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Review Article

A potential function for MicroRNA-124 in normal and pathological bone conditions

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ABSTRACT

Cells produce short single-stranded non-coding RNAs (ncRNAs) called microRNAs (miRNAs), which actively regulate gene expression at the posttranscriptional level. Several miRNAs have been observed to exert significant impacts on bone health and bone-related disorders. One of these, miR-124, is observed in bone microenvironments and is conserved across species. It affects bone cell growth and differentiation by activating different transcription factors and signaling pathways. In-depth functional analyses of miR-124 have revealed several physiological and pathological roles exerted through interactions with other ncRNAs. Deciphering these RNA-mediated signaling networks and pathways is essential for understanding the potential impacts of dysregulated miRNA functions on bone biology. In this review, we aim to provide a comprehensive analysis of miR-124's involvement in bone physiology and pathology. We highlight the importance of miR-124 in controlling transcription factors and signaling pathways that promote bone growth. This review reveals therapeutic implications for the treatment of bone-related diseases.

1. Introduction

Bone is one of the most prominent tissues within the musculoskeletal system. It is a dynamic, metabolically active tissue with an innate ability to heal through continuous remodeling [1]. Bone remodeling is characterized by resorption of old or damaged bone mediated by osteoclasts, and synthesis of new bone by osteoblasts [2]. The bone remodeling process consists of five steps: activation, resorption, reversal, formation, and termination [3]. Osteoblasts, osteocytes, and osteoclasts mediate bone remodeling. Osteoblasts are specialized fibroblast-like cells that originate from bone marrow-derived mesenchymal stromal cells (BMSCs) [4,5]. Osteoblasts' primary function is to synthesize extracellular matrix (ECM) components. Mature osteoblasts either become entrapped in newly synthesized matrix, differentiate into osteocytes, or remain on bone surface, transforming into flattened bone-lining cells after synthesizing the matrix. In a few instances, these cells undergo apoptosis instead of forming bone-lining cells [4,6]. Osteocytes are entrapped differentiated osteoblasts, playing a role in bone homeostasis by expressing the receptor activator of nuclear factor κB ligand (RANKL), essential for osteoclast formation [7]. Osteoclasts are multinucleated cells derived from hematopoietic stem cells. Osteoclasts aid in bone resorption through acidification and proteolysis of bone mineral matrix [8,9]. Various signaling pathways, including transforming growth factor-β (TGF-β) [10], parathyroid hormone (PTH) [11,12], wingless integration site (Wnt) [13,14], and neurogenic locus notch homolog protein 1 (NOTCH) [15], regulate bone remodeling at the molecular level. The NF-κB (RANK)/RANK ligand/osteoprotegerin and Wnt signaling pathways are the main pathways controlling bone breakdown by osteoclasts and bone growth by osteoblasts [16].

In recent years, endogenous and exogenous non-coding RNAs (ncRNAs) have been reported to regulate multiple signaling pathways in bone biology [13,28,29]. ncRNAs do not code for proteins directly but regulate gene expression at the post-transcriptional level. The main types of non-coding RNAs include small nuclear RNA), rRNA (ribosomal RNA), microRNAs (miRNAs), silencing interfering RNAs (siRNAs), long ncRNAs (lncRNAs), and circular RNAs (circRNAs). This review focuses on one of the most prevalent and widely studied regulatory ncRNA classes: miRNAs. Because of their ability to target mRNAs and their effective use as molecular markers, miRNAs have accrued increasing interest [30,31]. For instance, miR-4638-3p targets ATF3 in breast cancer cells, effectively suppressing cancer progression and bone metastasis [32]. MiRNAs are transcribed in the nucleus by RNA

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polymerase II (RNA Pol II), resulting in sequences characterized by a stem-loop structure called a primary miRNA (pri-miRNA). DGCR8 (RNase III) and DROSHA convert pri-miRNAs into precursor miRNAs (pre-miRNAs). In the cytoplasm, DICER cleaves the hairpin-loop structure of pre-miRNAs, resulting in mature miRNAs. To form the miRNA-induced silencing complex (miRISC), The argonaute (AGO) protein complex incorporates the selected guide strand to form an miRNA-induced silencing complex. The miRNA-RISC complex binds to cognate mRNAs via miRNA response elements (MREs), which are complementary miRNA seed regions. Depending on the degree of complementarity at their hybridization sites, miRNA-MRE interactions can result in mRNA cleavage or degradation, or inhibition of their translation [33,34].

miR-124 is among numerous miRNAs reported to exert effects governing diverse bone functions, including osteoclast and osteoblast differentiation [35]. miR-124 was first identified in mice [36] where it has been detected in multiple tissues including brain, liver, bone, pancreas, and colon [37–43]. miR-124 plays a crucial role as a diagnostic and prognostic biomarker of osteosarcoma development, and its downregulation in patients with osteosarcoma is associated with poor prognosis and adverse clinical outcomes. Overexpression of miR-124 effectively impedes core hallmarks of cancer, emphasizing its role as a tumor-suppressive factor in osteosarcoma. Additionally, miR-124 has been associated with bone diseases such as fracture healing and osteoporosis [35,17,44]. This review focuses on the various roles of miR-124 in bone, emphasizing its regulatory roles in several pathological and physiological conditions and its interactions with multiple signaling pathways. Furthermore, we discuss the roles of the lncRNA/circRNA/miR-124/mRNA axes reported to date and highlight the potential of miR-124 as a clinical target for treating bone diseases.

2. Role of miR-124 in bone: physiological and pathological conditions

miR-124 is specifically expressed in the central nervous system and is one of the most prevalent miRNAs in the adult brain [45]. miR-124 expression is observed in various other tissues [46,47]. Three members of this miRNA family, namely miR-124-1, miR-124-2, and miR-124-3, are encoded by genes located in distinct chromosomal regions. Remarkably, humans, mice, and rats produce the same mature form of this miRNA [47]. Recent studies have demonstrated roles for miR-124 in controlling cellular and molecular processes in bone. In this context, we emphasize its involvement in distinct physiological and pathological conditions in bone. We discuss a multitude of inhibitory effects due to miR-124 overexpression in BMSCs. At elevated levels, miR-124 targets the transcription factor Sp7, lowering markers of osteoblast differentiation including alkaline phosphatase (ALP), osteocalcin, osterix, and runt-related transcription factor-2 (Runx2), thereby inhibiting osteogenic differentiation. This inhibition can lead to osteoporosis [42]. Excessive miR-124 prevents BMSCs from differentiating into myogenic cells by turning off myogenic marker genes (Myf1 and Myod1), thereby retarding skeletal muscle development [48]. mir-124 targets STAT3, which inhibits cardiomyocyte differentiation in BMSCs, thereby diminishing the capacity for cardiac repair [49]. Excess miR-124-mediated inhibitory activity is implicated in the development of diverse pathological conditions.

Xia et al. aimed to determine the involvement of anthrax roxin receptor 2 (ANTXR2) in ankylosing spondylitis. They reported that ANTXR2 may dysregulate new bone formation. Bioinformatics analysis predicted ANTXR2 to be a target of miR-124. This prediction was later validated using a luciferase reporter assay. Compelling evidence suggests that high levels of miR-124 target and inhibit ANTXR2 expression, promoting autophagy [50]. Li et al. reported that miR-124 overexpression promotes BMSC osteogenesis by suppressing GSK-3β/β-catenin signaling pathway activity. This study provides insights into miR-124's primary role in regulating the Wnt pathway, making it ideal for diagnosing and treating diabetic osteoporosis [35]. Increasing miR-124 in MSC-derived extracellular vesicles (EVs) reversed the protective effect of MSC-circHIPK3-EVs against chondrocyte damage [51].

Another study by Cai et al. revealed miR-124 downregulation in metastatic bone tissue from patients with breast cancer. Restoring miR-124 expression suppressed bone metastatic breast cancer, whereas complete silencing of miR-124 promoted bone metastasis. At the molecular level, miR-124 inhibits bone metastasis in breast cancer cells by repressing IL-11 [52]. Subsequently, miR-124 is downregulated in osteosarcoma tumor tissues, and miR-124 downregulation is associated with tumor growth and differentiation. miR-124 overexpression suppresses cell growth and invasion *in vitro* [53].

3. Various signaling pathways regulated by miR-124 in bone

Existing research has reported an active role of miRNAs in positive and negative regulation of bone physiology and pathology. In one study, an exosomal miRNA, miR-144-5p, was reported to be expressed at acutely elevated levels in diabetic bone marrow-derived macrophages (dBMDM-exos), corresponding to low osteogenicity and fracture repair capacity compared to non-diabetics, by targeting SMAD1. When miR-144-5p was silenced, negative impacts on dBMDM-exos and their ability to heal fractures were rescued [38]. Using a mouse model, Wang et al. reported that miR-186 plays a vital role in regulating fracture healing by binding to SMAD6. Overexpression of miR-186 silenced SMAD6, increasing callus growth, bone mineral density (BMD), and BV/TV. In contrast, bone morphogenetic protein (BMP) 2 and BMP7 levels increased due to miR-186 upregulation and SMAD6 silencing. These results show that miR-186 activates the BMP signaling pathway by targeting SMAD6 to help bone regenerate [54]. Similarly, many studies implicate miR-124's regulatory role in bone through various signaling pathways. The molecular mechanisms by which miR-124 affects several signaling pathways in the bone are described in the following sections.

3.1. WNT signaling pathway

In ankylosing spondylitis, a condition of spastic and spinal joint disease characterized by pathological ossification, miR-124 was observed to regulate osteoblast differentiation by regulating GSK-3β expression, impacting Wnt/β-catenin pathway activity. Tang et al. induced differentiation of isolated ligament fibroblasts into osteoblasts. As osteoblasts differentiated, miR-124, β-catenin, Runx2, and Osterix expression levels progressively increased, while GSK-3β expression levels were gradually downregulated. These changes result in increased osteoblast differentiation. miR-124 downregulation increased GSK-3β expression, weakening Wnt/β-catenin signaling, which is essential in regulating osteoblast-specific genes, including Runx2, required for osteoblast differentiation. Inhibition of ligament fibroblast differentiation into osteoblasts was thus observed upon miR-124 silencing [55].

Multiple nutrient factors are crucial in bone remodeling, and researchers have identified glucose as a crucial nutrient for osteoblastic cells [56]. Li et al. demonstrated that miR-124-3p plays a pivotal role in intensified bone loss observed in patients with periodontitis and diabetes mellitus (DM). Gal-3 is a scavenging receptor of advanced glycation end products (AGE) that regulates bone cell interactions and homeostasis by stabilizing β-catenin to activate Wnt/β-catenin signaling. These results suggest that exosomes from osteocytes carrying miR-124-3p may control Gal-3 expression, especially when glucose levels are high. This could be a method for treating DM-related alveolar bone development deficiencies [57,58].

3.2. STAT3 signaling pathway

Li et al. investigated the effect of miR-124-3p on postmenopausal osteoporosis (POP) in rats via regulation of the STAT3 pathway.

Upregulation of the STAT3 pathway by miR-124-3p was observed to reduce BMD in POP rats, resulting in lower BMD in the femur [59]. A study by Cao et al. showed that astragaloside IV (AST-IV) helps human BMSCs grow and differentiate into osteogenic cells via the miR-124-3p.1/STAT3 axis. AST-IV is one of the main chemicals that comes from extracts of Astragalus membranaceus [60] and helps protect and differentiate BMSCs [61]. AST-IV promotes the cell cycle, viability, and osteogenic differentiation of human BMSCs. Results to date show that AST-IV raises STAT3 expression and lowers miR-124-3p.1 expression. Additionally, it accelerates healing of tibial bone defects in a concentration-dependent manner, showing that it promotes osteogenic differentiation in human BMSCs through the miR-124-3p.1/STAT3 axis [62].

3.3. RANK signaling pathway

Previous studies have shown that miR-124 controls osteoclastogenesis by targeting NFATc1 via RANK signaling pathways [63]. NFATc1 is an important factor underlying osteoclast activation and fusion. In the early stages of osteoclastic differentiation, the RANK signaling pathway activates NFATc1 through several transcription factors, including nuclear factor-κB [64,65]. Ohnuma et al. identified the modulatory activity of miR-124 in RANKL-independent osteogenesis, thereby providing a possible target for preventing bone damage in rheumatoid arthritis. miR-124 blocks TNF-α/IL-6-dependent osteoclastogenesis by controlling NFATc1 in both RANKL-dependent and-independent pathways. Overexpression of miR-124 inhibits RANKL-independent osteoclastogenesis *in vitro* and inhibits the bone resorption capacity of osteoclasts by suppressing various osteoclastic genes, such as CtsK, ACP5, DC-STAMP, and Itgb3 [63]. Many studies have elucidated miR-124 mediated regulation of bone homeostasis via signaling pathways. Further research could open new avenues to better understand bone physiology and develop various therapeutic methodologies for bone diseases.

3.4. BMP signaling pathway

Qadir et al. studied the detrimental effects of miR-124 on osteoblast differentiation by targeting the essential osteoblastic differentiation factor distal-less homeobox (Dlx). An inverse correlation was observed between miR-124 expression and osteogenic differentiation markers in human preosteoblastic cells and mouse BMSCs subjected to osteogenic differentiation induced by BMP2. miR-124 overexpression significantly decreases the expression levels of Dlx5, Dlx3, and Dlx2, which impacts alkaline phosphatase activity and matrix mineralization *in vitro* [66]. Similarly, Okamoto et al. investigated the involvement of various miRNAs, including miR-124a, in orchestrating osteoblastic differentiation induced by BMP4 in murine induced pluripotent stem cells. Their results suggest direct binding of miR-124a with the Dlx5 3′UTR, resulting in decreased Dlx5 expression. Thus, the development of anti-miR-124a antibodies could improve the clinical capability of inducing osteoblast differentiation [67] (Table 1).

4. Other ncRNA-mediated miR-124 regulation mechanisms in bone

Many studies describe miRNA regulation by other ncRNAs (miRNAs, circRNAs, and lncRNAs) in bone. The formed axes either positively or negatively regulate many bone conditions. Lai et al. showed that miR-27a-3p and miR-196b-5p help BMSCs differentiate into osteoblasts [68]. The miR-608/SP7 axis and circRNA hsa_circ_0001421/miR-608 partially control human adipose mesenchymal stem cell (hAMSC) osteoblastic differentiation, suggesting that hAMSCs can be used to treat osteoporosis [69]. The lncRNA ANCR negatively affects bone formation, starting with stem cells in the periodontal ligament. This is achieved by interacting with miRNA-758, which acts as a molecular sponge [70]. In the following sections, we discuss how ncRNAs such as lncRNAs and circRNAs regulate miR-124, and how ncRNA/miRNA/mRNA axes influence the outcome of bone remodeling genes.

Table 1
Signaling axes regulated by miR-124 in bone.

S. No.	Axis name	Target	Experimental Model	Effect	Reference
1.	miR-124-3p/BMP6	BMP6	Human osteosarcoma cells (OS-732)	BMP6, a direct target of miR-124, exerts a negative regulatory role in healing metaphyseal fractures of the distal tibia.	[17]
2.	miR-124/NFATc1	NFATc1	Mouse bone marrow macrophages	miR-124 plays a regulatory role in osteoclastogenesis of mouse bone macrophages. miR-124 inhibits NFATc1 expression. Active NFATc1 overexpression intercepts miR-124-mediated inhibition of osteoclastogenesis.	[18]
3.	miR-124/Rab27a	Rab27a	Female C57BL/6J mouse model	miR-124 inhibits osteoclastogenic differentiation of bone marrow monocytes by inhibiting Rab27a expression.	[19]
4.	miR-124/AKT/GSK-3β/SNAIL-1	AKT/GSK-3β/SNAIL-1	Human osteoblastic cells (MG-63) and Mouse preosteoblastic cells (MC3T3-E1)	miR-124 inhibits osteosarcoma growth by suppressing the TGF-β-mediated AKT/GSK-3β/SNAIL-1 axis.	[20]
5.	miR-124/Mycobacterium tuberculosis (Mt) sonicate/NFATc1	NFATc1	Bone marrow mononuclear cells	Mycobacterium tuberculosis sonicate upregulates miR-124 expression in osteoclasts. Overexpression of miR-124 inhibits NFATc1 and suppresses osteoclast differentiation and bone resorption.	[21]
6.	miR-124/NF-κB	NF-κB	Mouse osteoarthritis (OA) model; Primary chondrocytes	Curcumin effectively slows OA progression by regulating miR-124/NF-kB interaction. Curcumin treatment upregulates miR-124, and the 3′UTR of NF-κB is predicted to bind to miR-124.	[22]
7.	RANKL/MALAT1/miR-124	RANKL	RAW 264.7 and MCF-7 cells	Denosumab hinders MALAT1 expression via inhibition of RANKL, resulting in miR-124 upregulation, inhibiting spontaneous osteoclastogenesis caused by MCF-7 cells.	[23]
8.	SOX2/miR-124-3p/PI3K/Akt/mTOR	PI3K/Akt/mTOR	BMSCs	Inhibits osteogenic differentiation by inactivating PI3K/Akt/mTOR in rBMSCs.	[24]
9.	lncRNA MALAT1/miR-124-3p/IGF2BP1/Wnt/β-catenin	IGF2BP1	Ovariectomy-induced mouse model of osteoporosis	lncRNA MALAT1 promotes BMSC osteogenic differentiation and inhibits macrophage osteoclastic differentiation in osteoporosis via the miR-124-3p/IGF2BP1/Wnt/β-catenin axis.	[25]
10.	miR-124-3p/NFATc1/DLBCL	NFATc1	Human SU-DHL-6, SU-DHL-10 cells, and tumor xenograft nude mice	miR-124-3p overexpression downregulates the NFATc1/cMYC pathway and inhibits tumor growth in vivo and *in vitro*.	[26]
11.	MALAT1/miR-124/NFATc1	NFATc1	Mouse macrophage cells (RAW264.7)	lncRNA MALAT1 sponges miR-124 to regulate NFATc1 expression and increase osteoclastogenesis progression.	[27]

4.1. lncRNAs targeting miR-124

lncRNAs are non-protein-coding RNAs that regulate genes via epigenetic, transcriptional, and post-transcriptional mechanisms, affecting a range of biological functions, including growth, development, aging, and death. Transcripts of lncRNAs are typically longer than 200 nucleotides [71,72]. lncRNAs can serve as competing endogenous RNAs (ceRNAs) and interact with miRNAs through microRNA-responsive elements (MREs) to modulate gene expression. Yang et al. reported that MALAT1 functions as a molecular sponge for miR-34c, facilitating the upregulation of Special AT-rich sequence--binding protein (SATB2), enhancing osteogenic activity, and alleviating symptoms of osteoporosis [73]. Reports have indicated that miR-124 is regulated by lncRNAs. A study by Bin et al. elucidated the underlying mechanism of action of the lncRNA MALAT1 in osteosarcoma cell proliferation and migration by sponging miR-124-3p and upregulating the oncogenic sphingosine kinase 1 (SphK1). SphK1 is a direct target of miR-124-3p, and miR-124-3p upregulation downregulates SphK1 [74]. SphK1 is commonly upregulated in various cancer types, including osteosarcoma, and is correlated with poor prognosis [75]. A similar study by Cui et al. elaborated on the interaction between lncRNA HOXA11-AS/miR-124-3p/ROCK1 in patients with osteosarcoma. miR-124-3p inhibits tumor growth by directly binding to ROCK1 mRNA (encoding a transcription factor), halting colony growth, invasion, and the cell cycle. HOXA11-AS disrupts the tumor-suppressing activity of miR-124-3p by acting as an endogenous sponge, downregulating its expression, and simultaneously upregulating ROCK1 expression [76]. The lncRNAs HOXA11-AS and miR-124-3p have been implicated in fracture healing. Wang et al. have gathered conclusive evidence regarding the role of HOXA11-AS in their study. The CCK-8 assay revealed that HOXA11-AS overexpression inhibited cell proliferation and promoted cell apoptosis. The sites of miR-124-3p HOXA11-AS interaction were predicted using the bioinformatics tool DIANA LncBASE 2.0. miR-124-3p prevented the sponging activity of HOXA11-AS, rescued cells from apoptosis, and promoted cell growth. These findings may improve our understanding of fracture healing [77]. According to Wang et al., the cartilage tissues of patients with osteoarthritis (OA) were characterized by significant upregulation of lncRNA SNHG14, induced by IL-1β. lncRNA SNHG14 impeded the miR-124-3p-mediated anti-inflammatory effect by inducing the release of inflammatory mediators like Cox-2, iNOS, TNF-α, and IL-6. Downregulation of lncRNA SNHG14 suppresses Follistatin-like Protein 1 (FSTL-1)-mediated activation of NOD-like receptor family member pyrin domain containing 3 (NLRP3) and Toll-like receptor 4/nuclear factor κβ (TLR4/NF-κβ) signaling pathway activation by targeting miR-124-3p, thereby reducing inflammatory reactions in OA [Fig. 1A] [78].

4.2. CircRNA targeting miR-124

CircRNAs are another type of ncRNA distinguished by a covalently closed loop, eliminating 5′ and 3′ ends, and conferring stability on their structure. CircRNAs function as ceRNAs by competing with miRNAs for binding, thereby preventing miRNAs from blocking their target genes [79,80]. Ouyang et al. showed that hsa_circ_0074834 regulates the expression of zinc finger E-box-binding homeobox 1 (ZEB1) and vascular endothelial growth factor (VEGF) by acting as a ceRNA against miR-942-5p. Downregulating miR-942-5p and increasing ZEB1 and VEGF expression helps link angiogenesis to osteogenesis in BMSCs [81]. Similarly, a myriad of circRNAs regulate miR-124-3p function in the bones. A study by Liu et al. revealed mechanisms by which circRNAs regulate low-level laser irradiation (LLLI)-mediated promotion of BMSC proliferation in osteoporosis. Through the Wnt4/β-catenin signaling pathway, circRNA_0001052 negatively regulates BMSC proliferation by competitively binding to miR-124-3p. Hence, knockdown of circRNA_0001052 by LLLI enhanced miR-124-3p levels, upregulated Wnt4/β-catenin signaling and promoted BMSC proliferation [82]. Another study by Li et al. highlighted the significance of circHIPK3 derived from EVs secreted by MSCs. They underscored the importance of myosin heavy chain 9 (MYH9), which plays an important regulatory role in several diseases, including osteosarcoma. MSC-circHIPK3-EV noticeably rescued chondrocyte injury by downregulating miR-124-3p (through the ceRNA activity of circHIPK3) and upregulating MYH9 [52]. In a similar study on how circHIPK3 functions, Wu et al. reported that circHIPK3 correlated negatively with miR-124 in OA tissues and chondrocytes. Increasing circHIPK3 expression inhibits OA chondrocyte apoptosis by blocking miR-124 and increasing SOX8 expression (a direct target of miR-124). Wu et al. thus suggested that decreasing circHIPK3 expression could be a possible strategy to treat OA [Fig. 1B] [83].

5. *In vivo* studies of miR-124 on bone formation

Research into miRNAs in bone biology has increased substantially in recent years. Several in vivo experiments have indicated roles for miRNAs in osteogenesis, highlighting their potential as therapies [84–87].

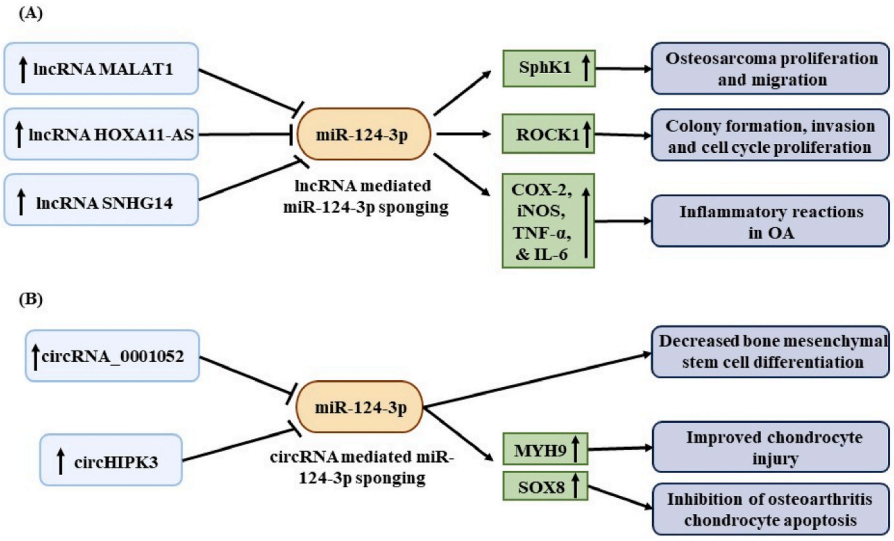

Fig. 1. Regulatory role of other ncRNAs on miR-124 in bone. (A) lncRNAs regulating miR-124-3p, validated targets of miR-124-3p, and their outcome in bone. **(B)** CircRNAs regulating miR-124-3p, validated targets of miR-124-3p, and their outcome in bone.

Nakamachi et al. examined the role of miR-124 in a rat model of adjuvant-induced arthritis (AIA). Injection of pre-miR-124 into the ankle joint repressed arthritis and improved the morphology of arthritic joints. Furthermore, in vivo assays were performed to assess the functions of the molecules that are prerequisites for arthritis. In AIA rats, miR-124 reduces NFATc1 expression through RANKL and NFATc1 pathways to suppress osteoclastogenesis. In addition to NFATc1, miR-124 reduced integrin beta-1 (ITGB1) expression, affecting osteoclast differentiation. miR-124 emerged from these studies as a key regulator of bone formation [88]. Another study on crosstalk between miR-124 and bone formation through bone remodeling was conducted by Cao et al., in which the effects of astragaloside IV on osteogenic proliferation and differentiation were evaluated. Studies conducted on female Lewis rats revealed that astragaloside IV decreased miR-124-3p.1 expression and increased STAT3 expression in rat tibial bones, resulting in bone marrow stem cell proliferation and differentiation [62].

6. miR-124 potential clinical and diagnostic applications

miR-124 has significant diagnostic applications in osteoporosis, osteosarcoma, and osteoarthritis [44,89,90]. In particular, miR-124 significantly regulates the osteoblastic differentiation of BMSCs, suggesting its potential as a therapeutic treatment for osteoporosis [42]. miR-124 expression levels are elevated in patients with osteoporosis and in postmenopausal women with or without fractures [91]. miR-124 inhibits cell proliferation and invasion by suppressing B7-H3 (also known as CD276) function and acts as a promising diagnostic marker and therapeutic target in osteosarcoma [54]. Delivery of miR-21/miR-124 using nanohydroxyapatite doped with iron oxide nanoparticles enhanced its pro-osteogenic effects due to exposure to magnetic fields. This complex increases osteoblast metabolism and differentiation, suggesting its use as a novel treatment for osteoporosis [92]. Additionally, miR-124 is a potential therapeutic agent for arthritis. Abnormal hyperplasia of fibroblast-like synoviocytes drives rheumatoid arthritis progression, and miR-124 inhibits cell proliferation and inflammation in these cells [93].

7. Other *functions* of miR-124

miR-124 mediates several regulatory roles in normal physiological and pathological bone conditions. In addition to bone environments, miR-124 modulates several functions in non-skeletal tissues. For instance, Guo et al. revealed that miR-124 overexpression inhibits delta-like canonical Notch ligand 4 (DLL4) expression and regulates the conversion of a significant number of astrocytes into functional neurons, thus contributing to recovery of motor deficits in an ischemic injury model [94]. A study of gastric fibroblasts (GF) by Li et al. reported that *Helicobacter pylori* infection intensified the expulsion of EVs carrying miR-124-3p, thereby initiating GF proliferation and migration. Reduced miR-124-3p expression enhances Snail Family Transcriptional Repressor 2 (SNAI2) expression (a potential contributor to the migratory and invasive capabilities of various cancers) [95]. Zhang et al. outlined an inverse correlation between miR-124-3p and the EYA transcriptional coactivator and phosphatase 1 (EYA1) gene using a zebrafish model. The EYA1 gene, which plays a crucial role in normal inner ear development, was shown to be affected by microinjection of agomiR-124-3p, resulting in reduced auricular area and inner ear dysplasia [96]. miR-124-3p is closely associated with allergic diseases, including rhinitis (AR). A study by Zhang et al. revealed that miR-124-3p is a potential upstream element of dipeptidyl peptidase-4 (DPP4), a serine protease that is abundantly distributed in plasma and body fluids, and a potential inflammatory mediator that initiates inflammation in various tissues. Upregulation of miR-124-3p alleviates allergy symptoms including nasal rubbing, sneezing, pathological changes, and eosinophil number by targeting DPP4 [97]. miR-124-3p acts as a key regulator of axes involving lncRNAs, miRNAs, and mRNAs. Yang et al. reported that the overexpression of lncRNA XIST in BV2 microglial cells sponges miR-124-3p and upregulates interferon regulatory factor 1. This promotes M1 polarization and inflammatory responses, causing spinal cord injury. This inverse mechanism promotes M2 polarization and alleviates SCI by decreasing the concentration of inflammatory cytokines [98]. Fig. 2 shows other functions of miR-124 in non-skeletal tissues.

8. Conclusion

Innumerable studies of relationships between miRNAs and bone metabolism have provided deep insight into the roles of miRNAs in bone and bone-related disorders. miR-124, an miRNA conserved among several species, plays pivotal roles in various cellular functions, including bone metabolism. miR-124 regulates bone remodeling events by controlling the activities of osteoblasts and osteoclasts via transcription factors and signaling pathways. Dysregulation of miR-124 by other ncRNAs can lead to several bone abnormalities. Future research should explore variations in miR-124 expression patterns as an informative biomarker for assessing bone-related diseases. Existing *in vitro* results supporting the roles of miR-124 in bone metabolism must be validated in vivo. Understanding the functional roles and impacts of miR-124 in physiological and pathological bone conditions will enable a broad spectrum of research and provide opportunities for therapeutic relief.

CRediT authorship contribution statement

Rushil Kolipaka: Writing – original draft. **Induja Magesh:** Writing – original draft. **M.R. Ashok Bharathy:** Writing – original draft. **S. Karthik:** Writing – original draft. **I. Saranya:** Writing – original draft. **N. Selvamurugan:** Writing – review & editing, Funding acquisition, Conceptualization.

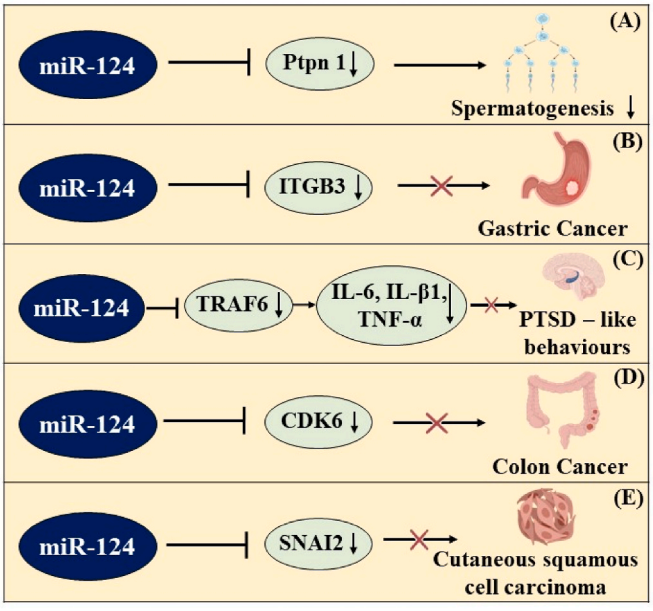

Fig. 2. A pictorial representation of other miR-124 functions in non-skeletal tissues. **(A)** miR-124-3p downregulates Ptpn1 expression, affecting testicular development and spermatogenesis [99]. **(B)** miR-124-3p suppresses gastric cancer progression by targeting ITGB3 [100]. **(C)** miR-124 targets TRAF6, decreasing pro-inflammatory cytokine levels, ameliorating post traumatic stress disorder (PTSD)-like behaviors [101]. **(D)** miR-124-3p downregulates CDK6, playing a vital role in attenuating colorectal cancer incidence [102]. **(E)** miR-124-3p targets SNAI2, thereby inhibiting cutaneous squamous cell carcinoma [103].

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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