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Recent advancements of miRNAs in the treatment of bone diseases and their delivery potential

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ABSTRACT

Advances in understanding miRNAs as endogenous posttranscriptional regulatory units have projected them as novel therapeutics for several untreatable diseases. miRNAs are endogenous non-coding small single-stranded RNA molecules (20–24 nucleotides) with specific gene regulatory functions like repression of mRNA translation by degrading mRNAs. Emerging evidence suggests the role of miRNAs in various stages of bone growth and development. Undoubtedly, due to their critical role in bone remodeling, miRNAs might be projected as a novel approach to treating bone-related diseases. However, the instability associated with miRNAs in their complex environment, such as degradation by nucleases, is a concern. Thus, recent attention is being paid to maintaining the miRNAs' safety and efficacy in the cells. Various efficient delivery systems and chemical modifications of miRNAs are being developed to make them a potential therapeutic option for bone diseases. Here, we have tried to recapitulate the recent advances in the role of miRNAs in bone disease, along with the potential delivery systems for their efficient delivery to the cells.

1. Introduction

The human skeletal system is responsible for various life-supporting functions like supporting soft tissues, locomotion, a reserve for phosphate and calcium, and the production of blood cells. Besides, it is constantly in a dynamic state of bone remodeling process mediated by bone-resorbing osteoclasts and bone-forming osteoblasts, and equilibrium between these two processes maintains bone homeostasis. However, any alteration in this equilibrium leads to several bone-related pathologies causing restriction in mobility and mortality. Various therapeutic interventions are available for bone-related diseases, but side effects associated with them are always a concern. Thus, therapeutic development for novel targets with minimum after-drug consequences is a prerequisite. The flexibility and strength of the bones are entirely dependent on a proper homeostatic balance between the osteoclast and osteoblast cells. As a person ages, there is a disruption in the homeostatic balance, which favors osteoclastogenesis, making the bones susceptible to fractures (Rodan and Martin, 2000). Furthermore, the alteration in the balance of these osteogenic events sometimes develops chronic bone disorders leading to a lack of mobility (Al-Bari and Al Mamun, 2020; Chindamo et al., 2020). An in-depth understanding of this equilibrium condition between bone resorption and bone formation is a key factor essential for developing therapeutics to treat bone diseases (Rodan and Martin, 2000). Presently, certain investigations have developed some drugs to treat bone-related ailments, but the administration of these drugs is causing certain side effects in several body organs (Chindamo et al., 2020). Generally, bone diseases range from the growth of osteolytic lesions to osteoporosis (OP). Sometimes the prevalence of both these ailments can be encountered in multiple myeloma disease. However, early diagnosis and treatment of bone-related diseases are essential to save people's lives (Hillengass and Merz, 2020). Besides, the complex process of bone metabolism is also responsible for bone-related ailments. This intricate process is mediated by various signaling pathways like Wingless-related integration site/beta-catenin (Wnt/β-catenin), (Transforming growth factor beta) TGF-β, and Bone morphogenetic protein (BMP). The differences in the regulation of these pathways lead to bone disorders like osteopenia, OP, osteoarthritis, etc. (Chen et al., 2018; Ensrud and Crandall, 2017).

A class of non-coding RNA, with sizes ranging from 20 to 22 bp, called microRNAs (miRNAs), can vary the expression of several genes in many

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biological events. miRNAs are strong intracellular mediators that are essential for different processes (Christopher et al., 2016; Landgraf et al., 2007). Recent studies highlight the role of different miRNAs in the progression of several diseases like myocardial infarction, hepatitis C, metabolic diseases, and various kinds of cancers. The miRNA profiling has proved that these non-coding RNAs can sometimes be overexpressed, or their expression can even be inhibited in a disease state (Lu et al., 2005). Recently, the role of different miRNAs involved in bone formation and bone-related disorders has been appreciated. MiR-133a, miR-21 (Li et al., 2014), and MiR-194-5p (Kanis et al., 2000) were suggested as biomarkers for osteoporosis. miR-34a is a potential prognostic biomarker for osteosarcoma (Lian et al., 2022). miR-10 and miR-326 were reported to significantly increase in Rheumatoid Arthritis (RA) patients (Paradowska-Gorycka et al., 2022). miR-29b-3p upregulate in *Staphylococcus aureus*-infected human bone mesenchymal stem cells. lncRNA KCNQ1OT1 has been projected for the treatment of osteomyelitis by sponging miR-29b-3p (Ding et al., 2022). miR-96, miR-144, miR-150, miR-326, miR-451 and let-7 have a crucial role in thalassemia bone disease by regulating γ-globin levels (Wang et al., 2021). Thus, miRNAs can be utilized as potential therapeutic agents in bone ailments because they can overcome the side effects caused due to the administration of certain drug molecules. Moreover, it can also be delivered very easily to the site of infection, a limitation of using conventional therapeutic agents (Bravo Vazquez et al., 2021). To enhance the functionality of miRNAs and their possibility of being used as a therapeutic molecule, several modifications are made to the RNA molecules in order to protect them and prevent the escape of miRNA from the endosomes (Sun et al., 2019).

In this review, we have elucidated the therapeutic role of different miRNAs in bone disorders. miRNAs play a major role in many kinds of diseases. The overexpression or the inhibition of the expression of several miRNAs regulates the expression of various genes involved in the disease landscape and leads to the progression of the disease. Some modifications of miRNA, along with the choice of appropriate delivery vehicle, can be an efficient approach for treating various kinds of orthopedic disorders like OP, osteogenesis imperfecta, osteomyelitis, osteonecrosis, etc. The administration of the miRNA as therapeutic molecules upregulates or downregulates the expression of several genes involved in the disease pathways leading to the differentiation of osteoblast cells. Furthermore, the use of miRNAs as therapeutics may help maintain a balance between the differentiation of osteoblast and osteoclast cells, restoring the bone mineralization and formation of the osteoblast cells.

2. Role of miRNA as a therapeutic agent

miRNAs can be used as a therapeutic agents because of their ability to regulate the translation of several proteins which are involved in a particular gene expression by choosing a variety of methods like degradation of mRNAs or deadenylation of the mRNAs. They can sometimes even insulate the mRNA molecules in the P bodies. The miRNAs can even interfere with the function of ribosomes, followed by the destruction of some nascent polypeptides (Morozova et al., 2012). The various evidence elucidating the therapeutic roles of miRNAs in treating bone-related disorders has been highlighted before. Some miRNA's, like miR-225 and miR-185, regulate the proliferation and expression of several osteoblast cells (Yao et al., 2018). Based on the differential levels of expression of the target miRNAs, therapeutic miRNAs can be broadly classified into two types, namely the “loss-of-function” or the “gain--of-function” (Adams et al., 2017). The miRNAs overexpress after adopting the strategy of “gain-of-function”. The exaggerated expression can be by some viral vectors or some imitation of the miRNA (Lima et al., 2018). On the contrary, the “loss-of-function” strategy can be achieved in various ways like miRNA sponging, anti-miRs, and miRNA masks (Sun et al., 2019).

The use of miRNAs as effective therapeutic agents mainly depends on the inhibition of expression or the overexpression of that particular miRNA. The anti-miRs or the miRNA masks generally inhibit the expression of that miRNA. The anti-miRs generally hinder the miRNA from binding with its mRNA target, which does not suppress the particular gene's function in that pathway. The anti-miRs are exactly similar to the naturally existing miRNAs, and they do not allow the formation of the RNA-induced silencing complex (RISC), an important step in miRNA biogenesis (Mendell and Olson, 2012; Peng et al., 2015). To improve the inhibitory effect, the anti-miRs are sometimes subjected to modifications that strengthen their function. The addition of 2′-O-methoxyethyl group (known as antagomiRs) or locked nucleic acids (LNA) is some of the common methods (Rupaimoole and Slack, 2017). However, recent studies have elaborated many facts suggesting the intense relationship of miRNAs in the several steps involved in bone formation, growth, and remodeling. Thus, given the close association of miRNAs in the process of several osteogenic disorders, miRNAs are being projected as a new generation of therapeutics for bone diseases. miRNAs also sometimes interfere with osteoblast differentiation, altering the osteogenic activities, metastasis, or even the proliferation of several cells. These versatile roles of the miRNAs in the alteration of osteogenic activities are therefore triggering the advancements of the miRNAs to be employed in treating several bone diseases (Bravo Vazquez et al., 2021).

3. Therapeutic role of miRNA in several bone diseases

The miRNAs have been employed as a therapeutic agent in many bone diseases. Some of the miRNAs and their therapeutic roles in bone diseases are listed below (Table 1). The secondary structures of the miRNAs is depicted in Fig. 1. Human miRNAs, their mature sequences, pre-microRNAs nucleotide, and miRBase ID having a significant role in bone disease are summarized in Table 2.

3.1. OP

The osteoblast and osteoclast cells are important for bone remodeling and bone matrix synchronization. OP results from the massive deterioration of the bone tissues, followed by a decrease in the density of the bones. This disorder is most prevalent in older ages and after menopause in females (Feng et al., 2019; Rozenberg et al., 2020). A disruption of the equilibrium between bone resorption and osteogenesis is majorly responsible for this ailment (Li et al., 2020). Similar to several diseases, miRNAs act as attractive therapeutic mediators in OP treatment. Some initial approaches have highlighted the superiority of Resveratrol in treating OP. The in-vitro studies in rats lacking one or more ovaries have elucidated that Resveratol could treat OP by altering the expression of miR-338-3p (Guo et al., 2015). Another miRNA, miR-365, can be employed for treating glucocorticoid-induced secondary OP by stimulating the process of osteogenesis. It targets one of the vital enzymes involved in histone acetylation named HDAC4 and nullifies the dexamethasone-induced suppression of osteogenesis in MC3T3 cells (Xu et al., 2017). Besides, two miRNAs, miR-150 and miR-214, might be considered novel agents for the OP treatment. The miR-150 is responsible for enhancing the process of bone formation by stimulating osteoblast functions and bone mineralization. Its agomir was shown to effectively increase the osteogenic markers in MC3T3 cells and was suggested as an effective agent for curing OP (Dong et al., 2015). On the contrary, miR-214 regulates the process of differentiation of osteoclast cells and might act as a therapeutic agent for preventing OP. Inhibition of miR-214 causes a decreased activation of the PI3K/Akt pathway by targeting phosphatase and tensin homolog (*Pten*), attenuating the process of osteoclastogenesis (Zhao et al., 2015). The estrogen hormone plays a vital role in protecting bone cells. It alters the levels of miRNAs in order to control the progression of bone-related diseases like OP, endometriosis, cancer, etc. It can even suppress the bone resorption process in the osteoclast cells (Hamilton et al., 2017; Hu et al., 2020). The anti-miR-148a exploits a similar strategy. Increased expression of miR-148a downregulated the expression of estrogen receptor alpha (ERa) by suppressing the activity of the PI3K/AKT signaling pathway in

Table 1
Chromosomal location and specific functions of miRNAs in bone.

Sl.no.	miRNA name	Chromosomal location	Functions	References
1	miR-185	Chr22	Represses cells growth and metastasis of osteosarcoma cells by targeting cathepsin E	(Wu et al., 2022)
2	miR-338-3p	Chr17	Enhances the proliferation of osteosarcoma cells by regulating the HIF-1/Rap1/PI3K-Akt pathway	(Li et al., 2021)
3	miR-365	Chr16	Helps in the progression of OP by inhibiting osteogenic differentiation by targeting RUNX2	Cheng et al. (2019)
4	miR-150	Chr19	Act as major epigenetic repressors and inhibits cell proliferation	Selvam et al. (2022)
5	miR-214	Chr1	Inhibits the osteoblast function by targeting ATF4 protein and promotes the function of osteoclast through phosphatase and tensin homolog	Wang et al. (2019)
6	miR-152	Chr17	Stimulates the viability and osteogenic differentiation of periodontal ligament stem cells by targeting integrin alpha	Wu and Ma (2020)
7	miR-134	Chr14	Augments the osteosarcoma chemoresistance through miR-134/PTBP1 signaling cascade	Zhang et al. (2021)
8	miR-544	Chr14	Deregulates a gene–protein network and contributes to the pathogenesis of osteosarcoma	Thayanithy et al. (2012)
9	miR-369-3p	Chr14	Deregulates a gene–protein network and contributes to the pathogenesis of osteosarcoma	Thayanithy et al. (2012)
10	miR-382	Chr14	Deregulates a gene–protein network and contributes to the pathogenesis of osteosarcoma	Thayanithy et al. (2012)
11	MiR-21	Chr17	Regulates the KLF3 protein to promote osteoblast proliferation	Zhai et al. (2019)
12	miR-186-5p	Chr1	Inhibits the PI3K/AKT signaling of non-traumatic osteonecrosis	Xu et al. (2019)
13	miR-127	Chr14	Helps in the progression of osteoarthritis by regulating the miR-127-5p/NAMPT axis	Liu et al. (2021)
14	miR-214	Chr1	Supports osteoclasts' differentiation through PI3K/Akt pathway by targeting PTEN.	Zhao et al. (2015)
15	miR-628-3p	Chr15	Upholds the growth and migration of osteosarcoma by targeting IFI44L protein.	Wang et al. (2020)
16	miR-381	Chr14	Controls the human bone mesenchymal stromal cells osteogenesis by suppressing the Wnt signaling pathway	Long et al. (2019)
17	miR-146a-5p	Chr5	Inhibits osteoclastogenesis in precursor	Yao et al. (2015)
18	miR-223-3p	ChrX	Upregulated in patients with RA and is involved in osteoclastogenesis.	Li et al. (2012)
19	miR-31a-3p	Chr9	Play an important role in non-union development	Waki et al. (2015)
20	miR-26b	Chr2	Helps in chondrocyte senescence and impairs the osteoarthritis progress by the TGF-beta1/Smad2 pathway	Liu et al. (2022)
21	miR-223	ChrX	Regulates the RA	Evangelatos et al. (2019)
22	miR-145	Chr5	Activates the expression of β-catenin and TCF-1	Sun et al. (2016)
23	miR-29b	Chr7	Inhibits the osteoblast apoptosis by restoring the down-regulated expression of Bcl-2 protein	Bourebaba et al. (2020)
24	miR-27a	Chr19	Helps in the chondrocyte apoptosis in osteoarthritis allied with the lipopolysaccharide.	Yu et al. (2022)

osteoblasts. anti-miR-148a rescued the ovariectomy-induced OP through ERα by PI3K/AKT signaling (Xiao et al., 2018). Feng et al. have highlighted that the reduction in the expression of miR-152 can stimulate the osteoblast cells' differentiation and upregulate the RICTOR protein that dominates the activities of the osteoblasts (Feng et al., 2019). The expression level of miRNA-151a-3p was found elivated in post-menopausal women with OP and promoted osteoclast differentiation. In a rat model of ovariectomy-induced osteoporosis, silencing of miRNA-151a-3p decreased osteoclastogenesis-related factors and raised BMD (He et al., 2021). miRNA-197-3p has been shown to inhibit osteogenic differentiation by downregulating KLF 10 in MC3T3-E1 cells (You et al., 2021). In OP patients' femoral neck trabeculae, the expression level of miR-874-3p is quite low compared to healthy individuals, while the leptin level is high. In human bone marrow mesenchymal stem cells, overexpression of miR-874-3p upregulated the gene expression levels of osteogenic markers like ALP, RUNX2, OCN, and OSX by suppressing leptin (Mei et al., 2021).

3.2. Osteosarcoma

Osteosarcoma is the most prevalent type of bone cancer observed in children and adult subjects. This type of cancer mostly affects the tubular bones resulting in extreme pain and swelling of such areas. It also causes joint afflictions (Zhao et al., 2021). The miRNAs employed for the treatment of osteosarcoma follow two possible mechanisms. The first way is to hinder the expressions of several oncogenic miRNAs by employing anti-miRs. The other way involves the re-establishment of the tumor suppressor miRNAs by employing mimics of miRNA. These structures are similar to the chosen miRNAs (Kobayashi et al., 2012). One of the most common types of miRNA employed as a therapeutic agent for various kinds of cancer, like lung cancer, breast cancer, colorectal cancer, etc. is miR-1 (Peng et al., 2020; Wu et al., 2020; Sheervalilou et al., 2019). miR-1 is also capable of acting as a therapeutic agent for treating osteosarcoma. It is very proficient in hindering the growth and invasion of osteosarcoma cells by VEGFA (vascular endothelial growth factor A), an essential factor required for the growth of tumor cells (Niu et al., 2016). Another miRNA capable of targeting osteosarcoma cells is miR-134. It downregulates the expression of VEGFR1 and VEFGA. Downregulation of these two enzymes arrests the process of angiogenesis and cell proliferation. Importantly, the binding of miR-134 to the 3' untranslated regions of the metalloproteinases (namely metalloproteinase 1 and 3) blocks the metastasis and invasion of the osteosarcoma cells (Chen et al., 2019). Some of the other miRNAs, like miR-544, miR-382, and miR-369-3p, are also potent therapeutic agents that are competent in repressing the expression of the *c-MYC* gene in the osteosarcoma cells (Thayanithy et al., 2012). The miR-21 has also been a good therapeutic candidate against osteosarcoma. MiR-21 down-regulates the expression of PTEN and enhances the apoptosis of the osteosarcoma cells (Yang et al., 2018). Recent research on the employment of miRNAs in treating osteosarcoma also elucidates the importance of miR-34 as an effective therapeutic agent. The miR-34 is a potent agent having the ability to destroy osteosarcoma cells (Vetter et al., 2017). Besides, the preliminary investigations using the mimics of miR-34 in animal models have also highlighted the capability of interfering in the process of metastasis of the cancer cells (Jian et al., 2017).

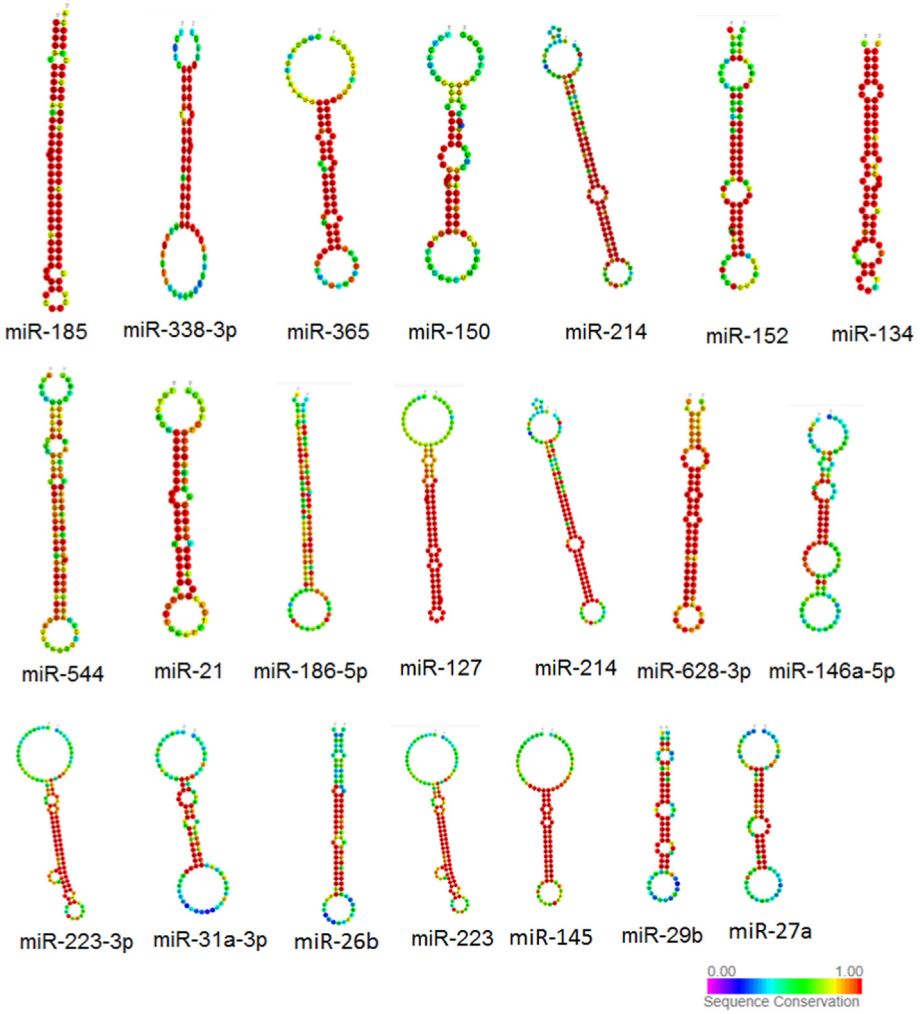

Fig. 1. Human miRNAs secondary structures (stem-loop) responsible for gene regulation and associated with bone disorders. Structure predicted by Rfam server (https://rfam.org/).

3.3. Osteonecrosis

A proper homeostatic balance between the osteoblasts and osteoclasts is essential for the proper functioning of the bones. Any kind of disruption in the homeostatic balance may downregulate the osteogenic activities with an increase in adipogenesis, resulting in osteonecrosis (Liu et al., 2020; Wang et al., 2018). Xu et al. have elucidated the significance of employing miR-186-5p as a therapeutic agent, as it downregulates the PI3K/AKT signaling pathway and controls the proliferation of human mesenchymal stem cells (Xu et al., 2019). The overexpression of miR-410 targets the Wnt signaling pathway, which dominates a balance between the osteoblast and osteoclast cells. The miR-410 can stimulate osteogenesis and downregulate osteoclasts' production. With such a regulation, miR-410 can offer an excellent way of treating osteonecrosis (Omar et al., 2019). Dai et al. have also pointed out the role of miR-127 in osteonecrosis. The miR-127 targets the *DKK1* gene, which is closely involved in several pathways of bone metabolism. The overexpression of this miRNA triggers osteoblast differentiation by downregulating the expression of the *DKK1* gene (Dai et al., 2019). The delivery of miR-214 using an adeno-associated virus has shown promising results in animal models of osteonecrosis. This miRNA plays a dual role in dominating both osteoblast and osteoclast differentiation. The upregulation of miR-214 represses osteoblast differentiation and promotes osteoclast differentiation. The downregulation of the miR-214 results in arresting osteonecrosis during the initiation of the disease (Wang et al., 2019). Moreover, the miRNAs like miR-27a, miR-548d-5p, and miR-708 can be employed as therapeutic agents against osteonecrosis because of their ability to stimulate the differentiation of osteoblast cells. Sometimes, they often regulate the phenomenon of adipogenesis which is a pivotal cause of osteonecrosis (Li et al., 2018).

3.4. Atrophic non-union

Atrophic non-union is caused when the individual loses the natural process of bone repair and healing after the occurrence of any fracture. In this disease, all sorts of osteogenic activities and the differentiation of osteoblast cells are delayed (Chen et al., 2017). Like many other bone disorders, miRNAs also have therapeutic roles in treating Atrophic non-union. For instance, miR-628-3p can be used for treating this disorder as it can inhibit the differentiation of the osteoblasts by altering the expression of the *RUNX2* gene (Chen et al., 2017). Alternatively, miR-381 is also a potential candidate for treating Atrophic non-union. miR-381 downregulates the functioning of the genes like *Wnt5A* and *FZD3* in the Wnt signaling pathway and exhibits an anti-osteogenic activity, as validated by administering miR-381 in rat models (Long et al., 2019). Moreover, Waki et al. have already illustrated that miR-146a-5p, miR-223-3p, miR-31a-3p, miR-146b-5p, and miR-146a-5p can be employed as therapeutic agents for the treatment of Atrophic non-union because these miRNAs are closely related with the pathogenesis of the disease as obtained from the samples examined

Table 2
Human miRNAs, their mature sequences, pre-microRNA nucleotides, and miRBase ID (having a role in bone diseases).

Sl.no.	miRNA name	Mature sequence	miRBase ID	Nucleotide length of Pre-mirRNA
1	miR-185	5′ - uggagagaaaggcaguuccuga - 3′	MIMAT0000455	22 nt
2	miR-338-3p	5′ - aacaauauccuggugcugagug - 3′	MIMAT0000763	22 nt
3	miR-365	5′ - agggacuuuuggggggcagaugug - 3′	MIMAT0009199	23 nt
4	miR-150	5′ - cugguacaggccugggggacag - 3′	MIMAT0004610	22 nt
5	miR-214	5′ - acagcaggcacagacaggcagu - 3′	MIMAT0000271	22 nt
6	miR-152	5′ - ucagugcaugacagaacuugg - 3′	MIMAT0000438	21 nt
7	miR-134	5′ - ugugacugguugaccagagggg - 3′	MIMAT0000447	22 nt
8	miR-544	5′ - auucugcauuuuuagcaaguuc - 3′	MIMAT0003164	22 nt
9	miR-369-3p	5′ - aauaauacaugguugaucuuu - 3′	MIMAT0000721	21 nt
10	miR-382	5′ - aaucauucacggacaacacuu - 3	MIMAT0022697	21 nt
11	MiR-21	5′ - uagcuuaucagacugauguuga - 3′	MIMAT0000076	22 nt
12	miR-186-5p	5′ - caaagaauucuccuuuuggcu - 3′	MIMAT0000456	22 nt
13	miR-127	5′ - ucggauccgucugagcuuggcu - 3′	MIMAT0000446	22 nt
14	miR-214	5′ - acagcaggcacagacaggcagu - 3′	MIMAT0000271	22 nt
15	miR-628-3p	5′ - ucuaguaagaguggcagucga - 3	MIMAT0003297	21 nt
16	miR-381	5′ - uauacaagggcaagcucucugu - 3′	MIMAT0000736	22 nt
17	miR-146a-5p	5′ - ugagaacugaauuccaugggguu - 3′	MIMAT0000449	22 nt
18	miR-223-3p	5′ - ugucaguuugucaaauacccca - 3	MIMAT0000280	22 nt
19	miR-31a-3p	5′ - ugcuaugccaacauauugccau - 3′	MIMAT0004504	22 nt
20	miR-26b	5′ - uucaaguaauucaggauaggu - 3′	MIMAT0000083	21 nt
21	miR-223	5′ - ugucaguuugucaaauacccca - 3′	MIMAT0000280	22 nt
22	miR-145	5′ - ggauuccuggaaauacuguucu - 3′	MIMAT0004601	22 nt
23	miR-29b	5′ - uagcaccauuugaaaucaguguu - 3′	MIMAT0000100	23 nt
24	miR-27a	5′ - uucacaguggcuaaguuccgc - 3′	MIMAT0000084	21 nt

from different subjects (Waki et al., 2015).

3.5. Rheumatoid arthritis (RA)

RA is one of the most severe inflammatory autoimmune disorders dominating the population (Firestein, 2003). Yang and his colleagues have elucidated the potential role of miR-221 as a possible therapeutic agent for RA. The repression of this miRNA can alter the entire disease landscape of RA as it causes variation in the expression of genes involved in the progression of this chronic disease. Besides, the repression of miR-221 even regulates the release of certain proinflammatory chemokines and cytokines (Yang and Yang, 2015). Some of the miRNAs, like miR-223-3p, miR-146a-5p, miR-125b-5p, miR-126-3p, and miR-16-5p, play important roles in the pathogenesis of RA. Thus, they can be considered as novel biomarkers against this autoimmune disease. The administration of anti-TNFα and DMARDs in patients has altered the regulatory function of these miRNAs, causing a decrease in the release of proinflammatory cytokines like TNFα, IL-17, and IL-6. (Castro-Villegas et al., 2015). The in-vitro trials for examining the efficacy of miRNAs as therapeutic agents have rendered promising results. The mimic of miR-26b stimulated the apoptosis of RA synovial fibroblast cells (RASF) with a decrease in the release of various cytokines (Sun et al., 2015). Alternatively, Kawano et al. also concluded that the administration of miR-124a drastically decreased the synthesis of the CDK-2 and MCP-1 proteins because it directly binds to the 3′-untranslated region of the mRNA for both CDK-2 and MCP-1, suggesting it as a possible therapeutic against RA (Kawano and Nakamachi, 2011). Moreover, the administration of miR-573 and miR-451 also mitigated the progression of RA via neovascularization and decreased the production of cytokines (Wang et al., 2015, 2016). Another possible therapeutic agent, miR-26a, administered as an intraperitoneal injection, hinders TLR3 with a downregulation in the production of cytokines secreted from the macrophages (Chen et al., 2018; Jiang et al., 2014). The inhibition of miR-223 improved the histological score and reduced bone erosion in collagen-induced arthritis, suggesting it as a potential treatment option for RA. (Li et al., 2012).

3.6. Osteogenesis imperfecta

Osteogenesis Imperfecta (OI) is an inherited bone disorder that occurs very rarely. The affected individuals are prone to fractures because of the lower mass and density of the bones (Monti et al., 2010; Shaker et al., 2015). The genes specifically responsible for this ailment are COL1A1, COL1A2, COL4A2, and COL5A3. These genes disrupt collagen production and weaken the bone (Kaneto et al., 2014; Lim et al., 2017). Some preliminary studies have indicated the use of miR-29b as a therapeutic agent. However, the amount of COL1A1 mRNA controls the induction of miR-29b, which is further responsible for collagen protein accumulation during mineralization. The findings concluded that the lower levels of COL1A1 mRNA seen in OI patients were insufficient to induce miR-29b. (Kaneto et al., 2014). The miR-145 can also be considered for therapeutic application against OI as it promotes the differentiation and proliferation of the osteoblast cells by targeting some of the genes involved in the Wnt signaling pathway (Sun et al., 2016).

3.7. Osteomyelitis

Osteomyelitis is a bacterial infection caused by *Streptococcus pneumoniae*, *Staphylococcus aureus,* or *Kingella kingae,* resulting in bone swelling. The disease gradually causes bone decay, leading to necrotic bone (Hatzenbuehler and Pulling, 2011; Birt et al., 2017). The research of using miRNA-based therapeutics against osteomyelitis has not been explored to a greater extent to date. Jin et al. reported that miR-24, a key regulator of osteogenesis, was downregulated in osteomyelitis patients. This miRNA targets the *CHI3L1* gene responsible for the secretion of several proteins responsible for inflammation. Thus, the overexpression of miR-24 can be a competent agent in preventing this bone infection caused by *Staphylococcus aureus* (Jin et al., 2015). However, treatment with algal extracts dramatically increased the expression of osteoblast-specific markers like Runx2, osteocalcin, alkaline phosphatase, and other miRNAs like miR-29b and miR-27a (Bourebaba et al., 2020). miR-146a suppressed inflammation response and induced osteogenesis in *Staphylococcus aureus*-induced osteomyelitis mice model (Jiang et al., 2022).

3.8. Multiple myeloma bone disease

Multiple myeloma bone disease is caused by excessive osteolysis due to increased osteoclastogenesis and decreased osteoblastogenesis, which is also the clinical symptom of multiple myeloma that is the second most common hematologic malignancy (Rajkumar and Kumar, 2016; Szudy-Szczyrek et al., 2022). miRNA-29b has been projected as a tumor

suppressor in multiple myeloma as it was shown to induce apoptosis in human myeloma cell lines and is antagonistic with IL-6 (Zhang et al., 2011). Exosomal miR-4261 can target and downregulate the ATP2B4 of the red blood cells with hypercalcemia, suggesting it to be an efficient therapeutic agent (Bian et al., 2022). The encapsulation of miR-34a into chitosan/PLGA nanoparticles can be employed as a potential therapeutic against multiple myeloma disease as it hindered the tumor growth in mice models (Cosco et al., 2015). The exosomal circ-ATP10A can also promote multiple myeloma angiogenesis by regulating the miRNAs like hsa-miR-1266-3p, hsa-miR-3620-3p, hsa-miR-3977, hsa-miR-6758-3p, and hsa-miR-6804-3p and their downstream mRNAs namely VEGFB, PDGF, HIF1A, and FGF) (Yu et al., 2022). Some previous study reported that miR-15, miR-16, miR-21, miR-34 family, and miR-221 are involved in the pathogenesis and progression of multiple myeloma (Handa et al., 2019). Papanota et al. provided the insight that circulating let-7b-5p, miR-143-3p, miR-17-5p, miR-335-5p, and miR-214-3p can be employed as a biomarker for the prognosis of multiple myeloma bone disease (Papanota et al., 2021).

3.9. Thalassemia bone disease

Thalassemia is chronic hemolytic anemia, and the underlying cause of the disease is the synthesis of mutant hemoglobin by the reduced production or absence of β-globin chains (Eltaweel et al., 2021). Additionally, one of the serious complications of thalassemia is thalassemia bone disease (Wang et al., 2021). Therefore, increasing the expression levels of fetal hemoglobin (HbF) or regulating the expression of α-, β- and γ-globin are considered promising and potential treatments against thalassemia bone disease (Eltaweel et al., 2021; Kuno et al., 2019). Importantly, in thalassemia bone disease eight miRNAs namely hsa-miR-146b-5p, hsa--miR-146a-5p hsa-miR-148b-3p, hsa-miR-155-5p, hsa-miR-192-5p, hsa--miR-335-5p, hsa-miR-7-5p, hsa-miR-98-5p were found to be upregulated followed by the downregulation of hsa-miR-320a, hsa-miR-92a-3p, hsa-let-7a-5p and hsa-miR-92a-3p (Das et al., 2021). Overexpression of MiR-486-3p suppresses the β-globin by targeting the *MAFK* gene and induces the HbF expression by regulating the *BCL11A*, *MTA1*, and *NR2F2* genes. Besides, the overexpression of miR-15a increases HbF expression by targeting the MAF proteins and *MYB* gene. Therefore, MiR-486-3p and miR-15a play pivotal roles in thalassemia bone disease (Eltaweel et al., 2021). miR-125b is expressed in higher amounts in monocytic cells of β-thalassemia patients and correlates negatively with abnormal red blood cells (RBCs) and hemoglobin levels. Thus, miR-125b might act as a potential therapeutic agent against thalassemia (Kuno et al., 2019). miR-30a also ameliorates thalassemia by regulating HbF expression by targeting the BCL11A gene (Gholampour et al., 2020).

4. Different ways of miRNA delivery

The delivery of miRNA as a therapeutic agent can be divided into two ways: first, the use of viral vectors to deliver the miRNAs appropriate for treating a particular disease. This strategy is considered very efficient because of the increased transfection of the therapeutic agents inside the host cells (Peng et al., 2015). The other way of delivering the miRNAs is the scaffold-mediated transfer in which the miRNA to be used as a therapeutic agent is immobilized and loaded over a scaffold material. The latter strategy is extremely beneficial for administering miRNAs in bone disorders (Sun et al., 2019). Some of the common methods of delivering miRNAs as therapeutic agents are discussed below.

4.1. Viral vectors

Viral vectors are extremely efficient in transferring genes into targeted cells. Engineering these viral vectors have proven to mediate the process of RNA interference and resulted in a prolonged expression of certain genes. Due to certain extraordinary characteristics, this delivery vehicle is immensely preferable. The commonly used viral vectors include lentivirus, adenovirus, retrovirus, and adeno-associated viruses (Fu et al., 2019). These vectors are engineered by altering some portions of the viral genome, inhibiting replication. This mode of delivery ensures the constant expression of miRNAs or the anti-miRs (Yang, 2015). Moreover, the use of viral vectors also nullifies the effects of several exogenous modulators of the miRNA, which properly facilitates the miRNA's function (Liu and Berkhout, 2011; Zhang and Godbey, 2006). Yao et al. delivered miR-146a into the peripheral blood mononuclear cells by constructing a bacteriophage-based VLP (MS2 VLP), and the investigation rendered promising results. The administration of this miRNA has suppressed osteoclast differentiation proving it to be an effective therapeutic agent (Yao et al., 2015). The transfer of miRNAs via retrovirus and lentivirus vectors provides a space of up to 8 kb for integrating the foreign particle. Importantly, the mode of transfer of miRNAs through these two viruses increases the expression of the miRNAs to a greater extent. Besides, using these vectors also provides higher transfection efficiency with greater stability of the expression of the incorporated miRNA (Yang, 2015). However, among all the types of vectors, adeno-associated vectors are the most suitable for miRNA delivery owing to the smaller size of the miRNA genes (Schultz and Chamberlain, 2008).

4.2. Lipid-mediated delivery

The lipid-mediated delivery is another prevalent delivery vehicle devoid of living viral vectors. The lipid-mediated delivery system comprises a mixture of lipid molecules with cationic groups at the head region and certain helper lipid molecules. Sometimes polyethylene glycol is also introduced into the medium to maintain the surface charge. A few times, the nucleic acids are made to interact with the cationic lipids, resulting in certain lipocomplexes. For instance, the delivery of pre-miR-107 using the lipid-nanoparticle based delivery was able to obstruct the tumorigenicity of head and neck squamous cell carcinoma (Piao et al., 2012; Hsu et al., 2013). Some of the therapeutic miRNAs transferred via this mode includes miR-39b, miR-133b, pre-miR-107, miR-34a, etc. (Wu et al., 2011, 2013; Shi et al., 2013). Furthermore, Endo-Takahashi et al. elucidated the construction of a structure called “bubble liposomes” in which the miR-126 was delivered to experimental models, and the expression of this miRNA triggered angiogenesis with an improvement in the blood flow (Endo-Takahashi et al., 2014). A greater degree of customization and formulation of the structure is required to render a well-established loading capacity of the lipid complexes (Akinc et al., 2008; Tseng et al., 2009). Nowadays, the formulation of neutral lipid complexes is a promising agent for delivering miRNAs compared to cationic lipids. The employment of this kind of lipids for transferring the miRNAs has been very successful because it eliminates the chances of accumulation in other body parts. Besides, using these neutral lipids as a vehicle to transfer miRNA therapeutics has also resulted in the even distribution of the therapeutic agent in the entire stretch of the cell or tissue (Li et al., 2014).

4.3. Polymer-mediated delivery

Polyethylenimines are the polymeric vector that can be chosen for delivering miRNAs and siRNAs into target regions. This is a positively charged moiety comprising a huge number of amine residues. This substance is suitable for forming complexes with smaller-sized RNA molecules facilitating easier uptake and release by the target cells (Hobel and Aigner, 2013). Previous studies have suggested that the polymer-based delivery of the therapeutic miRNAs is more efficient than the lipid-based vehicles (especially Lipofectamine 2000) (Lin et al., 2017). Polyethyleneimine possesses a special characteristic that can release oligonucleotides out of the endosomes. This is possible even if the cellular microenvironment is unfavorable, especially in an acidic environment using a mechanism termed “proton sponge effect” (Pereira et al., 2013). Successful results have been obtained in the trials of loading the miRNA

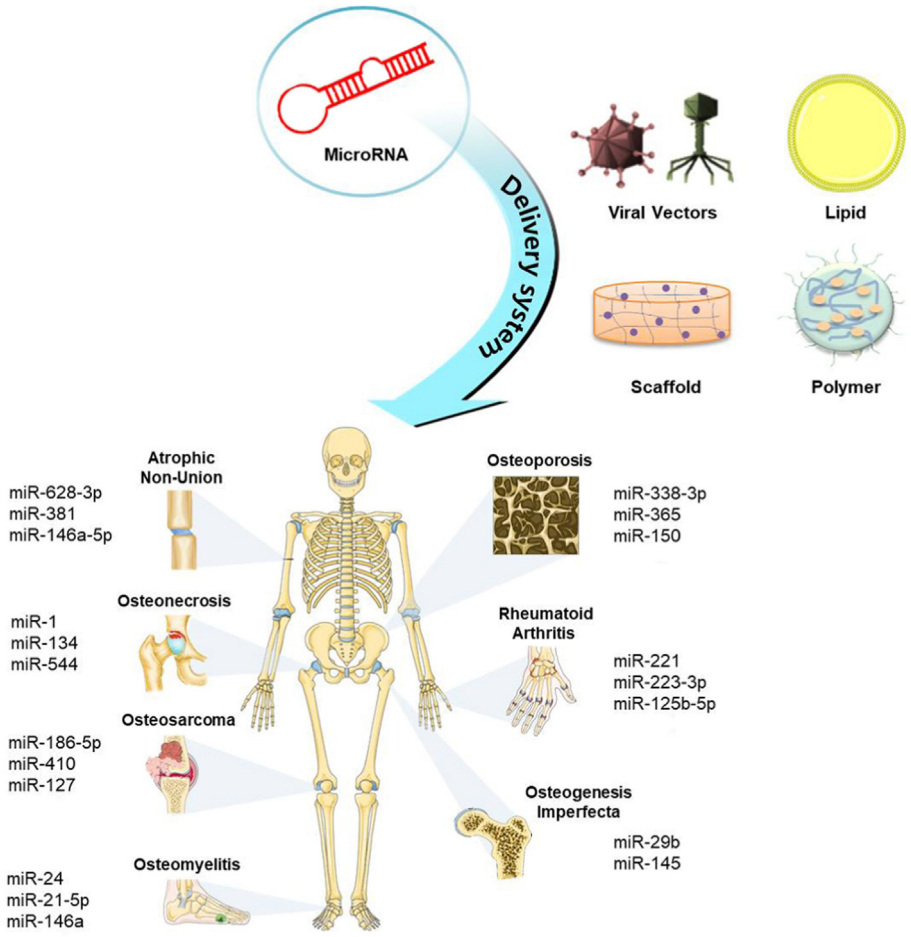

Fig. 2. A schematic illustration of the miRNAs and their delivery system in bone diseases.

therapeutics with the Polyethylenimines (PEI) complex. The administration of miR-145 or miR-33a in mice models has suppressed the growth of colorectal tumors with certain changes in the expression of ERK5 and the *c-Myc* gene (Ibrahim et al., 2011). On the other hand, certain miRNA mimics loaded with PEI have also shown efficient therapeutic potential in treating breast cancer (Gao et al., 2015; Dai and Zhang, 2019).

4.4. Scaffold-mediated delivery

The scaffold-mediated delivery vehicle has shown a promising approach in transferring several drugs and biomolecules to the specific sites of the target. This system is well-proposed in the domain of regenerative medicine due to its competence in mimicking the extracellular matrix (ECM) (Muniyandi et al., 2021). The use of scaffolds as delivery vehicles has been a boon in treating bone disorders, especially the repair of bones and osteoporotic fractures. Besides rendering support, the scaffold materials must be biodegradable and bioactive. The scaffolds also influence the bones' formation by supplying the required proteins and factors as and when required (Peng et al., 2015). The scaffold materials are widely used for transferring miRNAs and small therapeutic molecules very safely at the target site (Chew, 2015; Keeney et al., 2010). Most importantly, the cellular microenvironment created during these scaffold templates makes the therapeutic molecules less susceptible to being degraded and released from their target sites. This elucidates that scaffold-mediated delivery of miRNAs will provide protection for a much longer time (Nguyen et al., 2014). The popularly used scaffold materials which can be chosen for the introduction of miRNA therapeutics include electrospun gel, porous and spongy scaffolds, and hydrogels (Curtin et al., 2018). Furthermore, the significant application of this delivery vehicle in bone-related ailments is because of its exclusive characteristics like tissue anastomosis, increased porosity, and, most importantly, the response of these delivery agents to extreme cellular conditions. These factors make them extremely good delivery vehicles in orthopedic treatments (Liu et al., 2017; Olov et al., 2022).

5. Conclusion

Research studies in the last decade have provided crucial information about the functional roles of miRNAs and their role in diseases. Lately, studies have observed the role of miRNAs in the etiology and progression of numerous bone diseases, including osteosarcoma, OP, osteonecrosis, osteomyelitis, Osteogenesis Imperfecta, RA, and bone metastasis. In this review, we have summarized various miRNAs involved in bone-related diseases and delivery systems that may be utilized to deliver them to the target site (Fig. 2).

A combination of bioinformatic tools along with progress in experimental protocols has worked as a boon for deciphering the functional roles of miRNAs. Results are encouraging, and miRNAs as next-generation medicine therapeutics show promising potential. Nonetheless, the interaction between the miRNA transcriptome and bone disease-associated genes should be further researched for any risks associated with their use in vivo. Concerns like degradation from RNase in vivo, preventing unintentional triggering of an immune cascade, must be resolved before projecting miRNAs as future-generation medicine. Moreover, efforts must be put forward to detect (a profile of the expression pattern) miRNAs associated with bone-related diseases so that

miRNAs could be projected as potential biomarkers for properly diagnosing bone diseases and their severity.

To become a therapeutic candidate, miRNAs must undergo various refined animal experiments and clinical trials. The functionality of miRNAs might depend on certain factors like time of action, different concentrations, nature of microenvironments, and efficacy of delivery to the target. However, in this case, understanding miRNAs is still in its initial fancy stage. Studies focused on achieving safety, efficacy, and targeted delivery systems, along with optimized chemical modifications for miRNA as modulators, can be the answers to resolve these issues. Though progress has been made in delivering oligonucleotides to the cells and tissues, improved targeting ability, and the ability to stay long-term in the blood circulation, miRNA-based delivery systems need further research and continuous efforts by researchers. In this review, we have discussed some of the progress in the delivery systems of miRNAs to the bone. However, more studies are required to analyze new biomaterials with new methods for the delivery of miRNAs to the desired site of action. Recent studies have shown that cell-derived membrane vesicles, which include exosomes, microvesicles, and apoptotic bodies, can offer a great advantage as miRNA delivery systems. They have been projected as ideal delivery vectors because of their negligible antigenicity and low cytotoxicity. Moreover, these delivery systems are sufficiently stable for long-term storage and oral administration.

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CRediT authorship contribution statement

Ashish Ranjan Sharma: Writing – original draft, Writing – review & editing, Funding acquisition, Project administration, Supervision. **Yeon-Hee Lee:** Formal analysis, Validation. **Sang-Soo Lee:** Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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Data availability

Data will be made available on request.

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