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REVIEW

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Advances in periodontal stem cells and the regulating niche: From in vitro to in vivo

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Summary

Periodontium possesses stem cell populations for its self-maintenance and regeneration, and has been proved to be an optimal stem cell source for tissue engineering. In vitro studies have shown that stem cells can be isolated from periodontal ligament, alveolar bone marrow and gingiva. In recent years, more studies have focused on identification of periodontal stem cells in vivo. Multiple genetic markers, including Gli1, Prx1, Axin2, αSMA, and LepR, were identified with the lineage tracing approaches. Characteristics, functions, and regulatory mechanisms of specific populations expressing one of these markers have been investigated. In vivo studies also revealed that periodontal stem cells can be regulafrted by different niche and mechanisms including intercellular interactions, ECM and multiple secreted factors. In this review, we summarized the current knowledge of in vitro characteristics and in vivo markers of periodontal stem cells, and discussed the specific regulating niche.

KEYWORDS
alveolar bone, craniofacial biology, Gli1, niche, periodontal ligament, stem cell

1 | INTRODUCTION

The periodontium is a complex structure that consists of the gingival tissue, periodontal ligament (PDL), alveolar bone and the cementum of tooth. It provides protection and support to teeth and serves as transmitter of occlusal force. Periodontal diseases have been one of the most common diseases among people (Seo, Song, Um, & Lee, 2015). In addition to local tissue destruction and tooth loss, periodontal diseases are also risk factors of many systematic diseases including Alzheimer disease, cardiac diseases, and so forth (Parra-Torres et al., 2021; Zhou, Dong, Zha, & Liao, 2021; Zoellner, Chapple, & Hunter, 2002). Current efforts on regenerating periodontal tissue achieved only limited success due to the poor understanding of periodontal stem cells (Liang, Luan, & Liu, 2020).

Periodontium possesses stem cell populations for its self-maintenance and regeneration. Multipotent postnatal stem cells have been isolated and identified from gingiva, PDL, alveolar bone and dental follicle (Matsubara et al., 2005; Morsczeck et al., 2005; Seo et al., 2004; Zhang et al., 2009). Although complete anatomical and functional reconstruction of the complex periodontium remains challenging so far, tissue regeneration using stem cells has shown its potential in treatment (Li, Ouchi, Cao, Zhao, & Men, 2021). Thorough understanding of the identity and regulating mechanisms of these cells, especially their characteristics in vivo, is critical for their further clinical application.

In this review, we first discussed the isolation and in vitro characteristics of stem cells from periodontal tissues. We then summarized the current progress on in vivo studies on periodontal stem cells. Various in vivo stem cell markers and regulating niche were discussed. Finally, we provided our perspectives on future research directions.

2 | ISOLATION AND IN VITRO CHARACTERISTICS OF PERIODONTAL STEM CELLS

Mesenchymal stem cells (MSCs) were first identified in the 1960s by Friedenstein et al. as a heterogeneous colony-forming fibroblast-like cell

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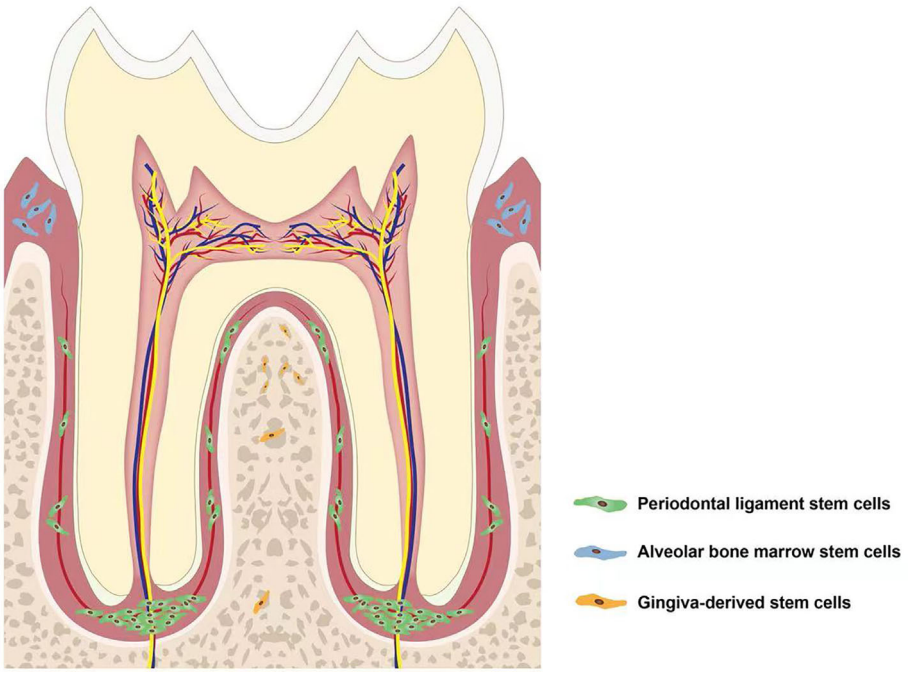

FIGURE 1 Diagram showing the anatomical structure of the tooth and location of periodontal stem cells, alveolar bone marrow stem cells and gingiva-derived stem cells

population (Friedenstein, Petrakova, Kurolesova, & Frolova, 1968) (Caplan, 1991). Historically, MSCs were identified based on their in vitro characteristics: (a) expression of surface markers (CD90+, CD73+, CD105+, CD44+, CD34−, CD45−, CD14−); (b) ability to expand and give rise to fibroblastic colonies (CFU-F) when cultured in vitro; (c) abilities to differentiate into various lineages. (Horwitz et al., 2005; Kurenkova, Medvedeva, Newton, & Chagin, 2020; Zhao & Chai, 2015).

To date, various reports have described the presence of MSCs in bone marrow, umbilical cord blood, peripheral blood, adipose tissue, placenta, lung, teeth, and so forth (Fukuchi et al., 2004; Gang et al., 2004; Tondreau et al., 2005; Tuli et al., 2003; Wexler et al., 2003; Zhao et al., 2014; Zheng et al., 2009; Zuk et al., 2001). Periodontium is considered a mesenchymal tissue and stem cells have been isolated from gingiva, PDL, and alveolar bone (Gang et al., 2004; Matsubara et al., 2005; Zhang et al., 2009) (Figure 1). Extensive studies have been performed on them, which showed great potential in tissue regeneration.

2.1 | Stem cells from the PDL

PDL stem cells (PDLSCs) were first isolated by Seo et al. from extracted human third molar teeth (B.-M. Seo et al., 2004). Multiple approaches have been designed for isolation and culture of PDLSCs. However, there's still controversy on whether enzyme digestion method or outgrowth technique is better for PDLSCs isolation (Rad et al., 2022; Zhu & Liang, 2015). PDLSCs share similar characteristic with MSCs obtained from many other tissues. They possess tri-lineage differentiation capacity in vitro, express surface markers including CD 73, CD90 and CD105, and are negative for CD45, CD34, CD14, CD79a, and HLA class II (Zhu & Liang, 2015). PDLSCs reside in perivascular region and exhibit pericyte characteristics. Besides, they show low immunogenicity and immunosuppressive effects on T and B cells. Lee group showed that compared to bone marrow MSCs, PDLSCs from supernumerary teeth presented better colony-forming efficiency (Song et al., 2012). Compared with dental pulp stem cells, PDLSCs show relatively low-proliferation potential and telomerase activity (Hakki et al., 2015). PDLSCs have been shown to possess the potential in periodontal tissue engineering, and in treatment of inflammatory imbalance-related disease including colitis and Crohn's disease (Földes et al., 2016).

2.2 | Stem cells from the alveolar bone

Alveolar bones have bone marrow space in the body part. Mason et al. reported isolation of alveolar bone marrow-derived MSCs (aBMSCs) (Mason, Tarle, Osibin, Kinfu, & Kaigler, 2014). The aBMSCs were aspirated or scraped from the marrow space. Cultured aBSMCs expressed surface markers including CD73, CD90, CD105, and Stro-1, and are negative for CD11b, CD19, and CD45. They exhibited multipotency, and could induce ectopic bone formation in a transplantation model. Further study showed that osteogenic differentiation ability of aBMSCs were higher than that of long-bone marrow MSCs. After being transplanted in a rabbit calvaria defect, aBMSC sheet showed strong bone regeneration capability (Y. Liu et al., 2020). This suggests that aBMSCs can be a potential stem cell resource for facial bone regeneration, especially for craniofacial defect repair.

2.3 | MSCs from gingiva

MSCs from gingiva are easily accessible in the oral cavity, without the need of tooth extraction or osteotomy preparation. They can be isolated from normal and healthy gingiva (Jiang et al., 2015). Gingiva-

TABLE 1 List of in vivo markers for identifying periodontal stem cells

Candidate markers	References	Distribution of cells expressing this marker	Contributions in periodontal tissues	Relationship with vasculature	In vitro characteristics
Gli1	Men et al., 2020; Hosoya et al., 2020; Yi, Stenberg, Luo, Feng, & Zhao, 2021	PDL, pulp, alveolar bone marrow	Gli1+ cells contribute to adult periodontium tissue turnover, support injured periodontium regeneration, support alveolar bone healing aftertooth extraction and dental implant osseointegration	Surrounding the NVB of the PDL	CD44+ CD146+ CD73+ CD31− CD34−.Osteogenic and chondrogenic differentiation, little adipogenic differentiation
Prx1	Bassir et al., 2019; Gong et al., 2022	PDL of both molars and incisors	Post-natal PRX1+ cells contribute to post-natal periodontal development, periodontium regeneration upon periodontal fenestration defects	Blood vessels were often accompanied by PRX1+cells in molar PDL. Prx1+cells are involved in the angiogenesis during PDL reconstruction	Highly expresses CD44, Pdgfra, Smo, Col2A1, Axin2, Wif1, Dll4, Jagged-1, Notch1, Notch 2, Itgb1, Foxo3, Pth1r
Axin2	Yuan et al., 2018; K. Wang et al., 2022; Xie, Xu, Zhao, Wang, & Feng, 2021	PDL, cementum surface	Limited contribution to periodontal tissue even after 90-day chase. Axin2+ cells contribute to new bone formation after tooth extraction, contribute to cementum growth	Not mentioned	Not mentioned
SMA	Kalajzic et al., 2008; Grcevic et al., 2012; Roguljic et al., 2013	Dental follicle, PDL and pulp (enriched in the apical region of the root)	SMA+ cells could differentiate into osteoblasts, cementoblasts, and cementocytes within the periodontium during normal growth and remodeling	The presence of SMA+ cells associated with microvasculature	Sca1+ (40%), CD90+ (25%), CD117−, CD11b−. Osteogenic differentiation ability. No odontoblastic differentiation ability
LepR	Zhang et al., 2020	PDL, alveolar bone marrow, trabecular bone of the root furcation area	LepR+ cells are largely quiescent and contribute partially to bone-lining osteoblastic cells and osteocytes. They are activated upon tooth extraction and contribute to alveolar socket healing	Not mentioned	Not mentioned

derived MSCs (GMSCs) contain both neural-derived MSCs (90%) and mesoderm-derived MSCs (10%) (Xu et al., 2013). Similar with other MSCs, they express typical mesenchymal surface markers, trilineage differentiation capability, and immunomodulatory properties. Based on our current knowledge, GMSCs display higher growth properties than BMSCs and PDLSCs (Moshaverinia et al., 2012), and higher proliferative rates than dental pulp stem cells (DPSCs) (Xing et al., 2019). They show high-regenerative potential after wounding, making them attractive source of MSCs in tissue engineering research.

3 | IN VIVO IDENTIFICATION OF PERIODONTAL STEM CELLS

Genetic lineage tracing is now the "golden standard" for identifying stem cells research. With the site-specific recombinase system (e.g., cre/loxP system), researchers can label specific stem cell populations and trace their fate for a long duration. Several molecules have been proposed as potential stem cell markers within the periodontium (Table 1, Figure 2).

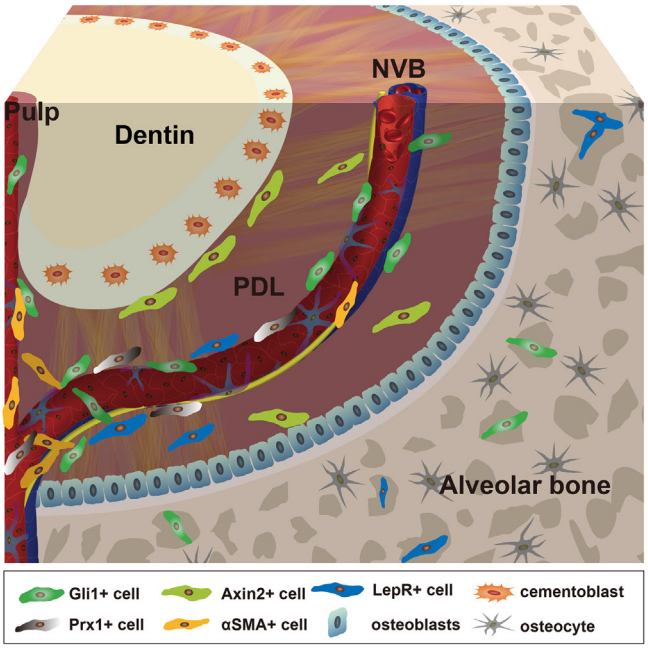

FIGURE 2 Diagram showing the periodontal stem cell niche, and the distribution of stem cells expressing specific markers within the periodontium. NVB, neurovascular bundle

3.1 | Gli1+ cells

The Hedgehog signaling pathway plays a critical role in development. Gli1, Gli2, and Gli3, are major mediators for canonical Hedgehog signaling transmission (Jing et al., 2021). Lineage tracing studies revealed that Gli1+ cells form an extensive perivascular network in bone-marrow, muscle, heart, lung, liver and kidney, and comprise a group of MSCs or progenitor cells (Kramann et al., 2015; Schneider et al., 2017; Shi et al., 2017; Zhao et al., 2014, 2015). These Gli + perivascular cells possess multi-lineage differentiation capacity in vitro, and participate in organ fibrosis after injury. They have been identified as stem cells for mouse incisor mesenchyme and calvaria bone (Zhao et al., 2014, 2015).

Men et al. identified Gli1+ cells in adult mouse molar PDL as multi-potential stem cells (Men et al., 2020). As in many other organs, these cells are surrounding the neurovascular bundle and are more enriched in the apical region, where blood vessels and nerves are more abundant. Gli1+ cells within the molar PDL could give rise to newly formed PDL, alveolar bone and cementum, and are regulated by alveolar bone osteocytes through sclerostin, a Wnt inhibitor. Akihiro Hosoya et al. also confirmed the stem cell properties of Gli1+ cells within the PDL in 2020, and they revealed that Gli1+ cells are involved in alveolar bone regeneration. In a tooth transplantation model, they showed that the osteoblasts and osteocytes in newly formed alveolar bone were derived from Gli1+ cells (Hosoya et al., 2020).

Consistent with Men et al., Yi et al. reported that Gli1+ cells locate not only within the PDL, but also in the alveolar bone marrow (Yi et al., 2021). These Gli1+ cells proliferated rapidly after tooth extraction and contributed to extraction socket healing and titanium implant osseointegration. As those in PDL, Gli1+ cells within the alveolar bone marrow were regulated by canonical Wnt signaling, as conditional knockout of β-catenin led to compromised bone healing around implants.

3.2 | Prx1+ cells

The paired-related homeobox gene-1 (Prx1) is a transcription factor closely related to limb development (Logan et al., 2002). In craniofacial bones, Prx1+ cells made significant contribution to craniofacial development in early embryonic stage (Martin, Bradley, & Olson, 1995). Recent studies revealed that Prx1+ cells were presented in the PDL of mouse molars and incisors, and were related to PDL development, turnover and regeneration (Bassir et al., 2019; Gong et al., 2022). DTA-mediated ablation of Prx1+ cells in 3-day-old mouse pups resulted in a significant enlargement of the PDL space after 18 days. Post-natal ablation of Prx1+ cells led to impaired regeneration in periodontal non-critical size defects. All defects by the incisors failed to heal in the test group. Defects by the molar tooth healed partially, accompanied by irregular and excessive bone formation (Bassir et al., 2019). The differentiation of Prx1+ cells was shown to be mediated by parathyroid hormone (PTH) signal, as conditional knockout of PTH1R exhibited significantly reduced alveolar bone formation, irregular PDL and reduced Periostin expression in mutant incisors (Cui et al., 2020).

3.3 | Axin2+ cells

Wnt signaling pathway is essential for stem cell proliferation and differentiation in various organs. Axin2, a critical component for canonical Wnt signaling pathway, has been shown to be expressed in stem cells for multiple tissues (Yuan et al., 2018). Axin2+ cells and their progeny were shown to be a quiescent population residing in the PDL proper. They migrated from the PDL remnants, populated tooth extraction site and differentiated into osteoblasts to support extraction socket healing. Wnt3A protein applied in the extraction socket increased the number of Wnt-responsive cells and facilitated bone formation (Yuan et al., 2018). Axin2+ cells in the periodontal tissue were sensitive to orthodontic tension force and were involved with PDL expansion and alveolar bone formation (K. Wang et al., 2022). Furthermore, Axin2+ cells were shown to support postnatal cementogenesis (Xie et al., 2021).

3.4 | αSMA+ cells

Smooth muscle alpha-actin (αSMA) is generally considered as a marker for smooth muscle cells and myofibroblasts (Frangogiannis et al., 2000). Apart from forming new myofibroblasts, αSMA+ cells also showed their potential in generating new osteoblasts and adipocytes

(Kalajzic et al., 2008). Lineage tracing studies based on *αSMA-Cre^{ERT2}*; *Ai9* model showed that αSMA+ cells might be a group of periodontal progenitor cells, and could differentiate into osteoblast and PDL fibroblasts. Upon injury, αSMA+ cells migrated from gingival tissues and PDL to give rise to new mesenchymal tissues within the periodontium (Grcevic et al., 2012; Roguljic et al., 2013).

3.5 | LepR+ cells

Leptin receptor (LepR)-expressing bone marrow stromal cells have been validated as major source of osteoprogenitor cells in adult mice. They can give rise to most bone and adipocytes, and thus are responsible for adult long bone homeostasis maintaining as well as fracture healing (Shu et al., 2021; B. O. Zhou, Yue, Murphy, Peyer, & Morrison, 2014). In jaw bone, Zhang et al. used a tooth extraction model to verify its role in alveolar bone healing (D. Zhang et al., 2020). By using *LepR-Cre; tdTomato*; *Col2.3-GFP* mice, LepR+ cells residing in alveolar bone and PDL were shown to be quiescent at physiological condition. After tooth extraction, these cells were activated into proliferation and differentiation. Ablation of LepR+ cells compromised the alveolar bone healing, suggesting the essential roles of LepR+ stem cells in alveolar bone injury repair.

4 | COMPONENTS OF PERIODONTAL STEM CELL NICHE

Stem cells rely on local micro-environment, which is called niche, for their maintenance and regulation (Schofield, 1978). Nowadays, stem cell niches have been identified to harbor hematopoietic, neural, intestinal, muscle, MSCs, and so forth (Kurenkova et al., 2020). Normally, a stem cell niche includes not only the specific architecture that cells reside in, but also their neighboring cells, extracellular matrix, secreted factors, as well as oxygen tension, shear stress, and so forth. Insights into stem cell niches would deepen the understanding of stem cell behavior, and provide insight for tissue engineering to regulate stem cell functions.

Many stem cells were located near vasculature (Putnam, 2014). Likewise, periodontal stem cells are prone to reside around vasculature. Men et al. revealed that periodontal Gli1+ MSCs are exclusively surrounding the vasculature using 3D imaging following tissue clearing. They are enriched in the apical region where the abundant pulp and PDL neurovascular structures converge (Men et al., 2020). Gli1+ stem cells within the alveolar bone marrow also proliferate along the vasculature after tooth extraction. They proliferated along the regenerating blood vessels upon injury, and then migrated out of the perivasculature niche to form new bone (Yi et al., 2021). Among various blood vessels, H-type blood vessels was shown to be essential for coupling angiogenesis with bone remodeling in alveolar bone. H-type vessels were detected at the site of extraction socket, along with the local enrichment of Runx2+ osteoprogenitors (Yan et al., 2020).

Endothelial cells may interact with periodontal stem cells. Single cell RNA sequencing showed that periodontal stem cells express NOTCH3, and that the adjacent endothelial cells express all five NOTCH ligands, JAG1, JAG2, DLL1, DLL3, and DLL4, acting as niche-derived modulator of periodontal stem cells (Pagella, de Vargas Roditi, Stadlinger, Moor, & Mitsiadis, 2021). Inhibition of Notch in vitro reduced the periodontal H type endothelium and down-regulated coupled osteogenesis.

Extracellular matrix (ECM) provides structural and biochemical support for stem cell migration, morphogenesis, proliferation, differentiation and apoptosis (Ahmed & ffrench-Constant, 2016). Stem cell adhesion to ECM is mediated by several classes of receptors. Integrins are a large ECM receptors family composed of an alpha (α) and a beta (β) subunit. In vertebrates, there are 18 kinds of α-subunits and 8 kinds of β-subunits, which can assemble into 24 different heterodimers (Barczyk, Carracedo, & Gullberg, 2010). In cultured human PDL cells, expression of integrin α3 and αV was upregulated upon osteogenic differentiation (Lee et al., 2020). Furthermore, over-expression of Integrin αV enhanced the proliferation, migration and osteogenic capacity of PDLSCs (H. Wang et al., 2018). According to Kawamura et al., anti-integrin α5 antibodies inhibited the migration of PDLCs, while anti-integrin α3 significantly enhanced their migration, suggesting their distinct roles in regulating cell behavior (Kawamura et al., 2019).

Secreted signaling factors are critical components of stem cell niche and have shown to be critical for regulating stem cells. Wnt signaling pathway has been shown to be essential for periodontal tissue turnover and regeneration. Periodontal stem cells could be regulated by sclerostin secreted by alveolar bone osteocytes (Men et al., 2020). Both in vitro and in vivo studies have shown that canonical Wnt signaling could promote osteogenic differentiation of PDLSCs (Bao, Yang, Xia, Sun, & Chen, 2021; C. Wang et al., 2021). Constitutive activation of β-catenin in periodontal stem cells might cause cementum hyperplasia (Xie et al., 2019, 2021). Moreover, Wnt5a, a prototypical β-catenin-independent Wnt family member also serves as a regulator of periodontal homeostasis. During development, its overexpression mediates moderated osteogenesis of dental follicle cells (Xiang et al., 2014). In adult periodontal stem cells, it suppresses their mineralization but enhance their collagen production, thus regulating PDL remodeling and preventing non-physiological mineralization (Wei, Liu, Guo, & Wu, 2021). TGF-β1 is highly expressed in the PDL, while its expression in alveolar bone and cementum is relatively low. Treatment of PDLSCs with TGF-β1 highly promoted their fibroblastic differentiation, and inhibited their osteo/cementoblastic differentiation (Lim, Bae, Lee, Ryu, & Jang, 2020). However, the roles of TGF-β1 on PDLSCs osteogenic differentiation is still controversial. In cultured PDLSCs, TGF-β1 induced the stabilization of HIF-1α (Z. Liu et al., 2019) and worked synergistically to inhibit osteogenesis of PDLSCs. It is also reported that TGF-β inhibits hard tissue formation by competing with BMP2 (Fan et al., 2019). Sonic hedgehog (Shh) is a member of the mammalian hedgehog family and plays a key role in tooth development (Martínez, Smith, Rodriguez, & Palma, 2011). Its expression is observed in Hertwig's epithelial root sheath,

cementoblasts, and PDL cells in developing mouse periodontal tissue (Wj et al., 2016). C. Martínez et al. reported that Shh increased the expression of GLI1 and PTC-1 and stimulated periodontal stem cell proliferation (Martínez et al., 2011). According to Won-Jung Bae et al., addition of cultured recombinant human SHH to human cementoblast-like cells could promote cell growth and cell osteoblastic/cementoblastic differentiation via BMP pathway (Bae et al., 2016). Fibroblast growth factors (FGF) have been shown to participate in both periodontal development and regeneration. FGF could stimulate PDL cell proliferation and its expression could be increased by low-oxygen level (Ratajczak et al., 2016; Sonmez & Castelnuovo, 2014). Moreover, FGF is a powerful angiogenic factor. It increases the expression of VEGF in PDLSCs, supports the angiogenesis process of endothelial cells, and thus regulating the stem cell niche, especially in cases of hypoxia (Ratajczak et al., 2016).

5 | IMPACT OF INFLAMMATION AND AGING UPON PERIODONTAL STEM CELLS

Despite of the presence of periodontal stem cells, periodontal tissue was notorious for its poor regeneration capability during or after inflammation. Unlike many other stem cell populations, periodontal stem cells tissue resides in a mixed environment where local bacteria co-exist with the host (Z. Zhang, Deng, Hao, & Tang, 2021). Immune cells must be a niche component for periodontal stem cells. It was proposed that prolonged periodontal inflammation may permanently disrupt functions of periodontal stem cells and their maintenance, leading to irreversible periodontal lesions.

Overactivated immune response upon pathogen infection in periodontal tissues is characterized by infiltration of immune cells and overproduction of proinflammatory cytokines including IL-1β, IL-6, IL-8, TNF-α, and so forth (Hasturk, 2022). In periodontitis tissues, the levels of plasma cells, naïve B cells, and neutrophils were elevated, and the ratio of activated CD4 memory T cells was relatively higher than in healthy periodontal tissues. With the periodontitis progressing, expansion of microvasculature and increased endothelial apoptosis could be detected (Zoellner et al., 2002). Increased number of blood vessels and expanded vascular diameter protected tissue from inflammation by increasing the supply of plasma defense factors. However, the production of perivascular hyaline and accumulation of basement membrane components could aggravate the periodontal inflammation (Zoellner et al., 2002).

Most research on the impact of inflammation upon periodontal stem cells were in vitro studies. LPS-induced inflammation on cultured PDLSCs would lead to increased apoptosis and decreased proliferation and osteogenic differentiation. NF-κB as an inflammation-sensitive regulator plays a key role in this process. The application of NF-κB inhibitor, pyrrolidine dithiocarbamate (PDTC), could reverse the above effects in vitro (M. Chen, Lin, Zhang, & Hu, 2022), and prevent alveolar bone loss in vivo (C. Li et al., 2014). Furthermore, canonical Wnt signaling pathway is also involved in regulating periodontal stem cells during inflammation. Inflammation induces hyperphosphorylation of GSK-3β and nuclear translocation of β-catenin of stem cells, which impairs their osteogenic differentiation. A possible feedback regulation of Wnt signaling was observed because antagonists of Wnt, including sclerostin and DKK1, were upregulated in periodontitis (X. Chen et al., 2013).

Aging has been recently introduced as a new disease in the International Classification of Diseases released by the World Health Organization (Zhavoronkov & Bhullar, 2015). Aging leads to stem cells number reduction, function decrease and cellular senescence (Oh, Lee, & Wagers, 2014). Occurrence and severity of periodontal disease tissue destruction was well known to be correlated with age. This strongly suggests potential roles of aging on periodontal microenvironment and periodontal stem cells.

Li et al isolated PDLSCs from individuals of different ages, and revealed that the proliferation, trilineage differentiation potential and immunosuppressive ability of PDLSCs decreased with aging, while their apoptosis increased (X. Li et al., 2020). In vivo study carried out by Kyaw et al. suggests that the number of MSCs within the periodontium was relatively low in the aged mice after ligation compared to that in young mice (Aung et al., 2020). Aged stem cells showed increased cell senescence-associated β-galactosidase and presented lower osteogenic ability. The number and function change of aged periodontal stem cells may attribute to reduced bone regeneration in ligature-induced periodontitis.

Aged periodontal stem cells were shown to be rejuvenated by young environment. When culturing aged PDLSCs with young PDLC-conditioned medium, the aged PDLSCs showed enhanced ability to produce cementum/PDL-like structures, while aged PDLC-conditioned medium decreased the young PDLSCs' capability to form mineralized tissues (Zheng et al., 2009). Bioactive molecules including paracrine growth factors and differentiation factors might be involved in this process(A.-Q. Liu, Hu, Jin, Zhang, & Xuan, 2018).

6 | CONCLUSIONS

In this review, we summarized the current understanding of periodontal stem cells, and their regulating niche. Although in vivo experiments based on lineage tracing models are currently golden standard for most other stem cell research, many periodontal stem cell studies still rely on in vitro approaches with cultured cells as the model. Characteristics of periodontal stem cell niche, during physiological or disease conditions, is far from enough. Identification of appropriate mouse models based on in vivo PDLSC markers is critical for future studies.

The same principle also applies for many PDL regeneration studies in which periodontal stem cells were acquired from donor and cultured in vitro before seeding into host for tissue engineering purposes. Removing stem cells from their in vivo niche can dramatically change their behavior and properties. Therefore, stem cells on the culture dish may present very different features as their in vivo properties. Still, an appropriate lineage tracing mouse model can be very helpful on analyzing the difference. Further understanding of how PDLSCs behave under various conditions will be critical for

designing better strategy for regenerating or healing PDL tissue in clinic.

AUTHOR CONTRIBUTIONS

Yating Yi, Yinghong Liu, Yi Men, Jun Wang, Hu Zhao co-wrote the manuscript. All authors approved the manuscript.

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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