ISSN 2706-6819 Vol.5, Issue 11: 63-68, DOI: 10.25236/IJFM.2023.051110

MicroRNAs positive and negative regulation of cellular osteogenesis and angiogenesis

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Abstract: *MicroRNAs(miRNAs) is a class of non-coding single composed of 21 to 25 nucleotides Chain small molecule RNA, which is mainly involved in the regulation of post-transcriptional gene expression, binds to the 3 ′ -UTR of target mRNA by inhibiting post-transcription gene expression and reducing corresponding protein synthesis, and plays extensive biological roles in the fields of osteogenesis and immunity. In recent years, a number of scientific studies have demonstrated that miRNAs is an important regulator of cell growth, differentiation and apoptosis, each miRNA has been shown to have hundreds of target mRNA, miRNA and target mRNA between formed a complex regulatory network involved in a variety of regulatory pathways, including development, virus defense, hematopoietic process, organ formation, cell proliferation and apoptosis, fat metabolism, etc. Currently, how to rationally utilize miRNA to regulate the function and differentiation of stem cells is an extremely attractive therapeutic direction in regenerative medicine. It is clear that small RNA (microRNA, miRNA) plays an important role in the growth, differentiation and function of bone cells, and miRNA is closely related to the survival and blood vessel formation of bone marrow mesenchymal stem cells. The miRNA can directly or indirectly participate in the process of osteoangiogenesis by inhibiting or promoting angiogenesis, regulating BMSC differentiation, activating or silent growth factor-mediated signaling pathways, and regulating the immune environment. This chapter will review the role of some microRNA in osteogenesis, and to study and explore the possible mechanisms behind their effects.*

Keywords: *MicroRNA; Angiogenesis; Bone angiogenesis; Bone regeneration*

1. Introduction

miRNA Is a class of non-coding, single-stranded RNA molecules, composed of approximately 21 to 25 nucleotides, which is responsible for the regulation of gene expression. These miRNA have become key post-transcriptional regulators of gene expression in multicellular animals and plants, blocking protein translation and regulating mRNA stability by binding to complementary sequences in the 3 ′untranslated region (UTR) of the mRNA .At the same time, miRNA has been used for bone defect repair and bone regeneration. Through recent years of research, the types of miRNA have been recognized as increasingly diverse, some of which have been focused on by scholars. Some scholars have found that [6], some miRNA, such as miRNA-7b, miRNA-9, miRNA-26a, miRNA-210, miRNA-378, all show positive effects in promoting angiogenesis and osteogenesis. While some miRNA, for example, MiRNA-10a, MiRNA-222, MiRNA-494 all show negative effects in the regulation of angiogenesis and osteogenesis. This review highlights some microRNA's positive regulation of stem cell function and differentiation and focuses on their osteogenesis-and angiogenesis-related parts. It is explained that some microRNA participates in the formation of physiological bone and blood vessels by targeting various transcription factors in osteoblasts, chondrocytes, osteoclasts and stem cells. Studying the regulation and differentiation of microRNA is help to broaden the thinking of gene therapy and regenerative medicine[1-5].

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2. The positively regulated miRNAs

2.1. MiRNA-7b

This miRNA is widespread as a developmental and functional biological activity in a wide variety of tissues [7].It is able to directly inhibit dendritic cell-specific transmembraneproteins(DC-STAMP) , essential proteins required for osteoclast fusion[8].Dou et al. [9] also represented that miRNA-7b delivery by GO-PEI increased ALP, Runx-2, and PDGF-BB expression after 3 days. Although it is thought to be required for osteoclast fusion, it is not essential for osteoclast differentiation. Therefore, it can be explained that miRNA-7b suppresses osteoclast fusion, maintains platelet-derived growth factor-bb secretion, and enhances new blood vessels and bone formation.

2.2. MiRNA-9

It has been shown that miRNA-9 is involved in the repair of [10] by nerve damage and also improves the angiogenesis of [11] in tumor cells. Qu et al. [14] demonstrated that miRNA-9 upregulates the amount of Runx-2 and bone hormones, which is an early marker of osteogenic differentiation. The positive regulation of the monophosphate-activated protein kinase (AMPK) of adenosine miRNA-9 and its signaling pathways was verified by [14]. Moreover, some have found that miRNA-9 can enhance cyclin D1 expression and cell cycle progression in HUVECs. MiRNA-9 promotes angiogenesis by improving endothelial progenitor cell migration and chemotaxis, which has been demonstrated by Transwell migration assay, VE GF and ve-cadherin upregulating [14]. This signaling pathway plays an important role in proinflammatory active [12], osteoblast differentiation [13], especially after hypoxic stress in endothelial cells. Thus, it seems that both osteogenic and angiogenic regulation underlie the signaling of amp-activated pathways. Other studies have also identified a role for miRNA-9 in tumor necrosis factor- α (TNF- α) and pathway [11], which regulate endochondral ossification and endothelial cell migration and angiogenesis.

2.3. MiRNA-26a

MiRNA-26a is the promoter of osteogenic differentiation in mesenchymal stem cell [15]. In the comparison of miRNA-21, -26a, and-29b, miRNA-26a was more highly expressed in the regenerated bone than in the other [15]. Furthermore, it induced a 2.4-to 10-fold increase in the expression of Runx-2 and BMP-2 (early osteogenic markers) and an 8.5-fold increase in cyanate (late osteogenic markers), VE GF and Ang-1 (angiogenic marker), demonstrating its ability to bind bone angiogenesis. Several studies have revealed their important role in bone regeneration in [16] and blood vessel formation in [17]. MiRNA-26a mainly targets GSK 3 β to activate Wnt signaling in BMMSCs; however, it targets Smad-1 in adipose-derived mesenchymal stem cells to interferes with BMP pathway [18] and osteogenic differentiation, which reveals various effects of MiRNA-26a on different stem cells. Moreover, BMP / Smad-1 signaling is regulated by miRNA-26a in endothelial [19] angiogenesis, which regulates angiogenesis, osteogenesis and other hard tissue formation, including tooth generation [20], which requires further investigation.

2.4. MiRNA-210

The therapeutic application of miRNA210miRNA-210 in patients with osteonecrosis revealed its involvement in the associated regulatory program [21]. A time-dependent promotion of VE GF expression in rat BMSCs by miRNA-210 was detected in [22] by Liu et al. Furthermore, RT-qPCR results showed a significant increase in the expression of osteoblast differentiation markers (ALP and osterix) compared with the control groups. On the other hand, miRNA-210 inhibited PPAR γ, which represents its inhibitory effect on adipogenic differentiation. They believe that this may be caused by VE GF signal regulation. In addition, Mizuno and others explained. [23] miRNA-210 inhibited the osteogenic ability of TGF pathway. However, the specific mechanism is still unclear and needs further study.

2.5. MiRNA-378

1) This miRNA is involved in several biological metabolic processes. MiRNA-378 inhibits apoptosis and promotes tumor proliferation and angiogenesis by interfering with Fus-1 expression and [24]. Moreover, miRNA-378 targets the triiodide K / Akt pathway to accelerate osteoblast differentiation at [25] under high glucose conditions. Zhang et al [26] demonstrated bone-angiogenic coupling capacity by

ISSN 2706-6819 Vol.5, Issue 11: 63-68, DOI: 10.25236/IJFM.2023.051110

assessing Runx-2, cyanate, ALP and VE GF markers significantly upregulated after miRNA-378 transfection. However, they do not approve exactly which pathway this miRNA targets.

2) Several studies have convincingly shown that excessive or weakened inflammatory response of macrophages is related to miRNA imbalance. It has been found that miRNAs play an important role in regulating macrophage polarization and subsequent inflammatory response [27]. In particular, some miRNA have been shown to regulate the expression of various adhesion proteins and transcription factors, and are considered to participate in macrophage[28-30] polarization. Macrophages were obtained from mouse bone marrow cells. miRNA-378 and miR-let-7c were used to analyze the arrangement of miRNA. The expression in M2 macrophages increased significantly.[31]Transfection of mouse peritoneal macrophages with 40nM miRNA-378 reduced the production of TNF-a and IL-6 by half. LPS-induced miRNA-378 acts by reducing the NF-kB protein and doubling the expression of the anti-inflammatory cytokine IL-10. Conclusion IL-10 has direct anti-inflammatory effect and promotes M2 polarization of macrophages. Chen Wei and others [32]. miRNA-378a has been shown to directly or indirectly regulate phagocytosis and macrophage polarization in SIRPA-mediated ApoE knockout mice. JiX [33]found that macrophages are closely related to capillarization and angiogenesis during mouse development. Especially when it appears in the form of M2.

3. The negatively regulated miRNAs

3.1. MiRNA-10a

MiRNA-10a, as an influencing factor, is involved in the pathogenesis of some diseases, including kidney and heart injury [34], and also inhibits tumor angiogenesis [35]. Li et al. [36] It was confirmed that the expression of miRNA-10a was significantly decreased by BMP-2-induced osteoblastic differentiation sig. Overexpression of miRNA-10 inhibits cyclin and typical Wnt signaling pathway, which leads to decreased therapeutic potential of bone disease, Runx-2, bone and distal homologous Box-5 gene expression [37]. In fact, in addition to mRNA (transcription effect), they also found mRNA reduction (TGF-/Smad2/STAT3/Static pathway [38] and other targets that may participate in this process. In addition, the anti-angiogenesis effect of these miRNA may be regulated by cyclin signaling pathway, but the elucidation of this mechanism needs further study.

3.2. MiRNA-494

MiRNA-494 interferes with VEGF in vitro, [38] interferes with angiogenesis in vivo. It was confirmed that he and others [39] miRNA-494 could target nitric oxide signal (angiogenesis-related pathway) and inhibit it 2 weeks after fracture, thus curing fracture in aged rats. Smad-9 and kinase-1 activated as growth factors are the main potential targets. In addition, miRNA-494 inhibits cartilage differentiation by targeting vector acid receptor signals [40] in pathway analysis. In vitro evaluation showed that miRNA-494 inhibited TAK-1, SMAD-9 and VEGF, which were involved in TGF-s signal transduction, retinoic acid receptor activation and nitric oxide signal transduction. Therefore, inhibiting these miRNA seems to have the potential to treat bone-related diseases.

3.3. MiRNA-222

MiroRNA-222 inhibitor can obviously promote bone formation, angiogenesis and cartilage formation, and improve fracture healing. Overexpression of MiRNA-222 can reduce the levels of Smad-5 and Runx-2 protein and regulate the formation of osteoclasts [41]. Although he left. Computer-aided analysis [42]was used to identify unverified miRNA-222 targets (BMP-2, Runx-2, osteocalcin). Ji Ju looks forward to the application of miRNA-222 inhibitor in the treatment of refractory fractures, and the results show that neovascularization has been greatly improved. On the basis of other studies, they suspect that miRNA may down-regulate angiogenesis through target signal converter and transcribe through low receptor 5 (STAT-5) and c-Kit. But these goals have not been verified in his research.

4. Conclusion

In conclusion, whether miRNA-7b, miRNA-9, miRNA-26a, miRNA-210, miRNA-378 that are able to positively regulate osteogenic vascularization, or miRNA that negatively regulate osteogenic vascularization, such as miRNA-10a, miRNA-494, miRNA-222, All are involved in the formation of

ISSN 2706-6819 Vol.5, Issue 11: 63-68, DOI: 10.25236/IJFM.2023.051110

physiological bone and blood vessels by targeting various transcription factors in stem cells, osteoblasts, macrophages, osteoclasts, and chondrocytes. Their different expression of Runx-2 and BMP-2, these early markers of osteogenic differentiation, also surface their ability to improve or slow their migration and chemotaxis to promote or hinder angiogenesis, can be explained by miRNAs inhibiting or promoting osteoclast fusion, maintaining or reducing platelet-derived growth factor-bb secretion, enhancing or hindering new blood vessels and bone formation.. Other studies have also identified the role of miRNAs in tumor necrosis factor- α (TNF- α) and pathways that regulate endochondral ossification and endothelial cell migration and angiogenesis. The corresponding index changes brought about by miRNAs regulation are also significant, and the expression of miRNA-26a is higher than that of other regenerated bone. Furthermore, it induced a 2.4-to 10-fold increase in the expression of Runx-2 and BMP-2 (early osteogenic markers) and an 8.5-fold increase in the expression of cyanate (late osteogenic markers), VE GF and Ang-1 (angiogenic markers).On a deeper level. miRNAs Overexpression inhibited or promoted cyclins and canonical Wnt signaling, resulting in reduced or elevated therapeutic potential for the expression of bone disease, Runx-2, bone, and distal homologous Box-5 genes. In fact, in addition to mRNA (transcriptional effects), they found reduced mRNA (TGF- / Smad 2 / STAT 3 / st static pathway [38]) and other targets that could be involved in this process. Moreover, the antiangiogenic effects of these miRNA may be regulated by the cyclin signaling pathway, but this mechanism needs further investigation. In some indirect aspects, the immune regulation of miRNA also promotes or suppresses osteogenesis to some extent. For example, the M2 polarization of miRNA-378a on macrophages reduces the inflammatory response in advance, providing a favorable environment for the healing and angiogenesis and bone regeneration. Therefore, promoting positive regulated miRNA or inhibiting negative regulated miRNA seems to have the potential to treat bone-related diseases. With the improvement of related research, miRNA is a potential and development path for gene therapy and regenerative medicine.

References

[1] Liu W, Miao Y, Zhang L, et al. MiR-211 protects cerebralischemia/reperfusion injury by inhibiting cell 12 apoptosis[J]. Bioengineered, 2020; 11(1):189-200.

[2] Chen L, Zhu Q, Lu L, et al. MiR-132 inhibits migration and invasion and increases chemosensitivity of cisplatin-resistant oral squamous cell carcinoma cells via targeting TGF-β1[J]. Bioengineered, 2020; 11(1):91-102.

[3] Martinez B, Peplow PV. MicroRNAs as disease progression biomarkers and therapeutic targets in experimental autoimmune encephalomyelitis model of multiple sclerosis[J]. Neural Regen Res, 2020; 15(10): 1831-1837.

[4] Han Z, Rosen ST, Querfeld C. Targeting microRNA in hematologic malignancies[J]. Curr Opin Oncol, 2020; 32(5):535-544.

[5] Poliseno L, Tuccoli A, Mariani L, Evangelista M, Citti L, Woods K, Mercatanti A, Hammond S, Rainaldi G (2006) MicroRNAs modulate the angiogenic properties of HUVECs. Blood 108:3068–3071

[6] Hosseinpour S, He Y, Nanda A, et al. MicroRNAs Involved in the Regulation of Angiogenesis in Bone Regeneration[J]. Calcif Tissue Int, 2019; 105(3):223-238.

[7] Dou C, Ding N, Luo F, Hou T, Cao Z, Bai Y, Liu C, Xu J, Dong S (2018) Graphene-based microRNA transfection blocks preosteoclast fusion to increase bone formation and vascularization. Adv Sci 5:1700578

[8] Yan B, Wang Z-H, Zhu C-D, Guo J-T, Zhao J-L (2014) MicroRNA repertoire for functional genome research in tilapia identifed by deep sequencing. Mol Biol Rep 41:4953–4963

[9] Dou C, Zhang C, Kang F, Yang X, Jiang H, Bai Y, Xiang J, Xu J, Dong S (2014) MiR-7b directly targets DC-STAMP causing suppression of NFATc1 and c-Fos signaling during osteoclast fusion and diferentiation. Biochim Biophys Acta Gene Regulat Mech 1839:1084–1096

[10] Brandenburger T, Castoldi M, Brendel M, Grievink H, Schlösser L, Werdehausen R, Bauer I, Hermanns H (2012) Expression of spinal cord microRNAs in a rat model of chronic neuropathic pain. Neurosci Lett 506:281–286

[11] Yoshizuka M, Nakasa T, Kawanishi Y, Hachisuka S, Furuta T, Miyaki S, Adachi N, Ochi M (2016) Inhibition of microRNA-222 expression accelerates bone healing with enhancement of osteogenesis, chondrogenesis, and angiogenesis in a rat refractory fracture model. J Orthop Sci 21:852–858

[12] Zhao X, Zmijewski JW, Lorne E, Liu G, Park YJ, Tsuruta Y, Abraham E (2008) Activation of AMPK attenuates neutrophil proinfammatory activity and decreases the severity of acute lung injury. Am J Physiol Lung Cell Mol Physiol 295:497–504

[13] Kanazawa I, Yamaguchi T, Yano S, Yamauchi M, Sugimoto T (2008) Metformin enhances the diferentiation and mineralization of osteoblastic MC3T3-E1 cells via AMP kinase activation as well as

ISSN 2706-6819 Vol.5, Issue 11: 63-68, DOI: 10.25236/IJFM.2023.051110

eNOS and BMP-2 expression. Biochem Biophys Res Commun 375:414–419
[14] Qu J, Lu D, Guo H, Miao W, Wu G, Zhou M (2016) MicroRNA-9 regulates osteoblast differentiation and angiogenesis via the AMPK signaling pathway. Mol Cell Biochem 411:23–33
[15] Li Y, Fan L, Liu S, Liu W, Zhang H, Zhou T, Wu D, Yang P, Shen L, Chen J (2013) The promotion of bone regeneration through positive regulation of angiogenic–osteogenic coupling using microRNA-26a. Biomaterials 34:5048–5058
[16] Lian JB, Stein GS, Javed A, Van Wijnen AJ, Stein JL, Montecino M, Hassan MQ, Gaur T, Lengner CJ, Young DW (2006) Networks and hubs for the transcriptional control of osteoblastogenesis. Rev Endocr Metab Disord 7:1–16
[17] Armulik A, Abramsson A, Betsholtz C (2005) Endothelial/pericyte interactions. Circ Res 97:512–523
[18] Su X, Liao L, Shuai Y, Jing H, Liu S, Zhou H, Liu Y, Jin Y (2015) MiR-26a functions oppositely in osteogenic diferentiation of BMSCs and ADSCs depending on distinct activation and roles of Wnt and BMP signaling pathway. Cell Death Dis 6:e1851
[19] Icli B, Wara A, Moslehi J, Sun X, Plovie E, Cahill M, Marchini JF, Schissler A, Padera RF, Shi J (2013) MicroRNA-26a regulates pathological and physiological angiogenesis by targeting BMP/SMAD1 signaling. Circ Res 113:1231–1241
[20] Qin W, Yang F, Deng R, Li D, Song Z, Tian Y, Wang R, Ling J, Lin Z (2012) Smad 1/5 is involved in bone morphogenetic protein-2-induced odontoblastic diferentiation in human dental pulp cells. J Endod 38:66–71
[21] Yamasaki K, Nakasa T, Miyaki S, Yamasaki T, Yasunaga Y, Ochi M (2012) Angiogenic microRNA-210 is present in cells surrounding osteonecrosis. J Orthop Res 30:1263–1270
[22] Mizuno Y, Tokuzawa Y, Ninomiya Y, Yagi K, Yatsuka-Kanesaki Y, Suda T, Fukuda T, Katagiri T, Kondoh Y, Amemiya T, Tashiro H, Okazaki Y (2009) miR-210 promotes osteoblastic diferentiation through inhibition of AcvR1b. FEBS Lett 583:2263–2268
[23] Liu X-D, Cai F, Liu L, Zhang Y, Yang A-L (2015) MicroRNA-210 is involved in the regulation of postmenopausal osteoporosis through promotion of VEGF expression and osteoblast diferentiation. Biol Chem 396:339–347
[24] Lee DY, Deng Z, Wang CH, Yang BB (2007) MicroRNA-378 promotes cell survival, tumor growth, and angiogenesis by targeting SuFu and Fus-1 expression. Proc Natl Acad Sci USA 104:20350–20355
[25] You L, Gu W, Chen L, Pan L, Chen J, Peng Y (2014) MiR-378 overexpression attenuates high glucose-suppressed osteogenicdiferentiation through targeting CASP3 and activating PI3 K/ Akt signaling pathway. Int J Clin Exp Pathol 7:7249–7261
[26] Zhang B, Li Y, Yu Y, Zhao J, Ou Y, Chao Y, Yang B, Yu X (2018) MicroRNA-378 promotes osteogenesis-angiogenesis coupling in BMMSCs for potential bone regeneration. Anal Cell Pathol 2018:8402390
[27] Bao L, Li X, et al. MicroRNA-32 targeting PTEN enhances M2 macrophage polarization in the glioma micro environment and further promotes theprogression of glioma[J]. Mol Cell Biochem, 2019, 460(1-2):67-79.
[28] Acuña SM, Aoki J, et al. Toll-Like Receptor and miRNA-let-7e Expression Alter the Inflammatory Response in Leishmania amazonensis-Infected Macrophages[J]. Front Immunol, 2018, 9:2792.
[29] Zhang Y, Li X, et al. Microarray analysis of circular RNA expression patterns in polarized macrophages [J]. Int J Mol Med, 2017, 39(2):373-379. 13
[30] Li H, Shen S, et al. Immunomodulatory Functions of Mesenchymal StemCells in Tissue Engineering [J]. Stem Cells Int, 2019, 2019(2):1-18.
[31] Damani T, Williams E, et al. microRNAs in Ex Vivo Human Adipose Tissue Derived Mesenchymal Stromal Cells(ASC)Undergo Rapid Culture-Induced Changes in Expression, Including miR-378 which Promotes Adipogenesis[J]. Int J Mol, 2020, 21(4):1492.
[32] Chen W, Li X, et al. miR-378a Modulates Macrophage Phagocytosis and Differentiation through Targeting CD47-SIRPαAxis in Atherosclerosis[J]. Scand JImmunol, 2019, 90(1):e12766.
[33] Ji X, Yuan X, et al. Mesenchymal stem cell-loaded thermosensitive hydrox ypropyl chitin hydrogel combined with a three-dimensional-printed poly(ε-caprol actone)/nano-hydroxyapatite scaffold to repair bone defects via osteogenesis, angiogenesis and immunomodulation [J]. Theranostics, 2020, 10(2):725-740.
[34] Aguado-Fraile E, Ramos E, Conde E, Rodríguez M, Liaño F, García-Bermejo ML (2013) MicroRNAs in the kidney: novel biomarkers of acute kidney injury. Nefrología (English Edition) 33:826–83475.
[35] Tang H (2013) miR-10a regulates epithelial-mesenchymal transition and adhesion and angiogenesis in hepatoma. In: Federation of American Societies for Experimental Biology, p lb153-lb153
[36] Day T F, Guo X, Garrett-Beal L, Yang Y (2005) Wnt/β-catenin signaling in mesenchymal progenitors

ISSN 2706-6819 Vol.5, Issue 11: 63-68, DOI: 10.25236/IJFM.2023.051110

controls osteoblast and chondrocyte diferentiation during vertebrate skeletogenesis. Dev Cell 8:739–750
[37] Sun W, Ma Y, Chen P, Wang D (2015) MicroRNA-10a silencing reverses cisplatin resistance in the A549/cisplatin human lung cancer cell line via the transforming growth factor-β/Smad2/STAT3/STAT5 pathway. Mol Med Rep 11:3854–3859
[38] Welten SM, Bastiaansen AJ, de Jong RC, de Vries MR, Peters EA, Boonstra MC, Sheikh SP, La Monica N, Kandimalla ER, Quax PH, Nossent AY (2014) Inhibition of 14q32 MicroRNAs miR-329, miR-487b, miR-494, and miR-495 increases neovascularization and blood fow recovery after ischemia. Circ Res 115:696–708
[39] He B, Zhang ZK, Liu J, He YX, Tang T, Li J, Guo BS, Lu AP, Zhang BT, Zhang G (2016) Bioinformatics and microarray analysis of miRNAs in aged female mice model implied new molecular mechanisms for impaired fracture healing. Int J Mol Sci 17:1260
[40] Cash DE, Bock CB, Schughart K, Linney E, Underhill TM (1997) Retinoic acid receptor alpha function in vertebrate limb skeletogenesis: a modulator of chondrogenesis. J Cell Biol 136:445–457
[41] Mizuno Y, Tokuzawa Y, Ninomiya Y, Yagi K, Yatsuka-Kanesaki Y, Suda T, Fukuda T, Katagiri T, Kondoh Y, Amemiya T, Tashiro H, Okazaki Y (2009) miR-210 promotes osteoblastic diferentiationthrough inhibition of AcvR1b. FEBS Lett 583:2263–2268
[42] Yu F, Cui Y, Zhou X, Zhang X, Han J (2011) Osteogenic diferentiation of human ligament fbroblasts induced by conditioned medium of osteoclast-like cells. BioSci Trends 5:46–51