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RNA-binding proteins in skeletal disorders: insights into molecular mechanisms and possible therapeutic targets

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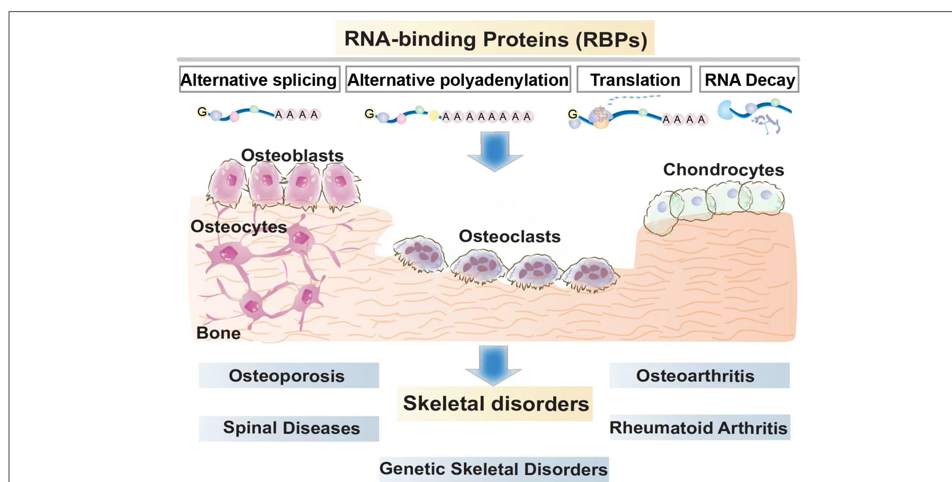
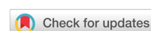


Abstract

RNA-binding proteins (RBPs) can form complex regulatory networks by binding to numerous transcripts, thereby exerting precise control over post-transcriptional gene regulation. Defects in their functions contribute to numerous human skeletal disorders by modifying RNA processing and regulation. Advancements in comprehending the molecular mechanisms of RBP functions are facilitating the development of effective therapies. Here, we delineated RBPs involved in bone development and skeletal disorders, highlighting recent advancements in this evolving field, focusing on mechanisms and therapeutic implications.



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INTRODUCTION

The skeleton is a metabolically active organ composed of cartilage and bone, comprising three principal cell types: osteoblasts (OBs), osteoclasts (OCs), and chondrocytes. OCs are formed through the fusion of mononuclear precursors, resulting in the formation of terminally differentiated mature and giant cells[1]. OBs differentiate directly from mesenchymal precursors or indirectly through a cartilage intermediate[2]. At sites of bone remodeling, OCs secrete regulatory factors that sequentially recruit osteoblast-lineage cells, thereby facilitating bone matrix deposition and mineralization[3,4]. Within this bone homeostasis, osteocytes are terminally differentiated OBs embedded within the bone matrix. They generate paracrine and endocrine factors, detect mechanical forces, regulate mineral metabolism, and sustain intercellular communications[5].

Any imbalance in bone remodeling, caused by inadequate activity of OBs or excessive activation of OCs, leads to diminished bone mass and weakened bone strength, thereby increasing the risk of fractures[6]. Although the role of post-transcriptional regulators, including microRNAs (miRNAs), is well-studied in cellular development, skeletal homeostasis, and disease conditions, the function of regulated RNA-binding proteins (RBPs) remains unclear.

Classic RBPs are modular proteins composed of well-defined RNA-binding domains (RBDs). They create ribonucleoproteins (RNPs) with cellular RNA molecules, affecting their fate from transcription through translation[7]. RBPs are evolutionarily conserved, with approximately 2% being tissue-specific, predominantly associated with mRNA- and non-coding affinities. These are attributed to the presence of one or more RBDs that interact with RNA in a sequence- and structure-dependent fashion, including the common RNA recognition motif (RRM), K-homology, DEAD/DEAH [Asp-Glu-Ala-Asp (referring to the conserved amino acid sequence D-E-A-D in the helicase motif II)/Asp-Glu-Ala-His (referring to the conserved sequence D-E-A-H in the corresponding motif)] helicase, and zinc-finger domains, and approximately 30 other less abundant domains[8].

However, there is another subfamily of RBPs that lack canonical RBDs, termed non-canonical RBPs (ncRBPs). Despite the identification of numerous ncRBPs and the characterization of their RNA interactomes, their roles in bone diseases remain unclear[9]. As "moonlighting" proteins, numerous ncRBPs are established metabolic enzymes, membrane proteins, or signaling molecules[10]. This dual functionality allows them to fulfill critical roles in the bone microenvironment and bone metabolism.

Mutations or expression alterations in RBPs frequently result in tissue-specific deficiencies, affecting skeletal development, mineral density maintenance, and bone integrity. Therefore, this study provides an updated overview of the role of RBPs in skeletal disorders and clarifies the underlying molecular mechanisms, highlighting potential therapeutic applications.

MOLECULAR MECHANISMS OF RBPs IN BONE HOMEOSTASIS

RBPs are a class of cytoplasm-nucleus shuttle proteins that regulate all stages of pre-mRNA processing, including 5'-end capping and splicing to 3'-end cleavage and polyadenylation in the nucleus. Additionally, RBPs closely regulate the encapsulation of mature mRNAs into RNP complexes, thereby facilitating their translocation into the cytoplasm for translation. RBP-mRNA interactions also influence mRNA stability and the timing and mechanisms of mRNA degradation [Figure 1][11,12]. Given the extensively documented studies on disabling RBP functions in skeletal disorders, we review the dysregulation or dysfunction of various RBPs affecting bone homeostasis and emphasize several well-studied RBPs of functional significance [Table 1].

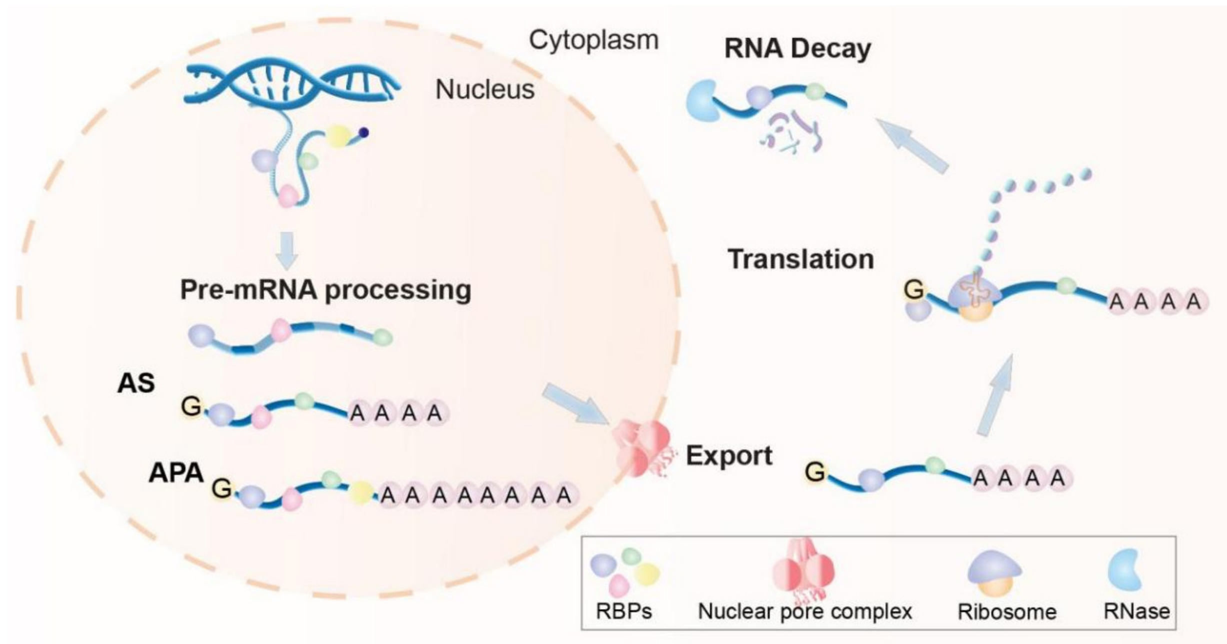

Figure 1. Interactions with RNA-binding proteins regulate RNA metabolism at multiple levels. From birth to decay, RNA fate is controlled by various dynamically changed RNA-binding proteins (RBPs, colored shapes), encompassing processes at the nuclear [alternative splicing (AS), alternative polyadenylation (APA)] and cytoplasmic (transport, translation, and degradation) levels.

Alternative splicing

Alternative splicing (AS) is a co-transcriptional mechanism facilitated by the spliceosome - commonly involving exon skipping, intron retention, alternative 5' splicing sites, alternative 3' splicing sites, and mutually exclusive exon splicing. In bone homeostasis, specialized RBPs modulate this process by identifying pre-mRNA sequence elements and guiding the splicing machinery to cleavage and ligation sites. This produces multiple mature mRNA isoforms from identical pre-mRNA, affecting mRNA stability and protein diversity[13,14].

For instance, splicing factor 3B subunit 4 (SF3B4) participates in RNA splicing in the nucleus, where it interacts with bone morphogenetic protein receptor-IA (BMPR-IA) to impede osteogenic and chondrocyte differentiation[15]. Similarly, the 54-kDa nuclear RNA-binding protein ($p54^{nrb}$) regulates chondrogenesis through specific AS. Minigene analysis and mutant $p54^{nrb}$ construction verified that it regulates collagen type II alpha 1 (*Col2a1*) mRNA splicing through two RRMs. Transgenic expression of mutant $p54^{nrb}$ (with Col2a1-Cre) impairs chondrogenesis and delays endochondral ossification[16]. Although these studies revealed the role of AS in OB and chondrocyte differentiation, its precise role in OC differentiation remains unclear, presenting a potential direction for subsequent studies.

Alternative polyadenylation

Alternative polyadenylation (APA) is a significant post-transcriptional regulation that produces a widespread mechanism that generates transcript isoforms with variable 3' untranslated regions (3'UTR) length by identifying distinct polyadenylation signals[17]. APA frequently alters solely the 3'UTR of the mRNA, which differs in its interactions with RBPs, consequently influencing mRNA localization, translation, and stability[18]. Although APA is frequently dysregulated in cancer, little information exists regarding APA events in the bone domain. To date, only one study has indicated that APA enhances gene expression during endochondral bone formation. Specifically, APA-induced *Col1a1/2* 3'UTRs shortening may evade repression by miR-29a-3p-mediated gene repression[19].

Table 1. Targets and dysregulation of RNA-binding proteins associated with bone homeostasis

RBP	Basic RBP mechanisms	Experimental system	Targets	Bone metabolism	Reference
SF3B4	Alternative splicing	C2C12 cells; ATDC5 cells	BMPR-IA	↓Osteogenic differentiation ↓Chondrocyte differentiation	[15]
p54^{nrb}	Alternative splicing	Transgenic mice	COL2A1	↑Chondrocyte differentiation	[16]
MSI1	Translation regulation	MC3T3-E1 cells	MACF1	↑Osteoblast differentiation	[21]
MSI2	Translation regulation	Bone marrow mesenchymal stem cells; bone marrow macrophages	Cebpα	↑Osteoblastogenesis ↑Osteoclastogenesis	[22]
SAMD4	Translation regulation	Mesenchymal progenitors	MIG6	↑Osteoblast differentiation ↑Chondrogenesis and chondrocyte differentiation	[24]
ZFP36	mRNA stability	Knockout mice	-	↓Osteoclast activity	[28]
ZFP36L1	mRNA stability	Knockout mice	PPARγ2; HSPA1A	↑Osteoblastic differentiation ↑Chondrocyte apoptosis	[29,30]
HuR	mRNA stability	Primary mouse osteoblasts; mesenchymal stromal cells	LARP6; HOTAIR	↑Osteoblast differentiation	[32,33]
METTL14	m6A writer	Bone marrow mesenchymal stem cells; bone marrow macrophages	BECLIN-1; GPX4	↑Osteogenic differentiation ↓Osteoclast differentiation	[36,37]
METTL3	m6A writer	MC3T3-E1 cells	BECLIN-1; SMAD7; SMURF1	↓Osteogenic differentiation	[38-40]
FTO	m6A eraser	Osteoclast precursors	Cyclin A2; CDK2	↑Osteoclast formation	[45,46]
ALKBH5	m6A eraser	Mesenchymal stem cells	PRMT6	↓Osteogenic differentiation	[47]
YTHDF1	m6A reader	Bone marrow mesenchymal stem cell	ZNF839	↑Osteogenic differentiation	[48]
IGF2BP2	m6A reader	MC3T3-E1 cells	SRF	↑Osteogenic differentiation	[49]
YTHDF2	m6A reader;	Umbilical cord mesenchymal stem cells	FBLN1	↓Osteogenic differentiation	[50]

SF3B4: Splicing factor 3B subunit 4; BMPR-IA: bone morphogenetic protein receptor-IA; p54^{nrb}: 54-kDa nuclear RNA-binding protein; COL2A1: collagen type II alpha 1; MSI1/2: musashi 1/2; MACF1: microtubule and actin crosslinking factor 1; Cebpα: CCAAT/enhancer binding protein alpha; SAMD4: sterile alpha motif domain containing protein 4; MIG6: mitogen-inducible gene 6; ZFP36: zinc finger protein 36; PPARγ2: peroxisome proliferator-activated receptor gamma 2; HSPA1A: heat shock protein family A member 1A; ZFP36L1: ZFP36 ring finger protein like 1; HuR: human antigen R; LARP6: la-related protein 6; HOTAIR: lncRNA HOX transcript antisense RNA; METTL14: methyltransferase-like 14; GPX4: glutathione peroxidase 4; METTL3: methyltransferase-like 3; SMAD7: sma-and mad-related protein 7; SMURF1: SMAD specific E3 ubiquitin protein ligase 1; FTO: fat-mass and obesity-associated protein; CDK2: cyclin dependent kinase 2; ALKBH5: AlkB homologue 5; PRMT6: protein arginine methyltransferase 6; YTHDF1/2: YT521-B homology domain family 1/2; ZNF839: zinc finger protein 839; IGF2BP2: insulin-like growth factor 2 mRNA binding protein; SRF: serum response factor; FBLN1: fibulin-1; RBPs: RNA-binding proteins.

Translation

RBP-mediated translation control mechanisms frequently focus on the translation initiation stage, where translation efficiencies fluctuate according to the binding affinities of RBPs with the 5' or 3' UTR of target mRNAs[20]. Musashi1 and Musashi2 belong to the Musashi (MSI) family, which regulates stem cell fate by modulating translational efficiency. They specifically bind to r(G/A)U1-3AGU sequences (MSI binding elements, MBEs) located at the 3' UTR of the target mRNA. This binding inhibits the poly-A binding protein from interacting with the extension initiation complex, suppressing translation. Recent studies demonstrated that MSI1 stabilizes microtubule and actin crosslinking factor 1 (*Macf1*), thereby promoting MC3T3-E1 osteogenic differentiation through the Wnt/β-Catenin pathway[21]. MSI2 may bind to MBEs at the 3'UTR of CCAAT (Cytosine-Cytosine-Adenine-Adenine-Thymine)/enhancer binding protein alpha (mouse *Cebpα*) mRNA, thereby promoting osteoblastogenesis in bone marrow mesenchymal stem cells (BMSCs)[22]. It is significantly expressed in OCs, facilitating nuclear factor-kappa B (NF-κB) activation, thereby stimulating OC formation and survival from bone marrow macrophages (BMMs)[23]. Furthermore, sterile alpha motif domain containing protein 4 (SAMD4) functions as a repressor of translational mechanisms, and its

deficiency in mesenchymal progenitors exhibits impaired OB differentiation, chondrogenesis, and chondrocyte differentiation. This correlates with increased synthesis of mitogen-inducible gene 6 protein, which binds to SAMD4 through stem-loop structures known as "Smaug recognition elements"[24].

Stability

RNA stability determinants encompass terminal structures of eukaryotic mRNAs, specifically the 5' cap and 3' poly(A) tail. Loss of either structure is adequate to impede translation and facilitate decay[25]. Specific cis-elements in the target mRNA, including AU-rich, CU-rich, or GU-rich elements, facilitate mRNA decay through interacting with various RBPs[26]. For instance, members of the zinc finger protein 36 families, including ZFP36 and ZFP36L1, are RBPs that facilitate mRNA degradation by binding to AU-rich elements in the 3'UTR[27]. According to Zhang *et al.*, *ZFP36* depletion in mice results in severe bone loss, inflammation, and increased OC activity[28]. Moreover, *Zfp36l1*+/- mice demonstrate cartilage degradation, osteophyte formation, and increased subchondral bone plate thickness. Mechanistically, ZFP36L1 facilitates osteoblastic differentiation by enhancing peroxisome proliferator-activated receptor gamma 2 (*Pparγ2*) mRNA degradation or inhibiting cartilage destruction by suppressing chondrocyte apoptosis, a process that targets heat shock protein family A member 1A (*Hspa1a*)[29,30].

Human antigen R (HuR) comprises three RRMs and a hinge region, with its activity partially dependent on its cellular localization. Upon activation, HuR translocates from the nucleus to the cytoplasm and interacts with ARE in the 3'UTRs of target mRNAs, thereby modulating their stability and translation. For instance, its interaction with la-related protein 6 (*Larp6*) has been demonstrated to stabilize RNA, thereby enhancing osteogenic differentiation[31,32]. This interaction is further stabilized by specific ncRNAs. For instance, circStag1 recruits the HuR protein or HuR-mediated lncRNA HOX transcript antisense RNA (HOTAIR) nucleocytoplasmic translocation into the cytoplasm to facilitate osteogenesis in mesenchymal stem cells (MSCs)[33]. Notably, in co-culture and conditioned-medium systems, HuR-deficient osteocytes inhibit OCs formation by indirectly regulating osteoprotegerin (OPG) expression, rather than by altering *OPG* mRNA stability[34].

Methylation of N6 nitrogen on adenosine is the primary internal modification observed in eukaryotic messenger RNA[35]. Recent studies suggest that N6-methyladenosine (m6A) methylation may affect RNA stability. Methyltransferase-like 14 (METTL14) is crucial for appropriate skeletal development. As an m6A methyltransferase, it promotes osteogenic differentiation of BMSCs and inhibits OC differentiation of BMMs by stabilizing *Beclin-1* mRNA or destabilizing glutathione peroxidase 4 (*Gpx4*) mRNA[36,37].

Conversely, another m6A methyltransferase, methyltransferase-like 3 (METTL3), functions as a suppressor of osteogenic differentiation of OBs by destabilizing *Beclin-1*, Sma-and Mad-related protein 7 (*Smad7)*, and SMAD-specific E3 ubiquitin protein ligase 1 (*Smurf1*) mRNA or by promoting miR-7212-5p maturation[38-40]. Additionally, it inhibits the extracellular matrix (ECM) synthesis in endplate chondrocytes and apoptosis and hypertrophic differentiation through m6A-mediated protein degradation[41-43]. METTL3 targets the m6A functional site in circ_0008542, and the upregulation of circ_0008542 enhances the target gene receptor activator of nuclear factor kappa beta (*Rank*) and initiates OC bone absorption by competing with miR-185-5p[44]. Although both are m6A methyltransferases, they serve distinct roles in bone homeostasis.

Fat mass- and obesity-associated protein (FTO), the first reported m6A demethylase, is essential in maintaining bone mass through its RNA demethylase activity. According to Zhuang *et al.*, FTO enhances osteoclastogenesis by activating NF-κB or stabilizing *Cyclin A2* and cyclin-dependent kinase 2 (*Cdk2*) in a YT521-B homology domain family 2 (YTHDF2)-dependent manner[45,46]. Another RNA demethylase, AlkB homolog 5 (ALKBH5), facilitates m6A methylation of protein arginine methyltransferase 6 (*Prmt6*) mRNA,

consequently inhibiting the osteogenic differentiation potential of MSCs[47]. Current studies indicate that the function of m6A demethylases in bone homeostasis remains controversial.

M6A readers contribute to bone homeostasis by regulating the translation, stability, and degradation of target mRNA. For instance, YT521-B homology domain family 1 (YTHDF1) and insulin-like growth factor 2 mRNA binding protein (IGF2BP2) enhance osteogenic differentiation of BMSCs or MC3T3-E1 by increasing zinc finger protein 839 (*Zfp839*) mRNA translation efficiency or stabilizing serum response factor (*SRF*) mRNA[48,49]. Conversely, YTHDF2 mediates fibulin-1 (*FBLN1*) mRNA degradation, thereby suppressing osteogenic differentiation of umbilical cord MSCs[50]. Collectively, these recent findings highlight the significant role of m6A modification mechanisms in maintaining bone homeostasis. M6A modification machinery may serve as a potential therapeutic target for skeletal disorders. Although the phenotypic effects of these RBPs on bone homeostasis are clear, the precise molecular mechanisms and biophysical interactions driving these processes remain an area requiring further comprehensive investigation.

RBPS AND SKELETAL DISORDERS

Notably, RBPs are crucial in directing the RNA life cycle and function, thereby influencing essential mechanisms for maintaining bone homeostasis. It can shuttle between the nucleus and cytoplasm, participating in nuclear pre-mRNA splicing and polyadenylation, and cytoplasmic mRNA decay and translation, respectively. Considering that RBPs exert precise and responsive control of gene expression, their dysregulation or potential mutations may lead to the emergence of disease phenotypes in complex disorders. Herein, we discuss bone diseases associated with RBP defects and delineate the most representative RBPs for each category, including osteoporosis, spinal diseases, rheumatic diseases, and genetic skeletal disorders, among others [Figure 2].

RBPs and osteoporosis

Osteoporosis, the predominant metabolic bone disease, is characterized by the loss of bone mass, degradation of bone microstructure, and increased bone fragility. As the influences of genetic lesions and environmental factors in osteoporosis are increasingly studied, post-transcriptional regulation mechanisms are becoming prominent in its pathogenesis. Recent studies highlight RBPs as critical players in osteoporosis[51]. For instance, numerous RBP-deficient mice exhibit RNA-binding defects that cause osteoporosis-related phenotypes or exacerbate osteopenia under pathological conditions, including METTL14, YTHDF1, Quaking (QKI), SAMD4, MSI2, iron regulatory protein 2 (IRP2), and METTL3[22,24,36,48,52-54]. Conversely, Src associated during mitosis of 68 kDa (*Sam68*)-deficient mice retained bone mass during aging, whereas *Pumilio2*-deficient mice maintained it under ovariectomized (OVX)-induced osteoporosis[55,56]. Given its proven efficacy and safety, targeted therapy aimed at RBP using siRNAs or adeno-associated virus (AAV) has demonstrated potential as an effective and safe approach for treating osteoporosis. The adenovirus-mediated HuR, METTL14, and METTL3 overexpression and the lentivirus-mediated shFTO or Wilms tumor 1-associated protein (WTAP) overexpression effectively mitigate osteoporosis-related symptoms in OVX mice[31,36,45,57]. CircStag1-loaded AAV (circStag1-AAV) and *lnc-PMIF* siRNA regulate interactions with HuR, effectively enhancing bone formation in OVX rats and aged mice, respectively[33,58]. Apigenin, another HuR activator, mitigates the deterioration of bone mass and trabecular bone micro-architecture in OVX mice and facilitates β-catenin nuclear translocation, thereby promoting osteogenesis[59]. Exosomes loaded with ALKBH5 injected into the tail vein or exosome-targeted delivery of METTL14 into the marrow cavity of the tibiae ameliorated the osteopenic phenotype in mice[44,60]. Despite some progress in targeted RBP therapy for osteoporosis models, significant advancements are required before these findings can be applied in clinical settings.

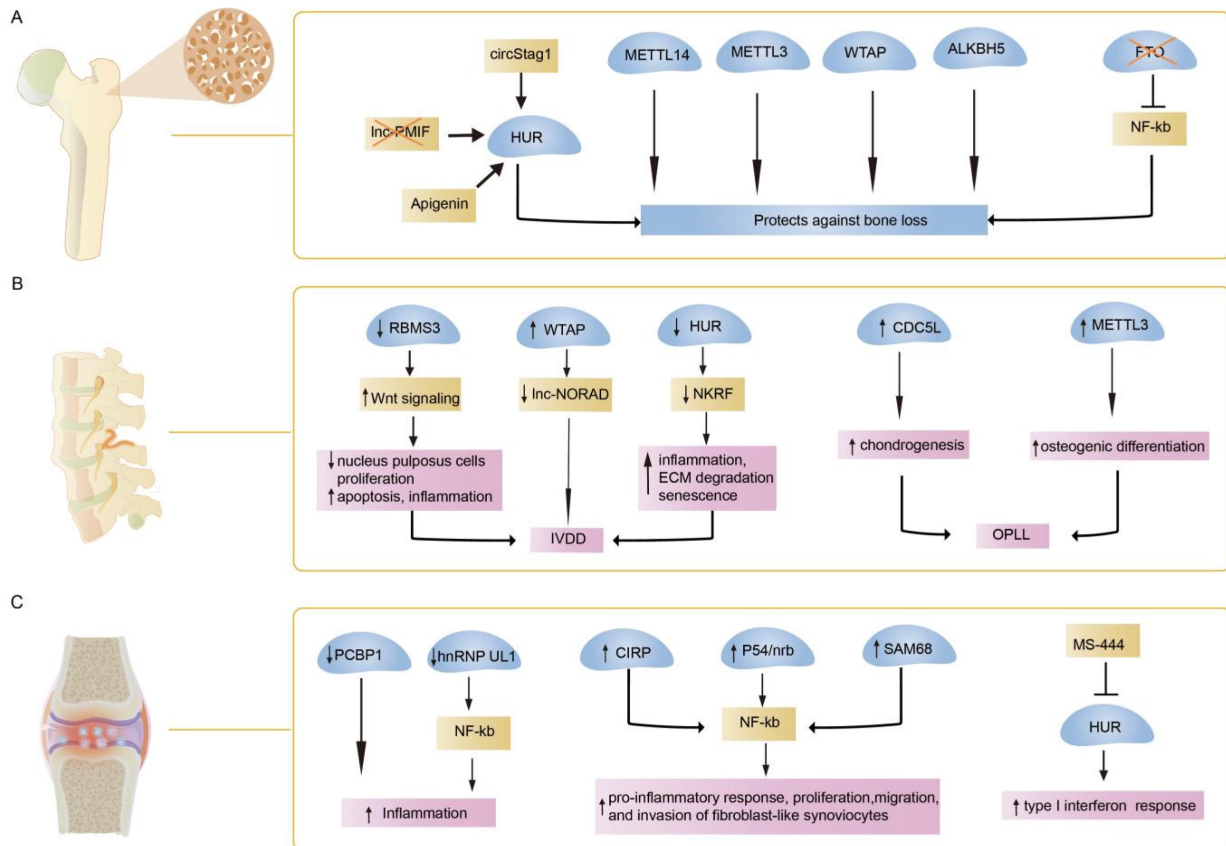

Figure 2. Functions of RNA-binding proteins in bone diseases. The main mechanism of RNA-binding proteins (RBPs) in osteoporosis (A), spinal diseases (B) and rheumatoid arthritis (C) is summarized in this figure. HUR: Human antigen R; lnc-PMIF: long non-coding RNA postulated migration inhibitory factor; circStag1: circular RNA Stag1; METTL14: methyltransferase-like 14; METTL3: methyltransferase-like 3; WTAP: wilms tumor 1-associated protein; ALKBH5: AlkB homologue 5; FTO: fat-mass and obesity-associated protein; NF-κB: nuclear factor-kappa B; IVDD: intervertebral disc degeneration; OPLL: ossification of the posterior longitudinal ligament; RBMS3: RNA binding protein motif single stranded interacting protein 3; lnc-NORAD: long non-coding RNA non-coding RNA activated by DNA damage; NKRF: NF-kappaB repressing factor; ECM: extracellular matrix; CDC5L: cell division cycle 5-like; PCBP1: poly(rC)-binding protein 1; hnRNP UL1: heterogeneous nuclear ribonucleoprotein U-like 1; CIRP: cold-inducible RBP; $p54^{nrb}$: 54-kDa nuclear RNA-binding protein; SAM68: Src associated during mitosis of 68 kDa.

RBPs and spinal diseases

Intervertebral disc degeneration

Intervertebral Disc Degeneration (IVDD) is the primary etiology of chronic lower back pain, which increases in incidence with advancing age. Progressive structural alterations coupled with severe disruptions in metabolic homeostasis facilitate IVDD progression (including abnormal apoptosis, senescence, and pyroptosis of IVD cells; ECM degradation and infiltration of immune cells)[61-63]. Therefore, comprehensively understanding the regulatory mechanisms of IVDD, particularly the primary genetic and epigenetic mechanisms, is essential.

Recent studies have demonstrated that RBPs can regulate degenerative changes in neural progenitor cells (NPCs), thereby influencing the risk of IVDD. Decreased levels of RBP motif single-stranded interacting protein 3 (RBMS3) and HuR have been noted in the nucleus pulposus tissue of patients with IVDD. RBMS3 enhances nucleus pulposus cell proliferation and inhibits their apoptosis and inflammation by inactivating the Wnt/β-catenin signaling pathway, thereby delaying IVDD progression. HuR mitigates inflammation, ECM degradation, and senescence by enhancing NF-kappaB repressing factor (*NKRF*) mRNA stability and autophagy[64-66]. Conversely, increased protein levels of WTAP enhance *lnc-NORAD* m6A modification in

senescent NPCs, whereas YTHDF2-mediated *lnc-NORAD* degradation facilitates cellular senescence during IVDD[67].

Ossification of posterior longitudinal ligament

Ossification of Posterior Longitudinal Ligament (OPLL) is an emerging spinal condition among older adults, leading to intractable myelopathy and radiculopathy due to heterotopic ossification of the posterior longitudinal ligament[68]. Recent evidence demonstrated increased levels of cell division cycle 5-like (CDC5L) and METTL3 in patients with OPLL, where they respectively enhance chondrogenesis and osteogenic differentiation[69,70].

Spondylitis

Ankylosing spondylitis is a common, highly heritable spondyloarthropathy that primarily affects the spine joints and pelvis, leading to severe chronic pain[71]. Limited information exists regarding RBP function in spondylitis, with one report indicating that decreased YTHDF2 is a risk factor for new-onset ankylosing spondylitis[72]. Another study found Rio Kinase 3 enriched in peripheral blood mononuclear cells obtained from ankylosing spondylitis, and its suppression reduces osteogenic differentiation in mouse MSC[73].

RBPs and rheumatic diseases

Osteoarthritis

Osteoarthritis (OA) is a leading cause of severe joint pain, creating a significant socioeconomic burden owing to the aging population, with no existing disease-modifying therapies available[74]. This progressive degenerative disease of the cartilage is marked by cartilage degradation, subchondral bone remodeling, and synovial inflammation[75]. Given recent comprehensive reviews regarding aberrant RBP expression and its role in OA regulation, we will concentrate on targeted RBP therapy for OA[76]. Recently, LIN28a was identified in damaged cartilage in humans and mice, where its overexpression enhanced ECM production. In OA mice (with Col2a1-Cre), the loss of Lin28a exacerbates cartilage degradation through high mobility group AT-hook 2 (HMGA2) and Sry HMG box protein 9 (SOX9)[77]. Cre-inducible Lin28 transgenic mice demonstrate increased articular cartilage thickness, which is diminished by the injection of the extracellular regulated protein kinase (ERK) signaling pathway inhibitor U0126[78]. In a surgical destabilization of the medial meniscus model of OA, intra-articular injection of synovium-targeted *METTL3* siRNA, adenovirus-mediated shZFP36L1, and lentiviral-mediated pumilio1 (PUM1) overexpression mitigates cartilage damage, preserves cartilage integrity, and inhibits OA pathogenesis[30,79,80]. Notably, ncRBP fascin actin-bundling protein 1 inhibition by NP-G2-044 could mitigate the progression of mechanical overload-induced OA in mice[81]. These data indicate that RBPs and their associated pathway activators or inhibitors may be potential candidates for targeted therapies in OA.

Rheumatoid arthritis

Rheumatoid Arthritis (RA) is a chronic immune-mediated disease characterized by inflammation and destruction of the bone and cartilage in affected joints[82]. M6A regulator level, including ALKBH5, FTO, and YTHDF2, is suppressed in patients with RA, indicating a potential risk factor associated with m6A regulators in RA[83,84]. Recent analyses have proficiently addressed RA-related m6A regulators, including those mentioned above[85].

Poly(rC)-binding protein 1 (PCBP1) and heterogeneous nuclear ribonucleoprotein U-like 1 (hnRNP UL1) - expressed at reduced levels in RA - modulate AS of immune response-related genes and inhibit NF-κB-mediated inflammation, respectively. The conditional deletion of *hnRNP UL1* in macrophages through Lyz2-cre enhances the synthesis of inflammatory cytokines[86,87]. Additionally, synovial tissues from

patients with RA demonstrate increased levels of cold-inducible RBP (CIRP), p54^{nrb}, and SAM68. They enhance NF-κB-induced pro-inflammatory response, proliferation, migration, and invasion of fibroblast-like synoviocytes in RA[87-89]. MS-444, a potential small-molecule inhibitor of HuR, impeded its dimerization and translocation, thereby diminishing the type I interferon (IFN) response in RA fibroblast-like synoviocytes[90]. Notably, HuR activators mitigate osteoporosis-related phenotypes in mice, whereas HuR inhibitors influence the IFN response in RA. Consequently, the future lies in targeting RBP as a potential therapeutic for skeletal disorders and in developing associated small-molecule compounds as novel therapeutic agents.

RBPs and genetic skeletal disorders

Bone development and homeostasis are disrupted by several genetic diseases. RBP mutations can impair skeletal development, resulting in a spectrum of musculoskeletal abnormalities, predominantly affecting the limbs, hip, and craniofacial skeleton [Table 2].

TARP syndrome

TARP syndrome (MIM # 311900) is an X chromosome-linked recessive genetic disorder characterized by Robin sequence (micrognathia, glossoptosis, and cleft palate), congenital heart defects, developmental delay, feeding difficulties, and talipes equinovarus. Mutations of RNA-binding motif protein 10 (RBM10) have been recognized as the causative factor, likely due to the loss of its splicing function for essential developmental regulators, thereby hindering normal palate development[91,92].

Nager syndrome

Nager syndrome (MIM # 154400) exemplifies preaxial acrofacial dysostosis, distinguished by craniofacial skeleton and limb malformations. Rodriguez syndrome has been proposed as a potentially severe variant. SF3B4 haploinsufficiency is confirmed as the primary etiology. Nager syndrome involves mutations that alter SF3B4 synthesis, leading to defective mRNA splicing and decreased expression of target genes in growth plate chondrocytes. The heterozygous mutant mouse (*Sf3b4*+/-) was initially noted to exhibit diminished body size, homeotic posteriorization of vertebral morphology, and flattened calvaria[93-96].

Craniofacial microsomia 1

Craniofacial microsomia 1 (MIM #164210) is the second most common congenital facial anomaly, characterized by microtia, mandibular hypoplasia, and preauricular tags. The predominant genetic etiology involves haplo-insufficient variants in splicing factor 3B subunit 2 (SF3B2), present in ~3% of sporadic and ~25% of familial cases. In Xenopus embryos, injecting *sf3b2* morpholinos leads to improper formation of cranial neural crest precursors and defective craniofacial cartilage[97,98]. Furthermore, an increase in cell death and a decrease in proliferative capacity have been observed in the differentiation of patient-derived induced pluripotent stem cells (iPSCs) into neural crest cells. Mechanistically, loss-of-function variants in the *SF3B2* gene induce extensive mRNA splicing disruption across the transcriptome, especially affecting TP53-dependent cell death, and contribute to these craniofacial features[99].

Robin sequence with cleft mandible and limb anomalies

Robin sequence with cleft mandible and limb anomalies (MIM #268305) (known as Richieri-Costa-Pereira syndrome) is an autosomal-recessive and unique acrofacial dysostosis type caused by mutations in non-coding expansions in the 5'UTR of the eukaryotic translation initiation factor 4A3 (*EIF4A3*) gene. It features a median cleft in the mandible, accompanied by craniofacial anomalies and considerable limb defects. In zebrafish, loss of *eif4a3* leads to underdevelopment of multiple craniofacial cartilage and bone structures. Moreover, impaired neural crest cell development clarifies craniofacial abnormalities identified in patient-derived iPSCs and conditional cre-mediated *Eif4a3* mouse models[100,101]. However, the mechanism by which the *EIF4A3* mutation affects the specific downstream targets remains unclear.

Table 2. RNA-binding protein mutations in genetic skeletal disorders with bone phenotypes

RBP	Disease (OMIM)	RNA metabolism defects	Experimental system	Bone phenotype	Refs
RBM10	TARP syndrome (MIM #311900)	Splicing function	Human case; mouse embryonic pharyngeal arch cell line	Micrognathia; talipes equinovarus	[91,92]
SF3B4	Nager syndrome (MIM #154400)	mRNA splicing	Human case; Knockout mice	Malformations of the craniofacial skeleton and the limbs	[93-96]
SF3B2	Craniofacial microsomia 1 (MIM #164210)	Splicing function	Human case; xenopus; zebrafish; iPSCs	Mandibular hypoplasia	[97-99]
EIF4A3	Robin sequence with cleft mandible and limb anomalies (MIM # 268305)	mRNA stability	Human case; Zebrafish; iPSCs	Mandibular median cleft associated with other craniofacial anomalies and severe limb defects	[100,101]
hnRNPA2B1	Paget disease of bone (MIM #602080)	m6A reader	Human case	Bone deformities, bone pain, and fragility fractures in the pagetic site	[102,103]
RBM8A	Thrombocytopenia-Absent Radius Syndrome (MIM #274000)	Splicing function	Human cohort; Zebrafish	A reduction in the number of platelets and the absence of one of the bones in the forearm	[104-106]
PUF60	Verheij syndrome (MIM #615583)	Splicing function	Human case	Craniofacial dysmorphism	[107]
EFTUD2	Mandibulofacial dysostosis with microcephaly (MIM #610536)	Splicing function	Human cohort; Knockout mice	Microcephaly, craniofacial anomalies	[108,109]
LARP7	Alazami syndrome (MIM #615071)	Splicing function	Human case; B-lymphoblastoid cell lines	Microcephalic primordial dwarfism	[110,111]
ASCC1	Spinal muscular atrophy with congenital bone fractures 2 (MIM #616867)	-	Human case; patient-derived fibroblasts	Arthrogryposis multiplex congenita and prenatal fractures of the long bones	[112,113]
hnRNPK	Au-Kline Syndrome (MIM #616580)	mRNA stability	Human cohort; Col2a1-Cre mice	Remarkable deformities in the limbs and spine	[114-116]
NIPBL	Cornelia de Lange Syndrome 1 (MIM #122470)	Protein translation	Human case; Knockout mice	Limb malformations	[117-121]
ERI1	Spondyloepimetaphyseal dysplasia, Guo-Campeau type（MIM #620663）	rRNA maturation, mRNAs decay	Human case; knockout mice	Severe bone dysplasia affecting the spine and long tubular bones	[122]
SH3BP2	Cherubism (MIM #118400)	-	Human case; knock-in mice	Excessive jaw-bone destruction	[123-125]

RBM10: RNA-binding motif protein 10; SF3B4: splicing factor 3B subunit 4; SF3B2: splicing factor 3B subunit 2; EIF4A3: eukaryotic translation initiation factor 4A3; hnRNPA2B1: heterogeneous nuclear ribonucleoprotein A2B1; RBM8A: RNA-binding motif protein 8A; PUF60: poly(U) binding splicing factor 60; EFTUD2: elongation factor Tu GTP binding domain containing 2; LARP7: La-related protein 7; ASCC1: activating signal co-integrator complex 1; hnRNPK: heterogeneous nuclear ribonucleoprotein K; NIPBL: nipped-B-like protein; ERI1: exoribonuclease 1; SH3BP2: c-Abl-SH3 domain binding protein-2; RBPs: RNA-binding proteins; iPSCs: induced pluripotent stem cells.

Paget disease of bone

Paget disease of bone (PDB) (MIM #602080) is a common metabolic bone disorder characterized by increased bone resorption and disorganized bone formation, leading to abnormal focal bone remodeling. Mutations in the m6A reader heterogeneous nuclear ribonucleoprotein A2B1 (hnRNPA2B1) were detected in patients with PDB, who frequently experience bone deformities, pain, and fragility fractures at the pagetic site[102]. Preliminary investigation into degenerative diseases indicates that these mutations may create more potent steric zippers within the prion-like domain of hnRNPA2B1, consequently modifying RNA granule assembly, impairing RNA metabolism, and accelerating fibrillization[103].

Thrombocytopenia-absent radius syndrome

Thrombocytopenia-Absent Radius (TAR) syndrome (MIM # 274000) is a hematological and skeletal disorder characterized by low platelet counts and the absence of one forearm bone. TAR syndrome is generally caused by mutations in RNA-binding motif protein 8A (RBM8A), with haploinsufficiency resulting in severe microcephaly and impaired neurogenesis in mouse models[104,105]. Recent research using the hypomorphic *rbm8a* zebrafish has demonstrated that the absence of RBM8A inhibits non-canonical Wnt/PCP signaling, resulting in abnormal lateral plate mesoderm patterning and hematopoietic defects[106].

Verheij syndrome

Verheij syndrome (MIM #615583) (8q24.3 microdeletion syndrome) is a rare craniofacial spliceosomopathy characterized by craniofacial dysmorphism, multiple congenital anomalies, and variable neurodevelopmental delay. Pathogenic variants in poly(U) binding splicing factor 60 (PUF60) have been recognized as causative for Verheij syndrome[107]. Although an increasing number of novel PUF60 variants have been identified in the literature, the underlying mechanisms remain a mystery.

Mandibulofacial dysostosis with microcephaly

Haploinsufficiency-inducing deletions or mutations in the spliceosome factor elongation factor Tu GTP binding domain containing 2 (EFTUD2, a GTPase and a core component of the U5 snRNP) were identified in patients with mandibulofacial dysostosis with microcephaly (MFDM, MIM #610536). Affected individuals display microcephaly, craniofacial anomalies, auditory impairment, and dysmorphic features. Conditional knockout models and mechanistic studies have demonstrated that EFTUD2 deficiency impairs cortical histogenesis and drives cortical neuronal attrition. By modulating the splicing patterns of the apoptosis regulators Caspase3 and apoptosis-inducing factor mitochondria-associated 1 (Aifm1), it activates programmed cell death[108,109].

Alazami syndrome

Alazami syndrome (MIM #615071) is an autosomal recessive microcephalic primordial dwarfism characterized by notable facial dysmorphisms and severe intellectual disability. The observed phenotypes may be ascribed to the depletion or loss of functional variants in La-related protein 7 (LARP7), resulting in splicing modification in affected patients, accompanied by diminished 2'-O-methylation of U6 small nuclear RNA[110,111].

Spinal muscular atrophy with congenital bone fractures 2

Spinal muscular atrophy with congenital bone fractures 2 (SMABF2) (MIM #616867) is a rare autosomal recessive neuromuscular disorder resulting from biallelic variants in activating signal co-integrator complex 1 (ASCC1). It is defined by congenital arthrogryposis multiplex and prenatal fractures of the long bones. Multi-omics analyses of patient-derived fibroblasts demonstrate that the downregulation of ASCC1 inhibits the TGF-β/SMAD signaling pathway, consequently suppressing osteoblastogenesis[112,113].

Au-Kline Syndrome

Au-Kline Syndrome (AKS) (MIM #616580) was initially characterized in 2015 as a multiple malformation syndrome distinguished by remarkable deformities in the limbs and spine. *De novo* missense or intronic variants in heterogeneous nuclear ribonucleoprotein K (HNRNPK) have been associated with AKS[114]. Recent studies demonstrated that depletion of hnRNPK during chondrogenesis using Col2a1-Cre results in dwarfism, marked by impaired survival and premature differentiation of growth plate chondrocytes. Mechanistically, hnRNPK deficiency extends the half-life of *Hif1a* mRNA, consequently activating the Hif-1

signaling pathway[115]. Recently, the RNA-binding motif protein 42 (RBM42) C-terminal A438T variant disrupted its interaction with hnRNP K, leading to a multisystem disease with musculoskeletal involvement[116].

Cornelia de lange syndrome

Cornelia de Lange Syndrome (CdLS) (MIM #122470) is the most common cohesinopathy, characterized by intellectual disability, growth retardation, limb malformations, and unique facial features. Heterozygous loss-of-function mutations in Nipped-B-Like protein (NIPBL) account for approximately 70% of CdLS cases[117,118]. Surviving *Nipbl*+/- mice exhibit significant reductions in body size, notable craniofacial changes, and anteriorization of thoracic vertebrae, with left-right asymmetry accompanied by collective changes in osteogenesis-regulatory pathways[119-121].

Spondyloepimetaphyseal dysplasia, Guo-Campeau type

Spondyloepimetaphyseal dysplasia, Guo-Campeau type (SEMDGC) (MIM #620663) is defined by severe bone dysplasia affecting the spine and long tubular bones, leading to substantial short stature with disproportionate extremities. Research has revealed that pathogenic variants in the exoribonuclease 1 (ERI1) gene are responsible for this novel form of bone dysplasia in patients from seven affected families. Mechanistically, missense mutations in the conserved 3'-5' RNA exonuclease impair enzyme activity, failing to catalyze 5.8S rRNA processing and affecting histone mRNA decay. Furthermore, *Eri1* knockout mice exhibit skeletal dysplasia that partially resembles human SEMDGC[122].

Cherubism

Cherubism (MIM #118400) is an autosomal dominant condition associated with severe craniofacial developmental anomalies, notably excessive jaw-bone destruction. Gain-of-function missense variants in c-Abl-SH3 domain binding protein-2 (SH3BP2) have been identified as being responsible for the condition in patients from 12 affected families[123]. In OCs, SH3BP2 phosphorylation seems to activate phospholipase C gamma 2 (PLCG2), resulting in excessive OC activity. Consistently, in the homozygous cherubism knock-in (KI) mouse model (*Sh3bp2* KI/+), systemic bone destruction has been observed owing to increased OC formation. Additionally, spleen tyrosine kinase (SYK) inhibitor, entospletinib, abolishes all observed cherubism phenotypes[124,125].

Others

Craniofacial malformations rank among the most common congenital disabilities. Considering the role of RBPs in modifying craniofacial disorders has recently been extensively reviewed[126,127], we presented fundamental research on craniofacial development. A homozygous frameshift variant in hnRNP UL1 was detected in patients exhibiting craniofacial and limb anomalies, consistent with the developmental role of hnRNP UL1 observed in zebrafish[128]. Studies utilizing animal models highlight the essential function of Serine-rich splicing factor 3 (SRSF3), nucleolin, RNA-binding Fox-1 homolog 2 (RBFOX2), and RBMS3 in regulating craniofacial development[129-132].

CONCLUSION AND PERSPECTIVES

This review offers a current and comprehensive overview of RBPs in bone homeostasis and skeletal disorders, elucidating their fundamental mechanisms, potential RBP-targeted therapeutic applications, and prospects. RBPs are recognized as essential regulators of intramembranous and endochondral bone formation. Recently, novel methods for profiling RNA-protein interactions have emerged, significantly expanding our knowledge of the RBP landscape[9,133,134]. However, understanding the roles of various bone homeostasis-specific RBPs and clarifying the complex regulatory network focused on RBPs remains

challenging.

Although the roles of RBPs in OBs and OCs have been thoroughly examined, their function in osteocytes has been historically neglected. Osteocytes have long been challenging to study *in vitro*, partly because these terminally differentiated cells are difficult to isolate and purify, leading to the lack of suitable *in vitro* cell models. Future studies may employ MLO-Y4 osteocyte-like cells, co-culture systems, and osteocyte-specific conditional knockout models to investigate the *in vitro* and *in vivo* function of specific RBPs in osteocytes.

To address the effect of RBP mutations in genetic skeletal disorders, novel cellular models of RBPs using iPSCs synthesized from the fibroblasts of patients offer promising avenues. Mouse models are essential in studying skeletal development, revealing that overexpression or inhibition of RBPs *in vivo* leads to multiple skeletal defects. Despite significant progress, much remains to be learned regarding how RBPs regulate bone development and homeostasis through mouse genetics. As additional RBPs are individually deleted in bone cells, their distinct and overlapping functions will be clarified.

A fundamental inquiry is determining the primary targets of RBPs. High-throughput platforms are utilized efficiently and dependably to evaluate these targets. Current evidence indicates that specific activators and inhibitors of HuR can alleviate bone loss and diminish the IFN response. Furthermore, the SYK inhibitor entospletinib has demonstrated therapeutic potential in the cherubism mouse model, indicating its potential for clinical application. However, further research is required to comprehensively clarify the underlying mechanisms of these effects. Understanding the *in vivo* specificity of RBPs in drug studies and their role in adult skeletons remains a major challenge.

RBPs interact with the target RNAs to regulate the protein synthesis of the target genes. In the rapidly advancing field of cancer, initial promising RBP therapeutic candidates are currently undergoing clinical trials, including FTO, splicing factor 3B subunit 1 (SF3B1), nucleolin, and RNA-binding motif protein 39 (RBM39). Specifically, small-molecule inhibitors (SMIs) targeting FTO have been formulated as anti-cancer drugs. These SMIs inhibit the catalytic pocket of FTO and impede the binding to m6A-modified targets. Therefore, this evidence endorses the prospective RBP-targeted therapies and aids in the investigation of their potential therapeutic applications in skeletal disorders. Interactions between ncRNAs and RBP are recognized as crucial factors in cancer, and investigating this research direction may reveal novel mechanisms underlying bone diseases. Employing ncRNA-loaded AAV to facilitate interactomes for RBPs may evolve into a simple and efficacious therapeutic strategy in the future. Continuous improvement of RBP-targeted therapies is essential to minimize side effects and enhance efficacy and safety. Addressing these inquiries is essential for comprehensively understanding the functions of RBPs in the skeleton and assessing the benefits and potential drawbacks of RBP-targeted therapies.

DECLARATIONS

Authors' contributions

Conceptualization, writing - original draft: Xu Y
Supervision, writing - review: Luan X, Wang Y
Validation, writing - editing: Chen S, Xu C
All authors reviewed the manuscript.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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