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Short Review

LncRNAs Regulate the PDLSCs Osteogenic Differentiation in Periodontitis

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Abstract

Periodontitis is a chronic infectious disease which would damage the connective tissue and alveolar bone. Inflammation micro-environment could destroy the osteogenic differentiation ability of PDLSCs, which would induce the periodontitis. Long non-coding RNA (lncRNA) had a very wide range of biological functions, including chromosomal inactivation and differentiation, pluripotent reprogramming, and apoptosis. Nowadays, many lncRNAs have been discovered regulating PDLSCs osteogenesis. Recent studies have demonstrated that lncRNAs were upregulated or downregulated in periodontitis tissues. LncRNAs were involved in the occurrence and development of periodontitis. We review research about lncRNAs in PDLSCs osteogenic differentiation and highlight the role of lncRNAs in the periodontitis. In the future, lncRNAs may be used for the treatment and diagnosis of periodontitis.

Keywords: LncRNA; Osteogenic differentiation; PDLSCs; Periodontitis

Introduction

Periodontitis is a chronic infectious disease which would damage the support tissue of teeth, resulting in periodontal tissue defects called "periodontal pockets" between teeth and alveolar bone. Periodontitis could cause tooth loss [1], which has a significant impact on people's oral health and life quality. Periodontal inflammation can be successfully alleviated through conventional treatment, but the loss of alveolar bone is irreversible. In order to improve the function and aesthetics of periodontitis patients, lots of research efforts have been made on the study of periodontal regeneration. In previous studies different strategies, using stem cells, growth factors or extracellular matrix scaffolds, have been developed to repair and reconstruct periodontal tissues [2].

Mesenchymal Stem Cells (MSCs) have been used for periodontal regeneration. MSCs first discovered in the bone marrow have the potential to differentiate into many types of cells, including osteoblasts, chondrocytes, myocytes and adipocytes [3]. Periodontal Ligament Stem Cells (PDLSCs) were first isolated from the periodontal ligament of third molars extracted from 25 patients by Seo et al., in 2004 [4]. PDLSCs can differentiate into adipocytes or osteoblasts, depending on the different culture conditions, and can contribute to the regeneration of periodontal ligament *in vivo*, thus, is considered to be a seed for periodontal regeneration.

In the human body, there are specific micro-environments that are suit for the proliferation and differentiation of stem cells, called stem cell nests [5]. Inflammation, as an influencing factor affecting the homeostasis of the nest, could change the function of various stem cells; therefore have a negative effect on tissue regeneration [6]. In 2011 Liu N et al., [7] first discovered that pPDLSCs (Periodontal Mesenchymal Stem Cells from periodontitis patients), compared to hPDLSCs (Periodontal Mesenchymal Stem Cells from healthy micro-environment), had enhanced proliferative capacity but reduced osteogenic differentiation ability. This explained why the PDLSCs-based treatment could hardly achieve periodontal regeneration. Therefore, currently improving the multiple differentiation ability of PPDLSCs and repairing damaged periodontal tissues is still challenging.

Long non-coding RNA (LncRNA) is one of non-coding RNAs, with the transcript length more than 200 nt. This type of RNA is transcribed in large quantities in cells, yet has been considered to be transcriptional "noise" in early studies, due to its lack of coding function. With the discovery of lncRNA-HOTAIR in 2007, the function of lncRNA has become clearer. Based on their structural features and cellular location, lncRNAs can be divided into five subcategories: antisense, long intergenic non-coding RNA (lincRNA), sense overlap, sense introns and processed transcripts [8]. Due to the flexibility of RNA, lncRNA can be folded into different unique secondary conformations, including the DNA binding domain, the RNA binding domain and the protein binding domain, enabling it to form a broad regulatory network with DNA, RNA particles and protein complexes [9-13]. LncRNA has been shown to affect transcription and post-transcriptional gene expression through a variety of mechanisms, for instances, by modulating chromatin remodeling, acting as competitive endogenous RNA (ceRNA), regulating mRNA stability or recruiting

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scaffold proteins [14-19]. This information helps to clarify their key role in normal and disease development. It is clear that lncRNA can regulate gene expression at epigenetic [20], transcription [21] and post-transcriptional [22] levels, and participate in X chromosome silencing, genomic imprinting. And a variety of important regulatory processes such as chromatin modification, transcriptional activation and inhibition, nuclear transport, etc., are pathophysiologically relevent.

The major mechanisms of lncRNA action are based on RNA and protein regulation, RNA and RNA interactions, and RNA-DNA interactions [23]. RNA-protein complexes can be formed, such as lncRNPs, to further mediate the correct localization of chromatin regulatory proteins or to recruit functional proteins with different protein interaction domains [24,25]. LncRNA is also involved in the regulation of pre-mRNA splicing, RNA editing, mRNA stability control, translational activation and can function as miRNA sponge [26]. In addition, lncRNAs play a key role in regulating biological processes by targeting RNA-DNA triplex targeting specific DNA sequences [23]. In recent years, lncRNA has been shown to affect the differentiation of PDLSCs, and certain lncRNAs can modulate the osteogenesis of PDLSCs [27]. Existing studies have demonstrated that lncRNA has two modes of action in osteogenic differentiation of PDLSCs (lncRNA-miRNA mode and RBP mode).

lncRNA-miRNA Pathway

A study had used lncRNA chip technology to screen the differential expressed lncRNAs in PDLSCs from healthy and periodontitis patients, and found that pPDLSC osteogenesis impairment-related lncRNA (lncRNA-POIR) and miR-182 constitute a regulatory network. This network is regulated by the NF-κB pathway in the inflammatory micro-environment and may influence the osteogenic differentiation of pPDLSC through the FoxO1 / canonical Wnt pathway [28,29]. LncRNA-POIR alleviated the periodontitis by improving the osteogenic differentiation of hPDLSCs. In addition, the study investigated the star molecule lncRNA anti-differentiation noncoding RNA (ANCR) and found that lncRNA-ANCR is up-regulated in PPDLSC and inhibits osteogenic differentiation of PPDLSC. In this model, lncRNA-ANCR directly targets miR-758, which can repress Notch2, a key regulator of PDLSC osteogenic differentiation [30]. The result of a luciferase reporter assay showed that the miR-758 bind with the Notch2. Overexpression of lncRNA-ANCR aggravated the periodontitis by inhibiting the osteogenic differentiation of PDLSCs. Another study found lncRNA MEG3 and Insulin-like Growth Factor 1 (IGF1) were down-regulated in periodontitis-derived PDLSCs, while miR-27a-3p was up-regulated. Therefore, lncRNAs may be used as the diagnostic molecular markers for periodontitis [31-33]. Overexpression of MEG3 inhibits the miRNA-27a-3p expression by increasing the IGF1 to promote osteogenic differentiation. The authors propose that MEG3 down-regulation inhibits osteogenic differentiation of PDLSC through the miR-27a-3p / IGF1 axis [34-36]. MEG3 up-regulation alleviated the periodontitis by promoting the osteogenic differentiation of PDLSCs. Previous study have proved that LncRNAs regulate the miRNAs [37,38]. LncRNAs could alleviate or aggravate the periodontitis by different molecular mechanisms [39-41].

RBP Pathway

RBPs comprise an RNA binding domain that can bind to lncRNA to exert biological functions. Studies have shown that the expression of lncRNA taurine up-regulated gene 1 (TUG1) is positively correlated with osteogenic differentiation of PDLSC. Knockdown of TUG1 inhibits osteogenic differentiation of PDLSCs. Lin28 A is an RBP that binds to TUG1 and promotes osteogenic differentiation of PDLSC [42]. These data indicate that lncRNA TUG1 can be used for periodontal tissue engineering and to treat the periodontitis. Maternal-expressed gene 3 (MEG3), a widely studied lncRNA, regulates osteogenic differentiation of MSCs in a number of ways. In a study by Liu et al., upregulation of MEG3 inhibits bone morphogenetic protein 2 (BMP2) by interacting with hnRNPI, whereas hnRNPI plays an active role in mRNA splicing and significantly inhibits hPDLC through this mechanism during osteogenic differentiation [16]. This study also suggests that lncRNA MEG3 in hPDLSCs can be used as a new method for the treatment of periodontitis. In addition, a bioinformatics study based on high-throughput RNA sequencing and microarray data on periodontitis, integrating lncRNA, miRNA and mRNA expression to construct putative competitive endogenous RNA (ceRNA) networks. By constructing a dysregulated ceRNA network, six genes (HSPA4L, PANK3, YOD1, CTNNBIP1, EVI2B, ITGAL) and three miRNAs (miR-125a-3p, miR-200a, miR-142-3p) were detected. Moreover, in this ceRNA network, three lncRNAs (MALAT1, TUG1, FGD5-AS1) simultaneously target miR-125a-3p and miR-142-3p. Protein-protein interaction network analysis identified several central genes, including VCAM1, ITGA4, UBC, LYN and SSX2IP. Three pathways (cytokine-cytokine receptor, cell adhesion molecule, chemokine signaling pathway) were identified, consistent with the results of previous periodontitis bioinformatics studies [43]. This study shows that lncRNAs are involved in the process of periodontitis and periodontal regeneration, and further research is needed.

A systematic characterization integrating 22 studies of periodontal regeneration using MSCs in animal models was performed. Apparently, MSCs have regenerative potential in animal models of periodontal defects, but there are differences in the reproductive potential of MSCs in different studies [44]. In addition, human studies have used PDLSC to achieve periodontal regeneration [45]. We found that LncRNA-TWIST1 promoted osteogenic differentiation both in PPDLSCs and in HPDLSCs by inhibiting TWIST1 expression [46]. Periodontitis induces the tooth loss by destroying the supporting structures of tooth. Chen et al showed the cell-based periodontal therapy is safe and efficient [47]. We propose that lncRNAs could be used to repair the damaged PDLSCs in periodontitis. It is expected that in-depth study of the role of lncRNA in osteogenic differentiation of PDLSCs would offer more insights into the mechanism of periodontal regeneration and for developing more effective therapeutic strategies to treat the diseases.

The present review summarizes the potential roles of lncRNAs in the PDLSCs osteogenic differentiation in periodontitis. Most of the studies proved that the lncRNAs regulate the PDLSCs osteogenic differentiation in periodontitis, but only few of them investigated the molecular mechanisms of lncRNAs on regulating PDLSCs osteogenic differentiation process. In summary, lncRNAs were proved to regulate the PDLSCs osteogenic differentiation in periodontitis by multiple regulatory effects, including periodontal inflammation and oxidative stress. Furthermore, miRNAs and proteins have been proved to be the direct targets of lncRNAs. However, the lncRNAs which could regulate the PDLSCs osteogenic differentiation in periodontitis are very limited. In the future study, the researchers should study deeply the regulative effects of lncRNAs and whether the

lncRNAs could regulate the other cells such as macrophage and periodontal cells. Furthermore, natural lncRNAs modulators may be used for the prevention and treatment of periodontitis.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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