ISSN 2616-5791 Vol.5, Issue 3: 54-60, DOI: 10.25236/AJMHS.2024.050310

Research progress of non-coding RNA-mediated regulation of the osteogenesis of periodontal tissues when mechanical tension is applied

Yanjun Pan[a], Zhiwen Sun[b], Zhihui Mai[*]

Department of Stomatology, The Third Affiliated Hospital of Sun Yat-sen University, 600 Tianhe Road, Guangzhou, 510630, China
[a]1563959495@qq.com, [b]524970406@qq.com
[*]Corresponding author: Maiya2007@126.com

Abstract: *Alveolar bone is the most active bone in the human skeleton. When stimulated by mechanical tension, periodontal osteoblast-related cells play a role in alveolar bone remodeling. During bone remodeling, non-coding RNAs (ncRNAs) actively participate in the regulation of osteogenesis, and mainly include microRNA (miRNA), long-chain non-coding RNA (lncRNA), and circular RNA(circRNA). This report aimed to review the current research of regulatory targets, pathways, and functions of cells and ncRNAs that play an important role in the osteogenesis in periodontal tissues when tension is applied.*

Keywords: *Mechanical tension; non-coding RNA; osteogenesis; alveolar bone remodeling*

1. Introduction

Alveolar bone is the most active bone in the human skeleton, and remodeling of alveolar bone includes bone absorption and generation. The dynamic balance between bone absorption and generation maintains the current shape of alveolar bone, and also reshapes alveolar bone [1]. The compression-tension theory is the most widely accepted theory of alveolar bone remodeling. According to this theory, the movement of teeth against alveolar bone is a process that produces mechanical strain that alveolar bone adapts to, and also produces slight, reversible damage to periodontal tissues. Alveolar bone remodeling requires efficient and coordinated alveolar bone absorption and formation, that is, a balance between the osteoblast and osteoclast activity [2].

The compression-tension theory suggests that under tension-pressure loading, mechanical signals are transformed into chemical signals via stress receptors of cells that are sensitive to mechanical forces. Within a few seconds after mechanical loading, the local stress on periodontal ligaments changes; the blood flow velocity on the pressure side decreases and the cells become relatively hypoxic, while the blood flow velocity of periodontal tissue on the tooth tension side remains unchanged or slightly increases, and cellular oxygen is relatively enriched [3-5]. These changes cause the cells in periodontal ligaments and alveolar bone to release prostaglandins and cytokines, such as interleukin (IL)-1b, resulting in a series of remodeling reactions. The difference of microenvironment changes between the tension and the pressure sides leads to the differences in chemical signals and cytokine secretion, which causes the expressions of osteoblasts and osteoclasts to be different on the two sides.

Previous studies have shown that periodontal bone cells, osteoblasts, fibroblasts, periodontal ligament stem cells (PDLSCs), and bone marrow mesenchymal stem cells (BMSCs) are sensitive to mechanical stress, and all participate in periodontal remodeling caused by mechanical stimulation [6-8]. Therefore, many studies have explored the functions of these cells under the stimulation of different mechanical forces, such as tension, pressure, vibration, and fluid shear force [9]. In the current study, we focus on periodontal changes caused by tension, since tension can stimulate periodontal osteogenesis activity and ensure the stable movement of teeth during remodeling of the periodontium.

As a result of advances in genetic technologies, such as microarray and high-throughput gene sequencing, the important role of non-coding RNAs (ncRNAs) has been recognized. A ncRNA is an RNA that is transcribed from genomic DNA, but does not have protein coding or translating functions. Notably, ncRNAs account for about 98% of the whole genome. However, ncRNAs can regulate the expression of target genes through interactions with proteins, DNA, RNA, and other molecules, and

ISSN 2616-5791 Vol.5, Issue 3: 54-60, DOI: 10.25236/AJMHS.2024.050310

ncRNAs have biological functions at the epigenetic, transcription, and post-transcription levels. In the periodontal cell model loaded with different mechanical forces, ncRNAs exhibit differential expressions, suggesting that ncRNAs are involved in periodontal remodeling due to mechanical stimulation. Studies suggest there is a precise and complex regulatory network that includes ncRNAs, microRNAs (miRNAs), long-chain non-coding RNAs (lncRNAs), circular RNAs (circRNAs), and mRNA(messenger RNAs), which is very important for the alveolar bone remodeling [10-12].

This report aims to review the current research in this field, examine the regulatory targets, pathways, and functions of several periodontal cell types that play an important role in osteogenesis under mechanical tension, and the role of ncRNAs in this process.

2. The effect of tension on ncRNAs and the mechanism of action

Osteoblasts and PDLSCs are mechanosensitive periodontal cells [10, 13-15]. They respond to tension mainly through mechanical sensors on the cell surface, and begin mechanical transduction from the inside out, or from the outside in. The receptors that respond to tension can be divided into two types; proximal mechanoreceptors that include integrins, primary cilia, ion channels, and cytoskeleton, and nuclear membrane proteins. Integrin is a heterogeneous dimer composed of α and β subunits, which senses extracellular matrix stimulation in a non-covalent manner by binding with extracellular ligands which results in a conformation change, and thus transmits a mechanical signal [16]. Talin and kindlin are mechanosensitive adaptor proteins, which bind with the integrin cytoplasmic tail. Studies have shown that when appropriate tension is applied, the two proteins synergistically increase the binding energy and combine with integrins to form an active complex, and then mediate the transformation of tension into intracellular chemical signals [17].

Primary cilia are microtubule-based organelles with unique lipids and unique receptors, which can detect changes in the extracellular environment and transmit information to the cell [18]. Tension causes local strain of primary cilia, resulting in the activation of specific proteins on the membrane which trigger a calcium ion reaction. Piezo1 and TRPV are important mechanosensitive ion channels that have been widely studied, and are composed of transmembrane proteins with complex structures. They are highly sensitive to mechanical forces, and changes of cell membrane tension result in their allowing an inflow of cations, and thus transforming a mechanical signal to a chemical signal [19, 20].

The cytoskeleton is a highly nonlinear intracellular network structure composed of actin fibers, microtubules, and intermediate filaments. Mechanical forces cause cytoskeleton deformation and recombination, which can stimulate other mechanical receptors on the cell membrane [21]. Studies have shown that the transmission of mechanical signals from the cell surface to the nucleus depend on transmission via the cytoskeleton and nuclear cytoskeleton, and the linker of nucleoskeleton and cytoskeleton(LINC) complex is the bridge between the two signals [22]. The LINC complex is connected with the SUN domain on the inner nuclear membrane through the nesprin domain on the outer nuclear membrane [23-25], and transmits tension and shear signals and regulates gene expression in the nucleus.

3. MiRNAs and osteogenesis under tension

3.1. Biological function of miRNAs

A miRNA is an evolutionarily conserved, non-coding small molecular RNA with a length of 21 to 23 nucleotides, and it has a number of functions. 1) It can bind with mRNA, and reduce the expression level of corresponding genes. 2) It can be translated into polypeptide. A Pri-mRNA (primary transcript messenger RNAs)can be recognized as a mRNA by ribosomes when it enters the cytoplasm, and then is translated into polypeptide. 3) It can bind with functional proteins. A miRNA can form RISC with AGO protein complex, target mRNA for degradation, and bind with other functional proteins to perform a non-classical regulatory function. 4) It can regulate the mRNA of mitochondrial related genes. A small number of miRNA generally contain an mRNA that simultaneously regulates multiple mitochondrial-related genes at the same time [26].

3.2. Regulation of miRNA during periodontal osteogenesis when tension is applied

Many miRNAs play a regulatory role in osteogenesis when stimulated by tension of periodontal

ISSN 2616-5791 Vol.5, Issue 3: 54-60, DOI: 10.25236/AJMHS.2024.050310

tissues [27-30]. Osteogenic markers of PDLSCs are increased after 12 hours of stimulation by 10% tension, and sequencing has shown that 26 miRNAs are up-regulated and 27 miRNAs are down-regulated. The most widely studied miRNA, miR-21, exhibits differential changes under fluid shear force and oscillation, but not under tension. The miRNA miR-21 promotes the osteogenesis of PDLSC induced by tension by acting on the transmembrane serine/threonine receptor kinase ACVR2B [31], which is an important part of TGF -β pathways, and affects the growth and differentiation of cells in many biological processes. The miRNA miR-1246 has the highest expression level of all miRNAs in PDLSCs stimulated by tension, and can activate the Wnt/β-catenin pathway by inhibiting the production of GSK3β and Axin2. Gu et al. [32] used the Flexcell®FX5000 TM tension system to culture human PDLSCs. Using RNA sequencing and real-time quantitative polymerase chain reaction (PCR) the researchers identified a ceRNA (Competing endogenouse RNA) network of lncRNAs, circRNAs, miRNAs, and mRNAs that involve the Wnt pathway, MAPK pathway, and signaling pathways that regulate stem cell pluripotency. The results predicted that 744 mRNAs will bind with 148 common miRNAs. The miRNAs miRNA-34a and miRNA-146a have a unique and common target, CELF3, which inhibits the osteogenic differentiation of PDLSCs under mechanical tension.

The periodontal ligament, located between teeth and alveolar bone, is the primary tissue that is stimulated by periodontal tension. Periodontal ligament cells conduct mechanical tension, and participate in the osteogenesis process induced by tension. Experiments have shown that periodontal ligament cells cultured under tension have osteogenic differentiation ability, and produce osteogenic related factors such as bone morphogenic protein (BMP)2, BMP6, alkaline phosphatase (ALP), and osteocalcin (OCN).

Many studies utilize mechanical devices to guide PDLCs to differentiate into osteoblasts. High-throughput sequencing showed that tension resulted in significant differences in the expression of 9 osteogenesis-related miRNAs, including miR-221-3p, miR-138-5p, miR-132-3p, miR-218-5p, miR-133a-3p, miR-145-3p, miR-143-5p, miR-486-3p, and miR-21-3p. In addition, a rat tooth movement experiment showed that there were significant changes in the expression of 6 of the 9 miRNAs. Chen et al. [33] also established a periodontal ligament stress stimulation model, and identified the differential expression of 818 mRNAs and 32 miRNAs. Results of the study predicted that miR-195-5p, miR-424-5p, miR-1297, miR-3607-5p, miR-145-5p, miR-4328, and miR-224-5p regulated osteogenic differentiation most likely by down-regulating downstream target genes Other study has shown that miR-195-5p down-regulates *SMURF1* by targeting *SMURF1* to activate the BMP-2/SMAD/Akt/RUNX2 pathway. In addition, miR-424-5p can be adsorbed by lncRNA 00638 to activate the *FGFR1* pathway and promote osteogenesis. A comparison of the differential expression of periodontal ligament cells between the compression side and the tension side showed that tension inhibited miR-3198, and up-regulation of miR-3198 inhibited the production of osteoprotegerin (OPG).

Mesenchymal stem cells are the main cells responsible for osteogenesis. Liu et al. [34] used miRNA chip detection technology to screen bone marrow mesenchymal stem cells subjected to stress, and found that 9 mechanosensitive miRNAs were differentially expressed in the process of osteogenic differentiation. The expressions of miR-326-5p and miR-34c-3p were up-regulated, while the expressions of miR-30a, miR-188, miR-345, miR-29b, miR-324, miR-503-5p, and miR-351-3p were down-regulated. Among them, miR-503-5p binds with the target gene *SORBS1* to inhibit osteogenic differentiation and bone formation during stimulation with tension. Li et al. showed that miR-326-5p is involved in the positive regulation of osteoblast differentiation using estrogen receptor α (ERα) and quercetin (QUE). MiR-21 is also involved in active osteogenic differentiation of bone marrow mesenchymal cells, and some studies have shown that down-regulation of miR-21 might be regulated by the lncRNA GAS5.[39]

Osteoblasts are the main functional cells of bone formation, and are responsible for the synthesis, secretion, and mineralization of bone matrix. Morphological changes of osteoblasts occur when stimulated by minimal force. The changes are usually accompanied by remodeling of the cytoskeleton and extracellular matrix, and through which mechanical signals can be transmitted to the cells to regulate bone formation and differentiation. Chen et al. reported that stimulation by a cyclic tensile force enhances the osteogenic differentiation ability of osteoblasts, and leads to a decrease of miR138-5p level. [11]

MACF1 is the key target of miR-138-5p, which results in activation of the β-catenin/TCF1-Runx2 pathway to promote osteogenic differentiation. The tension-sensitive miRNA -103a reduced the expression of Runx2 protein by acting on the gene *Runx2*, and thus inhibited the differentiation and bone formation of osteoblasts induced by tension.[10] The miRNA miR-214 has been shown to regulate the proliferation, apoptosis, and osteogenesis of osteoblasts by inhibiting the expression of

ISSN 2616-5791 Vol.5, Issue 3: 54-60, DOI: 10.25236/AJMHS.2024.050310

Sox4 in the blood of patients who have sustained a fracture, and thus participates in the process of fracture healing.

4. LncRNAs and osteogenesis under tension

A lncRNA is a ncRNA with a length greater than 200 nt. Based on the position relative to adjacent genes, lncRNAs can be divided into antisense lncRNAs, enhancer lncRNAs, intergenic lncRNAs, bidirectional lncRNAs, and intron lncRNAs.

4.1. Biological function of lncRNAs

A number of functions of lncRNAs have been identified. 1) Epigenetic regulation; lncRNAs can recruit chromatin remodeling complex to mediate the silencing of some genes, and also can participate in maintaining the stability of chromosome number. 2) Pre-transcriptional regulation; lncRNAs can bind with transcription factors and inhibit mRNA transcription. 3) Post-transcriptional regulation; lncRNAs can act as a "molecular sponge" and absorb miRNAs, and can directly combine with mRNA to degrade or inhibit mRNA translation. They can also bind with protein to activate or inhibit protein activity.

4.2. Regulation of lncRNAs during periodontal osteogenesis when tension is applied

The lncRNAs play a regulatory role in osteogenesis in periodontal tissue when stimulated by appropriate tension [35-38]. Gu et al. found that there were 147 lncRNA expressed differentially in the ceRNA network in tension-stimulated periodontal ligament stem cells. Among them, the lncRNAs encoded as tcon_00212979 and tcon_00212984 can interact with miRNA34a and miRNA146a, which regulate the osteogenic differentiation of PDLSCs through the MAPK pathway [39]. When healthy and inflammatory PDLSCs are subjected to 12% tension and cultured for 12 hours, the expression level of lncRNA-XIST was increased significantly on the 7th day after osteogenic differentiation of healthy PDLSCs. Another study showed that lncRNA-XIST can be used as a miRNA-214-3p sponge to promote osteogenic differentiation of PDLSCs. As a sponge of miR-424-5p, lncRNA 00638 activates the *FGFR1* pathway and promotes osteogenesis in periodontal ligament cells when subjected to tension. In addition, lncRNA GAS5 may inhibit the osteogenic differentiation of human BMSCs (hBMSCs) by down-regulating the expression of miR-21. Study has shown that lncRNA H19 can act as a ceRNA of miR-138, and induce osteogenesis by regulating hBMSCs tension [40]. Notably, lncRNA H19 and miR-675 encoded by exon 1 can form a new pathway, H19/miR-675/TGF-β1/Smad3/HDAC, which can regulate the osteogenic differentiation of BMSCs. Zhu et al. found that when 5% tension was applied to BMSCs, the level of lncRNA-MEG3 increased, which inhibited the expression of miR-140-5p and thus promoted the osteogenic differentiation of BMSCs [41]. In addition, lncRNA-XIST acts as a miR-29b-3p sponge in BMSCs, negatively regulates nicotinamide n-methyltransferase, and inhibits the osteogenic differentiation of BMSCs.

5. Osteogenesis under tension and circRNAs

5.1. Biological function of circRNAs

The circRNAs are endogenous ncRNAs with a unique covalently closed ring structure. Although its expression levels of most circRNAs is low, circRNAs play an active role in regulating physiological and pathological processes. The circRNAs can regulate transcription, and protein and miRNA functions in specific tissues through various mechanisms, and thus regulate gene expression. There are four main functions of circRNAs in cells. 1) They can act as molecular sponge of miRNA by competitively binding with miRNA, and thus indirectly regulate the transcription of downstream genes. 2) They can bind with RNA binding protein (RBP) to form a RNA- protein complex (RPC), which targets and regulates RNA. 3) When an internal ribosome entry site (IRES) is present, the modified circRNA can be translated into a protein. 4) A few circRNAs have the ability to encode proteins [42].

5.2. Regulation of circRNAs during periodontal osteogenesis under tension

In periodontal tissues, circRNA play a regulatory role in osteogenesis when stimulated by appropriate tension. In a periodontal ligament stem cell model stimulated by 10% tension, 1,382

ISSN 2616-5791 Vol.5, Issue 3: 54-60, DOI: 10.25236/AJMHS.2024.050310

circRNAs were predicted to be differentially expressed. Among them, circRNA BANP and circRNA ITCH can interact with miRNA34a and miRNA146a, and regulate the osteogenic differentiation of PDLSCs through the MAPK pathway [32]. As a miR-7 inhibitor, the mechanosensitive circRNA CDR1-AS triggers the up-regulation of *GDF5* and subsequent phosphorylation of Smad1/5/8 and p38 MAPK, which then promotes the osteogenic differentiation of PDLSCs.

5.3. Research summary of circRNAs

Despite technological advances, the small amounts of circRNAs in cells and their structural stability makes it hard to conduct extraction and detection experiments. In the current literature, a large number of potential circRNAs were identified through a cell overexpression experiment and predictive bioinformatics; however, only a few of them have been verified at the cellular level. There are very few animal studies in which the osteogenic activity regulated by circRNAs when tension is applied has been examined. There is currently no circRNA data set obtained using an animal model in the ncRNA database shared on the internet. Since only the overall activities of cells can show physiological activities, the differential changes of circRNAs obtained in an animal experiment have more physiological meaning. Therefore, appropriate experimental animals and sampling methods should be performed to increase the sample size and extraction rate. In addition, attention should be paid to the sample environment and processing during sample extraction to minimize the decomposition of ncRNAs.

Based on the current research of circRNAs, the circRNAs can regulate the gene transcription levels, and gene expressions include transcription and protein synthesis. Therefore, research of circRNAs should not be limited to the one-to-one relations of differential expressions of ceRNA after overexpression. The circRNAs can be regarded as an upstream gene to predict and explore their coding ability. They also can be regarded as an intermediate of transcriptome to perform correlation analysis with proteome and metabolome. Theoretically, there should be a high correlation between the transcriptome obtained from cells, tissues, or organs with the physiological state and protein data. However, in many studies they are not related, or even negatively correlated, which indicates that there are complex regulatory mechanisms that are in effect after transcription. Transcriptomics and proteinomics are closely related in the upstream and downstream, and a certain researches are required before metabolic researches are conducted.

6. Conclusion

In conclusion, when stimulated by mechanical tension, miRNAs, lncRNAs, and circRNAs are important regulatory factors in alveolar bone osteogenic differentiation. The miRNAs usually act directly on the target gene mRNA, and lncRNAs can bind with the osteogenic target gene mRNA and act as a ceRNA to competitively bind with miRNA, and thus regulate transcription level and post-transcriptional level. The circRNAs act primarily as a ceRNA to competitively inhibit miRNA. They form a precise and complex regulatory network comprised of lncRNA-circRNA-miRNA-mRNA, which can promote and inhibit the osteogenic activities and differentiation of alveolar bone.

The expressions of ncRNA and mRNA in the same cells will be different under different degrees of tension and the length of time the tension is applied, and the same ncRNAs may also exhibit different regulatory levels in different cells, which indicates that the mechanical transduction reaction of periodontal cells in different environments may involve different mechanisms. The ncRNAs regulate the occurrence of osteogenesis in cells, and also participate in extracellular signal transmission through exosomes.

Research on ncRNAs has developed rapidly, and more and more ncRNA expression profiles of cells involved in osteogenesis have been constructed. However, most of the current research is based on cell overexpression experiments and predictive models, and the specific sites of only a few ncRNAs have been identified; the functions and mechanisms of a large number of predicted ncRNAs have not been verified in related cells. Among them, the structural specificity of circRNAs and their small amounts in cells make the verification process difficult.

Although the gene level determines the basic properties of physiological activities, it cannot completely determine the final phenotype. It is difficult to comprehensively and systematically analyze the regulation mechanism of the complex physiological process of alveolar bone osteogenesis under tension using single-cell genomic data. The research design for studying ncRNAs should not be limited

ISSN 2616-5791 Vol.5, Issue 3: 54-60, DOI: 10.25236/AJMHS.2024.050310

to the confirmation of the role of predicted ncRNAs with differential expressions, but should also focus on combining proteomics and metabolomics.

The current results and pathways confirmed could not fully clarify the internal and external mechanisms of cells in the osteogenesis activity during alveolar bone remodeling. More researches are required to establish a more complete data system.

References

[1] Will LA: Orthodontic Tooth Movement: A Historic Prospective. Front Oral Biol 2016, 18:46-55.
[2] Wise GE, King GJ: Mechanisms of Tooth Eruption and Orthodontic Tooth Movement. Journal of Dental Research 2008, 87(5):414-434.
[3] Rodrigo F, Viecilli 1 TRK, Jie Chen, et al. Three-dimensional mechanical environment of orthodontic tooth movement and root resorption [J]. Am J Orthod Dentofacial Orthop. 2008. Jun; 133(6): 791. e11-26.
[4] Basdra EK KG. Osteoblast-like properties of human periodontal ligament cells: an in vitro analysis [J]. Eur J Orthod. 1997 Dec; 19(6):615-21.
[5] Kawarizadeh A, Bourauel C, Götz W, Jäger A: Early responses of periodontal ligament cells to mechanical stimulus in vivo. Journal of dental research 2005, 84(10):902-906.
[6] Wagh K, Ishikawa M, Garcia DA, Stavreva DA, Upadhyaya A, Hager GL: Mechanical Regulation of Transcription: Recent Advances. Trends Cell Biol 2021, 31(6):457-472.
[7] Li Y, Jacox LA, Little SH, Ko C-C: Orthodontic tooth movement: The biology and clinical implications. Kaohsiung J Med Sci 2018, 34(4):207-214.
[8] Basdra EK, Komposch G: Osteoblast-like properties of human periodontal ligament cells: an in vitro analysis. Eur J Orthod 1997, 19(6):615-621.
[9] Shen Y, Pan Y, Guo S, Sun L, Zhang C, Wang L: The roles of mechanosensitive ion channels and associated downstream MAPK signaling pathways in PDLC mechanotransduction. Molecular medicine reports 2020, 21(5):2113-2122.
[10] Wu Y, Ou Y, Liao C, Liang S, Wang Y: High-throughput sequencing analysis of the expression profile of microRNAs and target genes in mechanical force-induced osteoblastic/cementoblastic differentiation of human periodontal ligament cells. Am J Transl Res 2019, 11(6):3398-3411.
[11] Chen Y, Zhang C: Role of noncoding RNAs in orthodontic tooth movement: new insights into periodontium remodeling. J Transl Med 2023, 21(1):101.
[12] Yan L, Liao L, Su X: Role of mechano-sensitive non-coding RNAs in bone remodeling of orthodontic tooth movement: recent advances. Prog Orthod 2022, 23(1):55.
[13] Potekhina YP, Filatova AI, Tregubova ES, Mokhov DE: Mechanosensitivity of Cells and Its Role in the Regulation of Physiological Functions and the Implementation of Physiotherapeutic Effects (Review). Sovrem Tekhnologii Med 2021, 12(4):77-89.
[14] Shen T, Qiu L, Chang H, Yang Y, Jian C, Xiong J, Zhou J, Dong S: Cyclic tension promotes osteogenic differentiation in human periodontal ligament stem cells. Int J Clin Exp Pathol 2014, 7(11):7872-7880.
[15] Wang W, Wang M, Guo X, Zhao Y, Ahmed MMS, Qi H, Chen X: Effect of Tensile Frequency on the Osteogenic Differentiation of Periodontal Ligament Stem Cells. Int J Gen Med 2022, 15:5957-5971.
[16] Ji Y, Fang Y, Wu J: Tension Enhances the Binding Affinity of β1 Integrin by Clamping Talin Tightly: An Insight from Steered Molecular Dynamics Simulations. J Chem Inf Model 2022, 62(22):5688-5698.
[17] Lin T, Sun Y: Arl13b promotes the proliferation, migration, osteogenesis, and mechanosensation of osteoblasts. Tissue Cell 2023, 82:102088.
[18] Nguyen AM, Jacobs CR: Emerging role of primary cilia as mechanosensors in osteocytes. Bone 2013, 54(2):196-204.
[19] Nagai S, Kitamura K, Kimura M, Yamamoto H, Katakura A, Shibukawa Y: Functional Expression of Mechanosensitive Piezo1/TRPV4 Channels in Mouse Osteoblasts. Bull Tokyo Dent Coll 2023, 64(1).
[20] Yoneda M, Suzuki H, Hatano N, Nakano S, Muraki Y, Miyazawa K, Goto S, Muraki K: PIEZO1 and TRPV4, which Are Distinct Mechano-Sensors in the Osteoblastic MC3T3-E1 Cells, Modify Cell-Proliferation. Int J Mol Sci 2019, 20(19).
[21] Grandy C, Port F, Pfeil J, Oliva MAG, Vassalli M, Gottschalk K-E: Cell shape and tension alter focal adhesion structure. Biomater Adv 2023, 145:213277.
[22] Crisp M, Liu Q, Roux K, Rattner JB, Shanahan C, Burke B, Stahl PD, Hodzic D: Coupling of the nucleus and cytoplasm: role of the LINC complex. J Cell Biol 2006, 172(1):41-53.
[23] Roux KJ, Crisp ML, Liu Q, Kim D, Kozlov S, Stewart CL, Burke B: Nesprin 4 is an outer nuclear membrane protein that can induce kinesin-mediated cell polarization. Proceedings of the National

ISSN 2616-5791 Vol.5, Issue 3: 54-60, DOI: 10.25236/AJMHS.2024.050310

Academy of Sciences of the United States of America 2009, 106(7):2194-2199.
[24] Zhang Q, Skepper JN, Yang F, Davies JD, Hegyi L, Roberts RG, Weissberg PL, Ellis JA, Shanahan CM: Nesprins: a novel family of spectrin-repeat-containing proteins that localize to the nuclear membrane in multiple tissues. J Cell Sci 2001, 114(Pt 24):4485-4498.
[25] Haque F, Lloyd DJ, Smallwood DT, Dent CL, Shanahan CM, Fry AM, Trembath RC, Shackleton S: SUN1 interacts with nuclear lamin A and cytoplasmic nesprins to provide a physical connection between the nuclear lamina and the cytoskeleton. Mol Cell Biol 2006, 26(10):3738-3751.
[26] Dong H, Lei J, Ding L, Wen Y, Ju H, Zhang X: MicroRNA: function, detection, and bioanalysis. Chem Rev 2013, 113(8):6207-6233.
[27] Chen Z, Zhang Y, Liang C, Chen L, Zhang G, Qian A: Mechanosensitive miRNAs and Bone Formation. Int J Mol Sci 2017, 18(8).
[28] Cultrera G, Lo Giudice A, Santonocito S, Ronsivalle V, Conforte C, Reitano G, Leonardi R, Isola G: MicroRNA Modulation during Orthodontic Tooth Movement: A Promising Strategy for Novel Diagnostic and Personalized Therapeutic Interventions. Int J Mol Sci 2022, 23(24).
[29] Wang Y, Jia L, Zheng Y, Li W: Bone remodeling induced by mechanical forces is regulated by miRNAs. Bioscience reports 2018, 38(4).
[30] Wei FL, Wang JH, Ding G, Yang SY, Li Y, Hu YJ, Wang SL: Mechanical force-induced specific MicroRNA expression in human periodontal ligament stem cells. Cells, tissues, organs 2014, 199(5-6):353-363.
[31] Chen N, Sui BD, Hu CH, Cao J, Zheng CX, Hou R, Yang ZK, Zhao P, Chen Q, Yang QJ et al: microRNA-21 Contributes to Orthodontic Tooth Movement. Journal of dental research 2016, 95(12):1425-1433.
[32] Gu X, Li M, Jin Y, Liu D, Wei F: Identification and integrated analysis of differentially expressed lncRNAs and circRNAs reveal the potential ceRNA networks during PDLSC osteogenic differentiation. BMC Genet 2017, 18(1):100.
[33] Chang M, Lin H, Luo M, Wang J, Han G: Integrated miRNA and mRNA expression profiling of tension force-induced bone formation in periodontal ligament cells. In Vitro Cell Dev Biol Anim 2015, 51(8):797-807.
[34] Liu L, Liu M, Li R, Liu H, Du L, Chen H, Zhang Y, Zhang S, Liu D: MicroRNA-503-5p inhibits stretch-induced osteogenic differentiation and bone formation. Cell biology international 2017, 41(2):112-123.
[35] He Z, Sun F, Liu H: Differential expression of lncRNA in periodontal tissue of rats in model of orthodontic tooth movement. Minerva Pediatr (Torino) 2023.
[36] Hong S, Hu S, Kang Z, Liu Z, Yang W, Zhang Y, Yang D, Ruan W, Yu G, Sun L et al: Identification of functional lncRNAs based on competing endogenous RNA network in osteoblast differentiation. J Cell Physiol 2020, 235(3):2232-2244.
[37] Zhang Z, He Q, Yang S, Zhao X, Li X, Wei F: Mechanical force-sensitive lncRNA SNHG8 inhibits osteogenic differentiation by regulating EZH2 in hPDLSCs. Cell Signal 2022, 93:110285.
[38] Chang M, Lin H, Fu H, Wang B, Han G, Fan M: MicroRNA-195-5p Regulates Osteogenic Differentiation of Periodontal Ligament Cells Under Mechanical Loading. J Cell Physiol 2017, 232(12):3762-3774.
[39] Liu J, Yao Y, Huang J, Sun H, Pu Y, Tian M, Zheng M, He H, Li Z: Comprehensive analysis of lncRNA-miRNA-mRNA networks during osteogenic differentiation of bone marrow mesenchymal stem cells. BMC Genomics 2022, 23(1):425.
[40] Han H, Tian T, Huang G, Li D, Yang S: The lncRNA H19/miR-541-3p/Wnt/β-catenin axis plays a vital role in melatonin-mediated osteogenic differentiation of bone marrow mesenchymal stem cells. Aging (Albany NY) 2021, 13(14):18257-18273.
[41] Zhu G, Zeng C, Qian Y, Yuan S, Ye Z, Zhao S, Li R: Tensile strain promotes osteogenic differentiation of bone marrow mesenchymal stem cells through upregulating lncRNA-MEG3. Histol Histopathol 2021, 36(9):939-946.
[42] Prats A-C, David F, Diallo LH, Roussel E, Tatin F, Garmy-Susini B, Lacazette E: Circular RNA, the Key for Translation. Int J Mol Sci 2020, 21(22).