ISSN 1948-0210 (online)

# World Journal of *Stem Cells*

*World J Stem Cells* 2020 April 26; 12(4): 241-302

Published by Baishideng Publishing Group Inc

World Journal of Stem Cells

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**NAME OF JOURNAL**
*World Journal of Stem Cells*

**ISSN**
ISSN 1948-0210 (online)

**LAUNCH DATE**
December 31, 2009

**FREQUENCY**
Monthly

**EDITORS-IN-CHIEF**
Carlo Ventura

**EDITORIAL BOARD MEMBERS**
https://www.wjgnet.com/1948-0210/editorialboard.htm

**PUBLICATION DATE**
April 26, 2020



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*World J Stem Cells* 2020 April 26; 12(4): 251-265

DOI: 10.4252/wjsc.v12.i4.251

ISSN 1948-0210 (online)

*REVIEW*

# Overview of noncoding RNAs involved in the osteogenic differentiation of periodontal ligament stem cells

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**Author contributions:** Fang FC and Wu BL contributed to the conception and design of the review; Qiu W contributed to the writing and drafting of the manuscript; Fang FC and Qiu W contributed to the critical revision of the manuscript for important intellectual content; all the authors have given approval of the final version to be published and agree to be accountable for all aspects of the work.

**Supported by** National Natural Science Foundation of China, No. 81600882 and 81870755; China Postdoctoral Science Foundation, No. 2019M663009; and President Foundation of Nanfang Hospital, Southern Medical University, No. 2019B002.

**Conflict-of-interest statement:** The authors declare that they have no conflict of interest.



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## Abstract

Periodontal diseases are infectious diseases that are characterized by progressive damage to dental support tissue. The major goal of periodontal therapy is to regenerate the periodontium destroyed by periodontal diseases. Human periodontal ligament (PDL) tissue possesses periodontal regenerative properties, and periodontal ligament stem cells (PDLSCs) with the capacity for osteogenic differentiation show strong potential in clinical application for periodontium repair and regeneration. Noncoding RNAs (ncRNAs), which include a substantial portion of poly-A tail mature RNAs, are considered "transcriptional noise." Recent studies show that ncRNAs play a major role in PDLSC differentiation; therefore, exploring how ncRNAs participate in the osteogenic differentiation of PDLSCs may help to elucidate the underlying mechanism of the osteogenic differentiation of PDLSCs and further shed light on the potential of stem cell transplantation for periodontium regeneration. In this review paper, we discuss the history of PDLSC research and highlight the regulatory mechanism of ncRNAs in the osteogenic differentiation of PDLSCs.

**Key words:** Noncoding RNAs; Periodontal regeneration; Periodontal ligament stem cells; Osteogenic differentiation



**Core tip:** Periodontal ligament stem cells (PDLSCs) are widely utilized in therapeutic applications for periodontium repair and regeneration in periodontal disease treatment. However, more evidence is required to elucidate what determines and regulates the multilineage differentiation potential of PDLSCs. Noncoding RNAs (ncRNAs) are essential elements in gene expression and signal transduction, being involved in diverse cellular processes and diseases. Concerning ncRNAs that may collectively or individually alter the osteogenic differentiation of PDLSCs, this review is based on current studies and aims to summarize the most significant ncRNAs identified in the osteogenic differentiation of PDLSCs.

**Manuscript source**: Invited manuscript

**Received:** December 30, 2019
**Peer-review started:** December 30, 2019
**First decision:** February 20, 2020
**Revised:** March 16, 2020
**Accepted:** March 22, 2020
**Article in press:** March 22, 2020
**Published online:** April 26, 2020

**P-Reviewer:** Scuteri A, Hassan A, Politi L, Qiao L
**S-Editor:** Wang YQ
**L-Editor:** A
**E-Editor:** Xing YX

**Citation:** Qiu W, Wu BL, Fang FC. Overview of noncoding RNAs involved in the osteogenic differentiation of periodontal ligament stem cells. *World J Stem Cells* 2020; 12(4): 251-265
**URL**: https://www.wjgnet.com/1948-0210/full/v12/i4/251.htm
**DOI**: https://dx.doi.org/10.4252/wjsc.v12.i4.251

## INTRODUCTION

Periodontal diseases are infectious diseases characterized by progressive destruction of the periodontium (tooth-supporting tissue), which includes the periodontal ligament (PDL), cementum, alveolar bone, and gingiva[1]. Tooth loss mainly results from periodontal diseases in adults, which adds a substantial burden to public health worldwide[2,3]. Periodontal treatment is not as easy as only controlling inflammation and preventing disease development; the reconstruction of a healthy periodontium destroyed by diseases deserves equal attention[4,5]. Current therapies for periodontal diseases in the clinic, including conservative approaches, radicular conditioning, bioactive bone grafting/substitution, and guided tissue regeneration (GTR), encounter difficulty in regenerating the periodontium completely[6]. Therefore, the stem cell-based tissue regeneration approach involving transplantation of stem cells to enhance periodontal tissue regeneration has gradually taken the place of guided bone/tissue regeneration[7-9].

PDL is a specialized soft connective tissue that connects the cementum and alveolar bone; it shows the function of maintaining and supporting teeth *in situ*, preserving tissue homoeostasis and repairing damaged periodontal tissue[1]. In the 1980s, Bordin *et al*[10] reported that PDL tissue possessed periodontal regenerative properties due to its resident cells, which were considered to be seed cells and a reliable source for periodontium regeneration. In 2004, Seo *et al*[11] first identified and characterized multipotent stem cells in human PDL and termed them periodontal ligament stem cells (PDLSCs). PDLSCs show similar features to other postnatal mesenchymal stem cells (MSCs): Multilineage differentiation potential and potent self-renewal ability. PDLSCs can further differentiate into cementoblasts/osteoblasts, chondrocytes and adipocytes *in vitro* and regenerate cementum/PDL-like tissues *in vivo*[12]. As a consequence, PDLSC-mediated periodontium tissue regeneration is likely to be a practical cellular-based treatment for periodontal diseases[13]. However, what determines and regulates the multilineage differentiation potential of PDLSCs warrants further research.

Instead of the potential to encode proteins or peptides, noncoding RNAs (ncRNAs) are a category of unique RNAs that are widely present in eukaryotic cells[14-16]. Following the development of this field, scientists have determined that ncRNAs play a significant role in the regulation of gene expression by controlling the expression levels of protein-coding RNAs and are involved in diverse cellular processes, including cell proliferation, cell differentiation, and ontogenesis, and are thus closely related to embryonic development and disease pathogenesis[17-19]. However, there are currently no uniform criteria for ncRNA classification. ncRNAs can be divided into cytoplasmic and nuclear ncRNAs based on their subcellular localization. In addition, ncRNAs are generally categorized into structural and regulatory ncRNAs, as well as regarding their function in cellular processes[20]. Structural ncRNAs include ribosomal RNAs (rRNAs) and transfer RNAs (tRNAs), whereas regulatory RNAs can be further divided into categories based on their length, such as long noncoding RNAs (lncRNAs) (size from > 200 nt to 100 kb) and several types of small RNAs, which include small interfering siRNAs (18–30 nt), piwiRNAs (24–30 nt) and microRNAs (miRNAs, 20–24 nt)[21]. Circular RNAs (circRNAs) are covalently linked to the end of RNA molecules, in which the 3′ and 5′ ends are connected in a non-collinear way through the back-splicing process[22]. CircRNAs, which are a type of competing endogenous RNA (ceRNA), can act as miRNA sponges. Recently, growing research has indicated that circRNAs are involved in embryonic development, cellular activities, and many other human diseases[23-25]. In summary, the cell differentiation of PDLSCs is collectively or individually regulated by ncRNAs. This review focuses on the three most important ncRNAs, namely, miRNAs, lncRNAs and circRNAs, currently identified to play a role in osteogenic differentiation (Tables 1 and 2).

**Table 1 Expression profile of ncRNAs involved in the osteogenic differentiation of periodontal ligament stem cells**

| ncRNAs | Method | Subjects | Results | Ref. |
|---|---|---|---|---|
| mi-RNA | Microarray | 3 hPDLSCs from normal healthy premolars without periodontitis or caries cultured in mineralized medium and 3 in non-mineralized medium | 30 upregulated and 86 downregulated miRNAs ($P$ < 0.05, FC ≥ 2) | Hao *et al*[37] 2017 |
| mi-RNA | Microarray | 6 samples from untreated hPDLSCs and 6 hPDLSCs under osteogenic induction | miR-24-3p with the minimum fold change was significantly downregulated ($P$ < 0.05, FC ≥ 2) | Li *et al*[38] 2019 |
| mi-RNA | Microarray | 3 hPDLSCs cultured with 5.5 mmol/L glucose or 3 cultured with 25 mmol/L glucose mineralized medium | Analyzed 700 miRNAs and found miR-31 was the most upregulated in hPDLSCs cultured with 25 mmol/L glucose ($P$ < 0.01, FC ≥ 2) | Zhen *et al*[48] 2017 |
| mi-RNA | Microarray | 3 hPDLSCs from 3 volunteers not subjected to stretch and 3 hPDLSCs from 3 volunteers subjected to mechanical stretch | 26 miRNAs were up-regulated while 27 miRNAs were down-regulated with stretching ($P$ < 0.01, FC ≥ 2) | Wei *et al*[55] 2014 |
| lncRNA | RNA sequencing | 3 PDLSCs every group cultured in an osteogenic medium for 0, 3, 7, or 14 d | lncRNAs showed stage-specific expression, and 17 lncRNAs were up-regulated while31 were down-regulated in PDLSCs in an osteogenic medium for 3, 7, or 14 d ($P$ < 0.05, FC ≥ 2) | Zheng *et al*[68] 2018 |
| lncRNA | Microarray | 3 hPDLSCs both in osteoblast-induced group and non-induced group | 994 lncRNAs were up-regulated and 1177 lncRNAs were down-regulated during osteogenic differentiation in PDLSCs at 14 d ($P$ < 0.05, FC ≥ 2) | Qu *et al*[69] 2016 |
| lncRNA | RNA sequencing | 3 hPDLSCs subjected to static compressive stress (2 g/cm$^2$) for 12 h and 3 normal hPDLSCs | 72 lncRNAs were upregulated and 18 downregulated by compressive stress ($P$ < 0.05, FC ≥ 1.5) | Huang *et al*[70] 2019 |
| lncRNA | Microarray | 3 noninduced and 3 osteogenically induced hPDLSCs | 12 upregulated and 8 downregulated lncRNAs and MEG3 belonging to significant downregulation genes in induced cells ($P$ < 0.05, FC ≥ 2) | Liu *et al*[73] 2019 |
| lncRNA | Microarray | 3 hPDLSCs from 3 normal persons and 3 pPDLSCs from 3 periodontitis patients with osteogenic differentiation | 89 lncRNAs were differentially expressed between the two groups of cells and lncRNA-POIR was the most significantly altered between the non-induced group and osteogenic-induced group ($P$ < 0.05, FC > 2) | Wang *et al*[77] 2016 |
| lncRNA and circRNA | RNA sequencing | 3 samples from untreated hPDLSCs and 3 hPDLSCs under osteogenic induction | A total of 960 lncRNAs and 1456 circRNAs were found to be differentially expressed ($P$ < 0.05, FC ≥ 2) | Gu *et al*[67] 2017 |
| circRNA | RNA sequencing | 3 hPDLSCs were subjected to mechanical force and 3 hPDLSCs were not subjected to force | identified 2970 and 2788 circRNAs, respectively, in the control group and the force group, and 1191 circRNAs were significantly upregulated and 1,487 were downregulated in the force group ($P$ < 0.05, FC > 2) | Wang *et al*[89] 2019 |

miRNAs: MicroRNAs; lncRNAs: Long non-coding RNAs; circRNAs: Circular RNAs; hPDLSCs: Human periodontal ligament stem cells; PDLSCs: Periodontal ligament stem cells; MEG3: Maternally expressed gene 3; POIR: Osteogenesis impairment-related lncRNA of PDLSCs.

**Table 2 Overview of ncRNAs involved in the osteogenic differentiation of periodontal ligament stem cells**

| ncRNAs | Regulatory levels | Modes of action | Associated signaling pathways or biomarkers | Ref. |
|---|---|---|---|---|
| miR-24-3p | Posttranscriptional regulation | Interacting with Smad5 3′-UTR | Inhibits Smad5 and Runx2, BMP2, OCN biomarkers | Li *et al*[38] 2019 |
| miR-21 | Posttranscriptional regulation | Interacting with Smad5 3′-UTR | Inhibits Smad5 and Runx2, ALP, BSP, OSX biomarkers | Wei *et al*[39] 2017 |
| | | Interacting with Spry1 3′-UTR | Inhibits Spry1 and Runx2, OSX biomarkers | Yang *et al*[40] 2017 |
| | | Interacting with ACVR2B 3′-UTR | Inhibits ACVR2B and enhances Runx2, OCN, ALP biomarkers | Wei *et al*[56] 2015 |
| miR-203 | Posttranscriptional regulation | Interacting with Runx2 3′-UTR | Inhibits Runx2 and ALP, OCN, OPN biomarkers | Feng *et al*[41] 2019 |
| miR-1305 | Posttranscriptional regulation | Interacting with Runx2 3′-UTR | Inhibits Runx2 and ALP, OCN, OPN biomarkers | Chen *et al*[42] 2017 |
| miR-218 | Posttranscriptional regulation | Interacting with Runx2 3′-UTR | Inhibits Runx2 and OCT4, NANOG cytokines | Gay *et al*[43] 2014 |
| miR-214 | Posttranscriptional regulation | Interacting with ATF4 3′-UTR | Inhibits ATF4 and Runx2, ALP, OCN biomarkers | Yao *et al*[44] 2017 |
| | | Interacting with CTNNB1 3′-UTR | Activates Wnt/β-catenin signaling pathway and inhibits ALP, OCN, BSP biomarkers | Cao *et al*[45] 2017 |
| miR-17 | Posttranscriptional regulation | Interacting with TCF3 3′-UTR | Inhibits Runx2, ALP biomarkers | Liu *et al*[46] 2013 |
| | | Interacting with Smurf1 3′-UTR | Activates Smad family proteins and Runx2, ALP, OCN biomarkers | Liu *et al*[47] 2011 |
| miR-31 | Posttranscriptional regulation | Interacting with Stab2 3′-UTR | Inhibits Stab2 and Runx2, OSX, OCN biomarkers | Zhen *et al*[48] 2017 |
| miR-200c | Posttranscriptional regulation | Interacting with IL-6, IL-1β and CCL-5 3′-UTRs | Inhibits IL-6, IL-1β, CCL-5 and enhances Runx2, ALP, OCN, OPG biomarkers | Hong *et al*[49] 2016 |
| miR-543 | Posttranscriptional regulation | Interacting with TOB2 3′-UTR | Inhibits TOB2 and enhances Runx2, ALP, BSP, COL1A1 biomarkers | Ge *et al*[50] 2018 |
| miR-22 | Posttranscriptional regulation | Interacting with HDAC6 3′-UTR | Inhibits HDAC6 and enhances Runx2, OCN biomarkers | Yan *et al*[51] 2017 |
| lncRNA TUG1 | Transcriptional regulation | Binding with Lin28A protein | Promotes Lin28A and Runx2, ALP, OCN biomarkers | He *et al*[72] 2018 |
| lncRNA MEG3 | Transcriptional regulation | Suppresses BMP2 through binding with hnRNPI protein | Inhibits BMP2 and Runx2, ALP, OCN biomarkers | Liu *et al*[73] 2019 |
| lncRNA ANCR | Transcriptional regulation | Activates Wnt/β-catenin signaling pathway indirectly | Activates Wnt/β-catenin signaling pathway and inhibits ALP, BSP, DSPP, OCN, Runx2, Gsk3-β biomarkers | Jia *et al*[74] 2015 |
| | Posttranscriptional regulation | lncRNA ANCR/miR-758/Notch2 axis "ceRNA" | Activates Notch2-Wnt/β-catenin signaling pathway and inhibits ALP, Runx2, OSX biomarkers | Peng *et al*[78] 2018 |
| | Epigenetic regulation | Interacting with EZH2 and catalysis H3K27me3 of Runx2 | Inhibits Runx2 and ALP, OCN biomarkers | Zhu *et al*[82] 2013 |
| lncRNA POIR | Posttranscriptional regulation | LncRNA POIR/miR 182/FoxO1 axis "ceRNA" | Inhibits TCF-4-Wnt/β-catenin signaling pathway and promotes ALP, Runx2, COL1 biomarkers | Wang *et al*[77] 2016 |
| lncRNA PCAT1 | Posttranscriptional regulation | A feed-forward regulatory loop of lncPCAT1/miR-106a-5p/E2F5/ BMP2 axis "ceRNA" | Activates BMP2 and ALP, Runx2, OSX biomarkers | Jia *et al*[79] 2019 |
| lncRNA HIF1AAS2 | Posttranscriptional regulation | Base complementary pairing with the mRNA of HIF-1α | Inhibits HIF-1α and ALP, Runx2 biomarkers | Chen *et al*[80] 2017 |

| | | | | |
|---|---|---|---|---|
| circRNA CDR1as | Posttranscriptional regulation | circRNA CDR1as /miR-7/GDF5 axis "ceRNA" | Enhances Smad1/5/8 and p38 MAPK phosphorylation and promotes ALP, BMP2, Runx2, OCN biomarkers | Li *et al*[88] 2018 |
| circRNA3140 | Posttranscriptional regulation | CircRNA3140/miR-21/ACVR2B axis "ceRNA" | Promotes ACVR2B and inhibits Runx2, OCN, SP7 biomarkers | Wang *et al*[89] 2019 |

miRNAs: MicroRNAs; lncRNAs: Long non-coding RNAs; circRNAs: Circular RNAs; hPDLSCs: Human periodontal ligament stem cells; PDLSCs: Periodontal ligament stem cells; Smad5/: SMAD family member 5; Runx2: Runt-relatedtranscriptionfactor 2; BMP2: Bone morphogenetic protein-2; OCN: Osteocalcin; ALP: Alkaline phosphatase; BSP: Bone Sialoprotein; OSX: Osterix; Spry1: Palmitate phosphoprotein Sprouty1; ACVR2B: Activin A receptor type 2B; OPN: Osteopontin; OCT4: Octamer-binding transcription factor-4; NANOG: Homeobox transcription factor nanog; ATF4: Activated transcription factor 4; CTNNB1: Catenin beta 1; TCF3: Transcriptional factor 3; Smurf1: Smad ubiquitin regulatory factor 1; Satb2: Special AT-rich sequence-binding protein 2; IL: Interleukin; CCL-5: Chemokines-5; OPG: Osteoprotegerin; TOB2: Transducer of ERBB2; COL1A1: Collagen type I alpha 1 chain; HDAC6: Histone deacetylase 6; Lin28A: Lin-28 homolog A; hnRNP I: Heterogeneous nuclear ribonucleoprotein I; DSPP: Dentin sialophosphoprotein; GSK3β: Glycogen synthase kinase 3β; ANCR: Anti-differentiation noncoding RNA; Notch2: Neurogenic locus notch homolog protein 2; ceRNA: Competing endogenous RNAs; EZH2: Enhancer of zeste homolog 2; H3K27me3: Histone H3 trimethylated at lysine 27; POIR: Osteogenesis impairment-related lncRNA of PDLSCs; FoxO1: Forkhead box O1; TCF4: Transcription factor 4; COL1: Collagen type I; PCAT1: Prostate cancer-associated ncRNA transcript-1; HIF1AAS1/2: HIF1A antisense RNA 1/2; HIF-1α: Hypoxia-inducible factor-1α; CDR1as: Antisense to the cerebellar degeneration-related protein 1 transcript; GDF5: Growth differentiation factor 5; MAPK: Mitogen-activated protein kinase; ACVR2B: Activin A receptor type 2B; SP7: Transcription Factor Sp7.

## HISTORY OF PDLSCS

The progenitor cells residing within the PDL (periodontal ligament progenitor, PDLPs) were first described in seminal studies by Melcher in 1994[26]. Seo *et al*[11] described the identification and characterization of multipotent stem cells in human PDL in 2004, although these cells had been suspected to be present in the PDL for a long time. Nevertheless, there is no uniform standard for defining the features of PDLSCs. Often, reports suggest that the isolation of particular subsets of cells from bulk explant cultures is far less rigorous and was too liberal for the use of the term PDLSC[27]. Prateeptongkum *et al*[28] reported that the isolation methods of PDLPs and PDLSCs from PDL tissues are different and demonstrated that PDLPs could be isolated using outgrowth methods, while PDLSCs need single-cell isolation methods for isolation. PDLSCs can be further characterized by their cell surface expression of CD29, CD44, STRO-1, STRO-4, CD146, CD73, CD90, CD105 and CD166 and the lack of expression of endothelial (CD31), haematopoietic (CD14, CD34, CD45, and CD79a), and helper immune antigens (HLA-DR, CD40, CD54, CD80, and CD86)[10,29]. Functionally, PDLSCs have been determined to fulfil all of the criteria of identifiable MSC-like properties, including self-renewal capacity, multipotency *in vitro*, tissue regenerative capacity *in vivo*, and immunomodulation[30,31]. These processes are illustrated in Figure 1.

## MICRORNAS IN PDLSCS: ORCHESTRATING CELLULAR OSTEOGENIC DIFFERENTIATION

miRNAs are endogenous, single-stranded noncoding RNAs derived from genomic sequences[32]. The lengths of mature miRNAs are typically 20~24 nucleotides, 8 of which are identified as the "seed sequences" (with nt positions 2 to 7 that were 99% conserved)[33,34]. miRNAs have been extensively investigated in the past two decades, and the underlying mechanism is relatively clear. Mature miRNAs are targeted to a sequence in the 3′ UTR (untranslatedregion) of mRNAs matching the seed sequence and further influence the stability of mRNAs or inhibit their translation to eventually downregulate protein expression[35]. miRNAs are a leading representative of small ncRNAs, and they are closely associated with diverse biological and pathological processes.

miRNA microarrays are a widely accepted high-throughput method and are very effective in analysing miRNA expression levels during osteogenic differentiation of PDLSCs[36]. Our team used a miRNA microarray to detect the different expression profiles of miRNAs in PDLSCs during the osteogenic differentiation process *in vitro*[37]. The results showed a significant change in the expression level of 116 miRNAs, 30 of which were increased, while 86 miRNAs were downregulated in PDLSCs after 14 d of osteogenic induction. The results probably suggested an important regulatory role that miRNAs might play in the osteogenic differentiation of PDLSCs.

Similarly, a microarray was used in the study of Li *et al*[38] to detect the expression level of miRNAs in differentiated and undifferentiated PDLSCs and demonstrated that the expression level of miR-24-3p was significantly downregulated in

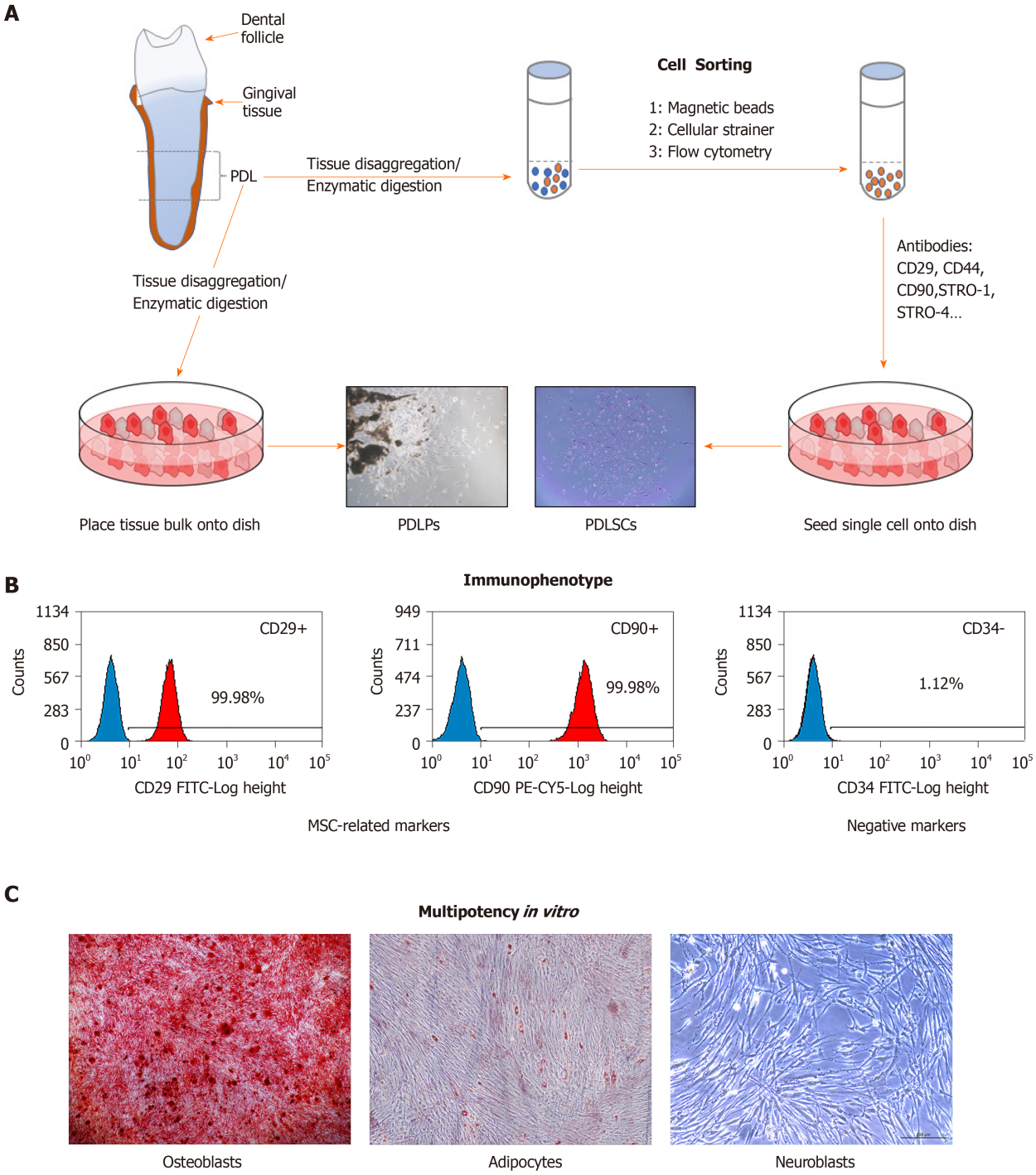


**Figure 1 Isolation and characterization of periodontal ligament stem cells.** A: Diagram of the isolation of periodontal ligament stem cells (PDLPs) and PDLSCs from human PDL tissue; B: Flow cytometric analysis to assess the immunophenotype of PDLSCs. Markers of mesenchymal stem cells (CD29, CD90) and non-mesenchymal stem cells (CD34); C: Assessment of the differentiation potential of PDLSCs *in vitro*. PDL: Periodontal ligament; PDLPs: Periodontal ligament progenitor; PDLSCs: Periodontal ligament stem cells.

osteogenically differentiated PDLSCs. Furthermore, double luciferase reporter assays and genetic engineering experiments demonstrated that miR-24-3p directly bound to the 3′-UTR of transduction protein 5 (SMAD family member 5, Smad5) and inhibited the transcription of the target gene.

The inhibition of the osteogenic differentiation of PDLSCs was the result of miR-21 downregulating the expression of Smad5 in the research of Wei *et al*[39]. Yang *et al*[40] found that the inhibition was attributed to the regulation of the miR-21/palmitate phosphoprotein Sprouty1 axis by tissue tumour necrosis factor-α. In addition, miR-203, miR-1305, and miR-218 have all been confirmed to target runt-related transcriptionfactor 2 (Runx2) and play important inhibitory roles in the osteogenic differentiation of PDLSCs[41-43]. miR-214 not only targeted activated transcription factor

4[44] but also bound with catenin beta 1 to modulate the Wnt/β-catenin signalling pathway, which is involved in osteogenic differentiation of PDLSCs[45]. Liu *et al*[46] found that miR-17 regulated the osteogenic differentiation of PDLSCs by reducing the expression of transcriptional factor 3 and inhibiting the Wnt signalling pathway. In contrast, Liu *et al*[47] demonstrated that miR-17 promoted differentiation by binding to the Smad ubiquitin regulatory factor one 3′-UTR in PDLSCs isolated from PDL tissue from periodontitis patients. miR-31 plays a regulatory role by targeting special AT-rich sequence-binding protein 2 in osteogenic differentiation mediated by a high dose of glucose in PDLSCs[48]. All of the abovementioned miRNAs exerted inhibitory effects on osteogenic differentiation by targeting osteogenesis-related transcription factors through the classic miRNA regulatory mechanism.

Although several miRNAs suppress the osteogenic differentiation of PDLSCs, recent research has revealed that miRNAs promote the osteogenic differentiation of PDLSCs, including miR-200c, miR-543 and miR-22. Hong *et al*[49] demonstrated that miR-200c decreased the levels of interleukin-6, interleukin-8 and chemokines-5 and increased the osteogenic differentiation of PDLSCs and BMSCs. miR-200c is a potentially effective means of preventing periodontitis-associated bone loss by arresting inflammation and osteoclast/osteogenesis and regenerating bone tissue. Previous research by our team found that miR-543 directly interacted with the 3′-UTR of transducer of ERBB2 and promoted osteogenesis in PDLSCs[50]. Yan *et al*[51] claimed that miR-22 promoted the osteogenic differentiation of PDLSCs by inhibiting the expression of histone deacetylase 6.

According to previous work, one of the factors affecting osteogenic differentiation of PDLSCs is mechanical stretch[52-54]. To investigate miRNA expression specifically in stretched PDLSCs, a microarray assay was utilized by Wei *et al*[55] to describe the differential expression of miRNAs in normal and stretched PDLSCs by using a tension system to achieve external mechanical stimulation. The results showed that 53 miRNAs were differentially expressed in stretched PDLSCs, and 26 of the miRNAs were upregulated, while 27 were downregulated. Noticeably, miR-21 directly targeted the 3′-UTR of activin A receptor type 2B (ACVR2B), thereby reducing the expression of ACVR2B and repressing the osteogenic differentiation of stretched PDLSCs[56].

The main regulatory mechanism of microRNAs is the posttranscriptional repression of target genes. However, several studies have reported that miRNAs function in other unconventional ways, including pri-miRNAs coding for short peptides and miRNAs interacting with non-AGO proteins, activating toll-like receptors, upregulating protein expression, targeting mitochondrial transcripts, directly activating transcription, and targeting nuclear ncRNAs[57-59]. To date, research has mainly focused on the classic regulatory mechanism of miRNAs in PDLSCs, and other regulatory mechanisms require further in-depth exploration.

## LNCRNAS INVOLVED IN OSTEOGENIC DIFFERENTIATION OF PDLSCs

LncRNAs are a family of RNA molecules with transcript lengths of 200 nt to 20000 nt. These RNAs are unable to encode proteins or are only translated into small peptides at a very low level. Initially, lncRNAs were identified as a by-product of RNA polymerase II transcription and thought to be the "noise" of genomic transcription (referred to as "the dark matter" of the genome) with no biological function[36,60,61]. However, research on lncRNAs has rapidly developed in recent years. According to their position relative to protein-coding genes in the genome, lncRNAs can be divided into five types: Sense, antisense, bidirectional, intronic, and intergenic lncRNAs[62]. Recent studies show that lncRNAs act as novel and important regulators of numerous biological, developmental, and numerous cellular processes, including chromatin modification, X-chromosome silencing, genomic imprinting, transcriptional activation or interference, and intranuclear transport[63], and act through such mechanisms as transcriptional regulation, posttranscriptional regulation, and epigenetic regulation[64-66].

Gu *et al*[67] compared the lncRNA profiles of PDLSCs on the 7th day with or without osteogenic differentiation medium using RNA sequencing. The results showed that 17 lncRNAs were upregulated and 31 were downregulated during osteogenic differentiation in PDLSCs. Zhang *et al*[68] also used RNA sequencing to detect the different expression profiles of lncRNAs in PDLSCs at different time points during osteogenic differentiation. These results indicated that 48 lncRNAs had significant changes on days 3, 7 and 14, of which 17 lncRNAs were upregulated and 31 were downregulated in PDLSCs. Our team used a lncRNA microarray to determine the expression levels of lncRNAs in osteoblast-induced and noninduced PDLSCs, and the

results showed that 994 lncRNAs were upregulated and 1177 lncRNAs were downregulated at 14 d of osteogenic differentiation in PDLSCs. Further GO analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis revealed that a total of 83 signalling pathways were involved in the osteogenic differentiation of PDLSCs, including the mitogen-activated protein kinase (MAPK) and transforming growthfactor-β signalling pathways. In addition, coding-noncodinggenecoexpression analysis indicated a potential regulatory relationship between the differentially expressed lncRNAs and the osteogenesis-related mRNAs, of which 131 pairs of lncRNAs and mRNAs had negative correlations and 262 pairs had positive correlations[69]. Huang *et al*[70] used RNA sequencing to describe the lncRNA landscape during osteogenic differentiation in PDLSCs subjected to compressive force. The results indicated that 90 lncRNAs and 519 mRNAs were differentially expressed in PDLSCs under compressive stress. Of the lncRNAs, 72 were upregulated, and 18 were downregulated. To summarize, investigations of the regulatory mechanisms of lncRNAs in the osteogenic differentiation of PDLSCs are mainly focused on transcriptional regulation and posttranscriptional regulation.

### *Transcriptional regulation by lncRNAs in PDLSCs*

Studies of the underlying mechanisms indicated that lncRNAs can specifically bind with a specific family of proteins called RNA binding proteins (RBPs) to regulate the biological functions of these proteins and then affect the transcriptional activation of downstream genes[71]. As a novel protein type, RBPs have been demonstrated to interact with lncRNAs and have attracted increasing attention from researchers. He *et al*[72] identified the novel lncRNA- taurine upregulated gene 1 (TUG1), which was significantly upregulated in osteogenically induced PDLSCs. Gain/loss-of-function experiments showed that lncRNA-TUG1 was positively correlated with the osteogenic differentiation of PDLSCs following induction. Meanwhile, bioinformatic analysis demonstrated that lin-28 homologue A (Lin28A, a member of the RBP family) containing multiple binding sites of lncRNA-TUG1 was a potential target in the process of osteogenic differentiation of PDLSCs. Further investigation demonstrated that suppression of Lin28A inhibited the expression of several osteogenic-related gene markers, such as alkaline phosphatase, osteocalcin, and Runx2, in PDLSCs. These results suggested that lncRNA-TUG1 might interact with Lin28A to form a positive regulatory network of osteogenic-related genes to promote osteogenic differentiation of PDLSCs. However, there is insufficient evidence about the direct binding between lncRNA-TUG1 and Lin28A in this study. In a study by Liu *et al*[73], lncRNA maternally expressed gene 3 (MEG3) was markedly downregulated in osteogenically differentiated human PDLSCs compared with undifferentiated cells, as determined by microarray analysis. Overexpression of lncRNA MEG3 inhibited the activation of bone morphogenetic protein-2 (BMP2) and reversed osteogenic differentiation induced by mineralizing solution in PDLSCs. Furthermore, RNA-binding protein immunoprecipitation (RIP) assays verified that lncRNA MEG3 suppressed BMP2 through direct interaction with heterogeneous nuclear ribonucleoprotein I (hnRNPI) during osteogenic differentiation in hPDLCs. These results indicated that lncRNA MEG3 could modulate the osteogenic differentiation of hPDLCs by interacting with hnRNPI and thus inhibiting the transcriptional activity of BMP2. Moreover, lncRNAs can also interfere with the transcriptional activation of mRNAs or other ncRNAs. Jia *et al*[74] found an inhibitory effect of ANCR (anti-differentiation noncoding RNA) on the gene expression of glycogen synthase kinase 3β and Runx2 and the classic Wnt/β-catenin signalling pathway, thereby suppressing osteogenic differentiation of PDLSCs.

### *Posttranscriptional regulation of lncRNAs in PDLSCs*

Recent studies revealed that lncRNAs might act as miRNA sponges to compete with target genes for miRNA binding sites, thereby affecting the activity of the targeted genes in various biological processes[75]. These regulatory mechanisms involving lncRNAs, miRNAs and mRNAs are one type of ceRNA[76] mechanism. Wang *et al*[77] successfully identified the novel lncRNA-POIR (osteogenesis impairment-related lncRNA of PDLSCs), which is an osteogenesis impairment-related lncRNA of PDLSCs, and the gradual reduction in the expression of this lncRNA in PDLSCs was recorded among periodontitis patients, as demonstrated by lncRNA microarray analysis. Overexpression or knockdown of lncRNA-POIR was performed, and lncRNA-POIR was shown to positively regulate osteogenic differentiation of PDLSCs both *in vitro* and *in vivo*. Further luciferase reporter assays and quantitative real-time PCRs demonstrated that lncRNA-POIR was likely to act as a ceRNA for miR-182, thereby leading to derepression of the target gene Forkhead box O1 (FoxO1). Activated FoxO1 could compete with transcription factor 4 for β-catenin binding and inhibit the classic Wnt signalling pathway, thereby promoting osteogenic

differentiation of inflammatory PDLSCs. On the other hand, Peng *et al*[78] suggested that lncRNA-ANCR targeted miR-758 directly as a molecular sponge *via* RNA immunoprecipitation, and a dual luciferase reporter assay was also performed to demonstrate that miR-758 modulates the transcript expression of neurogenic locus notch homolog protein 2 (Notch2) by targeting the 3′-UTR of Notch2. These findings suggest that the lncRNA-ANCR/miR-758/Notch2 axis plays an essential role in regulating the osteogenic differentiation of PDLSCs. In addition, prostate cancer-associated ncRNA transcript-1 (lncPCAT1) was significantly increased in osteogenically induced PDLSCs and could positively regulate osteogenic differentiation both *in vitro* and *in vivo* according to the study of Jia *et al*[79]. Thereafter, these researchers inferred a predicted interaction and then confirmed the direct binding sites of miR-106a-5p on lncPCAT1. In conclusion, lncRNA-PCAT1 promoted osteogenic differentiation of PDLSCs by sponging miR-106a-5p to upregulate the miR-106a-5p-targeted gene BMP2. Interestingly, the authors also found that another target of miR-106a-5p, E2F5, could bind to the promoter of lncPCAT1 and then form a feed-forward regulatory network targeting BMP2. Chen *et al*[80] studied two lncRNAs, HIF1A antisense RNA 1 and HIF1A antisense RNA 2, that regulated the mRNA expression of HIF1α. The results showed that HIF1A-AS2 exerted a remarkable negative regulatory function on hypoxia-inducible factor-1α (HIF-1α) through complementary base pairing with HIF-1α mRNA in PDLCs under hypoxia.

### *Epigenetic regulation of lncRNAs in PDLSCs*

Epigenetics plays a central role in regulating many critical cellular processes. From the perspective of epigenetics, several lncRNAs can interact with protein complexes and modulate the levels of DNA methylation as coordinators of chromatin modification, thereby regulating the expression of related genes at the epigenetic level[81]. Studies have claimed that lncRNAs affect the osteogenic differentiation of PDLSCs by epigenetic regulation. Zhu *et al*[82] found that lncRNA ANCR posed a physical interaction with enhancer of zeste homologue 2, and Runx2 expression was suppressed due to the catalysis of H3K27me3 in the Runx2 gene promoter, leading to the inhibiting effect on osteoblast differentiation of hFOB1.19 cells. At present, further exploration is needed to explore the function of lncRNAs in regulating the osteogenic differentiation of PDLSCs at the epigenetic level.

The discovery of lncRNAs greatly broadened the understanding of molecular regulatory mechanisms. LncRNAs regulate the expression of related genes via three different regulatory mechanisms at the levels of transcription, posttranscription, and epigenetics and participate in many important cellular processes. Current studies on lncRNAs regulating the osteogenic differentiation of PDLSCs have mainly focused on the transcriptional and posttranscriptional levels. However, most studies have not determined the subcellular localization of lncRNAs. Generally, the localization of an lncRNA in the cytoplasm is important when considering its functions, especially as a ceRNA sponge[83]. Due to the numerous lncRNAs and their complexity, the mechanisms of lncRNAs regulating osteogenic differentiation in PDLSCs need to be explored further.

## CIRCRNAS ASSOCIATED WITH OSTEOGENIC DIFFERENTIATION OF PDLSCS

circRNAs are a novel class of endogenous lncRNAs that are characterized by a structure of covalently closed continuous loops lacking 5′ or 3′ polarities and are widely present in eukaryotic cells[84]. The circRNAs are more stable than linear RNAs because of their covalently circular structure, making them more resistant to RNase R digestion. The majority of circRNAs are conserved across species and often exhibit cell type-specific, tissue-specific or developmental stage-specific expression[85]. Evidence is increasing that circRNAs might act as miRNA sponges and play critical roles in signal transduction in a posttranscriptional manner. The circRNA-miRNA axis is involved in several cellular processes, such as proliferation, differentiation and apoptosis[86].

Gu *et al*[67] conducted high-throughput sequencing to detect the different expression profiles of circRNAs in PDLSCs after 7 d of osteogenic differentiation. These researchers found that 766 circRNAs were significantly upregulated and 690 circRNAs were downregulated in PDLSCs. Furthermore, the authors predicted the potential functions of circRNAs as ceRNAs based on miRanda analysis and further investigated them using GO and KEGG analysis. The results showed that a total of 1382 circRNAs (including circRNA PTPRG, EXOC4, PRKCA, and SETBP1) were predicted to be able to interact with 148 miRNAs and compete for miRNA binding sites with 744 mRNAs, which were predicted to be significantly associated with

osteoblast differentiation and the MAPK and Wnt signalling pathways regulating pluripotency of mesenchymal stem cells. Among these circRNAs, one circRNA could bind with multiple miRNAs, and the same miRNA could also interact with multiple circRNAs. Li *et al*[87] revealed that circRNA antisense to the cerebellar degeneration-related protein 1 transcript (CDR1as) could act as a miR-7 adsorption sponge and then induce the upregulation of growth differentiation factor 5 and activate the Smad1/5/8 and p38MAPK signalling pathways, thereby promoting osteogenesis in PDLSCs. Wang *et al*[88] found that circRNA expression patterns were responsive to mechanical force in PDLSCs. Bioinformatic analysis showed that one circRNA could modulate one or several miRNA/miRNAs and vice versa. Importantly, the authors found that circRNA3140 was widely and highly related to microRNA-21, which played a key role in mechanical force-induced osteogenic differentiation of PDLSCs. These findings revealed that mechanical force induced the differential expression of circRNAs in PDLSCs, which might regulate the orthodontic tooth movement process and alveolar bone remodelling.

Overall, as a novel class of endogenous lncRNAs, circRNAs may modulate many pathophysiological processes, serve as diagnostic or predictive biomarkers for several diseases, and represent a novel and useful therapeutic method[89]. Compared with research on miRNAs and lncRNAs, research on circRNAs is in its infancy, and the potential functions and regulatory mechanisms of circRNAs are diverse. Investigating the regulatory mechanisms and functions of circRNAs in the osteogenic differentiation of PDLSCs may provide exciting potential therapies in periodontal regeneration.

## CONCLUSION

Numerous ncRNAs are associated with the osteogenic differentiation of PDLSCs (Figure 2). ncRNAs offer an additional and promising possibility of osteogenesis-related gene regulation that has not been fully elucidated to date. With increasing numbers of miRNAs, lncRNAs and circRNAs discovered in this process, it has become possible to use these ncRNA-related therapeutic methods in the field of periodontium repair and regeneration.

To date, ncRNA-related research on the osteogenic differentiation of PDLSCs has mainly focused on miRNAs. The demonstrated regulatory mechanism of miRNAs (miR-24-3p, miR-21, miR-203, miR-1305, miR-218, miR-214, miR-17, miR-31, miR-200c, miR-543 and miR-22) is to inhibit the mRNA levels or protein expression of targets. Other unconventional mechanisms could impact osteogenic differentiation. Currently, miRNAs are considered to be potential therapeutic targets based on their defined regulatory mechanism and clear functioning mode. miRNA-based therapeutic methods could become valuable in promoting periodontium repair and regeneration. Similarly, there are several studies on the role of lncRNAs during this process. Among these lncRNAs, lncRNA TUG1, MEG3 and ANCR regulate the osteogenic differentiation of PDLSCs in a transcriptional manner. The lncRNAs POIR, PACT1, HIF1A-AS2 and ANCR act as miRNA sponges and play critical roles during osteogenic differentiation of PDLSCs in a posttranscriptional manner (Figure 3). However, lncRNA-ANCR has been demonstrated to suppress osteogenic differentiation of PDLSCs in an epigenetic regulatory manner. To date, few studies have investigated circRNAs during osteogenic differentiation in PDLSCs. The demonstrated mechanism of circRNAs is to act as miRNA sponges to inhibit the mRNA levels of target genes (circRNA CDR1as and circRNA3140). Other types of ncRNAs involved in the osteogenic differentiation of PDLSCs warrant further exploration.

With the development of sequencing and microarray technologies, numerous novel ncRNAs have been screened out and identified in the past few years, and their regulatory mechanisms have also been predicted and explored, benefiting from the advancement of related bioinformatics databases. Subsequently, standard molecular biology experiments and genetic engineering methods, such as quantitative real-time PCR, western blotting, dual luciferase reporter assays, RNAi and overexpression plasmid transfections, have been used to characterize ncRNA functions and explore their regulatory mechanisms. In addition, some new experimental methods have emerged, such as RIP, RNA pull-down, chromatin isolation by RNA purification, cross-linking immunoprecipitation, cross-linking, ligation, and sequencing of hybrids, and capture hybridization analysis of RNA targets, which provide an ideal research platform for elucidating the signalling transduction mechanisms of ncRNAs. In addition, the regulatory mechanisms of ncRNAs, especially lncRNAs and circRNAs, in cellular processes and diseases are highly complex. However, there are few studies

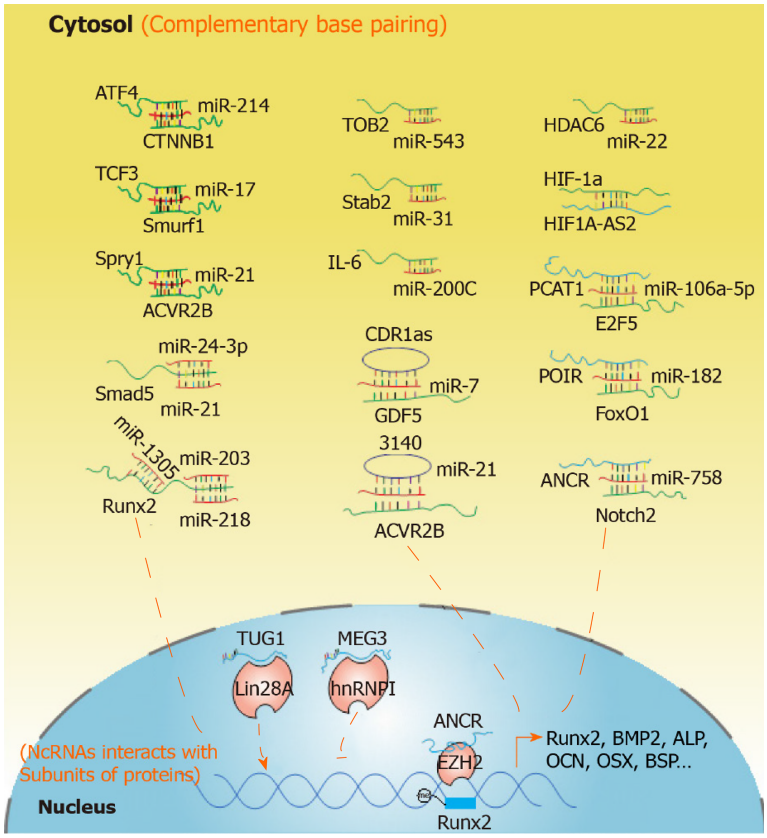


**Figure 2 Regulatory mechanisms of noncoding RNAs associated with the osteogenic differentiation of periodontal ligament stem cells.** Red indicates miRNAs, green indicates mRNAs, blue indicates long noncoding RNAs and purple indicates circular RNAs. Collectively, the regulatory mechanism of miRNAs is to directly bind to the 3'-UTR of target genes and inhibit the mRNA levels or protein expression. Long noncoding RNAs regulate the osteogenic differentiation of periodontal ligament stem cells at the transcriptional, posttranscriptional or epigenetic level. And the demonstrated mechanism of circular RNAs is to act as miRNA sponges to inhibit the mRNA levels of target genes. ATF4: Activated transcription factor 4; CTNNB1: Catenin beta 1; TCF3: Transcriptional factor 3; Smurf1: Smad ubiquitin regulatory factor 1; Spry1: Palmitate phosphoprotein Sprouty1; ACVR2B: Activin A receptor type 2B; Smad5: SMAD family member 5; Runx2: Runt-relatedtranscriptionfactor 2; TOB2: Transducer of ERBB2; Satb2: Special AT-rich sequence-binding protein 2; IL-6: Interleukin-6; CDR1as: Antisense to the cerebellar degeneration-related protein 1 transcript; GDF5: Growth differentiation factor 5; HDAC6: Histone deacetylase 6; HIF-1α: Hypoxia-inducible factor-1α; HIF1AAS1/2: HIF1A antisense RNA 1/2; PCAT1: Prostate cancer-associated ncRNA transcript-1; E2F5: E2F transcription factor 5; POIR: Osteogenesis impairment-related long noncoding RNA of periodontal ligament stem cells; FoxO1: Forkhead box O1; ANCR: Anti-differentiation noncoding RNA; Notch2: Neurogenic locus notch homolog protein 2; TUG1: Taurine upregulated gene 1; Lin28A: Lin-28 homolog A; MEG3: Maternally expressed gene 3; hnRNP I: Heterogeneous nuclear ribonucleoprotein I; EZH2: Enhancer of zeste homolog 2; BMP2: Bone morphogenetic protein-2; ALP: Alkaline phosphatase, OCN: Osteocalcin; OSX: Osterix; BSP: Bone sialoprotein; miR: MicroRNA; ncRNAs: Non-coding RNAs.

concerning the nonconventional mechanisms of ncRNAs during the osteogenic differentiation of PDLSCs.

Due to their osteogenic differentiation capability, PDLSCs show effective potential in the clinical application of periodontium repair and regeneration (Figure 4). However, reports have appeared that are less rigorous in the isolation and identification of PDLSCs. In addition, most current studies of ncRNAs involved in osteogenic differentiation in PDLSCs have focused on the cell level *in vitro*; therefore, *in vivo* experiments in this field warrant further in-depth exploration. Therefore, whereas interest and investigation in the contribution of ncRNAs to the osteogenesis of PDLSCs have increased considerably, the field is still a long way from understanding the full extent of the contribution of ncRNAs and the mechanisms by which ncRNAs exert their potential effects in this field.

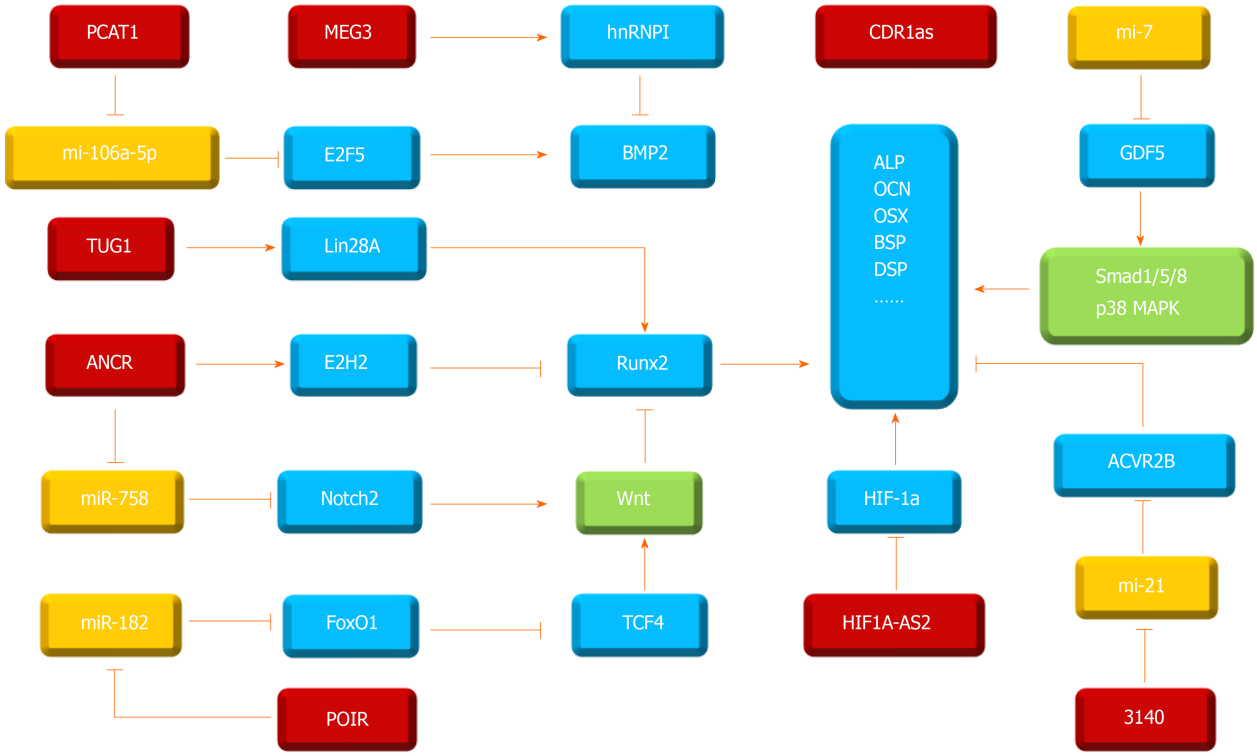


**Figure 3 Overview of the role of long noncoding RNAs and circular RNAs during osteogenic differentiation of periodontal ligament stem cells.** Red frame indicates long noncoding RNAs (lncRNAs) or circular RNAs (circRNAs), yellow frame indicates miRNAs interacted by lncRNAs and circRNAs, blue frame indicates target mRNAs or osteogenesis-related biomarkers, green frame indicates signaling pathways associated with osteogenic differentiation. These lncRNAs and circRNAs affect downstream factors to trigger related biomarkers or signaling pathways and then regulate the osteogenic differentiation of periodontal ligament stem cells. PCAT1: Prostate cancer-associated ncRNA transcript-1; E2F5: E2F transcription factor 5; MEG3: Maternally expressed gene 3; hnRNP I: Heterogeneous nuclear ribonucleoprotein I; BMP2: Bone morphogenetic protein-2; TUG1: Taurine upregulated gene 1; Lin28A: Lin-28 homolog A; Runx2: Runt-relatedtranscriptionfactor 2; ANCR: Anti-differentiation noncoding RNA; EZH2: Enhancer of zeste homolog 2; Notch2: Neurogenic locus notch homolog protein 2; FoxO1: Forkhead box O1; POIR: Osteogenesis impairment-related lncRNA of periodontal ligament stem cells; TCF4: Transcription factor 4; CDR1as: Antisense to the cerebellar degeneration-related protein 1 transcript; GDF5: Growth differentiation factor 5; Smad1/5/8: SMAD family member 1/5/8; MAPK: Mitogen-activated protein kinase; HIF-1α: Hypoxia-inducible factor-1α; HIF1AAS1/2: HIF1A antisense RNA 1/2; ACVR2B: Activin A receptor type 2B; ALP: Alkaline phosphatase, OCN: Osteocalcin; OSX: Osterix; BSP: Bone Sialoprotein; DSP: Desmoplakin; miR: MicroRNA.

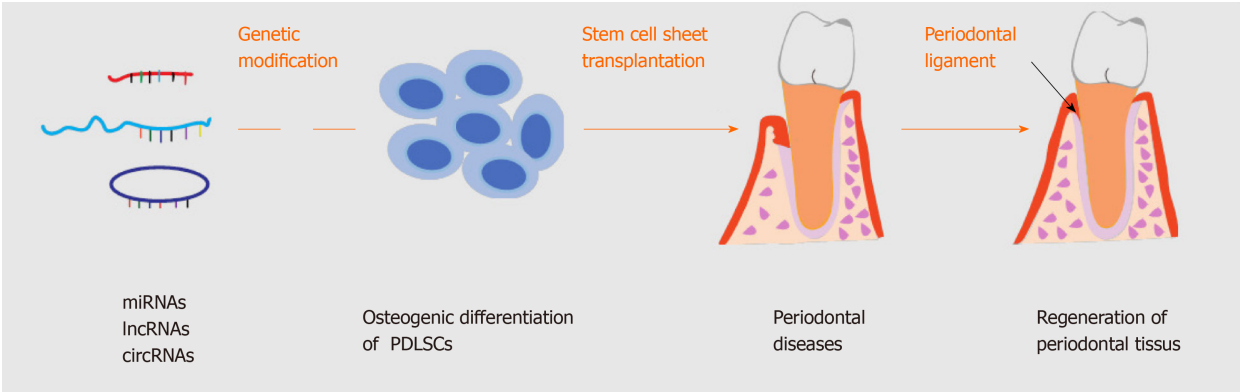


**Figure 4 Schematic diagram of noncoding RNAs genetic modification-based periodontal ligament stem cells transplantation therapy applications for periodontium regeneration of periodontal disease.** Genetic modification of noncoding RNAs in periodontal ligament stem cells can regulate the capability of osteogenic differentiation. periodontal ligament stem cells sheet with powerful osteogenic differentiation capability be injected or transplanted into the location of bone defects to regenerate the periodontium in periodontal diseases. miRNAs: MicroRNAs; lncRNAs: Long non-coding RNAs; circRNAs: Circular RNAs; PDLSCs: Periodontal ligament stem cells.

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