Deciphering the Epigenetic Code of Stem Cells Derived From Dental Tissues

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Stem cells derived from dental tissues (DSCs) exhibit multipotent regenerative potential in pioneering tissue engineering regimens. The multipotency of DSCs is critically regulated by an intricate range of factors, of which the epigenetic influence is considered vital. To gain a better understanding of how epigenetic alterations are involved in the DSC fate determination, the present review overviews the current knowledge relating to DSC epigenetic modifications, paying special attention to the landscape of epigenetic modifying agents as well as the related signaling pathways in DSC regulation. In addition, insights into the future opportunities of epigenetic targeted therapies mediated by DSCs are discussed to hold promise for the novel therapeutic interventions in future translational medicine.

Keywords: epigenetic regulation, stem cells derived from dental tissues (DSCs), cell differentiation, signaling pathways, regenerative therapies

INTRODUCTION

Dental stem cells (DSCs), a subgroup of mesenchymal stem cells (MSCs), are isolated mainly from dental pulp or periodontium-associated tissues. Current identified DSCs are dental pulp stem cells (DPSCs) (1, 2), stem cells from human exfoliated deciduous teeth (SHED) (3), periodontal ligament stem cells (PDLSCs) (4), dental follicle precursor cells (DFPCs) (5), stem cells from apical papilla (SCAP) (6), gingival-derived MSCs (GMSCs) (7), and alveolar bone marrow-derived MSCs (ABMSCs) (8, 9). In vitro identification demonstrated that DSCs positively expressed MSC-related markers, including CD13, CD29, CD44, CD59, CD73, CD90, CD105, CD146, and STRO-1; while negatively expressed hematopoietic markers, such as CD14, CD31, CD34, and CD45 (10–12). The key pluripotency markers (Oct4, Sox2, and Nanog) that are involved in maintaining the undifferentiated state were also expressed in DSCs with different levels (13). More importantly, a recent study revealed that Oct4 was only expressed in the nuclei of DPSCs, suggesting a better potential of DPSCs to differentiate into multi-lineage tissues (14). DSCs are easily accessible with no ethical controversies. Compared with other MSCs, DSCs presented better proliferative properties and odontogenic differentiation abilities, making them attractive candidates in the future application of tissue regeneration (15, 16).

It is generally believed that MSCs prefer to present regenerative potential corresponding to their origin in ectopic (17). In this regard, DSC-mediated oral and craniofacial regenerative therapies have lead a way in decades. Wang et al. revealed that the PDLSC/PRF/ABMSC sheet composites successfully regenerated periodontal ligament- and bone-like structures in nude mice (18). When
SCAP and PDLSCs were co-transplanted into the alveolar bone of mini-pigs, biological roots were formed (19). Expressing neural and angiogenic markers, such as neurofilament, nestin, vascular endothelial growth factor (VEGF), and angiogenin-1, SCAP presented great neurogenic and angiogenic potential (6, 20, 21). More importantly, clinical trials in recent years have provided more convincing evidence that the implanted DPSCs might induce functional dental pulp (22). Application of DPSCs in deep intrabony defects significantly improved clinical and radiographic parameters of periodontal regeneration 1 year after implantation (23). Nevertheless, despite the current encouragements, to improve the regenerative efficiency of DSCs, the underlying mechanisms that modulate DSC function are needed to be critically explored.

Emerging evidence has indicated that DSC fate is of great importance in directing their functions (11, 24). Potentiated to osteogenesis, adipogenesis, chondrogenesis, neurogenesis, and angiogenesis, DSCs may facilitate multiple tissue regeneration (25). To take full advantage of DSCs, key regulators that affect DSC fate should be critically discussed ahead of their applications. Various factors were reported to be involved in determining cell fate, of which epigenetic regulation has been considered as a vital cue (26). Without gene editing, epigenetic regulation plays a stable and heritable role in DSC function (27, 28).

Epigenetic modifications are generally orchestrated by DNA methylation, histone modifications, RNA modifications, and non-coding RNAs (29). DNA methylation, one of the most well-studied epigenetic modifications, is catalyzed by DNA methyltransferases (DNMTs) (24). In CpG islands, the C5 position of cytosine can be methylated into 5-methylcytosine [5-mC] by DNMTs, such as DNMT1, DNMT3A, and DNMT3B (24). DNA methylation can also be reversed by enzymes of the ten-eleven translocation (TET) family (e.g., TET1, TET2, and TET3) (30).

Histone methyltransferases (HMTs) result in chromatin compaction or relaxation (31). Histone 3 (H3) is the most extensively modified histone. Histone 3 lysine 9 (H3K9) and H3K27 are associated with specific and dynamic repression of transcriptional regulation. By contrast, H3K4, H3K36, and H3K79 facilitate gene transcriptional activation (32). Histone lysine demethylases (KDMs), removing methyl groups from histones, mainly include the lysine-specific demethylase 1 (LSD1) and Jumonji C (JMjC) families (33). Histone acetyltransferases (HATs) result in a more open chromatin structure for transcription factor binding that induces gene transcription (34). However, the effects of HATs can be counteracted by histone deacetylases (HDACs), leading to chromatin compaction and transcriptional repression (35).

Internal mRNA modifications, such as N6-methyladenosine (m6A), N1-methyadenosine (m1A), 5-mC, and 5-hydroxymethylcytosine (5-hmC), are critical in the maintenance of mRNA stability (36). As the most prevalent internal RNA modification, m6A modification is catalyzed by methyltransferases and reversed by demethylases (29). Abnormal regulation that leads to an imbalance in m6A levels might result in incompetent osteogenic differentiation of bone marrow MSCs (BMMSCs) (37) and impaired odontogenic differentiation of human DPSCs (38). Besides, micro-RNAs (miRNAs) (39), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs) (40) are critical components in epigenetic regulation mediated by non-coding RNAs. Dysregulation of these non-coding RNAs was found to have relevance with not only DSC fate but also their potential to regulate tissue regeneration.

To better understand how these epigenetic alterations are involved in DSC fate, the present review critically overviews the epigenetic modifiers in the regulation of DSCs and the relevant key pathways, providing a theoretical basis for the future translation of DSCs in regenerative medicine. Insights into the future perspectives are also provided for the identification of novel epigenetic targeted regenerative therapies mediated by DSCs.

**EPIGENETIC MODULATIONS OF DSCS**

**DNA Methylation**

It has been proved that DNA methylation profiles are associated with the osteogenic potential of DSCs. Using the HumanMethylation450 Beadchip, Ai et al. indicated that DPSCs, DFPCs, and PDLSCs showed highly similar DNA methylation patterns that were related to bone formation. Compared with DPSCs and DFPCs, PDLSCs had higher transcription levels of osteogenic-related factors indicating a better osteogenic capacity in vitro and in vivo (41). Besides the regulation of osteogenic differentiation, DNA methylation is also critical in modulating the odontogenic differentiation of DSCs. TET1 knockdown suppressed the proliferation and odontogenic differentiation of DPSCs, suggesting TET1-dependent DNA demethylation in dental tissue regeneration (42, 43). When DPSCs were treated with lipopolysaccharide, DNMT1 was downregulated, while the transcription of inflammatory cytokines was increased (44). This study provided a new rationale to reveal the molecular mechanisms of the inflamed dental pulp and was of instructive significance in revealing the effect of DNMT1 on the differentiation capacity of DPSCs in inflammatory conditions. It has also been indicated that by inducing DNMT3A/DNMT3B, the odontogenic differentiation of DPSCs was promoted, providing a potential target for DPSC mediated odontogenic regeneration (45). Taken together, DNA methylation is vital to the regulation of osteogenic and odontoblastic differentiation of DSCs, contributing to the regeneration of bone-related defects.

**Histone Methylation**

In addition to DNA methylation, histone modifications are also responsible for DSC fate, of which KDMs are of great importance. KDM3B enhanced the osteo-/odontogenic differentiation potential of SCAP (46). KDM4B removed H3K9me3 by binding with DLX promoters, leading to target gene activation (47). Yang et al. indicated that KDM4B and DLX5 regulated each other via a positive feedback loop in SCAP. DLX5 enhanced the alkaline phosphatase (ALP) activity and the expression of DSPP, DMP1, OPN, and OSX, inducing osteogenic differentiation. *In vivo* studies on nude mice further demonstrated that DLX5 promoted osteo-/dentinogenesis via
upregulating KDM4B in SCAP (48). KDM5A inhibited the odontogenic differentiation potentiality of DPSCs by removing H3K4me3 from DMP1, DSPP, OSX, and OCN promoters (49). KDM6A promoted osteoblastic differentiation of PDLSCs by decreasing H3K27me3 on promoters of ALP, Runx2, and OPN, suggesting a potential intervention for periodontal repair and regeneration (50). KDM6B was dynamically expressed in the bell stage of human tooth germs. KDM6B knockdown induced H3K27me3, which repressed the transcriptional activity of Wnt5A and ultimately suppressed odontogenic differentiation of SCAP (51). In addition, inhibition of KDM6B also resulted in a marked decrease of mineralization-related genes (ALP, BMP2, BMP4, Dlx2, Ocn, and OPN) during odontogenic/osteogenic differentiation of DPSCs (52).

**Histone Acetylation**

HATs and HDACs are also involved in DSC fate decisions. The acetyltransferase GCN5 regulated DKK1 expression by acetylation of H3K9 and H3K14 at its promoter region. Inhibiting the Wnt/β-catenin pathway through DKK1, GCN5 increased the osteogenic differentiation of PDLSCs. *In vivo* injection of aspirin that targeted GCN5 would rescue periodontitis of rats by promoting osteogenic differentiation of PDLSCs (53). By suppressing HDAC6, miR-22 would promote osteogenic differentiation of PDLSCs (54). Similarly, HDAC9 and miR-17 formed a loop of mutual inhibition during osteogenic differentiation of PDLSCs (55). Zhang et al. also revealed that PCAF knockdown resulted in critical repression of the osteogenic differentiation of BMMSCs by reducing H3K9 acetylation of BMP signaling (56), suggesting different osteogenic regulation of DSCs and other MSCs. Tao et al. indicated that the coordinated expression of p300 and HDAC3 was critical for odontoblast differentiation of SCAP providing new hints for restorative dentistry (57). It was also reported that the expression levels of SIRT7 and HDAC6 were decreased in stem cell aging models, whereas SIRT7 overexpression rescued the miR-152-3p-induced senescence phenotype of DPSCs (58). Li et al. further suggested that HDAC6 played an important role in PDLSC aging (59). The aforementioned literature provided candidate targets to improve the functional and therapeutic potential of DSCs.

**Non-coding RNAs**

It has been demonstrated that several miRNAs participated in the regulation of osteogenic differentiation in DSCs, such as miR-23a (60), miR-24-3p (61), miR-152-3p (62), miR-17 (63), and miR-22 (54). miR-23a acted as a negative regulator during osteogenesis of PDLSCs from patients with periodontitis by inhibiting the phosphorylation of Smad1/5/9, key transcription factors of the BMP pathway (60). In addition, miR-24-3p and miR-152-3p suppressed the osteogenic differentiation of PDLSCs (61, 62). On the contrary, miR-22 and miR-17 promoted the osteogenic differentiation of PDLSCs (54, 63). The above findings demonstrated miRNAs’ different effects on periodontal and alveolar bone regeneration.

The expression profiles of circRNAs and lncRNAs have revealed an extremely complex regulatory network (64). Specific circRNAs are involved in the osteoblastic differentiation of DSCs (65, 66). For instance, circRNA CDR1as inhibited miR-7 and alleviated the negative regulatory effect of miR-7 on osteoblastic differentiation (67). CircRNA124534 promoted the osteogenic differentiation of DPSCs by inhibiting miR-496, suggesting the functions and underlying mechanisms of circRNAs in the osteogenic differentiation (68). Anti-differentiation ncRNA (ANCR), a subclass of lncRNAs, can maintain the undifferentiated stem cell state (69, 70). Furthermore, lncRNA–miRNA–mRNA networks are also critical in osteogenesis. For instance, overexpression of ANCR downregulated miR-758, inhibiting the osteogenic differentiation of PDLSCs by reducing ALP, RUNX2, and OSX (71). The osteogenesis impairment-related lncRNA (lncRNA-POIR) competitively inhibited miR-182 in PDLSCs, leading to de-repression of its target gene FoxO1. FoxO1 increased bone formation of PDLSCs by competing for β-catenin with TCF-4 (a transcriptional cofactor) and inhibiting the canonical Wnt pathway (72). LncRNA MEG3 inhibited osteogenic differentiation of DPSCs via miR-543/RUNX2 regulatory network, which might contribute to the precise regulation of DPSC differentiation (73).

**KEY PATHWAYS REGULATED BY EPIGENETIC MECHANISMS**

**Wnt Signaling Pathway**

Wnt ligands bind to the Wnt receptors on the cell surfaces or induce β-catenin release to bind TCF in the nucleus to regulate downstream signaling (74). It has been proved that the Wnt signaling pathway is involved in the regulation of DSC stemness (75) and multipotency (76, 77). Through mass spectroscopy, Uribe-Etxebarria et al. revealed that activation of Wnt signaling induced epigenetic remodeling in DPSCs, mainly by inducing DNA demethylation, histone acetylation, and histone methylation (78). Moreover, SFRP1 (a Wnt antagonist) inhibited the mineralization of PDLSCs through H3K4me3-mediated regulation, maintaining the nonmineralized state of PDLSCs (79). EZH2 depletion activated the Wnt/β-catenin pathway led to the promotion of odontogenic differentiation in DPSCs (80).

**Notch Signaling Pathway**

Notch receptors and ligands are highly conserved type I transmembrane proteins. Once activated, Notch would release the Notch intracellular domain (NICD), allowing its consequent translocation to the nucleus and activating the expression of Notch targets (81). When nuclear NICD is absent, a repressor complex CSL/RBP-Jk will form in the nucleus by recruiting ubiquitous corepressors and HATs, repressing Notch targets (82). Activation of Notch enhanced the stemness and potency of DPSCs, providing a novel approach in DPSC related therapeutics (75). Notch signaling regulated by non-coding RNAs is also critical in DSC fate decisions. miR-146a-5p/Notch signaling played an important role in supporting odontogenic and osteogenic differentiation of STRO-1+ DPSCs, indicating that the application of DSCs may be facilitated by
epigenetic modifications in regenerative medicine and tissue engineering (83). miR-34a interacted with Notch signaling and promoted both odontogenic and osteogenic differentiation of SCAP (84).

**BMP Signaling Pathway**

Among the variety of signaling and transcription factors involved in osteogenesis, BMP/Smads signaling is considered to play a central role in controlling osteogenic differentiation. Exploration of all known factors affecting osteogenic differentiation and their interactions is of major importance in the field of DSC-mediated regenerative medicine. In the canonical BMP pathway, activated BMP phosphorylates the transcription factors Smad1/5/8. The phosphorylated Smads (pSmad1/5/8) form a heterodimeric complex with Smad4, which is then translocated into the nucleus to activate the expression of downstream osteogenic genes (85). At the epigenetic level, circRNA CDR1as activated pSmad1/5/8 by inhibiting the miR-7 expression and further promoted the osteogenesis of PDLSCs (67). Downregulation of miR-24-3p or miR-21 promoted osteogenic differentiation of PDLSCs by targeting Smad5 (61, 86). Under long-term BMP stimulations, DFPCs significantly increased ALP activity and mineralization (87).

**AKT/mTOR Signaling Pathway**

Phosphatidylinositol 3 kinases (PI3Ks), serine/threonine kinase AKT (also known as protein kinase B), and mTOR (also known as mechanistic TOR) are considered as core components of the PI3K/AKT/mTOR signaling cascade, participating in the regulation of DSC proliferation and differentiation. Under physiological conditions, the receptor tyrosine kinase (RTK) is activated by growth factors or cytokines and then phosphorylates the tyrosine residue to recruit PI3Ks (88, 89). It has been confirmed that the expression of vascular endothelial growth factor (VEGF) is repressed by HDACs, especially HDAC4. The VEGF/AKT/mTOR pathway promoted odontoblast differentiation of DPSCs after treatment with LMK235, a specific inhibitor of HDAC4 and HDAC5 (90). Additionally, the phosphatase and tensin homolog (PTEN) exhibited higher enrichment of DNA methylation and the repressive H3K9me2 in the promoter region of BMMSCs compared to DPSCs. PTEN suppression activated the AKT pathway to promote...
| Epigenetic modifiers | Regulators | Effects | In differentiation and regeneration | References |
|----------------------|------------|---------|-----------------------------------|------------|
| DNA methylation      | DNMT3A     | Methylation of Nanog promoter     | Promoted odontogenic differentiation of DPSCs | (45)       |
| DNA methylation      | DNMT3B     | /                                  | Promoted odontogenic differentiation of DPSCs | (42)       |
| DNA demethylation    | TET1       | /                                  | Promoted odontogenic differentiation of DPSCs | (42)       |
| Histone methylation  | EZH2       | Trimethylation of H3K27            | Inhibited odontoblastic differentiation of DPSCs | (90)       |
| Histone demethylation| KDM3B      | /                                  | Promoted osteogenic/odontogenic differentiation of SCAP | (46)       |
|                      | KDM4B      | Demethylation of the H3K9me3 from DLX5 promoter | Promoted osteogenic/odontogenic differentiation of SCAP | (49)       |
|                      | KDM5A      | Demethylation of the H3K4me3 from DMP1, DSPP, OSX, and OCN promoters | Inhibited odontoblastic differentiation of DPSCs | (49)       |
|                      | KDM6A      | Demethylation of the H3K27me3 from ALP, Runx2, and OPN promoters | Promoted osteoelastic differentiation of PDLSCs | (50)       |
|                      | KDM6B      | Demethylation of the H3K27me3 from the promoter | Promoted odontogenic differentiation of SCAP | (51)       |
| Histone acetylation  | GCN5       | Acetylation of H3K9 and H3K14 on DKK1 promoter | Promoted odontogenic differentiation of PDLSCs | (53)       |
|                      | PCAF       | Acetylation of H3K9 on the promoter | Promoted osteogenic differentiation of BMSCs | (56)       |
|                      | P300       | Acetylation of histone             | Promoted odontoblast differentiation of SCAP | (57)       |
| Histone deacetylation| HDAC3      | Deacetylation of histone           | Inhibited odontoblast differentiation of SCAP | (57)       |
|                      | HDAC6      | Deacetylation of Runx2 and OPN promoters | Inhibited osteogenic differentiation of PDLSCs. | (54)       |
|                      | HDAC9      | Deacetylation of miR-17-92a promoter | Protected stemness of PDLSCs. | (59)       |
| Non-coding RNAs      | miR-720    | Inducing DNMT3A or DNMT3B          | Promoted osteogenic differentiation of DPSCs | (45)       |
|                      | miR-153-3p | Downregulation of KDM6A to increase the H3K27me3 levels at the Runx2, OPN, and ALP promoters | Inhibited osteogenic differentiation of PDLSCs | (50)       |
|                      | miR-22     | /                                  | Promoted osteogenic differentiation of PDLSCs | (54)       |
|                      | miR-17     | /                                  | (63)       |
|                      | miR-23a    | /                                  | Inhibited osteogenic differentiation of PDLSCs | (60)       |
|                      | miR-24-3p  | /                                  | (61)       |
|                      | miR-152-3p | /                                  | (62)       |
|                      | circRNA CDR1as | /miR-7/GDF5 network          | Promoted osteogenic differentiation of PDLSCs | (67)       |
|                      | circRNA124534 | circRNA124534/miR-496        | Promoted osteogenic differentiation of DPSCs | (68)       |
|                      | IncRNA ANCR | /miR-758/mRNA network            | Maintained the undifferentiated state | (69)       |
|                      | IncRNA-POIR | IncRNA-POIR/miR-182/FoxO1 network | Inhibited osteogenic differentiation of PDLSCs | (71)       |
|                      | IncRNA MEG3 | IncRNA MEG3/miR-543/RUNX2 network | Promoted osteogenic differentiation of BMSCs | (72)       |
|                      | METTL3     | mRNA methylation (m6A)            | Promoted osteogenic differentiation of PDLSCs | (73)       |

**Comments:** GCN5, general control non-repressed protein 5; PCAF, p300/CBP-associated factor; p27Ki61, cyclin-dependent kinase inhibitor p27; GDF5, growth differentiation factor 5; IncRNA MEG3, IncRNA maternally expressed gene 3; METTL3, methyltransferase-like 3.
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adipogenesis and inhibit osteogenesis of DPSCs, suggesting a differed differentiation potential of DPSCs and BMMSCs (91).

**MAPK Signaling Pathway**

The MAPK pathways consist of extracellular signal-related kinases (ERK1/2), C-Jun N-terminal kinase (JNK), p38 MAPK, and ERK5 (92, 93). Decreased phosphorylation of MAPK mediated by circRNA CDR1as knockdown would lead to the inhibited osteogenic differentiation of PDLSCs (67). While lncRNA GAS5 enhanced the osteogenic differentiation of PDLSCs via GDF5 and p38/JNK signaling pathway (94). These findings provided the theoretical basis for understanding the osteogenesis mechanism in PDLSCs.

**NF-κB Signaling Pathway**

NF-κB is a transcription factor that is ubiquitous in the cytoplasm. It has pivotal roles in the regulation of inflammatory response and osteogenic differentiation of DSCs (95–97). NF-κB stays in an inactive state when it binds to the inhibitory protein IκB. Once activated by the activators, NF-κB dissociates from IκB and translocates into the nucleus to bind with the target genes and enhance their expression (98). Martins et al. revealed that NF-κB was involved in the epigenetic regulation of oral epithelial cells, suggesting a potential mechanism of their roles in DSCs (99). Activating NF-κB signaling by miR-132, the osteogenic ability of PDLSCs was inhibited, suggesting a potential role of NF-κB in future periodontal related therapy (95).

**FUTURE PERSPECTIVES**

Knowing the promising roles of epigenetic regulation in DSC fate (Figure 1, Table 1), new insights into future opportunities would provide promise for the identification of novel targets for DSC-mediated regenerative therapies. DSCs may partially lose their potential during long-term cell culture. In this context, how to ensure stemness of DSCs in normal culture conditions is critical to address. Diomede et al. revealed that 5-Aza (a DNMT inhibitor) induced the direct conversion of GMSCs into embryonic lineages. When treated with 5-Aza for 48 h, GMSCs were organized as round 3D structures and expressed markers related to three germ layers (100). Above findings suggested a possible application of epigenetic regulation in future translational medicine. It has further been demonstrated that 5-Aza treatment is responsible for GMSC dedifferentiation into embryonic lineages other than neural precursor cells after prolonged expansion (101, 102), suggesting the potential role of 5-Aza in DSC stemness maintaining for future application.

The key to regenerative medicine lies also in the differentiation of stem cells into specific tissues. Inhibition of DNMTs with RG108 increased the level of transcription factor Klf4, enhancing the efficiency of odontoblastic differentiation of DSCs, thus presenting great prospects in future application (103). DPSCs exhibited higher osteogenic as well as lower adipogenic potential compared with BMMSCs. As revealed by Shen et al. the PTEN promoter of BMMSCs presented higher levels of DNA methylation mediated by increased DNMT3B and enrichment of the repressive H3K9me2 (91). Altering epigenetics of PTEN that is responsible for inhibiting adipogenesis and

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**FIGURE 2** | Key pathways involved in the epigenetic regulation of DSC fate. The odontogenic and osteogenic differentiation of DSCs is mediated by the interaction of critical signal pathways such as Wnt, Notch, BMP, AKT/mTOR, MAPK, and NF-κB.
TABLE 2 | Key pathways regulated by epigenetic mechanisms.

| Pathways                  | Regulators        | Effects                                                                 | In differentiation and regeneration | References |
|---------------------------|-------------------|-------------------------------------------------------------------------|--------------------------------------|------------|
| WNT signaling pathway     | WNT-3a            | Increasement of DNA hypomethylation, histone acetylation, and histone trimethylation | Reversed osteogenic cell differentiation of DPSCs | (78)       |
|                           | SFRP1             | Inhibition H3K4me3 on RUNX2 and SP7 promoters                            | Inhibited mineralization of PDLSCs | (79)       |
|                           | EZH2              | Increasement of H3K27me3 on the β-catenin promoter                       | Inhibited odontogenic differentiation in DPSCs | (90)       |
| Notch signaling pathway   | miR-34a           | Crosstalk with Notch pathway                                             | Promoted odontogenic and osteogenic differentiation of SCAP | (84)       |
|                           | miR-146a-5p       | Partially suppression of Notch pathway                                   | Promoted odontogenic and osteogenic differentiation of DPSCs | (83)       |
| BMP signaling pathway     | circRNA CDR1as    | Activation of the pSmad1/5/8 by inhibiting miR-7 expression              | Promoted osteogenic differentiation of PDLSCs | (67)       |
|                           | miR-23a           | Inhibition of protein levels and phosphorylation of Smad1/5/9            | Inhibited osteogenic differentiation of PDLSCs | (60)       |
|                           | miR-24-3p         | Regulating Smad5                                                         | Inhibited osteogenic differentiation of PDLSCs | (61)       |
|                           | miR-21            |                                                                         |                                      | (86)       |
| AKT/mTOR signaling pathway| HDAC4 and          | Activation of VEGF expression to activate AKT/mTOR pathway              | Promoted odontoblast differentiation of DPSCs | (90)       |
|                           | HDAC5 inhibitor   |                                                                         |                                      |            |
|                           | (LMK 235)         |                                                                         |                                      |            |
|                           | PTEN              | Lower enrichment of DNA methylation and the repressive H3K9me2 in the promoter region | Promoted osteogenesis of DPSCs | (91)       |
| MAPK signaling pathway    | circRNA CDR1as    | Inhibition of p38 MAPK phosphorylation                                   | Inhibited osteogenic differentiation of PDLSCs | (67)       |
|                           | knockdown or      |                                                                         |                                      |            |
|                           | miR-7 overexpression |                                                         |                                      |            |
|                           | IncRNA GASS       | Activation of p38/JNK pathways                                           | Promoted osteogenic differentiation of PDLSCs | (94)       |
| NF-κB signaling pathway   | miR-132           | Activation of NF-κB pathway                                              | Inhibited osteogenic differentiation of PDLSCs | (95)       |

SFRP1, secreted frizzled related protein 1; EZH2, enhancer of zeste homolog 2.

promoting osteogenesis (104), we may control the lineage commitment of DSCs and facilitate their future translation. In this regard, histone deacetylase inhibitors (HDACi) have been critically studied. As a potent HDACi, trichostatin A (TSA) promoted odontoblast differentiation of DPSCs at certain concentrations (105). While at higher concentrations, TSA significantly accelerated mineralization of DPSCs by promoting DMP1 and DSPP expression (106). In rat models of periodontitis, TSA treatment resulted in increased alveolar bone volume and decreased inflammatory infiltration levels, suggesting HDACi as potential candidates for the treatment of periodontal disease (107).

CONCLUSIONS

Epigenetic modifications participate in the determination of DSC fate by regulating various critical signal pathways (Figure 2, Table 2). Summarizing the current state of knowledge regarding epigenetic cues would substantially promote the clinical research of DSCs to a new level. Moreover, deciphering the epigenetic code of DSCs would provide potential targets for DSC-mediated regenerative therapies, facilitating DSC applications from bench to bedside.

AUTHOR CONTRIBUTIONS

AL and YL contributed to the conception of the study. YL, XZ, and MS wrote the manuscript. DP and AL revised the manuscript. All authors approved the final manuscript.

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