complexes in bone biological functions

Normal bone development and aging are regulated by a complex interplay of biological and physiological processes that work in concert to sustain skeletal health throughout the lifespan (146). This section mainly focuses on chromatin remodeling complexes in three notable aspects: Proliferation, senescence and programmed cell death (Table I and Fig. 6), as they play crucial roles in regulating bone cell growth, influencing bone density and quality, affecting bone formation and repair processes as well as maintaining the balance of bone tissue (147).

Chromatin remodeling complexes and proliferation. Bone formation and remodeling during development are regulated by a network of transcription factors that facilitate the transition from proliferation to differentiation in osteoblastogenesis.

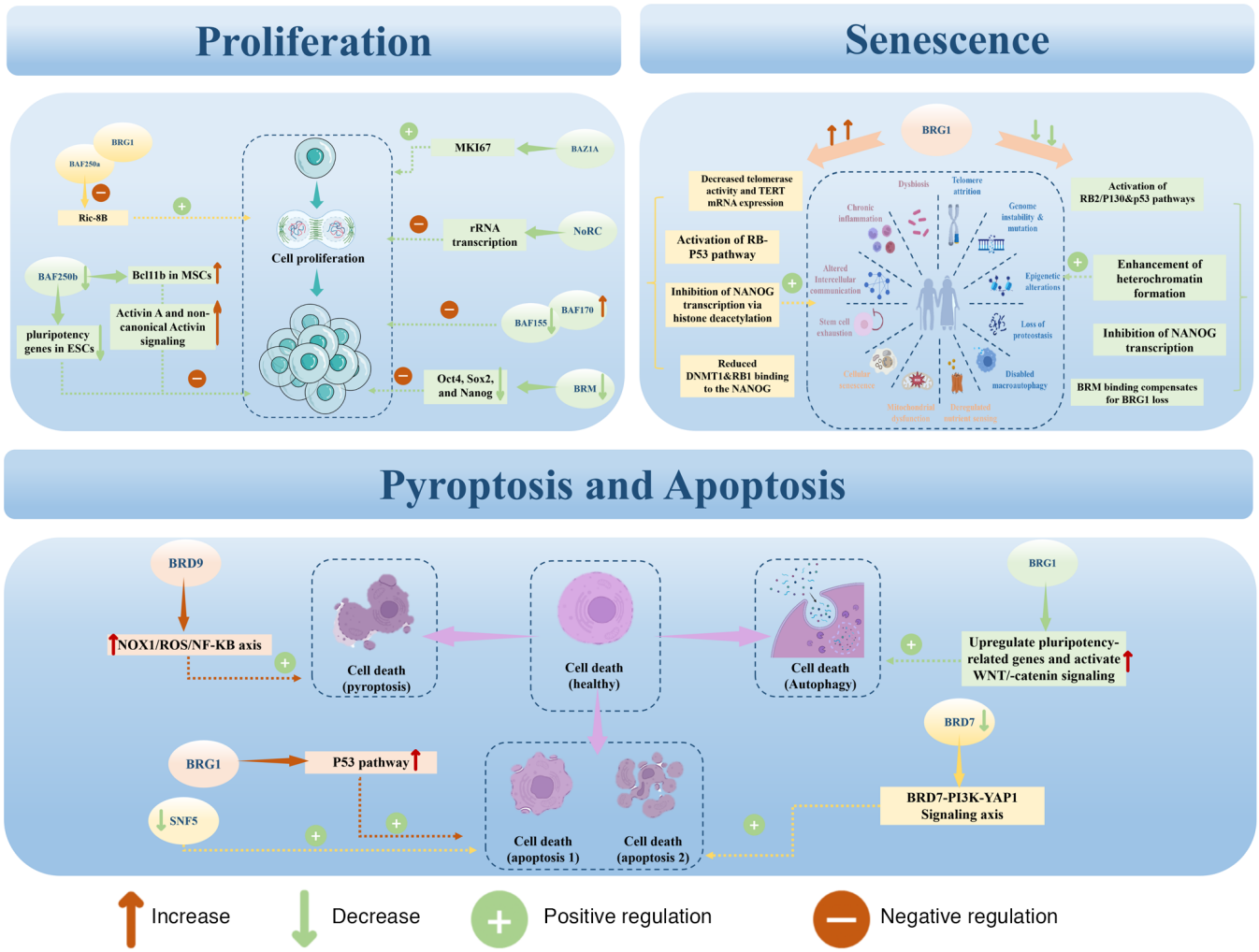

Figure 6. Epigenetic roles of chromatin remodeling complexes in bone biological functions. There are three other bone-related processes in which chromatin remodeling complexes and their essential subunits are involved. This figure demonstrates how each relevant subunit utilizes its distinct molecular mechanism to achieve epigenetic modifications, both under normal and pathological conditions. BAF, BRG1-associated factor; Ric-8B, regulator of G-protein signaling 8B; BRG1, brahma-related gene 1; Bcl11b, B-cell lymphoma/leukemia 11B; MKI67, marker of proliferation Ki-67; BAZ1A, bromodomain-adjacent to Zinc finger domain 1A; NoRC, nucleolar remodeling complex; Oct4, octamer-binding transcription factor 4; Sox2, sex-determining region Y-box 2; TERT, telomerase reverse transcriptase; DNMT1, DNA methyltransferase 1; RB1, Retinoblastoma 1; BRD, bromodomain-containing protein; NOX1, nicotinamide adenine dinucleotide phosphate oxidase 1; ROS, reactive oxygen species; NF-κB, nuclear factor-κB; YAP1, Yes-associated protein 1.

Grandy *et al* (148) reported that the Ric-8B gene, a pro-proliferative factor, is negatively regulated during osteoblast differentiation by the transcription factor C/EBPb, which, along with BRG1 and BRM, inhibits Ric-8B promoter activity. This repression of Ric-8B expression is crucial as it influences osteoblast proliferation and differentiation, ultimately impacting bone development (148).

During bone development and remodeling, the proper proliferation of MSCs and ESCs is essential for maintaining stem cell pluripotency and regulating differentiation. However, uncontrolled proliferation can lead to the loss of stem cell function or abnormal differentiation. In this context, chromatin remodeling complexes play a critical role in maintaining the delicate balance between proliferation and differentiation. For instance, the loss of BAF250b in MSCs results in the upregulation of Bcl11b, which induces activin A and activates non-canonical activin signaling through the pERK pathway, impairing MSC quiescence and proliferation, thereby disrupting tissue homeostasis (149). Similarly, the loss of BRG1 initially leads to reduced proliferation, self-renewal and altered colony morphology in ESCs. Long-term depletion results in the complete loss of key ESC determinants, including OCT4, SOX2 and NANOG (150). Additionally, depletion of BAF155 in ESCs decreases proliferation and increases cell death, while forced expression of BAF170 reduces the competitive self-renewal ability of ESCs in immunocompromised mice and impairs teratoma formation (150,151). Furthermore, biallelic inactivation of BAF250b in ESCs leads to reduced proliferation, downregulation of pluripotency genes, increased expression of lineage-specific genes, including mesodermal differentiation markers, and cell cycle abnormalities, along with downregulation of the cell cycle regulator Cdc20 (152). Lastly, the nucleolar remodeling complex (NoRC), assembled by the histone variant H2A.X at ribosomal DNA (rDNA) promoters, recruits NoRC to rRNA genes, leading to the formation of a heterochromatin-like structure that downregulates rRNA transcription and ultimately reduces the proliferation rate of ESCs (153). Therefore, these findings highlight the intricate interplay between chromatin remodeling complexes and

transcription factors in regulating proliferation, which is vital for proper bone development and tissue homeostasis.

Chromatin remodeling complexes and senescence. Cellular senescence, a pivotal aspect of biological aging, significantly influences bone development and related diseases (154). BRG1, serving as the ATPase subunit of the SWI/SNF chromatin remodeling complex, plays a crucial role in regulating cellular senescence in MSCs. Specifically, prior research has indicated that BRG1 is upregulated during the replicative senescence of MSCs, with forced BRG1 expression resulting in decreased telomerase activity and telomerase reverse transcriptase mRNA expression, coupled with the activation of RB- and p53-related pathways (155). Conversely, Alessio *et al* (156) reported that downregulation of BRG1 enhances senescence and heterochromatin formation via the activation of the RB2/P130 and p53 pathways, leading to reduced expression of stemness-related genes and compromised cellular physiology. Despite these seemingly inconsistent findings, the subsequent investigation by Squillaro *et al* (157) provided crucial insights, confirming that both forced upregulation and silencing of BRG1 in MSCs trigger cellular senescence. Specifically, in cells with silenced BRG1 expression, NANOG transcription is inhibited by RB1 and/or RB2-mediated DNA methyltransferase 1 (DNMT1) recruitment, causing methylation of the NANOG promoter, with BRM binding serving as a compensatory mechanism for the loss of BRG1. By contrast, in cells overexpressing BRG1, NANOG transcription is mainly suppressed through histone deacetylation, accompanied by reduced binding of DNMT1 and RB1 to the promoter, while histone deacetylase 1 and RB2 remain bound at E2F sites (157). Given these intricate interplays between BRG1 and cellular senescence in MSCs, it is evident that the role of chromatin remodeling complexes, particularly the SWI/SNF complex, in the senescence of osteoblasts, chondrocytes and osteoclasts remains an area ripe for further exploration.

Chromatin remodeling complexes and programmed cell death. Programmed cell death, including apoptosis, pyroptosis, autophagy and ferroptosis, plays a crucial role in the development, maintenance and repair of bone tissue (147). Apoptosis, a key form of programmed cell death, is essential for normal cell turnover, immune system function, embryonic development and the removal of damaged cells, ensuring the proper regulation of cellular processes (158). In bone development, chromatin remodeling complexes have been shown to regulate apoptosis, highlighting their critical role in maintaining cellular homeostasis. For example, BRG1 induces cell cycle arrest and apoptosis in MSCs, with p53 playing a central role in triggering programmed cell death (155). Similarly, SNF5 is vital for the survival of early embryonic cells, and its loss leads to apoptotic cell death and extensive DNA fragmentation (159). In the context of bone degeneration, BRD7 expression is decreased in severely degenerated NP tissues, and its knockdown promotes matrix degradation and apoptosis. Upregulation of BRD7 reverses these effects, enhancing matrix synthesis and reducing apoptosis through the PI3K and YAP1 pathways (160). These findings suggest that targeting the BRD7-PI3K-YAP1 axis, a chromatin remodeling pathway, could offer a potential therapeutic approach for treating intervertebral disc degeneration (IDD) by regulating apoptosis pathways.

Pyroptosis, an inflammatory form of programmed cell death typically triggered by inflammasomes and executed by gasdermin proteins in response to danger signals and pathogen infections, plays several crucial roles development, maintenance and repair, such as in osteogenic processes (161). Chai *et al* (162) discovered that tumor necrosis factor-α (TNF-α) induces pyroptosis in preosteoblastic MC3T3-E1 cells, negatively affecting osteogenic differentiation. Additionally, inhibiting Caspase-1-mediated pyroptosis promotes osteogenic differentiation, underscoring the complex relationship between these cell death pathways and bone development (163). A recent study has also shown that BRD9 contributes to bone degeneration through the regulation of inflammatory pathways via regulating pyroptosis (164). BRD9 expression increases as IDD progresses, and its inhibition reduces TNF-α-induced matrix breakdown, reactive oxygen species (ROS) production and pyroptosis in rat NP cells. BRD9 promotes IDD through the NADPH oxidase 1/ROS/NF-κB pathway, and *in vivo* inhibition of BRD9 helps mitigate IDD progression in a rat model (164). These findings suggest that targeting BRD9 and its chromatin remodeling functions may offer potential treatments for IDD, linking chromatin remodeling complexes and pyroptosis in bone development and degeneration.

Autophagy is a cellular process that facilitates the removal and recycling of damaged or unnecessary components to maintain bone homeostasis and function (165). A recent study has shown that BRG1 plays a crucial role in regulating bone development by upregulating pluripotency-related genes and activating pathways such as WNT/β-catenin signaling and autophagy, with inhibition of BRG1 leading to the opposite effect, suggesting an interconnected role of chromatin remodeling and autophagy in bone development and maintenance (166).

5. Role of chromatin remodeling complexes in the pathogenesis of bone-related diseases

The role of chromatin remodeling complexes in the pathogenesis of bone-related diseases is a critical area of study. Dysregulation of these complexes can impact bone cell differentiation, proliferation and apoptosis, resulting in a range of bone-related diseases, such as bone tumors, osteoporosis and OA. For example, low levels of BRD7 are associated with a poor prognosis in patients with osteosarcoma, while upregulation of BAF155 triggers OA (Table II). Understanding the mechanisms by which chromatin remodeling complexes contribute to these pathologies could reveal new therapeutic targets for treating bone-related diseases.

Chromatin remodeling complexes and bone tumors. Bone tumors refer to abnormal cellular proliferation occurring in the bone or surrounding tissues (such as cartilage and bone marrow) and can be classified as either benign or malignant (10,167). Although malignant bone tumors are rare [the annual incidence rate of osteosarcoma is 4-5 individuals per million (168)], the early symptoms are often subtle, leading

Table II. Key chromatin remodeling complexes in the pathogenesis of bone-related diseases.

Disease	Related subunits	Alias	Family	Expression	Targets	Biological function	(Refs.)
Ewing sarcoma	BRG1	SMARCA4	mSWI/SWF complex	Up	EWS-FLI1 or EWSR1	Contributes to Ewing sarcoma progression.	(65)
Ewing sarcoma	BAF155	SMARCC1	mSWI/SWF complex	Up	EWS-FLI1	Contributes to Ewing sarcoma progression.	(65)
Ewing sarcoma	BAF250a	ARID1a/ OSA1	mSWI/SWF complex	Up	EWS-FLI1	serves as an interface between EWS- FLI1 and the BAF complex.	(177)
Ewing sarcoma	CHD4	Mi-2β	CHD complex	Up	EWS-FLI1	Promotes Ewing sarcoma cell survival and its oncogenic gene expression program.	(176)
Synovial sarcoma	BAF47	SMARCB1/ INI1	mSWI/SWF complex	Down	-	Synovial sarcoma progression.	(29,99,104,105)
Synovial sarcoma	SS18	SSXT/SYT	mSWI/SWF complex	Up	SS18-SSX (t(X;18)	Synovial sarcoma progression.	(103-105)
Chondrosarcoma	BRG1	SMARCA4	mSWI/SWF complex	Up	esBAF complex	Chondrosarcoma progression.	(62)
Chondrosarcoma	BRM	SMARCA2	mSWI/SWF complex	Up	esBAF complex	Chondrosarcoma progression.	(62)
Extraskeletal myxoid chondrosarcoma	BAF47	SMARCB1/ INI1	mSWI/SWF complex	Down	-	-	(98)
Osteosarcoma	BAF47	SMARCB1/ INI1	mSWI/SWF complex	Down	-	-	(69,184)
Osteosarcoma	BRD7	-	mSWI/SWF complex	Down	APC/C-E3 ligase	Stabilizes and suppresses osteosarcoma progression.	(126)
Osteosarcoma	BAZ1A	ACF1	ISWI complex	Up	-	Induces senescence of osteosarcoma.	(198)
Osteosarcoma	BAF250a	ARID1a	mSWI/SWF complex	Down	-	-	(134,135)
Osteosarcoma	BRG1	SMARCA4	mSWI/SWF complex	Down	-	-	(134)
Poorly differentiated chordoma	BAF47	SMARCB1/ INI1	mSWI/SWF complex	Down	-	Binds with mSWI/ SNF complexes at different sites in the genome.	(183-185,190)
Skull base chordomas	BAF180	PBRM1	mSWI/SWF complex	Down	-	-	(191-193)
Osteoarthritis	BAF155	SMARCC1	mSWI/SWF complex	Up	IL-1β in chondrocytes	Silencing BAF155 impairs the pro-inflammatory response induced by IL-1β in chondrocytes.	(200)
Osteoarthritis	BRD7	-	mSWI/SWF complex	Up	-	Causes ferroptosis in osteoarthritis.	(201)

Table II. Continued.

Disease	Related subunits	Alias	Family	Expression	Targets	Biological function	(Refs.)
Bone-fat disorder	CHD7	-	CHD complex	Down	PPARγ signaling with H3K4me patterns	Disrupts the balance between osteogenesis and lipogenesis.	(127-129)
Adolescent idiopathic scoliosis	CHD7	-	CHD complex	Down	-	-	(205)
Osteoporosis	BRM	-	mSWI/SWF complex	Up	Osteoblast progenitors	BRM depletion results in an increased proportion of cells that express markers for osteoblast precursors and provides substantial resistance to osteoporosis.	(64)
Osteoporosis	BRD9	-	mSWI/SWF complex	Down	Osteoblast progenitors	BRD9 deficiency promotes the specification of the osteoclast lineage and increases bone resorption.	(14)
Postmenopausal osteoporosis	CHD1	-	CHD complex	Up	-	-	(210)

BRG1, brahma-related gene 1; EWS-FLI1, Ewing sarcoma breakpoint region 1-Friend leukemia virus integration 1 transcription factor; EWSR1, Ewing sarcoma breakpoint region 1; BAF, BRG1-associated factor; ARID1a, AT-rich interactive domain-containing protein 1a; OSA1, other SANT/Myb-associated protein 1; CHD, Chromodomain-helicase-DNA-binding protein; Mi-2β, microphthalmia-associated transcription factor-interacting protein 2 β; INI1, integrase interactor 1; SS18, synovial sarcoma translocation protein 18; SSXT/SYT, synovial sarcoma X-breakpoint translocation/synovial sarcoma translocation; SSX, synovial sarcoma X-breakpoint gene; esBAF complex, embryonic stem cell BAF; BRD, bromodomain-containing protein; APC/C-E3 ligase, anaphase-promoting complex/cyclosome-E3 ligase; BAZ1A, bromodomain-adjacent to zinc finger domain 1A; ACF1, accessory chromatin assembly factor 1; ISWI complex, imitation switch complex; PBRM1, polybromo-associated BRG1-associated factor 1; IL-1β, Interleukin-1 β; PPARγ, peroxisome proliferator-activated receptor γ; H3K4me, histone H3 lysine 4 methylation.

to misdiagnosis as 'growing pains' or arthritis, which delays treatment (169-171). Common types of bone tumors include benign tumors, such as chondroma and giant cell tumor of the bone, the latter of which may undergo malignant transformation (172). Malignant bone tumors can be primary, including osteosarcoma (predominantly affecting adolescents), chondrosarcoma (more common in middle-aged and elderly individuals) and Ewing sarcoma (frequently seen in children and adolescents) (173,174). Alternatively, malignant bone tumors can be metastatic, originating from cancer types such as lung or breast cancer and subsequently spreading to the bone (175).

Chromatin remodeling complexes play a critical role in regulating tumor cell proliferation, survival and metastasis across various bone tumors. In Ewing sarcoma, for example, CHD4 depletion leads to increased DNA accessibility, which in turn increases DNA damage (176). Moreover, Ewing sarcoma is driven by the EWS-FLI1 fusion protein, which alters gene expression through the prion-like domains of EWS and ARID1A, facilitating the formation of biomolecular condensates crucial for tumor progression. ARID1A condensates localize to EWS/FLI1 target enhancers, driving long-range chromatin remodeling and the formation of functional hubs at oncogenic genes (177). Selvanathan *et al* (178) describe a novel feed-forward cycle in Ewing sarcoma, where EWS-FLI1 promotes the splicing of the ARID1A isoform protein variant ARID1A-L, driving tumor growth, while ARID1A-L, in turn, stabilizes EWS-FLI1, revealing potential targets for cancer-specific therapies. Additionally, in the presence of EWS-FLI1, multimerization at GGAA repeats and the prion-like domains of EWSR1 facilitate the recruitment of BAF complexes to tumor-specific enhancers, driving oncogenic gene expression (179). Autocrine neural EGFL like 2 (NELL2) signaling in Ewing sarcoma cells regulates BAF chromatin remodeling complexes and promotes cell proliferation by inhibiting Cdc42 and upregulating EWS-FLI1,

with NELL2, CD133 and EWS-FLI1 positively regulating each other to enhance proliferative capacity (180). Similarly, in synovial sarcoma, the SS18-SSX fusion protein disrupts normal chromatin remodeling, leading to tumorigenesis (181). Additionally, ncBAF complexes uniquely localize to CTCF sites and promoters, acting as synthetic lethal targets in synovial sarcoma, with BRD9 subunit depletion effectively reducing cell proliferation (182). In chondrosarcoma, proline-rich polypeptide-1 inhibits chondrosarcoma cancer stem cell proliferation by targeting the SWI/SNF chromatin-remodeling complex, reducing the expression of key oncogenic players such as BRG, BAF170 and BRM (62). EMC is characterized by alterations in BAF47, although the precise mechanisms remain unclear (98,99). Osteosarcoma, the most prevalent primary bone sarcoma, is associated with reduced levels of BAF47 and BAF250a, suggesting their potential involvement in tumor progression (69,173,183-185). BRD7 also functions as a tumor suppressor in osteosarcoma and is degraded by the APC/C complex during the cell cycle. A BRD7 mutant resistant to APC/C degradation more effectively suppresses tumor growth, suggesting that targeting the APC/C-BRD7 pathway, along with APC/C inhibitors such as proTAME, could provide a novel therapeutic approach for osteosarcoma (126). Additionally, in response to doxorubicin treatment in U2OS cells, the INO80 complex regulates the removal of H2A.Z at the p21 promoter, facilitating p21 activation and contributing to the DNA damage response in osteosarcoma (186). Another study uncovered that pRB directly activates the osteoblast differentiation marker, Alpl, by recruiting the BRG1-containing SWI/SNF chromatin-remodeling complex, which displaces BRM-containing complexes, marking the onset of differentiation and highlighting the critical role of pRB in osteosarcoma susceptibility (187). Moreover, cohesin and PBAF play a crucial role in suppressing gene transcription near DNA double-strand breaks during interphase, and their absence results in extensive genome alterations, potentially driving genomic instability in osteosarcoma (188). The PHD domain of the KAP1 corepressor acts as an intramolecular E3 SUMO ligase, facilitating sumoylation of the adjacent bromodomain, which is crucial for KAP1-mediated gene silencing in osteosarcoma by recruiting SETDB1 and the CHD3/Mi2 NuRD complex, thereby enhancing histone methyltransferase activity (189). Similarly, poorly differentiated chordoma also exhibits BAF47 loss, implicating its role in tumor biology (69,183,185,190). In skull base chordomas, BAF180 mutations are linked to poor prognosis, underscoring the importance of chromatin remodeling complexes in determining tumor aggressiveness (191-193).

Given their central role in tumor progression, chromatin remodeling complexes present viable targets for therapeutic intervention. Trabectedin, for instance, has been shown to evict the SWI/SNF complex from chromatin in Ewing sarcoma, redistributing EWS-FLI1 and altering histone modifications to suppress tumor growth (194). The loss of CHD4 in Ewing sarcoma not only delays tumor growth and enhances overall survival but also, when combined with PARP inhibition using olaparib, significantly boosts the antitumor effects of genotoxic agents, positioning CHD4 as a promising therapeutic target (171). In synovial sarcoma, BRD9 inhibitors, such as FHD-609 (NCT04965753) (195) and CFT8634 (NCT05355753), have been developed to degrade BRD9, effectively impairing tumor proliferation (196,197). In osteosarcoma, BAZ1A and BRD7 have emerged as potential therapeutic targets, with BAZ1A influencing senescence and BRD7 stabilizing tumor suppression pathways (126,198). These findings suggest that targeting specific chromatin remodeling subunits could provide novel treatment strategies for sarcomas driven by epigenetic dysregulation.

Several chromatin remodeling components are frequently mutated or lost in bone and soft tissue sarcomas, highlighting their diagnostic and prognostic significance. In osteosarcoma, BRG1 mutations and the downregulation of BAF47 and BAF250a suggest a disrupted chromatin landscape (69,173,183-185). Similarly, synovial sarcoma is characterized by the SS18-SSX fusion, which affects SMARCB1 function (104,105). BAF47 loss is a hallmark of poorly differentiated chordoma and EMC, whereas BAF180 mutations in skull base chordomas are associated with poor prognosis (98,99,191-193). These genetic alterations could serve as valuable biomarkers for the early detection, risk stratification and treatment response monitoring, reinforcing the clinical relevance of chromatin remodeling complexes in sarcoma pathology.

Chromatin remodeling complexes and OA. OA, the most common joint disorder primarily affecting the aging population, is a leading musculoskeletal cause of impaired mobility, with the majority of individuals >65 years experiencing this condition (199). Wang *et al* (200) reported that interferon regulatory factor 1 (IRF1) regulates BAF155 expression, playing a crucial role in OA development, as knockdown of either IRF1 or BAF155 alleviates OA-like symptoms and inflammatory responses. Epigenetic modifications near the BAF155 promoter, mediated by GCN5 and SETD2, are key drivers of its expression, with upregulation of these enzymes worsening OA symptoms (200). Additionally, a study found that reduced levels of BRD7 activates the main immunodeficiency pathway. By contrast, increased levels of BRD7 may activate the ECM receptor interaction pathway and inhibit the primary immunodeficiency pathway, ultimately leading to ferroptosis in OA (201).

Chromatin remodeling complexes and bone-fat disorder. Bone marrow is the only tissue where bone and fat are adjacent and collaborate in various processes such as metabolic homeostasis, hemopoiesis and osteogenesis (202). Successful osteogenesis and adipogenesis are tightly regulated processes that must maintain a balance for proper skeletal and metabolic function. It has been reported that PPARγ serves as a differentiation switch between osteoblastogenesis and adipogenesis in the bone marrow, inhibiting the process of osteoblastogenesis (128). Depletion of CHD7 in MSCs and preosteoblasts disrupts this balance, leading to low bone mass and increased marrow adiposity through enhanced PPARγ signaling and trimethylated H3K4-mediated activation of lipogenic genes (127-129).

Chromatin remodeling complexes and AIS. AIS is defined by a lateral curvature of the spine (Cobb angle) of at least 10 degrees, occurring in the absence of any underlying congenital

or neuromuscular abnormalities (203). The Cobb angle is calculated by drawing lines along the most tilted vertebrae at the curve's top and bottom and measuring the intersection (204). Studies have found that genetic variants of CHD7 play a vital role in AIS. According to a comparison of genotype and allele frequency between patients with AIS and healthy controls, rs121434341 of CHD7 is significantly associated with AIS susceptibility (205). Meanwhile, the rs1017861 polymorphism in the CHD7 gene is associated with susceptibility idiopathic scoliosis in Caucasian female patients, averaging 16.8±4.2 years old (range, 12.3-50.1). Additionally, the rs1017861 and rs4738813 polymorphisms are associated with higher curvature severity and progression rate (206). Lower expression of CHD7 has also been observed in patients with AIS compared with controls, which may be associated with the etiology of aberrant bone mass in AIS, but the pathogenetic mutation mechanism remains to be determined (205,207).

Chromatin remodeling complexes and osteoporosis. During senescence, the bone marrow has a reduced number of MSCs and an impaired balance between osteogenesis and osteoclastogenesis, leading to age-related osteoporosis (131,208,209). Therefore, the chromatin remodeling complex that contributes to osteogenesis and osteoclastogenesis may play a significant role in osteoporosis, such as BRM, BRD9 and CHD1 (14,64,210). BRM plays a crucial role in maintaining the balance of MSC lineage commitment between adipocytes and osteoblasts. BRM-null mice show a marked resistance to osteoporosis as the population of osteoblast progenitors is enhanced at the expense of increased adipocyte differentiation (64). Glucocorticoids, while effective for treating inflammatory and autoimmune disorders, cause bone loss by repressing osteogenic genes through the glucocorticoid receptor (GR), particularly involving the BRM. A study has revealed that BRM, unlike the essential ATPase BRG1, cooperates with the GR to repress genes such as Bglap, Per3 and FasL, disrupting osteoblast differentiation and promoting bone degradation (211). Moreover, BRD9 deficiency enhances osteoclast commitment and accelerates the development of osteoporosis (14). Postmenopausal bone loss, related to estrogen deficiency, is the predominant contributor to osteoporosis. Serum levels of CHD1 are elevated during postmenopausal osteoporosis (PMOP) and may play a role in pathogenesis. This elevation could potentially serve as an effective marker for diagnosing PMOP (210).

6. Conclusions and perspectives

Chromatin remodeling complexes are crucial for maintaining normal bone development and are implicated in various bone-related diseases. The present review provides a detailed examination of the diverse roles of these complexes, revealing their functions as regulators, promoters, inhibitors and stabilizers in bone biology. The present review emphasizes that understanding the specific mechanisms by which chromatin remodeling complexes influence bone homeostasis is essential for developing targeted therapies. For instance, certain subunits of these complexes may play critical roles in modulating gene expression during osteoblast differentiation, and disruptions in their function could lead to conditions such as osteoporosis or other metabolic bone diseases. Identifying these specific subunits and their interactions will be vital for designing interventions that can restore normal bone function.

However, the significant gap in research regarding the impact of aging on the functionality of chromatin remodeling complexes in bone health should be noted. The few studies available suggest that age-related changes in these complexes may contribute to impaired bone regeneration and increased fracture risk. This highlights the need for longitudinal studies that examine how the activity and composition of chromatin remodeling complexes evolve with age, and how these changes correlate with clinical outcomes in bone health. Understanding these dynamics will be crucial for developing strategies to mitigate the effects of aging on bone integrity.

Furthermore, it is important to consider the potential therapeutic implications of targeting chromatin remodeling complexes. Given their central role in regulating gene expression, pharmacological modulation of these complexes could provide a novel approach to treating bone-related diseases. For example, small molecules that enhance the activity of specific chromatin remodeling complexes may promote osteoblast differentiation and function, offering a new avenue for osteoporosis treatment. Conversely, small molecule inhibitors that target dysfunctional subunits of these complexes could help restore normal gene expression patterns, thereby addressing the underlying causes of metabolic bone diseases, such as using dBRD9 to treat synovial sarcoma and trabectedin for Ewing sarcoma (194,196). Controlled lineage selection in MSCs offers a promising strategy for cell engineering and tissue regeneration. For instance, CHD7-silenced MSCs show comprised osteogenic ability when cultured with a scaffold *in vivo* (84). Since BRM remains unchanged during normal osteogenesis, targeting it may enhance bone formation, and developing BRM inhibitors holds promise as a potential osteoporosis treatment (64). Targeting BRM, a key mediator of GR-induced repression in osteogenesis, may also offer a therapeutic strategy to counteract glucocorticoid-induced bone loss and potentially aid in reversing age-related osteoporosis by relieving repression on osteogenic genes (211). Furthermore, a study has shown that transfection of MSCs with small interfering RNA targeting INO80 results in impaired mineral deposition under osteogenic induction conditions, and mice implanted with INO80-silenced MSCs also exhibit reduced bone formation. This highlights the critical role of the INO80 complex in MSC osteogenic differentiation and its potential applications in clinical tissue engineering and osteoporosis treatment (131). BAF250a, another subunit, acts as a key link between EWs:Fli1 and the BAF complex; its capacity to form condensates is crucial for the dysregulated gene expression that fuels growth. As a result, the absence of condensate-competent BAF250a significantly obstructs tumor advancement, highlighting it as a possible therapeutic target. Nonetheless, the transient nature of these interactions complicates efforts to effectively target condensate formation, posing challenges in creating suitable inhibitors (177). In clinical trials, some new drugs are still under development and in the early phase such as FHD-609, a heterobifunctional degrader of BRD9 that treats advanced synovial sarcoma or SMARCB1-deficient tumors, which is in phase I study (195). Moreover, tazemetostat has demonstrated some efficacy in treating certain

SMARCB1-deficient tumors in a subset of patients. However, it still faces limitations such as inconsistent efficacy, unclear indications and ambiguous dosing guidelines (212). Therefore, the potential therapeutic role of chromatin remodeling complexes in bone-related diseases needs further studies and research.

Additionally, through the continuous exploration of the assembly and 3D structures of chromatin remodeling complex subunits, there is potential for the discovery and development of specific chemical modulators that can optimize therapeutic outcomes. Understanding the structural nuances of these complexes will facilitate the design of targeted interventions that can more effectively influence their activity in bone biology. By leveraging structural biology techniques, such as X-ray crystallography and cryo-electron microscopy, researchers can gain insights into the conformational changes and interactions that govern the function of these complexes. For example, a potent and selective BRD9 bromodomain inhibitor series was developed based on a novel pyridinone-like scaffold, with crystallographic data guiding the optimization of its potency for BRD9 (213). Moreover, the integration of artificial intelligence in structural analysis presents a transformative opportunity for advancing our understanding of chromatin remodeling complexes. This approach can significantly accelerate the discovery of small molecules that specifically target the active or allosteric sites of chromatin remodeling complexes, enhancing their therapeutic efficacy.

In conclusion, while there has been progress in understanding the role of chromatin remodeling complexes in bone-related diseases, our knowledge remains limited and fragmented. We consider that utilizing advanced techniques, such as CRISPR-based gene editing and high-throughput sequencing, will allow for a more comprehensive exploration of these complexes and their interactions within the bone microenvironment. Additionally, integrating insights from systems biology could help elucidate the complex regulatory networks involving chromatin remodeling in bone biology. This deeper understanding could ultimately lead to innovative therapeutic strategies aimed at enhancing bone health and effectively treating degenerative bone conditions, thereby improving patient outcomes and quality of life.

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Authors' contributions

WW prepared the first draft of the manuscript; YW, YN and CZ performed the literature search; WW and YC wrote and edited the manuscript; WW and QY drew the figures; WS and QY supervised and polished the manuscript. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

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