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Research Progress on the Mechanism of LIPUS Inducing MicroRNA to Promote Osteogenesis

Zijian Wang, Yuan Ji, Xi Chen, Lifang Feng*

North China University of Science and Technology, Tangshan 063000, China

Abstract

Low intensity pulsed ultrasound (LIPUS) is a therapeutic method that transmits mechanical energy into human tissues and cells in the form of ultrasonic resonance, and then produces a series of biological effects. It can regulate a series of signal transduction pathways in osteoblasts and osteoclasts. Some scholars have proposed that a series of biological effects produced by LIPUS are realized by regulating a series of non-coding Rnas (Ncrnas), especially micrornas. In this paper, the latest research progress and possible research direction of LIPUS on a series of biological effects of LIPUS on osteoblasts through non-coding RNA were discussed from the related mechanisms of LIPUS on osteoblasts and the related mechanisms of miRNA promoting bone healing.

Keywords

Low-intensity Pulsed Ultrasound; Micrornas; Osteoblast; Osteoclast.

1. Introduction

LIPUS has been widely used in clinical practice in recent years as a new type of physical therapy in recent years. As a non-invasive physical therapy, LIPUS has unique biological effects in the human body. LIPUS can be applied to diseases of soft and hard tissue system, nervous system, cardiovascular system and urinary system, and is often used in the rehabilitation of various diseases. Some scholars have applied LIPUS in the treatment of bone nonunion and temporomandibular joint disorders, and achieved ideal results in the end. Several studies have demonstrated that LIPUS affects osteoblasts by adjusting various signaling pathways. It has been proposed that LIPUS exerts a series of biological effects on osteoblasts partly by regulating the expression level of a series of microRNA (miRNA). In this paper, the latest research progress and possible research direction of LIPUS on a series of biological effects of LIPUS on osteoblasts through non-coding RNA were discussed from the related mechanisms of LIPUS on osteoblasts and the related mechanisms of miRNA promoting bone healing.

2. Mechanisms of LIPUS Promoting Osteogenesis

2.1 LIPUS Can Promote the Proliferation and Differentiation of Osteoblasts

LIPUS has a positive effect on the proliferation, differentiation and mineralization of osteoblasts. Bone marrow stem cells differentiate and divide into osteoblasts, and osteoblasts mainly undergo three stages in the process of osteogenesis: proliferation, differentiation and calcification [1]. LIPUS promotes calcium and phosphate uptake and mineralization of MC3t3-E1 [2].LIPUS can promote the differentiation of osteoblasts, but different scholars hold different opinions on whether LIPUS can promote the proliferation of osteoblasts[3].The differences in these studies may be caused by different cell types, different cell culture environments, different ultrasound propagation in two-dimensional or three-dimensional environments, and different ultrasound parameters[5].A variety of studies have confirmed that LIPUS regulates the effects of osteoblasts by regulating the integrin α5β1/P13K/Akt pathway, Rock-COT/TP12-MEK signaling pathway and m-TOR pathway, etc.[7]. Some scholars have found[8] that inhibition of sonic hedgehog (SHH) pathway reduces the migration, proliferation

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and differentiation ability of osteoblasts, and reduces the promoting effect of LIPUS on the osteogenic function of osteoblasts. Zhang[9] et al proposed that Piezo1 played a key role in the mechanical-effects-related pathways of osteoblast differentiation induced by LIPUS. Under LIPUS 'stimulation, Piezo1 clipped restricted the migration and proliferation of Mc3t3-e1 cells. They demonstrate that LIPUS promotes bone formation in the Mc3t3-e1 cell line by Piezo1 ion channels in the cell membrane.Some scholars[10] explored the optimal frequency for MC3T3-E1 cell osteogenesis stimulated by ultrasound[11] , and respectively loaded different intensities of ultrasound (0, 10, 30, 60 and 100mW/cm2), and concluded that 30mW/cm2 frequency had the best influence on the biological behavior of Mc3t3-e1 cell line osteogenesis differentiation in mice.

2.2 LIPUS Can Inhibit the Proliferation and Differentiation of Osteoclasts

Not only osteoblasts participate in the process of osteogenesis, but also osteoclasts play a role in the process of osteogenesis. Some scholars found in the experiment of ultrasound promoting the repair of rat normal root malformation that the number and activity of osteoclasts in Wistar rats in the LIPUS irradiation group were lower than those in the unirradiated control group. Further experimental study and detection found that TNF-α expression of osteoclasts in the LIPUS irradiation group was down-regulated compared with that in the control group. The ratio of OPG (osteoprotectin) to RANKL (osteoclast differentiation factor) increased. Some scholars[12] explored the internal mechanism of LIPus inhibiting osteoclast differentiation, and the results showed that LIPus inhibited ranKL-induced osteoclast differentiation in vitro. Their results showed that LIPus inhibited erK-C-fos -NFATC1 cascade by inhibiting ERK-C-FOS -NFATC1. Thus, osteoclast differentiation and osteoclast specific gene expression are affected. In recent years, many scholars have explored the effects of LIPUS on the proliferation and differentiation of osteoblasts and related mechanisms[13], but there are few studies on the effects of LIPUS on osteoclasts, and the research on its mechanism is even less rare. The study and exploration of the internal mechanism of osteoclast may be a worthy topic.

3. Effect of LIPUS on miRNA Expression Level

MicroRNA can affect the osteogenesis of osteoblasts by regulating Smad5, MAPK, WNT and other signaling pathways[14]. Experimental studies have shown that LIPUS can change the expression level of miRNA. Studies have shown[17] that LIPUS can inhibit the expression of Mir-182 in hPDLCs cells. Overexpression of Mir-182 inhibits FOXO1 protein accumulation, which in turn inhibits the expression of osteogenic markers ALP and Runx2. Ultrasound can also promote the release of Mir-629-5p, Mir-374-5p and Mir-194-5p in the extracellular space of prostate cancer cell lines (PCa), and these mirnas are expected to become biomarkers with diagnostic and predictive value of disease[18]. Low-intensity ultrasound can also increase the expression of Mir-34A in cisplatin (DDP) treated hepatocellular carcinoma (HCC) cells, and enhance the chemical sensitivity of HCC cells to DDP by altering the Mir-34a pathway[20].

4. LIPUS Altered miRNA Levels to Promote Osteogenesis

Feng et al.[21] conducted whole transcriptome and miRNA sequencing on Mc3t3-e1 cell line on porous titanium alloy scaffold and Mc3t3-e1 cell line without LIPUS under the action of LIPUS, and the results showed miRNA with a difference of more than 1.5 times. These results suggest that LIPUS can significantly change the expression level of miRNAs in Mc3t3-e1 cell line by mechanical stimulation. Through relevant biological analysis[22], Mir-31-5p was confirmed to be lipUS-induced miRNA, and this was confirmed by subsequent experiments. Through a series of experiments, it was found that LIPUS stimulation could promote the expression of Mir-31-5p. Mir-31-5p can target HIF-1 α signaling and cytoskeletal proteins to affect human bone marrow mesenchymal stem cells (hMSCs). LIPUS can also negatively regulate the expression of some mirnas to inhibit the osteogenic effect of a variety of cells.

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5. Conclusion

LIPUS, as a non-invasive physical therapy, has a reliable therapeutic effect and is easy to be accepted by patients, which has a broad application prospect. LIPUS can promote osteogenic differentiation of osteoblasts and inhibit osteoclast differentiation. LIPUS can promote osteoblast differentiation by regulating integrin α5β1/P13K/Akt pathway, ROCK-Cot/Tp12-MEK signaling pathway, m-TOR pathway and other pathways. Osteoclast differentiation and osteoclast specific gene expression can also be effectively inhibited by inhibiting the ERK-c-Fos-NFATC1 cascade reaction. LIPUS stimulation can affect the expression levels of some miRNA, thus regulating the osteogenic function of osteoblasts. There are few experimental studies on the effect of LIPUS on miRNA and then osteogenesis, and the effect of LIPUS on other non-coding Rnas such as lncRNA and circRNA has not been mentioned. It may be a good research direction to thoroughly explore the mechanism of various biological phenomena produced by LIPUS from the molecular level, and then develop the clinical therapeutic function of LIPUS.

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References

[1] Epstein F H , Manolagas S C , Jilka R L . Bone Marrow, Cytokines, and Bone Remodeling — Emerging Insights into the Pathophysiology of Osteoporosis[J]. New England Journal of Medicine, 1995, 332(5): 305-311.

[2] Tassinary J, Lunardelli A, Basso B, et al. Low-intensity pulsed ultrasound (LIPUS) stimulates mineralization of MC3T3-E1 cells through calcium and phosphate uptake[J]. Ultrasonics, 2017, 84:290-295.

[3] Fang T , Wu Q , Zhou L , et al. miR-106b-5p and miR-17-5p suppress osteogenic differentiation by targeting Smad5 and inhibit bone formation[J]. Experimental Cell Research, 2016:74-82.

[4] Cao H , Feng L , Wu Z , et al. Effect of low-intensity pulsed ultrasound on the biological behavior of osteoblasts on porous titanium alloy scaffolds: An in vitro and in vivo study[J]. Materials Science and Engineering C, 2017, 80(nov.):7.

[5] Kc A , Yj B , Quan Q A , et al. Improved activity of MC3T3-E1 cells by the exciting piezoelectric BaTiO 3 /TC4 using low-intensity pulsed ultrasound[J]. Bioactive Materials, 2021, 6(11):4073-4082.

[6] Song Y, Wu G, Wang J, et al. Effects of low-intensity pulsed ultrasound on the osteogenic differentiation of bone marrow mesenchymal stem cells with different titanium surfaces [J]. Journal of Applied Stomatology, 2017, 33(4):6.

[7] Qin L, Wu L, Wu Z. Effect of ultrasonic wave on the biological behavior of osteoblasts on porous titanium alloy scaffolds [J]. Journal of China Medical University, 2018, 47(8):5.

[8] Zhang Z C , Yang Y L , Li B , et al. Low-intensity pulsed ultrasound promotes spinal fusion by regulating macrophage polarization[J]. Biomedicine & Pharmacotherapy, 2019, 120:109499.

[9] Zhang G , Li X , Wu L , et al. Piezo1 channel activation in response to mechanobiological acoustic radiation force in osteoblastic cells[J]. Bone Research, 2021, 9(1).

[10] Zheng X , Dai J , Zhang H , et al. MicroRNA-221 promotes cell proliferation, migration, and differentiation by regulation of ZFPM2 in osteoblasts[J]. Brazilian Journal of Medical and Biological Research, 2018, 51(12).

[11] Tutar Y , ME Coşkun, KA Coşkun. Determination of Optimum Operation Parameters for Low-Intensity Pulsed Ultrasound and Low-Level Laser Based Treatment to Induce Proliferation of Osteoblast and Fibroblast Cells[J]. Photomedicine & Laser Surgery, 2018, 36(5):246.

ISSN: 2414-1895 DOI: 10.6919/ICJE.202208_8(8).0026

[12] Meng J , Hong J , Zhao C , et al. Low-intensity pulsed ultrasound inhibits RANKL-induced osteoclast formation via modulating ERK-c-Fos-NFATc1 signaling cascades[J]. American Journal of Translational Research, 2018, 10(9):2901-2910.

[13] Jiang X , Savchenko O , Li Y , et al. A Review of Low-Intensity Pulsed Ultrasound for Therapeutic Applications[J]. IEEE Transactions on Biomedical Engineering, 2018, PP(99):1-1.

[14] Liu Y, Zhu D. Experimental study on the effect of cytoskeleton and MAPK signaling pathway on osteoblast proliferation under low load mechanical vibration [J]. Medical Biomechanics, 2019(A01):1.

[15] Chen N , Wu D , Li H , et al. MiR-17-3p inhibits osteoblast differentiation by downregulating Sox6 expression[J]. FEBS Open Bio, 2020.

[16] Zhou X Y , Wu S Y , Zhang Z C , et al. Low-intensity pulsed ultrasound promotes endothelial cell-mediated osteogenesis in a conditioned medium coculture system with osteoblasts[J]. Medicine, 2017, 96(43):e8397.

[17] Dcab C , Mxab C , Ygab C , et al. LIPUS promotes FOXO1 accumulation by downregulating miR-182 to enhance osteogenic differentiation in hPDLCs[J]. Biochimie, 2019, 165:219-228.

[18] Claes L , Willie B . The enhancement of bone regeneration by ultrasound[J]. Progress in Biophysics and Molecular Biology, 2007, 93(1-3):384-398.

[19] ? Erdogan, Esen E . Biological aspects and clinical importance of ultrasound therapy in bone healing.[J]. Journal of Ultrasound in Medicine, 2009, 28(6):765–776.

[20] Garg P , Mazur M M , Buck A C , et al. Prospective Review of Mesenchymal Stem Cells Differentiation into Osteoblasts[J]. Orthopaedic Surgery, 2017, 9(1).

[21] Feng L F. Effect of low intensity pulsed ultrasound on osteogenesis of porous titanium alloy and bioinformatics analysis and prediction [D]. China Medical University, 2018.

[22] Viviana, Costa, Valeria, et al. miR-31-5p Is a LIPUS-Mechanosensitive MicroRNA that Targets HIF-1α Signaling and Cytoskeletal Proteins.[J]. International Journal of Molecular Sciences, 2019.

[23] Meng J , Hong J , Zhao C , et al. Low-intensity pulsed ultrasound inhibits RANKL-induced osteoclast formation via modulating ERK-c-Fos-NFATc1 signaling cascades[J]. American Journal of Translational Research, 2018, 10(9):2901-2910.