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Reviews

RNA-Binding Proteins: Biological Mechanisms and Their Impact on Osteoporosis Development

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Osteoporosis is a common bone disease characterized by reduced bone mass and increased fracture risk, largely driven by imbalances in osteoblast and osteoclast activity. Recent studies highlight the critical role of RNA-binding proteins (RBPs) in the regulation of bone metabolism, specifically in osteoblast and osteoclast function. These proteins have also been implicated in other bone diseases, suggesting a broader influence on skeletal health. This review explores the molecular mechanisms through which RBPs impact bone cells, discusses their potential as therapeutic targets in osteoporosis, and outlines future research directions and challenges in harnessing RBPs for clinical applications.

Introduction

Osteoporosis (OP) is a progressive bone disorder that leads to diminished bone strength, manifesting as decreased bone density and the degradation of bone tissue integrity, which consequently increases fracture susceptibility [1]. The underlying pathophysiology of OP is driven by a multifaceted interaction of genetic factors, molecular mechanisms (such as the pivotal RANK/RANKL/OPG [2] and Wnt/β-catenin [3] pathways), as well as environmental influences that collectively modulate bone formation and resorption processes [4-6]. Recent studies have brought attention to the significant functions of RNA-binding proteins (RBPs) in numerous biological activities, including the regulation of gene expression, RNA splicing, RNA stability, and translation processes [7]. These proteins are being increasingly acknowledged as important regulators of bone homeostasis, particularly through their influence on transcription factors and signaling pathways critical to the function of osteoblasts and osteoclasts. Aberrant RBP function has been associated with various chronic conditions such as cancer [8, 9], metabolic abnormalities [10], and neurodegenerative disorders [11], but their precise involvement in OP pathogenesis is still in its early stages of investigation. This review seeks to clarify the biological pathways through which RBPs impact bone health, with a focus on their role in gene expression and signaling regulation relevant to osteoblast and osteoclast activity, as well as their potential as therapeutic targets in the treatment of OP.

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RBPs are widely expressed across most human tissues and play a pivotal role in regulating RNA metabolism, with variations in expression depending on tissue and cell type. These proteins, by recognizing specific binding sequences or secondary structures in RNA molecules, control various processes both at the nuclear level, such as indirectly influencing transcription through RNA stability and protein interactions, and directly regulating splicing, capping, and polyadenylation. At the cytoplasmic level, they regulate processes including RNA transport through nuclear-cytoplasmic trafficking, localization, translation, and degradation (Fig.1). The ability of RBPs to bind to a diverse range of RNA targets, such as messenger RNA (mRNA) exons, introns, untranslated regions (UTRs), as well as non-coding RNAs like long non-coding RNA (lncRNA), microRNA (miRNA), circular RNA (circRNA), ribosomal RNA (rRNA), transfer RNA (tRNA), small nucleolar RNA (snoRNA), small interfering RNA (siRNA), telomerase RNA (TERC), and splicing small nuclear RNA (snRNA), highlights their versatility in gene expression regulation [12, 13]. Moreover, RBPs are crucial in the initiation of translation by regulating the recruitment of ribosomal subunits to target mRNA. This regulation affects the translational rate and efficiency, thereby altering the protein expression of mRNAs [14, 15]. The extensive role of RBPs in RNA metabolism and gene expression underscores their importance in cellular function and suggests their potential as key targets in the study and treatment of various diseases, including those with emerging roles in OP development (Table 1).

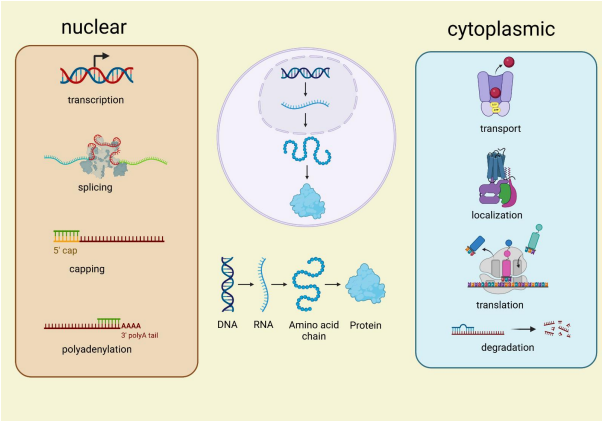

Fig.1 RNA is Primarily Regulated by RNA-Binding Proteins. RNA-binding proteins (RBPs), by recognizing specific binding sequences or secondary structures in RNA molecules, control various processes both at the nuclear level, including transcription, splicing, capping, polyadenylation, and at the cytoplasmic level, encompassing transport, localization, translation, and degradation.

Table 1. Roles of RNA-Binding Proteins in Osteoporosis Development. Protein amino acid content and molecular weight data are from the UniProt database: https://www.uniprot.org/ (accessed on October 1, 2024).

RBPs	Amino acids	Mass/Da	Expression or activity in Osteoporosis	Function	Targets	Organism	Refs.
Irp2	963	104920	Increased: Leads to bone loss and osteoporosis	Regulates iron metabolism in bone tissue	Transferrin receptor 1 (TfR1), Ferroportin-1 (FPN1)	Mus musculus	[16]
Irp1	790	87089	Increased activity due to excess iron	Regulates iron homeostasis by controlling NOX4 transcription, leading to osteoporotic bone loss	NOX4, influences ferroptosis in osteoblasts	Homo sapiens	[17]
QKI	341	37671	Increased osteoclast formation and impaired bone metabolism	Regulates osteoclastogenesis and inhibits osteoblast formation through the inflammatory microenvironment	TRAP, Ctsk, NFATc1, NF-κB, MAPK	Mus musculus	[18, 19]
RBM5	815	92154	Increased: Impairs osteoclast differentiation	Regulates RNA splicing and osteoclast differentiation, inhibiting bone-resorbing activity	Genes involved in RNA splicing and osteoclast differentiation	Homo sapiens	[20]
PUM1	1186	126473	Increased risk for osteoporosis in gene-gene interactions	Regulates genetic interactions influencing bone mineral density	Genes involved in osteoporosis risk, such as AKAP11, KCNMA1, SPTBN1	Homo sapiens	[21, 22]
ELAVL1	313	35283	Increased: Upregulated in diabetes-related diseases affecting bone metabolism	Regulates DMT1 to control iron accumulation and oxidative stress, promoting osteogenesis in bone tissue	DMT1	Mytilus edulis (Blue mussel)	[23]
HuR	326	36169	Increased: Promotes osteoblast differentiation and alleviates osteoporotic phenotypes in ovariectomized mice	Regulates LRP6 mRNA translation to activate the Wnt pathway, promoting osteoblast differentiation	LRP6	Mus musculus	[24, 25]
Msi2	328	35197	Decreased: Leads to increased adipocyte differentiation and impaired bone metabolism with aging	Regulates BMSC lineage commitment and inhibits adipocyte formation through PPARγ signaling	Cebpα, PPARγ	Homo sapiens	[26]
SAMD4B	687	74994	Increased: Impairs osteoblast differentiation and bone development	Regulates protein translation by binding Mig6 mRNA, inhibiting MIG6 protein synthesis, and affecting osteogenesis	MIG6, PPAR	Mus musculus	[27, 28]
Cpeb4	704	77297	Increased: Required for RANKL-induced osteoclast differentiation	Regulates osteoclast differentiation and expression of key differentiation markers in osteoclastogenesis	TRAP, Acp5, Ctsk, Nfatc1, Dcstamp	Homo sapiens	[29, 30]

DDX21	82	9376	Increased; involved in cancer metastasis, but its role in bone metabolism remains unclear	Regulates CRC metastasis through EMT pathway and phase separation mechanisms, potentially affecting cellular differentiation and proliferation	MCM5, EMT pathway, CRC cells	Homo sapiens	[31]
DDX24	859	96332	Not clearly established in osteoporosis	Regulates ribosome biogenesis and nucleolar homeostasis	NPM1, ribosome biogenesis	Homo sapiens	[32]
IGF2BP2	605	66786	Increased expression; plays a crucial role in osteoblast differentiation and normal bone mass acquisition in mice	Regulates IGF2BP2-mediated osteoblast differentiation through interaction with RPTPβ, crucial for AKT activation and osteocalcin expression	RPTPβ, AKT signaling, osteocalcin	Homo sapiens	[33]
IGF2BP3	582	63352	Increased: Promotes osteosarcoma progression by regulating RNA-binding activity in bone tumor cells	Regulates translation inhibition and impacts cellular translation processes affecting cell viability in osteosarcoma	Myc (transcription factor), IGF2	Zebrafish	[34]
RBM10	930	103533	Overexpression decreases osteosarcoma cell proliferation and migration	Acts as a tumor suppressor in osteosarcoma	Bcl-2, TNFα	Homo sapiens	[35]
RBM34	430	48565	Increased: Overexpression is related to poor prognosis in osteosarcoma and associated with immune response and tumor progression.	Regulates cancer immune response and tumor proliferation, may influence osteosarcoma cell migration and immune infiltration	Tumor-infiltrating lymphocytes (TILs), immunomodulators, chemokines	Homo sapiens	[36]
IGF2BP1	577	63451	Increased expression in Ewing's sarcoma (ES), contributes to tumor proliferation and survival	Regulates mRNA translation and stability, influencing IGF signaling	IGF1, IGF2, IGF1R	Mus musculus	[37, 38]

Basic Concepts of RNA-Binding Proteins

RBPs are characterized by their ability to bind to RNA through one or more RNA-binding domains (RBDs), significantly impacting the fate and function of the bound RNA, as well as the expression of the associated target gene [39]. The mechanisms and structures by which RBPs bind and regulate RNA are diverse and complex [40], often depending on the recognition of specific RNA sequences or secondary structures. The classification of RBPs is often based on the specific RBDs they contain, which influence their binding preferences and target specificity [15]. Commonly, RBPs feature domains such as the RNA recognition motif (RRM), K homology (KH) domain, DEAD-box helicase domain, double-stranded RNA-binding motif (DSRM), or a zinc-finger domain [15]. This diversity in domains underscores the versatility of RBPs in gene regulation, enabling them to participate in various cellular processes, including RNA splicing, transport, translation, and degradation. Such a wide range of functionalities highlights the pivotal role of RBPs in the post-transcriptional regulation of gene expression, including RNA stability, translation, and splicing, and offers a promising area for research.

Molecular Mechanisms and Therapeutic Targets in Osteoporosis

As cells age, physiological changes in bone cells can lead to dysregulation of RBPs, thereby affecting bone composition and increasing the risk of OP [41]. OP is a chronic and progressive condition that leads to reduced bone mineral density and a decline in bone mass, greatly increasing the likelihood of fractures [42]. In women, particularly after menopause, the decline in estrogen and androgen levels causes bone resorption to outpace bone formation, accelerating bone loss. Both men and women experience age-related bone loss, partly due to a reduction in mesenchymal stem cells (MSCs), which leads to an inadequate supply of osteoblast precursors [43]. Moreover, specific medical conditions, such as glucocorticoid-induced OP, further deteriorate bone health. Large doses of glucocorticoids drastically diminish the quantity and function of osteoblasts and osteocytes, thus suppressing bone formation [44]. Regardless of its underlying causes, bone loss is often accompanied by the accumulation of adipose tissue in the bone marrow. Studies indicate that the depletion of osteoblast precursors and increased adipogenesis both contribute to the pathogenesis of osteoporosis [45]. Thus, maintaining a balance between osteoblasts and adipocytes is essential for preserving bone homeostasis [46].

Mice lacking Iron regulatory protein 2 (Irp2) show reduced bone mineral density (BMD) and bone iron content, along with signs of bone iron deficiency and hepatic iron overload. This condition is further linked to decreased serum levels of 25(OH)D3 and lower expression of bone formation biomarkers (Balp, BGP, Col I α1), while markers of bone resorption (Ctsk, Trap) are elevated [16]. These findings underscore the importance of iron regulation in bone metabolism. Beyond Irp2, research indicates that iron regulatory protein 1 (Irp1) may play a role in OP through ferroptosis. Irp1 typically binds to iron-response elements (IREs), regulating the translation of target mRNAs. However, in iron-overload conditions, Irp1 dissociates from these elements, leading to NOX4 enzyme activation. Elevated NOX4 levels result in lipid peroxide accumulation, impairing mitochondrial function in osteoblasts, which contributes to bone loss associated with osteopenia and OP. This suggests that dysregulated Irp1 activity in iron-overloaded environments can accelerate bone deterioration and increase OP risk [17]. Iron regulatory proteins, such as Irp1 and Irp2, post-transcriptionally control cellular iron metabolism by interacting with IREs in mRNAs, such as those of ferritin and transferrin receptor, which manage iron storage and uptake [16, 47-49] (Fig.2). The link between iron regulation and bone health is evident, indicating that disruptions in iron homeostasis could be a significant risk factor for OP, thereby offering a promising target for therapeutic intervention.

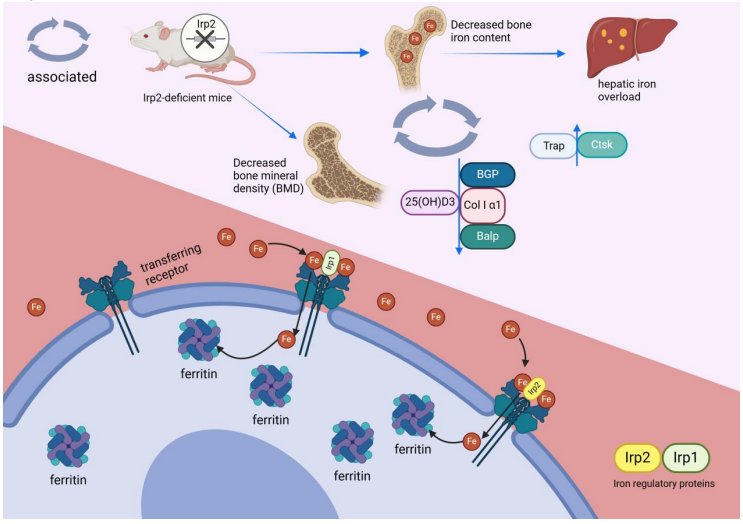

Fig.2 Iron Homeostasis and Bone Density. Irp2-deficient mice show lower bone mineral density and iron levels, with signs of bone iron deficiency and hepatic iron overload, linked to altered serum vitamin D and bone metabolism markers, highlighting Irp1 and Irp2's role in regulating cellular iron metabolism. Irp2: Iron regulatory protein 2, a key regulator of iron metabolism, plays a crucial role in preventing osteoporosis by regulating bone iron content and controlling the expression of genes involved in bone formation, such as Balp, BGP, and Col I α1, while modulating osteoclast activity in bone tissue. Irp1: Iron regulatory protein 1, a key regulator of iron homeostasis, plays a crucial role in preventing osteoporotic bone loss by controlling NOX4 transcription and modulating lipid peroxide accumulation in osteoblasts, thereby maintaining mitochondrial function and reducing iron-induced cell death in bone tissue.

Quaking (QKI), an RNA-binding protein, is essential for regulating osteoclastogenesis by modulating the stability or translation of osteoclast-related mRNAs. Its deficiency leads to increased osteoclast formation and upregulates osteoclast-specific markers, including Tartrate-resistant acid phosphatase (TRAP) and Cathepsin K (Ctsk). This enhanced osteoclastogenesis is driven by the activation of the Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF-κB) and Mitogen-Activated Protein Kinase (MAPK) signaling pathways, which subsequently promote the expression of Nuclear Factor of Activated T-cells, cytoplasmic 1 (NFATc1), a critical transcription factor in osteoclast differentiation. Moreover, QKI deficiency impairs osteoblast formation by disrupting signaling pathways involved in osteoblast differentiation and maturation, underscoring QKI's pivotal role in maintaining bone metabolic homeostasis [18]. Additionally, RNA-binding motif protein 5 (RBM5), another RNA-binding protein, is overexpressed in OP patients and is believed to contribute to the pathogenesis of OP by regulating genes involved in bone resorption. Knockdown of RBM5 has been shown to inhibit osteoclast differentiation, likely through the p38 MAPK/NFATc1 signaling pathway [20] (Fig.3). RBPs such as QKI and RBM5 are fundamental to bone metabolism, as they regulate both osteoclastogenesis and osteoblast formation. Therefore, targeting these proteins could offer novel therapeutic approaches to restore bone metabolic balance and treat OP by regulating the interplay between osteoclast

s and osteoblasts.

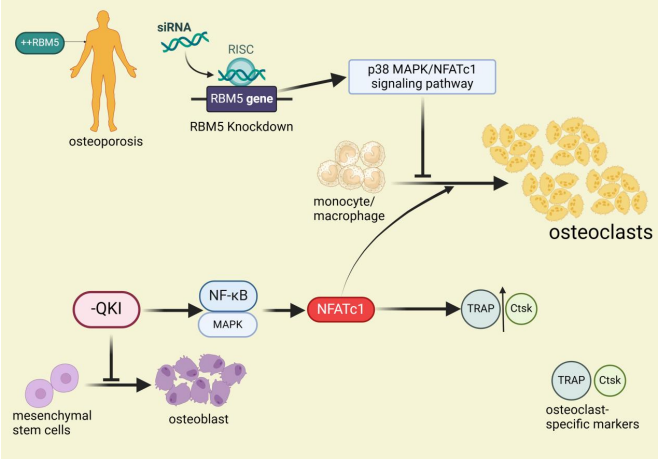

Fig.3 RNA-binding Proteins and Bone Metabolism. QKI deficiency leads to increased osteoclast formation and impaired osteoblast production via NF-κB and MAPK signaling, disrupting bone metabolism, while RBM 5 overexpression in osteoporosis inhibits osteoclast differentiation thro ugh the p38 MAPK/NFATc1 pathway. QKI: Quaking, an RNA-binding pro tein, plays a crucial role in promoting osteoporosis by regulating osteoc last differentiation and controlling the expression of osteoclast-specific genes, such as TRAP and Ctsk, while inhibiting osteoblast activity in bon e tissue through the NF-κB and MAPK signaling pathways. RBM5: RNA-binding motif protein 5, a key regulator of RNA splicing, plays a crucial r ole in the pathogenesis of osteoporosis by regulating osteoclast differe ntiation and controlling the expression of genes involved in osteoclasto genesis, such as TRAP and Ctsk, while inhibiting bone-resorbing activity in bone tissue.

Pumilio homolog 1 (PUM1), a gene situated on chromosome 1p35.2, functions as a translational regulator by binding to th e 3' untranslated region (UTR) of certain mRNAs, thereby infl uencing their stability and translation efficiency to modulate gene expression [22]. Research has indicated that PUM1 inte racts with genes discovered through genome-wide associatio n studies (GWAS) to be linked to OP, such as A-kinase anchor ing protein 11 (AKAP11), Jagged canonical Notch ligand 1 (JA G1), and Spectrin beta, non-erythrocytic 1 (SPTBN1), potenti ally co-regulating signaling pathways related to bone metabo lism [50]. Specifically, SPTBN1, alongside Mitogen-Activated Protein Kinase 3 (MAPK3) on chromosome 2p16.2, contribut es to bone formation by activating mechanisms like the MAP K pathway and is correlated with differences in bone mineral density (BMD) and susceptibility to fractures [51, 52]. These f indings are consistent with the current study, which identifie d AKAP11 and SPTBN1 as key genetic factors in OP risk model s. Moreover, the PUM1 variant PUM1_rs7529390 may modul ate bone metabolism by interacting with AKAP11_rs238340 a nd SPTBN1_rs6752877 at the RNA level, potentially influenci ng OP pathology by altering the translation or stability of the se genes and ultimately affecting bone health [21] (Fig.4). OP is genetically complex, involving multiple genes and pathway s.

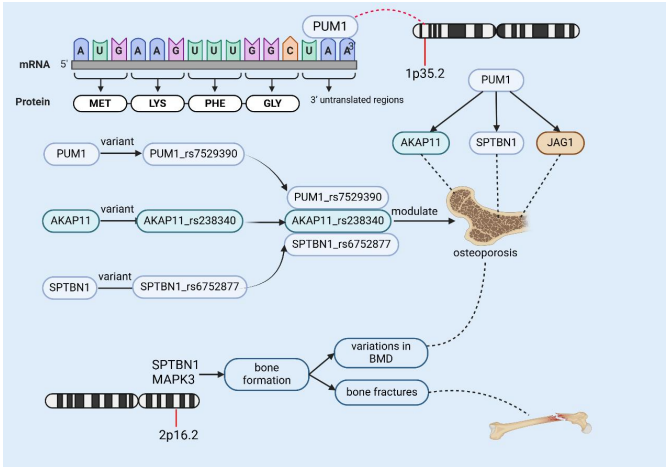

Fig.4 Genetic Regulation and Osteoporosis Susceptibility. PUM1, linked to osteoporosis genes via GWAS like AKAP11 and SPTBN1, regulates th eir expression and impacts bone health, with specific variants influenci ng osteoporosis risk by affecting bone formation and fracture susceptib ility. PUM1: Pumilio homolog 1, a key regulator of RNA stability, plays a crucial role in embryogenesis and cell differentiation by binding to targ et RNA sequences and controlling the expression of genes involved in d evelopment, such as those related to translation and cell division, while maintaining gene structure and function across various tissues.

The upregulation of ELAV-like RNA binding protein 1 (ELAVL1) has been linked to diabetes-induced bone impairment. In a h igh-glucose environment, ELAVL1 affects bone metabolism b y modulating the activities of both osteoblasts and osteoclast s. Specifically, ELAVL1 modulates gene expression and oxidati ve stress levels, impacting the activity of these bone cells. Kn ocking down ELAVL1 has shown promise in mitigating diabeti c bone disease by reducing oxidative stress, enhancing bone cell function, and promoting bone formation [23]. Human an tigen R (HuR), a post-transcriptional regulator, plays a critical role in LRP6-mediated osteogenic differentiation by stabilizin g low-density lipoprotein receptor-related protein 6 (LRP6) m RNA and increasing its translation. LRP6, a key co-receptor in the Wnt signaling pathway, regulates osteoblast developmen t and differentiation. Overexpression of HuR may activate th e Wnt signaling pathway by upregulating LRP6 translation, th us promoting osteoblast differentiation, presenting a potenti al therapeutic approach for OP [24] (Fig.5). RBPs such as ELA VL1 and HuR are emerging as promising therapeutic targets f or OP due to their central roles in regulating bone cell functio n and signaling pathways.

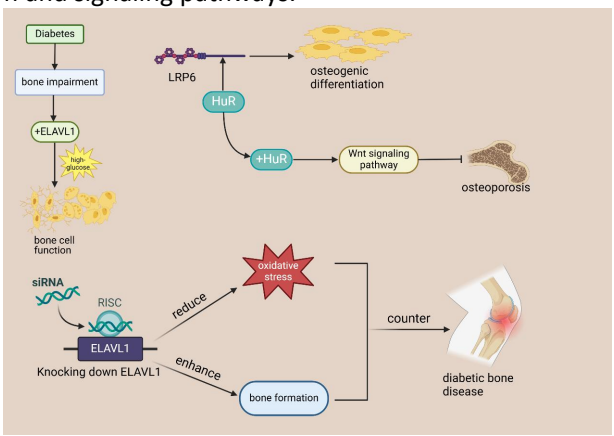

Fig.5 Osteoporosis Therapeutic Targets. ELAVL1 upregulation under high glucose impairs bone cells in diabetes, but knocking it down can mitigate oxidative stress and improve bone formation, while HuR might enhance osteogenesis via the Wnt pathway, offering potential osteoporosis treatments. ELAVL1: ELAV-like RNA binding protein 1, a key regulator of iron metabolism in diabetic osteoporosis, plays a crucial role in preventing bone loss by regulating the expression of DMT1, controlling iron accumulation and promoting osteogenesis in bone tissue while mitigating oxidative stress. HuR: Human antigen R, a key regulator in bone metabolism, plays a crucial role in preventing osteoporosis by stabilizing LRP6 mRNA and promoting the expression of genes involved in osteoblast differentiation, such as Runx2 and Osterix, while modulating Wnt signaling in bone tissue.

Role of RNA-Binding Proteins in Osteoblast and Osteoclast Function

RBPs are vital for bone remodeling, as they control mRNA stability and translation, which in turn affects the equilibrium between osteoclast-driven bone resorption and osteoblast-driven bone formation [53, 54]. Studies have shown that Musashi homolog 2 (Msi2) not only promotes osteoblast differentiation but also inhibits adipocyte differentiation by repressing Peroxisome Proliferator-Activated Receptor Gamma (PPAR γ), thus regulating the balance between osteogenesis and adipogenesis in mesenchymal stem cells (MSCs). Furthermore, Msi2 binds to the 3′ UTR of target mRNAs, inhibiting their translation and further modulating the fate of MSCs [26]. Sterile Alpha Motif Domain Containing Protein 4 (SAMD4) ensures proper bone formation and development during early embryonic bone development by regulating mRNA stability and translation repression. SAMD4 knockout mice exhibit significant defects in ossification and mineralization, highlighting its critical role in skeletal development [27, 28]. Cytoplasmic polyadenylation element-binding protein 4 (Cpeb4) is upregulated during osteoclast differentiation, and it is speculated that it regulates osteoclastogenesis by repressing the translation of specific target mRNAs [29]. QKI, a member of the STAR family, plays an essential role in osteoclastogenesis and bone metabolic balance by influencing osteoclast differentiation and bone cell function through signal transduction regulation. QKI deficiency promotes osteoclast differentiation by activating the NF-κB and MAPK pathways. Additionally, QKI deficiency affects the fate of Bone Marrow Mesenchymal Stem Cells (BMSCs), impairing their osteogenic differentiation potential while promoting adipogenesis through Wnt pathway activation, ultimately leading to a significant impact on bone mass [18, 19, 55]. These studies demonstrate that RBPs such as Msi2, SAMD4, Cpeb4, and QKI play pivotal roles in regulating bone metabolism. A deeper understanding of their functions could offer novel therapeutic targets and strategies for treating bone diseases such as OP.

RNA-Binding Proteins in Other Bone Diseases

Recent genomic sequencing studies have identified numerous genetic mutations and abnormal expression of RBPs in malignant tumors, including bone cancers, suggesting that these proteins play key roles in the onset, progression, and metastasis of cancer [56, 57]. Although bone cancers account for a small percentage of global malignancies—around 5% of childhood cancers and less than 1% of adult cancers—they include highly aggressive types such as osteosarcoma (OS) and Ewing's sarcoma (ES) [58]. Gene Ontology (GO) enrichment analysis reveals that most RBPs are downregulated in OS, particularly in pathways related to RNA metabolism, ribosome biogenesis, and protein synthesis [59]. For instance, the expression levels of DEAD-Box Helicase 21 (DDX21), DEAD-box helicase 24 (DDX24), and Insulin-like growth factor binding protein 2 (IGF2BP2) are significantly lower in OS cell lines compared to osteoblast cell lines, and these proteins are known to be involved in ribosomal RNA synthesis and osteoblast differentiation [31, 33]. Further research has shown that Insulin-like growth factor 2 mRNA-binding protein 3 (IGF2BP3), through a positive feedback loop with the transcription factor transcription factor (Myc), regulates cellular translation and tumor cell survival, positioning it as a potential therapeutic target in OS [34]. In U2 Osteosarcoma (U2OS) cell lines, RNA Binding Motif Protein 10 (RBM10) acts as a tumor suppressor by limiting cell proliferation, migration, and invasion, while inducing apoptosis via the downregulation of B-cell lymphoma 2 (Bcl-2) and the activation of caspase-3 and Tumor Necrosis Factor-alpha (TNF α) [35]. Similarly, RNA Binding Motif Protein 34 (RBM34) promotes cell proliferation and migration in OS by regulating the cell cycle, and its knockdown leads to a greater proportion of cells in the G1 phase, highlighting its role in tumor growth [36]. ES, a highly aggressive bone cancer that primarily affects children and young adults, exhibits elevated levels of Insulin-like Growth Factor 2 mRNA-binding Protein 1 (IGF2BP1) and IGF2BP3, which enhance oncogene expression, cell migration, and metastasis [37, 38]. Collectively, these findings emphasize the significant role of RBPs in bone cancer development and suggest that targeting these proteins could provide new therapeutic strategies for treating bone cancers.

Future Directions and Challenges

RBPs have been extensively studied in the context of various diseases, including bone pathologies [60]. As previously noted, RBPs bind to their target RNA in a sequence- and structure-dependent manner via their unique domains. This feature offers potential therapeutic strategies for directly targeting specific RBPs or RBP-RNA interactions, particularly in the treatment of bone disorders [61]. As research on RBPs and their interaction networks in OP pro

gresses, drugs that modulate RBPs and their downstream signaling pathways are emerging as promising therapeutic approaches for managing OP. For instance, mammalian Samd4 has been identified as a novel regulator of osteogenesis. By reducing the expression of Mitogen-inducible gene 6 (Mig6), Samd4 limits protein translation and controls bone growth, which may make it a viable target for treating metabolic bone diseases such as OP [28]. Additionally, endoplasmic reticulum stress (ERS) has been strongly implicated in the development of skeletal diseases, particularly OP. ERS activates multiple signaling pathways, leading to cellular stress responses and apoptosis, with RBPs playing a crucial regulatory role in these processes [62]. For example, HuR regulates endoplasmic reticulum stress through the formation of stress granules (SGs), affecting osteoblast differentiation and bone formation. In aged mice, both HuR expression and stress granule formation decline, but they can be restored through HuR overexpression. Conversely, inhibiting stress granule formation reduces osteoblast differentiation, underscoring the critical role of HuR and stress granules in bone formation. These findings suggest that targeting HuR and stress granules may represent a promising strategy for treating age-related OP [63]. Consequently, therapies targeting RBP-RNA interactions have garnered increasing attention in both laboratory and clinical research, particularly for the treatment of OP and related bone disorders. While this review offers important perspectives on the roles of RBPs in bone metabolism and regeneration, several gaps remain. For instance, although HuR plays a critical role in osteoblast differentiation, its involvement in osteoclast differentiation and bone resorption has not been adequately explored. Thus, further research is required to investigate potential off-target effects and to validate the safety and efficacy of RBP-targeting therapies in clinical trials. This includes understanding the expression patterns of RBPs across different tissues and considering the possible side effects of targeting these proteins. Future studies should focus on elucidating the regulatory mechanisms of RBPs in osteoclast differentiation and their role in bone resorption. Moreover, new therapeutic strategies should be evaluated for their clinical translatability, particularly regarding the long-term effects on bone health. The application of RBPs in other diseases is also a subject of interest. For example, the involvement of RBPs in neurodegenerative disorders, such as amyotrophic lateral sclerosis (ALS), has been well-established, and RBP-RNA interaction-targeting therapies have shown promise in cancer treatment. These advancements suggest that RBPs are not only potential therapeutic targets for OP but also hold broad potential in the treatment of various other diseases. In conclusion, RBPs and their interactions with RNA offer novel avenues for disease treatment. By further investigating the regulatory roles of RBPs in bone metabolism and developing more precise and safe targeted therapies, new treatment strategies for OP and other bone disorders can be realized. As preclinical and clinical research continues to progress, RBPs are likely to demonstrate even greater therapeutic potential across a wide range of medical fields.

Conclusion

In summary, RBPs play a crucial role in the regulation of osteoblast and osteoclast function, offering new insights into the molecular mechanisms underlying OP. These proteins not only contribute to bone metabolism but are also involved in other bone diseases, highlighting their potential as therapeutic targets. Despite significant advances in understanding RBPs' roles, further research is needed to fully uncover their therapeutic potential and address the challenges in developing targeted treatments. Future directions should focus on exploring novel RBPs and their regulatory networks to pave the way for innovative therapeutic strategies in OP and other bone-related disorders.

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