SCOPING REVIEW

MicroRNAs in Aseptic Loosening of Prosthesis: Pathophysiology and Potential Therapeutic Approaches

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Abstract

Objectives: Aseptic loosening (AL) is one of the leading causes of total joint arthroplasty (TJA) revision. Discovering the roles of microRNAs (miRNA/miR) in ontogenesis and osteolysis has attracted more attention to diagnosing and treating bone disorders. This review aimed to summarize miRNA biogenesis and describe the involvement of miRNAs in AL of implants.

Methods: A detailed search was carried out on scientific search engines, including Google Scholar, Web of Science, and PubMed, to find appropriate papers related to subjects. The search process was performed using the following keywords: "Implant", "miRNAs", "Wear particles", "Osteoclasts", "Total joint replacement", and "Osteolytic diseases".

Results: miRNAs play an essential role in the regulation of gene expression. AL is associated with several pathologic properties, including wear particle-induced persistent inflammatory response, unbalanced osteoclastogenesis, abnormal osteoblast differentiation, and maturation. Recent researches have revealed that these pathological events are closely associated with miRNA deregulation, confirming the relationship between miRNA and AL of prostheses.

Conclusion: With the results of the new approaches to target miRNA, the essential role of miRNA is further defined. Understanding the mechanisms of miRNAs and related signaling pathways in the pathophysiology of AL will help scientists illuminate novel therapeutic strategies and specific targeted drugs.

Level of evidence: V

Keywords: Implant, MiRNAs, Osteoclasts, Osteolytic disease, Wear particles

Introduction

Total joint arthroplasty (TJA), also known as artificial joint replacement, is a highly effective surgical procedure for treating osteoarthritis. This procedure offers significant improvements in the quality of life for patients suffering from this condition.[1,2] However, complications can arise, leading to pain and discomfort after TJA. These complications may include ligamentous instability, stress fractures, late infections, polyethylene wear, or loosening of the artificial joint.[3] The findings of recent studies have proven that aseptic loosening (AL) of joint implants induced by wear particle-mediated osteolysis is the common cause of revision arthroplasty.[4]

AL has been recorded to be one of the most frequent long-term complications of total hip arthroplasty (THA) and total knee arthroplasty (TKA).[5,6] AL is caused by chronic inflammation induced by the activation of inflammatory cells in contact with prosthetic wear debris. However, the development of chronic infection is associated with the septic loosening of joint implants.[7] The amount of wear particles generated from the articular joint into the

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periprosthetic fluids is a key factor affecting the implant survival rate. Besides, wear particles can induce inflammatory responses in cultured macrophages and lead to osteolysis in numerous animal models.[8] At present, no effective therapeutic approach except for revision surgery has been described.

Among therapeutic strategies to target inflammatory pathways, the role of microRNAs (miRNA/miR) and their potential for treating inflammatory diseases has been investigated.[9] miRNAs are classified as a non-protein-coding RNA family, represented by evolutionarily conserved, single-stranded RNA molecules with about 18-22 nucleotides in length. They play an important role in regulating gene expression at the translational level. Likewise, miRNAs can repress the mRNA translation initiation by multiple mechanisms, such as mRNA degradation.[10] They can exert their functions by interacting with the 3′ untranslated region (3′ UTR) of specific target mRNA to promote mRNA degradation and translational inhibition. miRNAs are involved in the modulation of numerous life processes, including inflammation, cell death, and osteoblast-osteocyte differentiation.[11] In recent years, several studies have revealed that the changes in the expression of miRNAs are involved in the pathogenesis of various human diseases. Therefore, these tiny molecules are remarkable factors to be used as clinical diagnostics and potential therapeutic targets.[12] According to recent information, miRNAs represent promising targets for the detection and improvement of AL following TJA. In this review, we provided a highlight of the recent important research on the biological and therapeutic effects of miRNAs in the development of AL.

Materials and Methods

For our review, we conducted a comprehensive literature search using databases such as PubMed, Scopus, Web of Science, and Google Scholar. Employing a combination of keywords including "MicroRNAs," "Aseptic loosening," "Prosthesis," "Orthopedics," "Pathophysiology," and "Therapeutic Approaches," we identified relevant original research articles, reviews, and meta-analyses published in the last years in English language. Following the screening of titles and abstracts, we selected articles that provided insights into the involvement of microRNAs in the pathophysiology of aseptic loosening and potential therapeutic interventions, ensuring the inclusion of credible and scientifically sound information. Our rigorous search and selection process aimed to present a comprehensive overview of the current understanding of microRNAs in aseptic loosening and the potential therapeutic strategies, while adhering to ethical considerations and ensuring the representation of diverse perspectives in the review.

Results

Biogenesis of miRNAs

miRNAs are single-stranded RNA that can mediate post-translational regulation of gene expression in various eukaryotic organisms.[13] Different pathophysiological events are regulated by a number of miRNAs, such as hematopoietic function, cellular development, cell proliferation, differentiation, organogenesis, tumorigenesis, and apoptosis. Typically, half of all previously detected miRNAs are transcribed commonly from introns. A few exons of protein-coding genes also are involved in the transcription of miRNAs. The remaining miRNAs are independently transcribed from a host gene and controlled by their own intronic promoters.[14] It is also possible that miRNAs are presented as long transcripts called clusters. These clusters usually have similar seed regions and encode miRNAs of the same family.[15] In general, the biogenesis of miRNA can be grouped into canonical and non-canonical pathways; the canonical biogenesis process of miRNAs starts when RNA polymerase II (pol II) encodes miRNA genes long primary to miRNAs (pri-miRNAs) in the nucleus.[16] Subsequently, the microprocessor complex, conformed by DiGeorge Critical Region 8, processes microRNA maturation by cleavage of pri-miRNAs into hairpin-loop structures known as precursor miRNAs (pre-miRNAs) within the nucleus. After completing the Drosha-associated procedure, exportin-5 (XPO5) exports pre-miRNAs to the cytoplasm, where they are further processed by Dicer RNase III to produce mature miRNA products. Afterward, one of two miRNA strands, known as the guide strand, selectively binds to an Argonaute (Ago) protein and is incorporated into the miRNA-induced silencing complex (miRISC). Finally, the interaction of miRISC with complementary target mRNA regulates its expression.[17] The non-canonical pathways are initiated with primary cleavage of small hairpin RNA through microprocessor complex and their transfer into the cytoplasm by using GTP-binding nuclear protein Ran (RanGTP)/XPO5, where the Argonaute 2-mediated cleavage further cleave activity occurs. Dicer is an important factor for cytoplasmic maturation of Mirtrons and 7-methylguanine capped (m^7G)-pre-miRNA; however, they are different in their nucleocytoplasmic exportation. The PHAX-Exportin-1 pathway is responsible for the transfer of m^7G-pre-miRNA, while mirtrons are transferred via RanGTP/XPO5. All signaling pathways eventually result in the activation of miRISC complex.[18] Most frequently, miRISC target mRNAs to induce translational suppression; this is most likely accomplished by interference with the eukaryotic initiation factor 4F (eIF4F) complex. Then, GW182 family proteins bound to Ago recruit the poly (A)-deadenylases PAN2/3 and CCR4-NOT. Deadenylation is initiated by PAN2/3 and completed by the CCR4-NOT complex, which allows the decapping complex to remove the m7G cap from the target mRNA. The exoribonuclease XRN1 may then cause 5′-3′ degradation of the decapped mRNA[18] [Figure 1].

MicroRNA in the pathogenesis of aseptic loosening

To develop new therapeutic approaches to prevent AL of prosthetics, it is important to investigate the molecular mechanisms that cause periprosthetic osteolysis (PPO), which is considered the primary cause of AL in patients with TJA surgery.[19] Wear debris from an implant surface may trigger a number of biological reactions that result in the development of AL. PPO is the process by which mechanical or biological factors induce local inflammatory responses in periprosthetic tissue (PPT) that finally lead to prosthesis failure. The type of material, the character of the prosthesis implanted, and the size of particulates have implications for this process.[20] Numerous cell types, such as fibroblasts, macrophages, and other cell types, might be triggered to

express several hundreds of genes after several hours or Osteolysis is a result of misbalances in the bone homeostatic process, which includes bone resorption by osteoclasts and bone formation by osteoblasts.[22] Wear debris may worsen the aggregation of bone marrow-derived macrophages (BMDMs) and boost the expression of inflammatory mediators, which decreases osteoblastic bone formation and enhances osteoclastic bone resorption.[23] These particles provoke inflammatory responses and promote macrophage activation through a number of molecular mechanisms, such as Toll-like receptor (TLR) pathways. Many inflammatory cells, notably those of the monocytic lineage, are able to produce TLRs, and their stimulation enhances phagocytosis and starts an innate immune response that is regulated by activating nuclear factor kappa B (NF-κB).[24] The results of an in vitro study demonstrated that TLR2 and TLR1/2 could be directly stimulated by Ultra High Molecular Weight Polyethylene particles, which resulted in their phagocytosis and subsequent immunological activation.[25] Osteoclastogenesis (OCG) is triggered by NF-κB, which is referred to as the master regulator of innate immunity.[26] The innate immunity system is activated through the days of prosthesis wear particles-related stimulation.[21] upregulation of NF-κB/NLR family pyrin domain containing 3 (NLRP3) inflammasome observed in the PPT.[27] NF-κB signaling pathways are essential prerequisites for the proper stimulation of the NLRP3 inflammasome. Upon activation, NLRP3 and the adapter ASC form an inflammasome platform, which results in the caspase-1-associated formation of inflammatory mediators (including interleukin-1β (IL-1β) and IL-18 from pro-forms) and leads to gasdermin D-mediated cell death (known as pyroptosis).[28] The stimulated immune cells, particularly macrophages, are triggered to secrete proinflammatory mediators, such as IL-1β, IL-11, IL-6, tumor necrosis factor α (TNFα), nitric oxide (NO), and prostaglandin E2 (PGE2), into PPT, aggravating the immune responses.[29] These inflammatory mediators disrupt osteoblast activity and mediate the overproduction of receptor activator of NF-κB (RANK) ligand (RANKL) in osteoblasts. Finally, these events result in osteolysis and AL of the prosthesis. Consequently, targeting a particular factor to reduce the inflammatory response of macrophages is a prospective therapy to lengthen the device's life.[30]

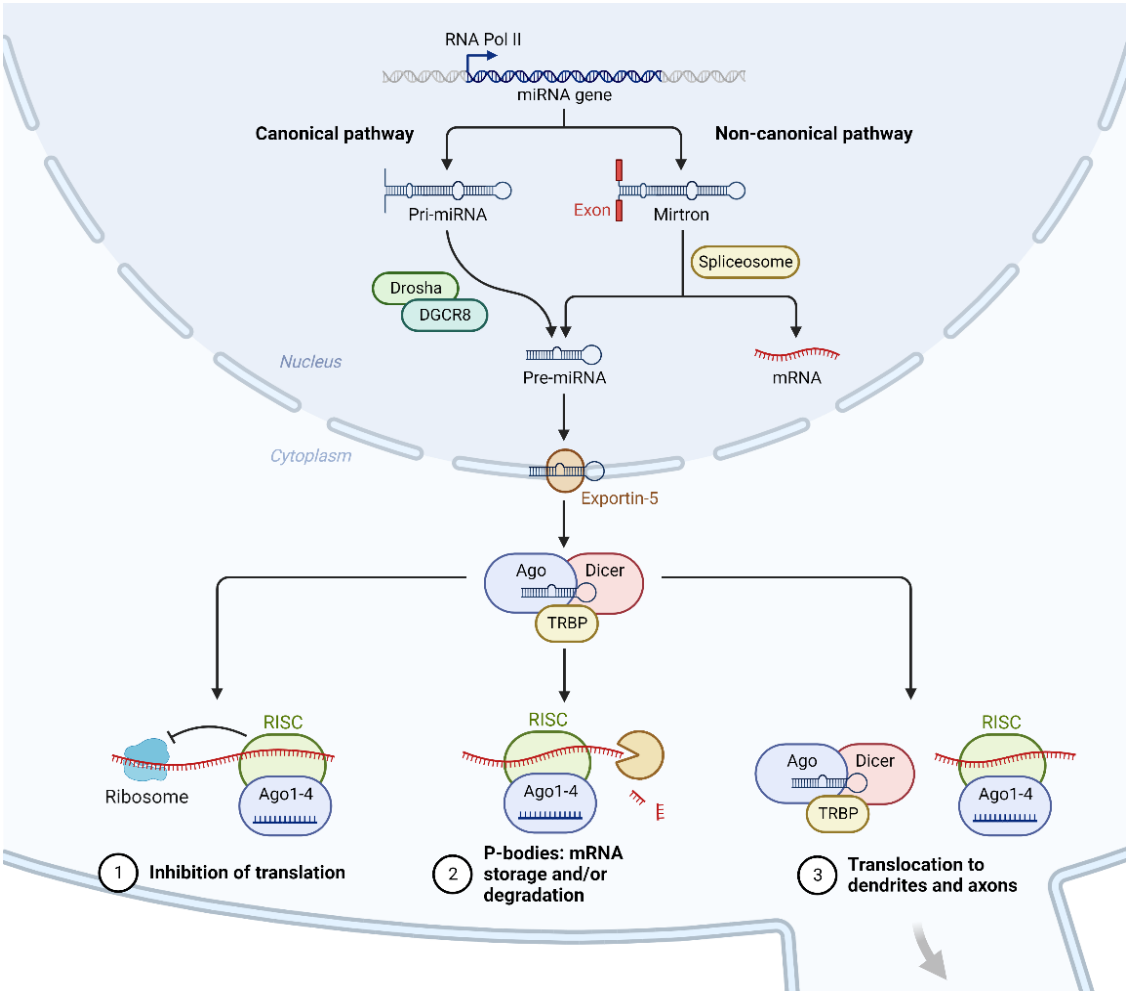

Figure 1. Biogenesis of miRNAs

microRNAs play an essential role in the regulation of periprosthetic inflammation. miRNAs have a crucial role in bone formation, bone disorders, and bone cell differentiation and function.[31] A number of miRNAs control osteoblastic activity and bone formation and are crucial for controlling bone remodeling and regeneration. miR-125b, miR-26a, miR-133, and miR-135 have reportedly been associated with the differentiation of osteoblasts and osteogenesis.[32] Among several miRNAs, miR-7b, miR-9, miR-21, miR-26a, miR-27a, miR-210, miR-378, miR-195~497 cluster, miR-378, and miR-675 positively promoted both angiogenesis and osteogenesis, whereas miR-10a, miR-222, and miR-494 inhibited both processes.[33] Previous studies about OCG found that miRNAs might serve as essential mediators in RANKL-induced osteoclast differentiation.[34] It has also been investigated how miRNA expression changes when mature osteoclasts are differentiated from osteoclast precursors.[35] miRNAs show a greater than 2-fold increase in expression throughout this process.[36] In addition, the facts that Dicer, a member of the Rnase III family, which cleaves double-stranded RNA or pre-miRNA into short double-stranded RNA fragments, is involved in the regulation of bone resorption by osteoclasts suggests that miRNAs are new regulatory elements of OCG.[37] The significance of miRNAs in post-transcriptional control of skeletal development was previously evaluated by several researchers.[31] Previous reviews have outlined the roles of miR-155, miR-223, and miR-21 in osteoclast differentiation.[38]

miRNAs are vital in bone regeneration and fracture healing.[39] By suppressing the expression of leucine-rich repeating G protein-coupled receptor 4 (LGR4), miR-137 has been demonstrated to block alkaline phosphatase (ALP) expression and activity, increasing the risk of osteoporosis fracture in patients. In addition, it has been shown that miR-185, which targets the parathyroid hormone gene by downregulating the Wnt/β-catenin pathway, prevents osteoblastic growth and proliferation during the healing of fractures.[40] The essential role of miRNAs has been proven in the post-operative follow-up of TJA. An upregulation of miR127, miR-409, miR-211, and miR-146a was observed in trabecular bone specimens of cases with primary THA and patients undergoing revision surgery. Furthermore, osteogenic genes, including SMAD4, fibroblast growth factor receptor 1 protein, TGF-β1, runt-related transcription factor 2 (RUNX2), COL1A1, and WNT4, were downregulated. miR127, miR-409, miR-211, and miR-146a were suggested to be potential biomarkers to predict osteolysis and therapeutic targets.[41] In another study, serum levels of miRNA-142 and bone morphogenetic protein 2 (BMP2) were reported as a biomarker of recovery of patients with THA, which were positively associated with the osteoprotegerin (OPG) and RANKL levels. At one month following surgery, the blood levels of BMP2 and miR-142 in patients with satisfactory recovery were considerably greater than those in patients with poor recovery.[40] Whole transcriptome analysis was used to evaluate the titanium (Ti) debris-activated RAW264.7 cells. According to the results, the expression of 159 mRNAs, 31 circRNAs, 96 lncRNAs, and 12 miRNAs were considerably different. Moreover, Lmf2-206, BC049715-OT4, Snx24-OT3, and 2010111I01Rik-AS1 were found to act as ceRNAs to attenuate the suppressive effects of mus-miR-3065-3p on Myo18a, which closely participates in suppressing inflammatory responses of macrophages via pathway regulating CD14 trafficking.[42] In another study, miR-130b was reported to participate in PPO via reducing the gene expression of frizzled-related protein (FRZB) in mice model induced by implantation of cobalt-chromium-molybdenum alloy debris. Additionally, debris-treated MC3T3-E1cells showed suppressed proliferation and differentiation.[43] Furthermore, miR-130b is involved in wear debris-triggered inflammation and osteolysis via the FOXF2/NF-κB signaling pathway.[44] The results of an animal study also revealed that miR-21 was significantly increased in an animal model of particle-induced osteolysis.[45] miR-9-5p was recorded to activate the SIRT1/NF-κB signaling pathway to boost debris-induced OCG.[46] Therefore, the upregulated miRNAs could function as one vital modulator of PPO progress. Moreover, miRNAs may provide a novel therapeutic approach for the pharmacological management of bone disorders, especially wear-induced osteolysis.

Discussion

Targeting MicroRNA in aseptic loosening

One strategy for the development of specific biomarkers and targeted treatment is to concentrate on the role of miRNAs in the pathophysiology of PPO. Here, we summarized the targeting of different miRNAs to develop new therapeutic approaches [Table 1].

miR-21

miR-21 is one of the earliest microRNAs to be discovered and is found on chromosome 17 at the vacuole membrane protein 1 (VMP1) locus.[47] Compared to other miRNAs, the control of miR-21 regulation is more intricate. Pri-miR-21 found within the VMP1 locus contributes to miR-21 transcription. Cytokines, such as interferons and hypoxia, may regulate miR-21.[48] One miRNA that has drawn a lot of interest as a potential role in bone disorders is miR-21. The differentiation of osteoblasts and osteocytes from mesenchymal stem cells (MSCs) is controlled by miR-21 through a number of pathways. The stimulation of the extracellular signal-regulated kinase/mitogen-activated protein kinase signaling pathways through miR-21 has been reported to promote osteogenesis in MSCs. Bone marrow MSCs undergo osteogenic differentiation by miR-21 through regulating the SMAD7-SMAD1/5/8-RUNX2 axis.[49] Osteogenic differentiation and mineralization is positively regulated by miR-21. It could successfully upregulate the main osteogenic bio-factors, such as ALP, osteopontin, RUNX2, and osterix in MC3T3-E1 cells, and this finding also was confirmed in miR-21-deficient mice.[50] Likewise, osteogenic differentiation is promoted by miR-21 through suppression of SMAD7 translation in MC3T3-E1 cells.[51] Icariin, a flavonoid glycoside, was shown to mitigate the suppressive effects of Ti particulates on the differentiation of osteoblast and mineralization of matrix by increasing the

gene expression of miR-21-5p in MC3T3-E1 cells, confirming the potential role of miR-21-5p in osteoblast differentiation and matrix mineralization.[52] Besides, miR-21 was demonstrated to promote OCG through targeting PTEN/phosphatidylinositol-3 kinase (PI3K)/protein kinase B or Akt signaling in RAW264.7 cells.[53] In another study, it was reported that miR-21 deficiency could improve osteolysis symptoms in the debris-induced tissue. Moreover, the feedback loop of miR-21, activator protein 1, and PDCD4 might be involved effectively in the development of debris-induced osteolysis.[45] The findings suggested that miR-21 could be used as a potential targeting factor for implant loosening therapies.

Table 1. Targeting NLRP3 inflammasome as potential therapeutic implications for the treatment of EMS

Author	Model	Medication	Results
Murakami et al. (2022)	**In vitro:** Human ESCs & CSCs **In vivo:** C57BL/6 N female mice/ ovarian EMS	MCC950, NLRP3 inhibitor	- Reduced IL-1β and IL-18 secretion in CSCs - Reduced levels of caspase-1 in CSCs - Decreased volume of lesions - Decreased number of Ki67+ epithelial cells in the endometriotic lesions (proliferative activity) - Diminished IL-1β+ area in the epithelial cells - Decreased lipid peroxidation and oxidative stress in the granulosa cells of ovarian follicles
Zhou et al. (2022)	**In vitro:** Human ESCs **In vivo:** NLRP3-/- C57BL/6 mice	Targeted inhibition of NLRP3	- Reduced lesion development - Suppressed the migration ability of ESCs
Hang et al. (2021)	**In vitro:** Human ESCs	TRIM24	- Negatively regulation of NLRP3/Casp1/IL-1β-triggered pyroptosis - Reduced cell migration of hESC,
Zhao et al. (2019)	**In vitro:** Human ESCs & CSCs	Targeted inhibition of AEG-1 by by shRNA	- Increased SOCS1 level (inhibitor of TLR/NF-κB signaling pathways) - Reduced levels of inflammatory cytokines (IL-1β, IL-6, and TNF-α) - Inhibited the formation of NALP3 inflammasome
Fusco et al. (2018)	**In vivo:** Fpr1 KO mouse model of EMS	Targeted inhibition of Fpr1	- Increased regression of endometriotic lesion and reduced development of cysts - Reduced duration of uterine pain behaviors - Reduced numbers of mast cells and neutrophils - Altered gene expression of VEGF and ICAM-1 associated with the pathology - Regulation of NF-κB /NRLP3 inflammasome signaling - Reduced resistance to the apoptosis
Palmer et al. (2016)	**In vivo:** Nude mouse model of EMS	Bentamapimod (AS60280), a JNK1 (activator of NLRP3) inhibitor	- Prevent disease progression - Decreased levels of inflammatory cytokines - Increased NK cell activity
Murakami et al. (2022)	**In vivo:** Randomized placebo-controlled study in baboons	Bentamapimod (AS60280), a JNK1 (activator of NLRP3) inhibitor	- Reduced total surface area and volume of endometriotic - No severe adverse effects or negative impacts on effect on cycle length or serum levels of sex hormones,

EMS: Endometriosis, ESCs: Endometrial stromal cells with endometriosis, CSCs: Cyst-derived stromal cells, NLRP3: Nucleotide- binding oligomerization domain (NOD)-like receptor pyrin domain containing 3, JNKs: c-Jun N-terminal kinase, VEGF: Vascular endothelial growth factor, ICAM-1: Intercellular adhesion molecule-1, AEG-1:Astrocyte elevated gene-1, TLR: Toll-like receptors (, NF-κB: Nuclear factor kappa , IL-1β: interleukin-1β, KO: Knockout, NK: Natural killer

miR-29

miR-29 family includes miR-29a, miR-29b, and miR-29c. miR-29b is further classified into two types, miR-29b-1 and miR-29b-2. miR-29a was first identified in cervical tumor cells (HeLa).[54] Numerous researches have proved that miR-29 has a significant role in the differentiation of osteoclasts. A decrease in the expression of miR-29a was discovered in glucocorticoids-induced osteoporosis. In contrast, gaining miR-29a function decreased the differentiation of osteoclasts induced by glucocorticoids in vitro. Moreover, treatment of animals with pre-miR-29a precursor significantly improved bone loss caused by glucocorticoid, whereas miR-29a deficiency enhanced osteoclast-mediated bone resorption, bone fragility, and cortical bone porosity. In addition, miR-29a has been found to support osteoblast development and mineral deposition in bone via participating in the Wnt and Dickkopf related protein 1 (Dkk-1) signaling pathways.[55] Additionally, miR-29b overexpression has substantial negative impacts on the expression of tartrate-resistant acid phosphatase (TRAP), the breakdown of collagen, and the generation of lacunae, all of which are indicators of osteoclast activity.[56] In osteoclasts, nuclear Factor I A (NFIA) acts as a negative modulator of the M-CSF receptor, and the miR-29-mediated downregulation of NFIA mRNA may contribute to the promotion of OCG.[57] In an in vitro study, pretreatment of THP-1 cells with wear debris, including zirconiumoxide (ZrO_2), polymethylmethacrylate (PMMA), Ti alloy (Ti-6Al-7Nbs), and commercially pure Ti (cpTi), upregulated IFN-γ

gene via miR-29b. The inhibitor of miR-29b downregulated the expression of IFN-γ in these cells. In addition, treatment of wear debris-stimulated THP-1 cells with TNF-α neutralizing antibody downregulated miR-29b. According to the results, wear debris suppressed the IFN-γ production through TNF-α-triggered miR-29b upregulation in human monocytes.[58] In short, the miR-29 family is essential for the differentiation of osteoclasts and wear-induced osteolysis. Thus, targeting miR-29 can be a new approach for the management of PPO.

miR-92a

Seven members of the miR-17∼92 cluster, found at 13q22 region, include miR-17-5p, miR-92a, miR-17-3p, miR-18a, miR-20a, miR-19a, and miR-19b.[59] Suppression of miR-92a via locked nucleic acid technology was revealed to promote fracture healing via enhancing angiogenesis in a stabilized fracture model and had therapeutic potential for bone repair in young mice models of rib and femoral fracture.[60] Higher expression of miRNA-92a-3p was detected in the callus and plasma of patients who have suffered from concomitant extremity fractures. On the other hand, overexpression of miRNA-92a-3p was reported to suppress the expression of integrin binding sialoprotein (IBSP) and promote the differentiation of osteoblasts, while miRNA-92a-3p silencing suppressed osteoblast function in vitro. Moreover, agomiR-92a-3p pre-injection resulted in enhanced bone development.[61] Furthermore, overexpression of miR-92a boosted the osteogenic differentiation of BMCs by impeding Smad6-mediated RUNX2 degradation.[62] miR-92a/Krüppel-like factor 4 (KLF4)/p110δ (belongs to Class I PI3Ks with ability to manage cell migration, differentiation, and survival) was reported to regulate Ti debris-triggered inflammation and osteolysis by modulating NF-κB pathway and polarizing M1/M2 macrophage.[63] These results indicate the vital role of miR-92a signaling pathways in wear-induced osteolysis.

miR-106b

A recently identified miRNA, called miR-106b, is a member of the miR-106b-25 cluster. Recent research has demonstrated that miR-106b has a crucial role in the control of bone mass.[64] miR-106b was reported to partially inhibit bone formation, and the suppression of miR-106b reduced osteoporosis induced by glucocorticoid via the BMP2-SMAD signaling cascade.[65] In a mice model of collagen-induced rheumatoid arthritis (RA), the suppression of miR-106b expression was shown to decrease joint inflammation and bone destruction.[66] Besides, miR-106b inhibition was revealed to attenuate the degree of synovial inflammation and joint bone destruction by regulating RANKL/OPG signaling pathways and decreasing the number of mature osteoclasts in a mice model of RA.[67] In another animal study, the administration of the lentivirus-mediated miR-106b inhibitor significantly downregulated miR-106b in the distal femur and improved Ti debris-triggered bone loss and osteolysis in a rat model of implant loosening. Moreover, the miR-106b inhibitor promoted osteoblast activity, lowered $TRAP^+$ cell counts, repressed osteoclast development, and increased bone formation. The polarization of macrophages was considerably controlled by MiR-106b inhibition, which also reduced the inflammatory response. Additionally, miR-106b suppression inhibited NF-κB activation and PTEN/PI3K/Akt signaling.[68] These findings confirmed that the suppression of miR-106b inhibits wear debris-triggered osteolysis and bone degradation, suggesting a possible treatment for PPO and AL.

miR-130

miR-130b is localized at chromosomal region 22q11. The relationship between miR-130b and PPO has already been demonstrated. In a functional study, miR-130b inhibition reversed the debris-triggered suppressive effects on the gene expression of FRZB and cell proliferation and differentiation. According to luciferase report assays, miR-130b was demonstrated to negatively modulate FRZB expression, whereas FRZB might improve the negative impacts of miR-130b inhibition on PPO establishment.[43] In Raw264.7 cells, transfection with miR-130b inhibitor significantly decreased the production of pro-inflammatory cytokines (TNF-α, IL-6, and IL-1β), and elevated the production of anti-inflammatory cytokines (IL-10). FOXF2 siRNA was confirmed to target miR-130b and regulate the production of these cytokines. Additionally, BAY 11-7082, NF-κB inhibitor, was reported to further reduce the production of TNF-α, IL-1β, and IL-6 and enhance IL-10 level.[44] Thus, the elevated miR-130b expression in PPO could function as a vital modulator of osteolysis progress, partially because of its negative modulatory effects on FRZB.

miR-135b

miR-135b-mediated osteoblast differentiation has been demonstrated in recent works.[69] The results of an in vitro study showed that miR-135b might regulate the osteoblastic differentiation of unrestricted somatic stem cells isolated from human umbilical cord blood via the modulation of osteogenic genes IBSP and Osterix.[70] The alterations of various miRNAs, including miR-135, were recorded during the BMP2-triggered osteogenesis of C2C12 mesenchymal cells. miR-135 may promote an osteogenic program through controlling osteogenic signaling pathways, such as transducer and activator of transcription 6 (STAT6), BMP receptor type 1A (BMPR1A), BMPR2, Janus kinase 2 (JAK2), SMAD5, and MSX2.[71] In another investigation based on an online prediction website, it was found that JAK2 could be targeted by miR-135b. The JAK-STAT signaling pathway was revealed to be involved in oxidative stress, cell inflammatory responses, apoptosis, and cell injury. Furthermore, the upregulation of miR-135b participated in the abnormal osteogenic differentiation of MSCs isolated from patients with multiple myeloma.[72] To inhibit wear particle-induced osteolysis5p in hip chondrocytes, it was demonstrated that LINC01534 (enhanced in severe osteolysis patients) acted as a competing endogenous RNA (ceRNA) by sponging miR-135b. In addition, CCHC-type zinc finger nucleic acid binding protein (PTPRT) could be used for the regulation of downstream target of miR-135b-5p. Knockdown of PTPRT mitigated the IL-1β-associated innate immunity in chondrocytes. Moreover, overproduction of PTPRT or

suppression of miR-135b-5p was reported to antagonize the effects of LINC01534 deficiency on the reduction of inflammation in these cells.[73] Therefore, miR-135b can be used for developing a targeted therapeutic strategy to manage AL of implants.

miR-155

miR-155 is involved in the regulation of various inflammatory cytokines and is associated with different inflammatory diseases. Increased levels of miR-155 expression have been recorded in the synovial tissue, synovial fluid, fibroblasts, and peripheral blood mononuclear cells of patients with RA, indicating its importance as a key biomarker for bone loss.[74] In a murine model of RA known as K/BxN serum-transfer arthritis, the localized bone loss was considerably reduced in miR-155$^{-/-}$ mice, and these findings were associated with the reduction of OCG.[75] In Dicer-deficient mice, trabecular thickness and bone mass were increased and osteoclast formation and the gene expressions of TRAP and nuclear factor of activated T cells 1 were reduced compared to wild-type mice. RANKL treatment could inhibit MiR-155 levels in BMDMs from osteoclast-specific Dicer-deficient mice. However, the levels of miR-155 were not affected by RANKL in BMDMs from wild-type mice. Dicer-deficient osteoclasts suppressed the development of RANKL-induced TRAP^{+} cells. Findings demonstrated that Dicer deficiency inhibited miR-155 expression upon RANKL treatment.[76] miR-155 was found to suppress the differentiation of RAW264.7 cells into osteoclast by suppressing microphthalmia-associated transcription factor (MITF), an essential marker for the differentiation of osteoclast.[77] In addition, IFN-β-stimulated inhibition of osteoclast differentiation was mediated by miR-155 expression, which interacted with positive regulators of OCG, including MITF and suppressor of cytokine signaling 1.[78] It was also revealed that the regulation of miR-155-5p/FOXO3 axis via tanshinone (extracted from the roots of Salvia miltiorrhiza) could reduce bone loss and osteolysis induced by polyethylene in a mouse model via the inhibition of FOXO3 and improvement of balance between OPG and RANKL.[79] In summary, these findings prove that the modulation of miR-155 can improve particle-induced osteolysis by regulating various essential transcriptional factors.

Conclusion

PPO is accompanied by increased osteoclastic bone resorption compared to osteoblastic bone development, resulting in AL of prosthesis. Generally, the management of osteolysis has focused on the suppression of excessive activation of osteoclasts and osteoblast dysfunction. It is necessary to conduct further investigations of signaling pathways regulating the differentiation and maturation of osteoclasts for the development of novel treatments for PPO. Among several pathways, the regulation of OPG/RANK/RANKL signaling pathways in the differentiation and maturation of osteoclast has attracted more attention as a major landmark in debris-induced osteolysis research. Many biological functions are regulated by the function of miRNAs. An overview of the role of miRNAs confirms that miRNAs deeply contribute to the modulation of bone resorption via regulating osteoclast differentiation. On the other hand, ontogenesis and osteoblast function are modulated by miRNAs, which can be affected by wear particles. The inhibition or overproduction of specific miRNAs effectively regulates osteoclast differentiation and bone resorption or promotes osteoblast function to regulate bone formation. In the preclinical studies, miRNA-based targeted therapies have shown some promise for the treatment of PPO. Additionally, these biomarkers can be used to evaluate the TJA in the postoperative follow-up. Nevertheless, further studies are necessary to show the effectiveness and safety of miRNA-based therapeutic approaches to be utilized in the clinic.

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