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# The application of dental mesenchymal stem cells (DMSCs) in the repair of oral and maxillofacial defects

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Dental mesenchymal stem cells (DMSCs) are important seed cells for oral and maxillofacial tissue regeneration due to their wide availability, multi-directional differentiation potential, strong proliferation ability, maintenance of stemness after multiple proliferations, and immunomodulatory capacity. DMSCs have a wide range of sources, and different subtypes have different properties. They can promote tissue regeneration through direct differentiation into tissue cells, improvement of the local regeneration microenvironment through immunomodulatory functions, and release of various bioactive components. The article reviews the classification of DMSCs, their performance comparisons in recent years, methods of promoting tissue regeneration, and their applications in maxillofacial bone and soft tissue. Furthermore, the review explores DMSCs' excellent abilities to promote bone tissue repair when supported by various materials and repair maxillofacial soft tissue defects by promoting the regeneration of special structures of teeth such as dentin, cementum, and dental pulp vessels and nerves.

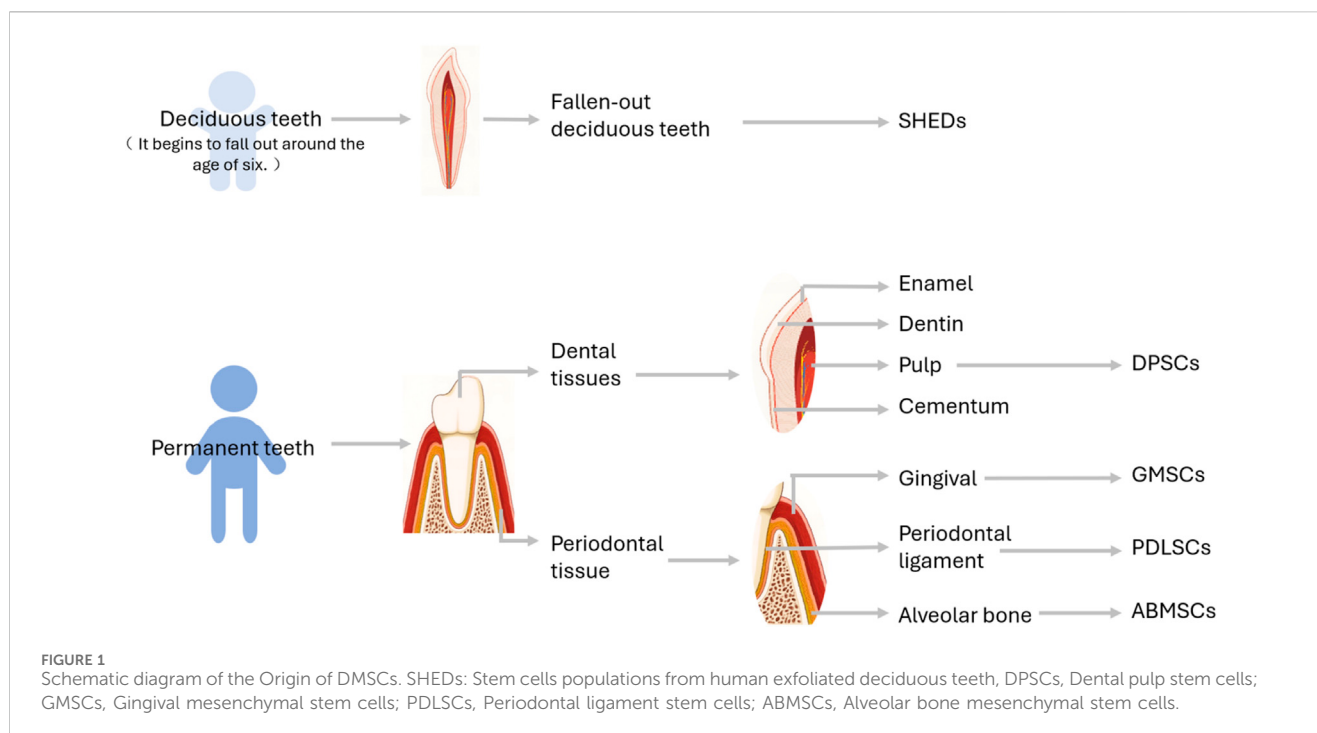
## KEYWORDS

dental mesenchymal stem cells, dental pulp stem cells, periodontalligament stem cells, deciduous tooth pulp stem cells, gingival mesenchymal stemcells, apical papilla stem cells, dental follicle precursor cells, tissue regeneration

## 1 Introduction

Oral and maxillofacial defects are often caused by trauma, tumors or congenital diseases. For a long time, traditional repair methods have faced many insurmountable bottlenecks in restoring the function of the oral and maxillofacial region and meeting aesthetic needs. However, in recent years, with the vigorous development of the frontier field of tissue regeneration medicine, a brand-new exploration direction has been opened up for the repair of oral and maxillofacial defects. Among many innovative approaches, dental mesenchymal stem cells (DMSCs) have stood out due to their wide availability, multi-directional differentiation potential, and low immunogenicity, becoming one of the most notable hotspots in current oral medicine research.

Mesenchymal stem cells (MSCs) are a type of non-hematopoietic adult stem cells. They can be isolated from various tissues and organs, including bone marrow, skin, adipose tissue, and umbilical cord. These cells possess the potential for both proliferation and differentiation (Li et al., 2023). DMSCs are a type of adult stem cells among mesenchymal



stem cells and can be isolated from dental pulp, periodontal ligament, apical papilla, gingiva, dental follicle and human deciduous teeth. Due to their multi-directional differentiation potential, strong proliferation ability, maintenance of cell stemness after multiple proliferations, and immunomodulatory capacity, they have become an important seed cell in the clinical application of tissue regeneration.

## 2 The classification of DMSCs

DMSCs are characterized by a diverse array of sources, and their properties vary notably among different subtypes. In the subsequent part, the sources of DMSCs are introduced in Figure 1. Additionally, several common types of DMSCs and their properties are expounded upon. Moreover, Figure 2 illustrates the sources and differentiation potential of DMSCs.

### 2.1 Dental pulp stem cells (DPSCs)

Dental pulp refers to the loose connective tissue within the pulp cavity surrounded by dentin, which has functions such as forming dentin, sensing pain, providing nutrition, and resisting bacterial invasion. Dental pulp stem cells are cells isolated from dental pulp with mesenchymal stem cell characteristics. In 2000, Gronthos et al. successfully isolated DPSCs (Gronthos et al., 2000). As the earliest isolated dental stem cells, they revealed that mesenchymal stem cells also exist in dental-related tissues besides bone marrow, adipose tissue, placenta, umbilical cord, etc. Compared with the extraction of bone marrow mesenchymal stem cells which requires anesthesia, DPSCs are easier to obtain and can be isolated from healthy first premolars, third molars, or

other teeth extracted for orthodontic purposes, thus causing less ethical disputes (Hwan and Woo, 2022).

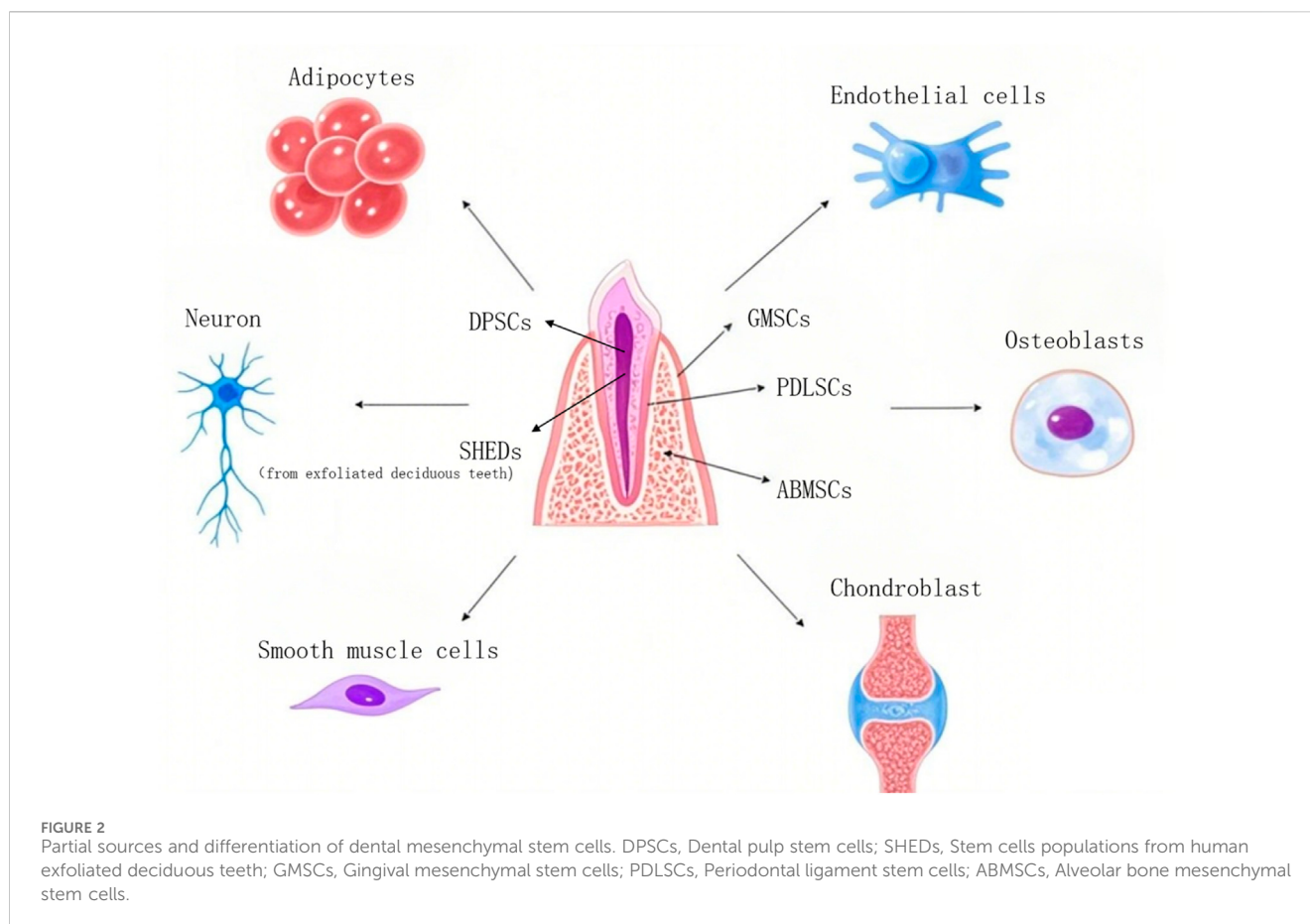
With the deepening of research, DPSCs can be traced back to neural crest cells, thus having the ability to differentiate into neurons and glial cells. Under certain environmental conditions, they can also produce capillary-like structures by synthesizing and secreting angiogenic regulators. Based on their potential for neural differentiation and angiogenesis, dental pulp stem cells have become the best seed cells for dental pulp regeneration.

### 2.2 Periodontal ligament stem cells (PDLSCs)

The periodontal ligament is a dense connective tissue connecting the alveolar bone and cementum. As a connection between the alveolar bone and cementum, it plays a crucial role in resisting and regulating the pressure on teeth during chewing. In 2004, Seo et al. successfully isolated periodontal ligament stem cells (Seo et al., 2004). *In vitro* experiments have shown that when periodontal tissue is damaged, periodontal ligament stem cells can migrate to the damaged area and repair it, revealing the possibility of periodontal tissue regeneration (Hwan and Woo, 2022).

### 2.3 Stem cells populations from human exfoliated deciduous teeth (SHEDs)

In 2003, Miura et al. discovered and isolated SHEDs (Miura et al., 2003). Due to the growth and development differences between deciduous teeth and permanent teeth, deciduous dental pulp stem cells exhibit different characteristics from permanent dental pulp stem cells, such as a strong



proliferation tendency, higher mineralization ability, and unique osteoinductive ability. Therefore, they have become a new direction for the repair of dental and bone tissues in the future (Forough et al., 2023).

## 2.4 Gingival mesenchymal stem cells (GMSCs)

GMSCs were first proposed by Zhang et al., in 2009 (Zhang et al., 2009). The gingiva is a tough oral mucosa surrounding the cervical part of the tooth and the alveolar ridge, and it participates in oral mucosal immunity as a mucosal barrier. Studies have found that gingival mesenchymal stem cells have the potential for bone regeneration, neural regeneration, and the regeneration of muscle, cartilage, and synovial tissues, but their osteogenic potential is lower than that of other sources of dental mesenchymal stem cells (Gamilah et al., 2021).

## 2.5 Other DMSCs

In addition to the above-mentioned stem cells, there are also dental follicle stem cells (DFSCs) (also known as dental follicle progenitor cells, DFPCs), (Karamzadeh et al., 2017), alveolar bone mesenchymal stem cells (ABMSCs), (Mason et al., 2014), and stem cells from apical papilla (SCAPs), etc (Sonoyama et al., 2006).

## 3 Comparison of various cellular properties of DMSCs

The following table compares the proliferation ability, differentiation potential and immune regulation characteristics of several types of cells (Table 1).

## 4 The modalities by which dental mesenchymal stem cells facilitate tissue regeneration

Previous studies have shown that dental mesenchymal stem cells mainly promote tissue regeneration through three ways: (1) differentiation into tissue cells; (2) improvement of the local regeneration microenvironment through immunomodulatory functions; (3) promotion of tissue regeneration by releasing various bioactive components.

### 4.1 Differentiate into tissue cells

During the development of the tooth germ, the enamel organ composed of the ectodermal epithelium undergoes significant morphological changes. In the cap stage, an intermediate layer appears between the inner enamel epithelium and the stellate reticulum. In the late stage, acidic mucopolysaccharides and

**TABLE 1 Comparison of various properties of DMSCs (Guanlin et al., 2021; Linglu et al., 2021; Lu et al., 2020; Sabbagh et al., 2020; Al-Qadhi et al., 2021; Deng et al., 2024; Kotova et al., 2021; Nowwarote et al., 2020; Abe et al., 2022).**

| Cellular type | Proliferation capacity                                                                                                                                                                                                                             | Differentiation potential                                                                                                                                                                                                       | Immune regulation                                                                                                                         | Cell markers                                             |
|---------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------|
| DPSCs         | The proliferation rate is similar to that of PDLSCs but lower than that of DFPCs. The proliferation capacity and osteoinductive ability are higher than those of DPSCs                                                                             | Endothelial cells, osteoblasts, adipocytes, chondroprogenitor cells, hepatocytes and cardiomyocytes have neurogenic differentiation potential. Among them, the osteogenic differentiation ability is greater than that of DFPCs | It has immunomodulatory properties, can inhibit T cell proliferation, trigger M2 macrophage polarization, and suppress inflammation, etc. | Stro-1, CD49f, CD29, CD44, CD105, CD90                   |
| SHEDs         | The proliferation rate is similar to that of PDLSCs but lower than that of DFPCs. The proliferation capacity and osteoinductive ability are higher than those of DPSCs                                                                             | Osteocytes, chondrocytes, adipocytes, odontoblasts, endothelial cells and hepatocytes<br>Unique dental tissue and osteoinductive ability*<br>Can be used as a neuroprotective agent*                                            | /                                                                                                                                         | CD73, CD90, CD105<br>CD146                               |
| PDLSCs        | /                                                                                                                                                                                                                                                  | The differentiation potential of osteocytes, endothelial cells, cardiomyocytes, islet-like cells and retinal ganglion-like cells<br>It can form typical cementum and periodontal ligament-like structures                       | /                                                                                                                                         | Stro-1, CD146, CD29, CD44, CD106                         |
| GMSCs         | Greater than PDLSCs, and the degree of senescence after continuous passage <i>in vitro</i> culture is less than that of PDLSCs. Compared with DPSCs and PDLSCs, it has a unique ability to automatically differentiate into gingiva <i>in vivo</i> | Neurogenic differentiation, adipocytes, chondrocytes and endothelial cells                                                                                                                                                      | /                                                                                                                                         | CD13, CD29, CD44, CD54, CD73, CD90, CD105, CD166, Stro-1 |

Unique dental tissue and bone induction ability\*: Capable of differentiating into odontoblasts and forming dentin-like or pulp-like tissues, rather than complete dentin-pulp-like complexes. *In vivo*, it recruits host osteoblasts to induce new bone formation, unlike *in vitro* where it differentiates into osteoblasts.

Can act as a neuroprotective agent\*: Promotes neural function recovery through paracrine action and inhibits the formation of glial scars after spinal cord contusion.

Unique ability to automatically differentiate into gingiva *in vivo*\*: Transplantation forms connective-like tissue expressing collagen I, a capability not possessed by DPSCs, and PDLSCs. DPSCs, Dental pulp stem cells; SHEDs, Stem cells populations from human exfoliated deciduous teeth; PDLSCs, Periodontal ligament stem cells; GMSCs, Gingival mesenchymal stem cells; DFPCs, Dental follicle progenitor cells.

glycogen deposits can be observed in the cytoplasm of the intermediate layer cells, and they have high alkaline phosphatase activity. Subsequent studies have demonstrated that alkaline phosphatase is involved in the formation of enamel, dentin, and bone. Furthermore, its high enzymatic activity can serve as a marker for cells associated with the development of these tissues (Yu et al., 2015). Stem cell surface markers are often used to routinely identify the differentiation potential of pluripotent mesenchymal stem cells (i.e., to confirm the strength of the stemness of cells). CD51/CD140α and CD271 have been used to isolate and identify neural crest cell progenitors, while the STRO-1/CD146 combination has been used to isolate mesenchymal stem cells (MSCs) located in blood vessels (Mao et al., 2012). Since the success of craniofacial defect repair depends on the ability to separate specific subpopulations of DMSCs with strong differentiation ability into appropriate cell types, it is crucial to identify effective markers for isolating pluripotent DMSCs. The mRNA expression of dental source genes can indicate whether mesenchymal stem cells have differentiated into dental lineage tissue cells.

In the experiment by Alvarez et al. (Ruth et al., 2015), primary dental pulp cells (DPCs) from the dental pulp tissue of adult third molars were obtained in α-modified Eagle's medium (containing 20% fetal bovine serum (FBS), non-essential amino acids, 100 units/mL of penicillin, and 100 units/mL of streptomycin) in a humidified incubator at 37 °C with 5% CO<sub>2</sub> to obtain DMSCs. Then, fluorescence-activated cell sorting (FACS) technology was used to sort out suitable DMSCs. These cells are induced to

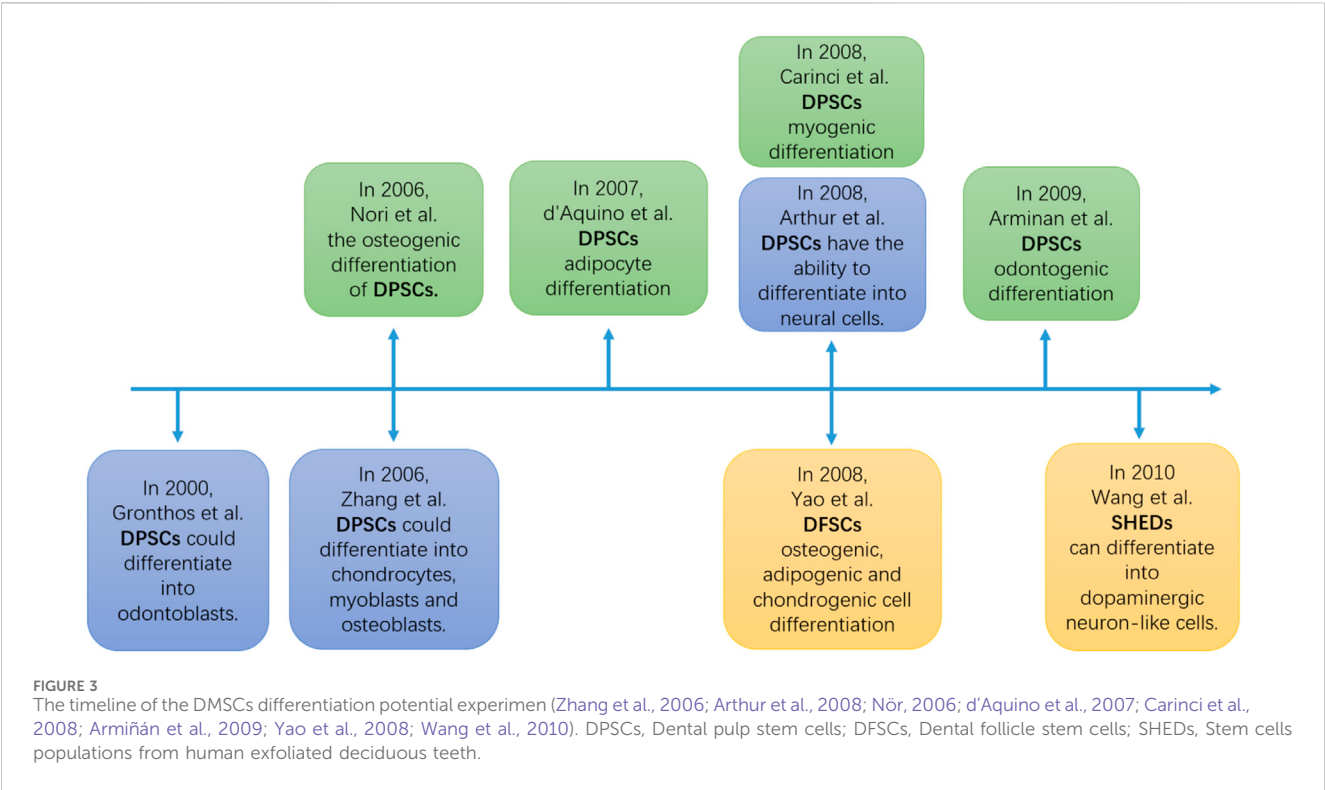
undergo odontogenesis through a specific tooth-inducing medium or what is known as odontogenic induction medium (OIM). The results (Table 2) showed that various surface markers (including CD51/CD140α, CD271, and STRO-1/CD146 DMSCs) could be isolated from the surface of DMSCs. Their alkaline phosphatase (ALP) activity was measured to determine their differentiation ability, and the mRNA expression of dental source genes at different time points was detected to confirm that DMSCs with surface markers may exhibit the ability to differentiate into dental lineage cells. Furthermore, numerous researchers have uncovered the differentiation potential of DMSCs. Figure 3 illustrates some of the studies on DMSCs - derived differentiated cells.

## 4.2 Improve the local regenerative microenvironment through immune regulation function

After various injury factors cause damage to the body's tissues and cells, sentinel cells around the injured tissue (such as macrophages) mediate the production of inflammatory mediators by recognizing injury factors and necrotic tissue. This is the reason why the body often experiences an inflammatory response in cases of tissue damage and infection (such as fractures, trauma, tumors, etc.). The body can repair damage by confining or eliminating injury factors. However, if tissue cells are chronically exposed to an

TABLE 2 ALP activity and expression of dental source marker genes under different induction media cultivation (Ruth et al., 2015).

| Experimental group category   | Alkaline phosphatase (ALP) activity                     | The mRNA expression of odontogenic marker genes (including DLX5, RUNX2, BGLAP, DMP1 and DSPP) at different time points                                               |
|-------------------------------|---------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Non-induced CD51/CD140a DMSCs | Control group                                           | /                                                                                                                                                                    |
| Induced CD271 DMSCs           | Increased by five times compared with the control group | On Day 10, concurrently with the notable induction of BGLAP expression, the expressions of DMP1 and DSPP were significantly upregulated during the induction process |
| Induced CD51/CD140a DMSCs     | Increased by 2.5 times compared with the control group  | On Day 7, the expression of DLX5 was significantly increased. On Day 10, the expressions of DMP1 and DSPP were significantly upregulated after induction             |
| Induced STRO-1/CD146 DMSCs    | Increased by 1.25 times compared with the control group | On Day 10, the expressions of DMP1 and DSPP were significantly upregulated                                                                                           |



inflammatory environment (such as without using drugs to block the continuous inflammatory process), the inflammatory mediators in the inflammatory environment will activate the host's vascular response and leukocyte response. The aggregation of a large number of activated cells and the excessive release of enzymes and chemokines will instead impede the process of tissue repair. Timely blocking the development of the inflammatory response through immune regulation function becomes an important factor for tissue regeneration (Wang et al., 2020).

DMSCs can exert immunomodulatory functions by releasing or inhibiting the expression of factors, influencing the proliferation, differentiation, apoptosis and other physiological processes and morphological functions of T cells and macrophages, thereby improving the local regenerative microenvironment to promote tissue repair and regeneration (Table 3).

### 4.3 By releasing a variety of bioactive components, it promotes tissue regeneration

Dental pulp stem cells share the same characteristics as other mesenchymal stem cells, such as high proliferation capacity and multi-lineage differentiation ability. Besides differentiating into various mesodermal tissue cells, dental pulp stem cells also exhibit differentiation capabilities in non-mesodermal tissues, such as neurons. In experiments, researchers have found that dental pulp stem cells in the culture medium for regeneration secrete various bioactive substances. Ogata et al. discovered that the culture medium derived from dental pulp stem cells contains anti-inflammatory cytokines, IL-10, IL-13, follistatin, TGF-β1, hepatocyte growth factor (HGF), neural cell adhesion molecule-1

TABLE 3 Immune regulation pathways of DMSCs.

| DMSCs  | Research scholars        | Mechanism of action                      | Experimental conditions                                                                                         | Specific approaches                                                                                                                                                                                    | References                             |
|--------|--------------------------|------------------------------------------|-----------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------|
| DPSCs  | KWACK et al.             | Inhibit the proliferation of T cells     | Phytohemagglutinin-activated monocytes, IFN- $\gamma$ pretreated culture medium                                 | IFN- $\gamma$ activation of DPSCs can inhibit the proliferation of T cells and reduce the production of IL-17                                                                                          | Kwack et al. (2017)                    |
|        | ZHAO et al.              | Inducing apoptosis of T cells            | CD3 <sup>+</sup> T cells activated by phytohemagglutinin                                                        | It can inhibit T cell proliferation, induce T cell apoptosis, and stimulate the formation of Treg                                                                                                      | Zhao et al. (2012)                     |
|        | OMI et al.               | Influence macrophage polarization        | Transplantation of DPSCs into the unilateral hind limb skeletal muscle and DPSCs treated with lipoteichoic acid | Trigger M2 macrophage polarization and inhibit inflammation                                                                                                                                            | Omi et al. (2016)                      |
|        | RUFAS et al.             | Activate the complement system           | /                                                                                                               | It can express the vast majority of factors required to activate the complement system                                                                                                                 | Rufas et al. (2016)                    |
| PDLSCs | LIU et al.               | Inhibit the differentiation of T cells   | Periodontal ligament stem cells isolated from an inflammatory environment                                       | Inhibit the secretion of IFN- $\gamma$ to suppress the differentiation of T cells into Th1                                                                                                             | Liu et al. (2012)                      |
|        | LI et al.<br>SHIN et al. | Inhibit T cell proliferation             | Concanavalin A-activated peripheral blood mononuclear cells                                                     | Indirect soluble mediators and direct cell-to-cell contact inhibit T cell proliferation, or inhibit the expression of non-classical MHC-like glycoprotein CD1b in DCs to suppress T cell proliferation | Li et al. (2014)<br>Shin et al. (2017) |
| SHEDs  | YAMAZA et al.            | Inhibit T cell differentiation           | Peripheral blood mononuclear cells activated by anti-CD3/CD28 antibodies and immature CD4 <sup>+</sup>          | Inhibiting Th17 differentiation, its effect is greater than that of bone marrow mesenchymal cells                                                                                                      | Yamaza et al. (2010)                   |
|        | GAO et al.               | Enhance the ability of DC to induce Treg | /                                                                                                               | Reduce the secretion of IL-2, TNF- $\alpha$ and IFN- $\gamma$ by DC and increase the secretion of IL-10                                                                                                | Gao et al. (2018)                      |

DMSCs, Dental mesenchymal stem cells; DPSCs, Dental pulp stem cells; PDLSCs, Periodontal ligament stem cells; SHEDs, Stem cells populations from human exfoliated deciduous teeth.

(NCAM-1), and other bioactive substances. The presence of these bioactive substances is highly beneficial in reducing inflammation, effectively reducing infection, promoting stem cell proliferation, and improving the tissue repair environment (Kwack et al., 2017).

In addition, Zhang et al. found that DPSCs can secrete neuron-related proteins such as DCX, NeuN and NF200, thereby restoring the neurological function of rats with Alzheimer’s disease (Zhang et al., 2021).

Moreover, Roato et al. demonstrated that both PDLSCs and DPSCs can secrete VEGF and generate substances such as proteoglycans when cultured in osteogenic medium (OM). These secretions play a significant role in promoting angiogenesis (Roato et al., 2025).

Through the secretion of growth factors, chemokines, etc., DMSCs exert a paracrine effect. This effect serves to regulate the microenvironment of the injured area, inhibit cell apoptosis and local inflammatory responses, and facilitate angiogenesis and tissue repair.

## 5 The application of DMSCs in the repair of maxillofacial bone tissue

In bone tissue repair, DMSCs can promote bone regeneration, enhance bone repair capacity, improve bone quality, and repair bone defects. They can be applied in periodontal disease treatment and

alveolar bone repair. The following is a detailed description of the currently well-studied DPSCs in bone tissue repair.

### 5.1 DPSCs

According to the studies by Amiryaghoubi et al. (2020) and Imanishi et al. (2021), DPSCs were investigated using different materials and scaffolds. The results demonstrated that DPSCs exhibited excellent regenerative performance when supported by hydrogel scaffolds and a mixed scaffold composed of three substances including collagen (COL). This can achieve the goal of micro-repairing mandibular and facial bone defects by efficiently inducing the proliferation of DPSCs and promoting their differentiation into osteoblasts, without inducing inflammation. It is a material that can balance safety and efficiency in mandibular and facial bone regeneration. Meanwhile, Alksne et al. (2022) delved into the biological characteristics of DPSCs themselves and discovered that they can secrete a unique extracellular matrix (ECM) protein network, broadening the understanding of the repair mechanism of DPSCs: this protein network can promote biological behaviors of cells such as adhesion, migration, proliferation or immune regulation by forming a suitable microenvironment, thereby achieving biological processes such as recruiting endogenous stem cells, osteogenesis and angiogenesis (Table 4).

TABLE 4 Applications of DPSCs in bone tissue repair.

| Cell type | Material/scaffold                                                                    | Experimental model | Experimental subject | Results and conclusions                                                                                                                                                                                                            | References                                 |
|-----------|--------------------------------------------------------------------------------------|--------------------|----------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------|
| DPSCs     | Injectable thermosensitive hybrid hydrogel containing graphene oxide and chitosan    | hydrogel           | culture medium       | It can significantly upregulate the expression of Runx2 and OCN, enhance ALP activity and mineral deposition                                                                                                                       | <a href="#">Amiryaghoubi et al. (2020)</a> |
| DPSCs     | The combination of DPSC-EVs and three scaffold materials: COL, $\beta$ -TCP, and HA. | Skull defect       | rat                  | Micro-CT analysis at 4 weeks and histological examination at 16 weeks revealed that the amount of central bone formation was comparable to that in the live cell transplantation group, and no signs of inflammation were detected | <a href="#">Imanishi et al. (2021)</a>     |
| DPSCs     | ECM protein network                                                                  | Skull defect       | rat                  | It can enhance the ability of cell adhesion, migration and proliferation, and promote osteogenesis and angiogenesis                                                                                                                | <a href="#">Alksne et al. (2022)</a>       |

DPSCs, Dental pulp stem cells; OCN, osteocalcin; ALP, alkaline phosphatase; EVs, Extracellular vesicles; COL, collagen;  $\beta$ -TCP,  $\beta$ -Tricalcium phosphate; HA, hydroxyapatite; ECM, extracellular matrix.

TABLE 5 Applications of SHEDs in bone tissue repair.

| Cell type | Material/scaffold                           | Experimental model  | Experimental subject | Results and conclusions                                                                                                                                                                                                                    | References                            |
|-----------|---------------------------------------------|---------------------|----------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|
| SHEDs     | SHED-CM                                     | Skull defect        | mouse                | It can significantly increase the volume of new bone, the proportion of mature bone, and vascular density, and is rich in osteogenic and angiogenic factors                                                                                | <a href="#">Hiraki et al. (2020)</a>  |
| SHEDs     | PGH                                         | Skull defect        | mouse                | The expression of osteogenic genes such as ALP, RUNX2, and OCN was significantly upregulated. The amount of new bone formed within 8 weeks was high, and mature bone and blood vessels grew in synchrony without any inflammatory response | <a href="#">Sattary et al. (2022)</a> |
| SHEDs     | PLGA-10% bioactive glass composite scaffold | Alveolar bone cleft | rat                  | Within 14 days, the activity of ALP and the expression of RUNX2, OCN and Col1 were significantly increased, mature bone matrix could be formed, and osteocalcin was positive                                                               | <a href="#">Kunwong et al. (2021)</a> |

SHEDs, Stem cells populations from human exfoliated deciduous teeth; CM, conditioned medium; PGH, Polycaprolactone/gelatin/hydroxyapatite Nanoparticles; PLGA, Poly (lactic-co-glycolic acid); ALP, alkaline phosphatase; OCN, osteocalcin.

## 5.2 SHEDs

[Hiraki et al. \(2020\)](#) used a 5 mm critical-sized mouse calvarial defect model to demonstrate that both human exfoliated SHEDs and their conditioned medium (SHED-CM) could significantly promote bone regeneration, with SHED-CM showing a superior effect compared to direct SHEDs application. This study was the first to prove that transplanting only the secretome of SHEDs could achieve bone regeneration comparable to that of live cells without immunosuppression, making it particularly suitable for repairing alveolar clefts in children with cleft lip and palate. [Sattary et al. \(2022\)](#) used polycaprolactone/gelatin/hydroxyapatite nanoparticles (PGH) as a scaffold to culture SHEDs and found that PGH scaffolds seeded with SHEDs could accelerate bone repair, which could be further translated into clinical applications for repairing craniofacial bone defects. [Kunwong et al. \(2021\)](#) further explored the application of SHEDs in a poly (lactic-co-glycolic acid) (PLGA)-bioactive glass composite scaffold. The results showed that a scaffold composed of 10% bioactive glass and PLGA performed well in promoting the adhesion, proliferation, and osteogenic differentiation of SHEDs, and could promote new bone formation at the site of rat alveolar bone defects without inducing inflammatory responses, providing

important experimental evidence for the development of new and efficient bone regeneration materials ([Table 5](#)).

## 5.3 SCAPs

[Cui et al. \(2020\)](#) demonstrated that injecting berberine (BBR) into the root canals of a rat model of apical periodontitis activated the Wnt/ $\beta$ -catenin signaling pathway in SCAPs, significantly promoting root apex repair in immature teeth with apical periodontitis. This finding suggests that pharmacological activation of SCAPs can drive root reconstruction and may be used for the treatment of root apex defects in children and adolescents. [Wu L. et al. \(2021\)](#) found that a low concentration (0.2 mg/mL) of injectable root canal sealer (iRoot SP) significantly promoted the proliferation, migration, and osteogenic differentiation of SCAPs. By regulating the activity of SCAPs, it provides a favorable microenvironment for the repair of periapical bone tissue and is expected to become an efficient biomaterial for promoting periapical bone regeneration. [Ramírez et al. \(2024\)](#) discovered that both platelet-rich fibrin (PRF) and low-level laser therapy (LLLT) alone could promote the osteogenic differentiation

TABLE 6 Applications of SCAPs in bone tissue repair.

| Cell type | Material/scaffold                             | Experimental model                       | Experimental subject | Results and conclusions                                                                                                                                                                                                          | References            |
|-----------|-----------------------------------------------|------------------------------------------|----------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| SCAPs     | BBR                                           | Immature teeth with apical periodontitis | rat                  | $\mu$ CT results at 3 weeks indicated remarkable root reconstruction. Significantly enhanced expression levels of Runx2, ALP, and Col1 $\alpha$ 1 were observed, which effectively promoted the formation of mineralized nodules | Cui et al. (2020)     |
| SCAPs     | 0.2 mg/mL iRoot SP                            | Osteogenic culture medium                | culture medium       | It can enhance ALP activity and the ability to form mineralized nodules, significantly up-regulating the mRNA and protein expressions of OCN, OSX, Runx2 and DSPP.                                                               | Wu L. et al. (2021)   |
| SCAPs     | LLLT combined with platelet-rich fibrin (PRF) | Osteogenic culture medium                | culture medium       | It can promote the formation of osteogenic nodules, significantly upregulate the expression of genes such as OCN, OPN, MSX1, TGF- $\beta$ 1 and SMAD1, as well as the protein levels of BMP-2 and BMP-4                          | Ramírez et al. (2024) |

SCAPs, Stem cells from apical papilla; BBR, berberin; ALP, alkaline phosphatase; iRoot SP, injectable root canal sealer; LLLT, Low-level laser therapy; PRF, Platelet-rich fibrin; OCN, osteocalcin; OPN, osteopontin.

TABLE 7 Applications of PDLSCs in bone tissue repair.

| Cell type | Material/scaffold                                   | Experimental model   | Experimental subject | Results and conclusions                                                                                                                                                                | References           |
|-----------|-----------------------------------------------------|----------------------|----------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------|
| PDLSCs    | GelMA hydrogel                                      | Alveolar bone defect | rat                  | The bone volume fraction was as high as 67.2% at 8 weeks, with abundant new bone and high ALP activity                                                                                 | Pan et al. (2020)    |
| PDLSCs    | MSM                                                 | Skull defect         | mouse                | The expression of genes and proteins such as ALP, OPN, OCN, and Runx2 doubles, which can promote osteogenic differentiation <i>in vitro</i> and <i>in vivo</i> and produce bone matrix | Ha and Choung (2020) |
| PDLSCs    | The combination of PDLSCs-Exos and Gel-Alg hydrogel | Alveolar bone defect | rat                  | It significantly promotes the proliferation and osteogenic differentiation of bone marrow mesenchymal stem cells, enhances their ALP activity, and can form more new bone              | Zhao et al. (2022)   |

PDLSCs, Periodontal ligament stem cells; GelMA, methacrylated gelatin; ALP, alkaline phosphatase; OPN, osteopontin; OCN, osteocalcin; MSM, methylsulfonylmethane; Exos, Exosomes; Gel-Alg, GelMA-Alginate.

of SCAPs, and their combined use produced a synergistic effect, significantly enhancing the formation of mineralized nodules and the secretion of osteogenic-related proteins (such as BMP-2 and BMP-4) by SCAPs. This study indicates that the combination of PRF and LLLT can serve as an efficient tool for the repair of maxillofacial bone tissue, providing a new combined treatment strategy and holding promise for more effective bone regeneration in clinical practice (Table 6).

5.4 PDLSCs

Pan et al. (2020) encapsulated PDLSCs in liquid methacrylated Gelatin (GelMA) hydrogel and demonstrated in a rat critical alveolar bone defect model that GelMA hydrogel could effectively fill any irregularly shaped alveolar bone defects and provide a suitable physicochemical microenvironment for the adhesion, viability, and osteogenic differentiation of PDLSCs, protecting PDLSCs from being lost due to bone defects in the early stage of transplantation. PDLSCs encapsulated in GelMA hydrogel exhibited significant alveolar bone regeneration potential. Ha and Choung (2020) proved that methylsulfonylmethane (MSM) could

significantly promote the proliferation and osteogenic differentiation of PDLSCs and enhance the regeneration efficiency of PDLSCs in the repair of maxillofacial bone defects. Zhao et al. (2022) demonstrated that exosomes derived from periodontal ligament stem cells (PDLSCs-Exos) could significantly promote the repair of mandibular bone defects. Their combined application with sodium GelMA-Alginate hydrogel (Gel-Alg) could be used to repair initial alveolar bone defects in SD rats, promoting bone regeneration. This is a promising strategy for the repair of mandibular bone defects, breaking through the limitations of traditional stem cell therapy and providing new ideas for future clinical applications (Table 7).

5.5 DFSCs

Meng et al. (2022) focused on the effects of N-acetylcysteine (NAC) on the osteogenic properties of DFSCs and alveolar bone repair. The study found that treatment with 5 mM NAC significantly enhanced the proliferation ability of DFSCs, reduced the senescence rate, and increased the expression of stem cell-specific markers and immune-related factors. It also promoted the strongest osteogenic

TABLE 8 Application of DFSCs in bone tissue repair.

| Cell type | Material/scaffold | Experimental model   | Experimental subject | Results and conclusions                                                                                                                                                                                                 | References         |
|-----------|-------------------|----------------------|----------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|
| DFSCs     | NAC               | Alveolar bone defect | rat                  | It has the potential to enhance the osteogenic differentiation ability. It enriches genes associated with the “developmental process”, decreases the intracellular ROS levels, and strengthens the antioxidant capacity | Meng et al. (2022) |
| DFSCs     | HOTAIRM1          | Skull defect         | rat                  | Regulating the demethylation of H3K27 promotes osteogenic differentiation of DFSCs and shows stronger ALP activity and mineralized nodule formation ability under hypoxic conditions                                    | Chen et al. (2023) |

DFSCs, Dental follicle stem cells; NAC, N-acetylcysteine; ROS, reactive oxygen species; ALP, alkaline phosphatase.

differentiation ability. An appropriate concentration of NAC enhanced the osteogenic properties of DFSCs through the PI3K/AKT/ROS signaling pathway, providing clinical potential for alveolar bone regeneration based on stem cells. Chen et al. (2023) revealed the important role of long non-coding RNA HOTAIRM1 in DFSC-mediated bone regeneration. The study found that HOTAIRM1 was induced under hypoxic conditions and activated HIF-1 $\alpha$ , which in turn upregulated oxygen-sensing histone demethylases KDM6A/B and inhibited the methyltransferase EZH2. By targeting HIF-1 $\alpha$ , HOTAIRM1 regulated the demethylation of H3K27 and promoted osteogenic differentiation of DFSCs. This study provided a new molecular mechanism and potential therapeutic target for the application of DFSCs in the repair of maxillofacial bone tissue, indicating that HOTAIRM1 may promote the osteogenic ability of DFSCs and bone regeneration by regulating the HIF-1 $\alpha$ /KDM6/EZH2/H3K27me3 axis (Table 8).

## 6 The application of DMSCs in the repair of soft tissues in the maxillofacial region

The oral and maxillofacial region plays a crucial role in chewing, pronunciation, and facial expressions. However, its high exposure rate makes it vulnerable to trauma and infection. Defects in the soft tissues of the oral and maxillofacial region not only cause functional problems for patients, bringing many inconveniences to their lives, but also seriously affect their appearance and mental health. In recent years, as people's demands for aesthetic restoration have increased, how to functionally reconstruct the damaged tissues while restoring their appearance as much as possible and achieving good aesthetic restoration results has become the focus of soft tissue repair. Utilizing dental mesenchymal stem cells to achieve soft tissue regeneration in the oral and maxillofacial region will become an effective approach for treating and restoring maxillofacial soft tissues in the future.

### 6.1 PDLSCs

The periodontal ligament is a connective tissue located between the alveolar bone and cementum, capable of absorbing mechanical pressure exerted on the teeth during chewing. PDLSCs are heterogeneous, clonal, highly proliferative and pluripotent cells

that can differentiate into osteoblasts, cementoblasts, chondrocytes and adipocytes, promoting the new formation of periodontal tissues, including periodontal ligament fibers similar to Sharpey fibers, bone and cementum (Queiroz et al., 2021).

You et al. (2024) confirmed through a rat periodontal window defect model that PDLSCs injection could reduce the reverse diversity during periodontal repair and increase the abundance of non-pathogenic bacteria such as Bifidobacterium and *Lactobacillus*, demonstrating that PDLSCs have the ability to influence the oral microbiota and promote periodontal regeneration. Meanwhile, the studies by Zhao et al. (2020) and Hu et al. (2020) indicated that PDLSCs, when combined with different carriers, could improve periodontal tissue regeneration. They found that the expression of type I collagen, alkaline phosphatase and bone sialoprotein genes was significantly upregulated on the polycaprolactone (PCL) membrane scaffold containing simvastatin (SIM), and the formation of mineralized matrix increased. In the tissue derived from PDLSC sheets combined with HA/TCP, the fibers showed obvious directionality, meeting the functional requirements of the periodontal soft tissue for the ordered structure of fibers. This suggests that PDLSCs materials provide a molecular and structural basis for the repair of periodontal soft tissue, which may contribute to periodontal tissue regeneration (Table 9).

### 6.2 SCAPs

SCAPs are a type of MSC population residing in the apical region of immature permanent teeth, characterized by high proliferation potential, self-renewal ability, and low immunogenicity (Sonoyama et al., 2006), and thus hold great potential for stem cell therapy.

Combining the *in vitro* and *in vivo* experimental results of Jing et al. (2022) on the exosomes of stem cells from apical papillae (SCAP-Exo), it was found that SCAP-Exo demonstrated excellent angiogenic and osteogenic properties, and this ability was still significantly manifested in diabetic (diabetes mellitus, DM) rats. The experiments showed an increase in the number of trabeculae in the alveolar bone of DM rats, a reduction in trabecular space, and a significant improvement in bone healing. This indicates that SCAPs have outstanding potential in promoting periodontal tissue regeneration. Meanwhile, Li et al. (2018) focused on the clinical translation potential of SCAPs, taking the key clinical assessment indicators in periodontitis treatment - probing pocket depth (PPD)

TABLE 9 Research on PDLSCs in soft tissue repair.

| Author      | Year | Subjects          | Source of stem cells | Carrier | Results and conclusions                                                                                        | References                         |
|-------------|------|-------------------|----------------------|---------|----------------------------------------------------------------------------------------------------------------|------------------------------------|
| You et al.  | 2024 | rat               | human                | /       | Injection of PDLSCs can enhance periodontal regeneration and regulate oral microbiota                          | <a href="#">You et al. (2024)</a>  |
| Zhao et al. | 2020 | Athymic nude mice | human                | PCL-SIM | Promoting the formation of cementum-like tissue, it has the feasibility of improving periodontal regeneration  | <a href="#">Zhao et al. (2020)</a> |
| Hu et al.   | 2020 | Athymic nude mice | human                | HA/TCP  | PDLSCs have the ability to form mineralized tissue and express proteins related to periodontal ligament tissue | <a href="#">Hu et al. (2020)</a>   |

PDLSCs, Periodontal ligament stem cells; PCL, polycaprolactone; SIM, simvastatin; HA, hydroxyapatite; TCP, tricalcium phosphate.

TABLE 10 Research on SCAPs in soft tissue repair.

| Author      | Year | Subjects                    | Source of stem cells | Carrier                 | Results and conclusions                                                                    | References                         |
|-------------|------|-----------------------------|----------------------|-------------------------|--------------------------------------------------------------------------------------------|------------------------------------|
| Jing et al. | 2022 | Diabetic rats               | human                | PEG/DNA hybrid hydrogel | SCAP-Exo can promote angiogenesis and bone regeneration                                    | <a href="#">Jing et al. (2022)</a> |
| Li et al.   | 2018 | Porcine periodontitis model | human                | /                       | The improvement of the gingival condition promoted the regeneration of periodontal tissues | <a href="#">Li et al. (2018)</a>   |

SCAPs, Stem cells from apical papilla; PEG, polyethylene glycol; Exo, exosome.

and attachment loss (AL) - as the core research objects. Through experiments, it was confirmed that SCAPs could effectively improve the PPD and AL indicators in a porcine periodontitis model. By using clinical assessment data such as PPD and AL, a bridge was built between laboratory research and clinical application, which has a positive effect on the application of SCAPs in soft tissue repair (Table 10).

### 6.3 SHEDs

SHEDs are regarded as a promising cell population for cell-based or cell-free therapy and tissue engineering due to their proliferative, pluripotent and immunomodulatory properties. Studies have found that in addition to their osteogenic and odontogenic potential, SHEDs also exhibit remarkable neuroregenerative capabilities (Tsutsui, 2020).

According to the research of Wu M. et al. (2021), it was found that the exosomes of SHEDs (SA-Exo) can upregulate the expression of angiogenesis-related proteins such as VEGF, angiopoietin 2 and PDGF in SHEDs. This reflects the endothelial differentiation potential of SHEDs and also indicates from a histological perspective that SA-Exo can enhance the regeneration of the dentin-pulp complex and angiogenesis. Guo et al. (2020) focused on the regeneration of blood vessels and nerves. Through histological analysis, it was shown that the extracted pulp permanent incisors of miniature pigs implanted with SHEDs contained regenerated pulp tissue with a similar structure to normal pulp. Moreover, the positive expression of platelet endothelial cell adhesion molecule (CD31) and neurofilament (NF) in the regenerated pulp tissue confirmed the regeneration of blood vessels and nerves. In summary, SHEDs have the ability to regenerate host pulp tissue *in vivo*. The clinical case report by Ghana Shyam Prasad et al. (2019) provided key practical evidence: after

treating tooth #46 with SHEDs for apical periodontal lesions, the patient's periapical radiolucency completely disappeared, and tooth #46 responded positively to the electric pulp test, which may indicate the reinnervation of pulp tissue in the root canal. It can be seen that the application of SHEDs in humans shows the ability to effectively treat apical periodontal lesions of permanent teeth (Table 11).

### 6.4 GMSCs

The gingiva is firmly attached to the teeth and jawbone, forming a mucoperiosteum, which has the ability to resist masticatory and minor traumatic forces. It plays a crucial role in maintaining oral health and exhibits a unique fetal-like scarless healing process after injury, suggesting that this tissue may be a source of stem cells (Chen et al., 2012).

Qiu et al. (2020) transplanted GMSCs into periodontal defects in rats and found that periodontal tissue regeneration occurred, with significantly lower expression levels of tumor necrosis factor (TNF- $\alpha$ ) and interleukin (IL-1 $\beta$ ) compared to the control group, and significantly higher expression of BSP-II and Runx2. This indicates that GMSC-CM may have the effect of inhibiting inflammation, promoting periodontal regeneration, and osteogenic differentiation. Sun et al. (2019) transplanted GMSCs into C57BL/6 J mice with periodontitis and found that the alveolar bone height of the mice increased significantly, and GMSCs were detected in the newly formed periodontal ligament and alveolar bone. This suggests that systemically transplanted GMSCs can return to the periodontal injury site and promote the regeneration and repair of periodontal tissue. Fawzy El-Sayed et al. (2015) transplanted GMSCs into periodontal defects in miniature pigs and found that compared to the control group, they showed better clinical attachment levels, PPD, GR, periodontal attachment levels, cementum regeneration and bone regeneration, as well as shorter

TABLE 11 Research on SHEDs in soft tissue repair.

| Author       | Year | Subjects                                        | Source of stem cells             | Results and conclusions                                                                                                                           | References                       |
|--------------|------|-------------------------------------------------|----------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------|
| Wu et al.    | 2021 | Immune-deficient mouse model                    | deciduous teeth                  | It can promote the regeneration of the dentin-pulp complex                                                                                        | Wu M. et al. (2021)              |
| Guo et al.   | 2020 | Porcine dental pulp regeneration model          | deciduous teeth                  | The accompanying blood vessels and nerves were discovered, suggesting that the regenerated dental pulp may be capable of sensing external stimuli | Guo et al. (2020)                |
| Ghana et al. | 2019 | A 12-year-old patient with apical periodontitis | The same child's deciduous teeth | Four months after the operation, regenerated dental pulp tissue appeared in the root canal                                                        | Ghana Shyam Prasad et al. (2019) |

SHEDs, Stem cells populations from human exfoliated deciduous teeth.

TABLE 12 Research on GMSCs in soft tissue repair.

| Author       | Year | Subjects                          | Source of stem cells | Results and conclusions                                                                                                                | References                   |
|--------------|------|-----------------------------------|----------------------|----------------------------------------------------------------------------------------------------------------------------------------|------------------------------|
| Qiu et al.   | 2020 | Rat periodontal defect model      | human                | GMSCs transplantation promoted periodontal defect regeneration in rats, inhibited inflammation and promoted osteogenic differentiation | Qiu et al. (2020)            |
| Sun et al.   | 2019 | Mouse periodontitis model         | human                | GMSCs can locate the sites of inflamed periodontal tissues and be used for the formation of new tissues                                | Sun et al. (2019)            |
| Fawzy et al. | 2015 | Miniature pig periodontitis model | Self                 | It demonstrated the significant periodontal regeneration potential of GMSCs                                                            | Fawzy El-Sayed et al. (2015) |

GMSCs, Gingival mesenchymal stem cells.

junctional epithelium length and better improvement in probing bleeding. This indicates that GMSCs have excellent potential for periodontal regeneration (Table 12).

## 7 Summary and prospects

In summary, DMSCs have demonstrated excellent performance in preclinical and clinical studies for the repair of bone and cartilage tissues in the maxillofacial region under the support of various culture media. Despite the promising application prospects of DMSCs, there are still bottlenecks for their large-scale clinical application.

### 7.1 Challenges in the clinical application of DMSCs

#### 7.1.1 Lack of standardized isolation and culture procedures for DMSCs

One of the challenges in the clinical application of DMSCs is how to obtain a large number of stem cells from tissues. This goal cannot be achieved without the isolation of stem cells, multiple passages, and cryopreservation. Although enzymatic methods are generally applicable in the process of isolating stem cells, there are no unified regulations for the physical operations of tissue separation for different types of DMSCs. Moreover, multiple passages may reduce the differentiation potential of cultured cells, thus leading to the development of various culture media to regulate their performance. Additionally, different cryopreservation strategies, such as controlled-rate freezing and non-controlled-rate freezing, are still controversial (Khaseb et al., 2021).

#### 7.1.2 Difficulties in quality control of DMSCs

Compared with chemically synthesized drugs, the cell culture conditions of DMSCs, including cell passage number and density, may lead to inconsistencies among different batches of DMSCs. Moreover, studies have found that the conditioned medium functions of DMSCs from different sources may be affected by their cell sources (Joo et al., 2018). The age and diseases of DMSC donors may also influence the composition of DMSC culture media (Bhandi et al., 2021).

#### 7.1.3 Rejection and tumorigenic risks

When DMSCs are used for allogeneic transplantation, the risks of immunogenicity and tumorigenicity cannot be ignored. Since DMSCs, such as DPSCs, have unique immunomodulatory functions, if their upregulated genes are enriched in immune and inflammatory-related cell pathways, they often exhibit higher immunogenicity, increasing the risk of immune rejection during allogeneic transplantation. Additionally, the differential expression of tumor-related genes and the presence of undifferentiated induced pluripotent stem cells during the induction and differentiation process of DMSCs may also lead to tumor formation (Taoran et al., 2024).

#### 7.1.4 Cost issues in large-scale production

Exosomes are extracellular vesicles that carry various bioactive molecules such as proteins, genetic material, and lipids, playing a crucial role in intercellular communication and material transport (Lu et al., 2024). Exosomes can be extracted from DMSCs, and studies have found that their functions are highly dependent on the source cells and their physiological states (Huang et al., 2016). In recent years, multiple studies have discovered that exosomes play a

role in various aspects such as angiogenesis (Ribeiro et al., 2013) and neural repair (Jarmalavičiūtė et al., 2015) by regulating intracellular signaling pathways. Like other bioactive components, exosomes, as an important component of DMSCs, must be stored under appropriate conditions. Wu J et al. (2021) found that different exosome storage conditions can affect their biological utilization rate. Generally, it is recommended to store them at  $-80^{\circ}\text{C}$ , but this condition is costly (Zhang et al., 2025).

Although a large number of proteins, nucleic acids, lipids and metabolic enzymes have been identified in Exos, little is known about their functions and sorting mechanisms. Moreover, the concentration of effective substances in Exos depends on the surrounding environment and the metabolic state of the host cells, making the condition control in the clinical application of Exos rather complex. Despite extensive research on Exos in chronic wound healing and skin regeneration, the exact molecular mechanisms and roles of Exos in tissue repair and regeneration still need further investigation. In addition, to use Exos as a research tool, extensive research is still needed in the fields of EV biosynthesis, cellular uptake and transport, which still has a long way to go (Hade et al., 2022).

## 7.2 Prospects for the clinical application of DMSCs

DMSCs, with their multi-directional differentiation and immunomodulatory properties, show great potential in the repair of maxillofacial defects. In the future, through technological optimization and more preclinical and clinical trials, overcoming issues such as quality control and safety, DMSCs may become a core force in regenerative medicine.

## Author contributions

YC: Data curation, Formal Analysis, Visualization, Writing – original draft, Writing – review and editing. XM: Data curation, Writing – review and editing. HM: Data curation,

Writing – review and editing. PL: Data curation, Writing – review and editing. RH: Conceptualization, Supervision, Writing – review and editing. AA: Conceptualization, Supervision, Writing – review and editing.

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## References

- Abe, S., Kaida, A., Kanemaru, K., Nakazato, K., Yokomizo, N., Kobayashi, Y., et al. (2022). Differences in the stemness characteristics and molecular markers of distinct human oral tissue neural crest-derived multilineage cells. *Cell Prolif.* 55 (10), e13286. doi:10.1111/cpr.13286
- Al-Qadhi, G., Aboushady, I., and Al-Sharabi, N. (2021). The gingiva from the tissue surrounding the bone to the tissue regenerating the bone: a systematic review of the osteogenic capacity of gingival mesenchymal stem cells in preclinical studies. *Stem Cells Int.* 2021 (1), 1–26. doi:10.1155/2021/6698100
- Alksne, M., Kalvaityte, M., Simoliunas, E., Gendviliene, I., Barasa, P., Rinkunaite, I., et al. (2022). Dental pulp stem cell-derived extracellular matrix: autologous tool boosting bone regeneration. *Cytotherapy* 24 (6), 597–607. doi:10.1016/j.jcyt.2022.02.002
- Amiryaghoubi, N., Pesyan, N. N., Fathi, M., and Omid, Y. (2020). Injectable thermosensitive hybrid hydrogel containing graphene oxide and chitosan as dental pulp stem cells scaffold for bone tissue engineering. *Int. J. Biol. Macromol.* 162, 1338–1357. doi:10.1016/j.ijbiomac.2020.06.138
- Armiñán, A., Gandía, C., Bartual, M., García-Verdugo, J. M., Lledó, E., Mirabet, V., et al. (2009). Cardiac differentiation is driven by NKX2.5 and GATA4 nuclear translocation in tissue-specific mesenchymal stem cells. *Stem Cells Dev.* 18, 907–918. doi:10.1089/scd.2008.0292
- Arthur, A., Rychkov, G., Shi, S., Koblar, S. A., and Gronthos, S. (2008). Adult human dental pulp stem cells differentiate toward functionally active neurons under appropriate environmental cues. *Stem Cells* 26, 1787–1795. doi:10.1634/stemcells.2007-0979
- Bhandi, S., Al Kahtani, A., Mashyakh, M., Alsofi, L., Maganur, P. C., Vishwanathaiah, S., et al. (2021). Modulation of the dental pulp stem cell secretory profile by hypoxia induction using cobalt chloride. *J. Pers. Med.* 11 (4), 247. doi:10.3390/jpm11040247
- Carinci, F., Papaccio, G., Laino, G., Palmieri, A., Brunelli, G., D'Aquino, R., et al. (2008). Comparison between genetic portraits of osteoblasts derived from primary cultures and osteoblasts obtained from human pulpar stem cells. *J. Craniofac Sur* 19, 616–625. doi:10.1097/scs.0b013e31816aabc8
- Chen, F., Sun, H., Lu, H., and Yu, Q. (2012). Stem cell-delivery therapeutics for periodontal tissue regeneration. *Biomaterials* 33 (27), 6320–6344. doi:10.1016/j.biomaterials.2012.05.048
- Chen, Z., Gan, L., Chen, X., Zheng, J., Shi, S., Wu, L., et al. (2023). LncRNA HOTAIRM1 promotes dental follicle stem cell-mediated bone regeneration by regulating HIF-1 $\alpha$ /KDM6/EZH2/H3K27me3 axis. *J. Cell. Physiology* 238 (7), 1542–1557. doi:10.1002/jcp.31028
- Cui, Y., Xie, J., Fu, Y., Li, C., Zheng, L., Huang, D., et al. (2020). Berberine mediates root remodeling in an immature tooth with apical periodontitis by regulating stem cells from apical papilla differentiation. *Int. J. Oral Sci.* 12 (1), 18. doi:10.1038/s41368-020-0085-7

- Deng, Y., Li, Q., Svoboda, K. K. H., Opperman, L., Ruest, L., and Liu, X. (2024). Gli<sup>+</sup> periodontal mesenchymal stem cells in periodontitis. *J. Dent. Res.* 103 (3), 279–288. doi:10.1177/00220345231220915
- d'Aquino, R., Graziano, A., Sampaioles, M., Laino, G., Pirozzi, G., De Rosa, A., et al. (2007). Human postnatal dental pulp cells co-differentiate into osteoblasts and endothelial cells: a pivotal synergy leading to adult bone tissue formation. *Cell Death Differ.* 14, 1162–1171. doi:10.1038/sj.cdd.4402121
- Fawzy El-Sayed, K., Mekhemar, M., Beck-Broichsitter, B., Bähr, T., Hegab, M., Receveur, J., et al. (2015). Periodontal regeneration employing gingival margin-derived stem/progenitor cells in conjunction with IL-1ra-hydrogel synthetic extracellular matrix. *J. Of Clin. Periodontology* 42 (5), 448–457. doi:10.1111/jcpe.12401
- Forough, J. M., Benyamin, P., Ezatolah, K., and Ayyoob, K. (2023). Hopes and opportunities of stem cells from human exfoliated deciduous teeth (SHED) in cartilage tissue regeneration. *Front. Bioeng. Biotechnol.*, 111021024–1021024. doi:10.3389/fbioe.2023.1021024
- Gamilah, Q. A., Iman, A., and Niyaz, S. A. (2021). The gingiva from the tissue surrounding the bone to the tissue regenerating the bone: a systematic review of the osteogenic capacity of gingival mesenchymal stem cells in preclinical studies. *Stem Cells Int.*, 20216698100–6698100. doi:10.1155/2021/6698100
- Gao, X., Shen, Z., Guan, M., Huang, Q., Chen, L., Qin, W., et al. (2018). Immunomodulatory role of stem cells from human exfoliated deciduous teeth on periodontal regeneration. *Tissue Eng. Part A* 24 (17–18), 1341–1353. doi:10.1089/ten.tea.2018.0016
- Ghana Shyam Prasad, M., Juvva, R., and Babu Duvvi, N. (2019). Towards a new era in the management of large periapical lesion in permanent tooth using stemcells: a 2-year clinical application report. *J. Dent. (Shiraz, Iran)* 20 (2), 137–140. doi:10.30476/DENTJODS.2019.44925
- Gronthos, S., Mankani, M., Brahimi, J., Robey, P. G., and Shi, S. (2000). Postnatal human dental pulp stem cells (DPSCs) in vitro and in vivo. *Proc. Natl. Acad. Sci.* 97 (25), 13625–13630. doi:10.1073/pnas.240309797
- Guanlin, Q., Yan, L., Lu, C., Qin, C., Duohong, Z., Chi, Y., et al. (2021). Comparison of osteogenic differentiation potential of human dental-derived stem cells isolated from dental pulp, periodontal ligament, dental follicle, and alveolar bone. *Stem Cells Int.*, 20216631905–6631905. doi:10.1155/2021/6631905
- Guo, H., Zhao, W., Liu, A., Wu, M., Shuai, Y., Li, B., et al. (2020). SHED promote angiogenesis in stem cell-mediated dental pulp regeneration. *Biochem. and Biophysical Res. Commun.* 529 (4), 1158–1164. doi:10.1016/j.bbrc.2020.06.151
- Ha, S. H., and Choung, P. H. (2020). MSM promotes human periodontal ligament stem cells differentiation to osteoblast and bone regeneration. *Biochem. Biophysical Res. Commun.* 528 (1), 160–167. doi:10.1016/j.bbrc.2020.05.097
- Hade, M. D., Suire, C. N., Mossell, J., and Suo, Z. (2022). Extracellular vesicles: emerging frontiers in wound healing. *Med. Res. Rev.* 42 (6), 2102–2125. doi:10.1002/med.21918
- Hiraki, T., Kunimatsu, R., Nakajima, K., Abe, T., Yamada, S., Rikitake, K., et al. (2020). Stem cell-derived conditioned media from human exfoliated deciduous teeth promote bone regeneration. *Oral Dis.* 26 (2), 381–390. doi:10.1111/odi.13244
- Hu, L., Zhao, B., Gao, Z., Xu, J., Fan, Z., Zhang, C., et al. (2020). Regeneration characteristics of different dental derived stem cell sheets. *J. Of Oral Rehabilitation* 47, 66–72. doi:10.1111/joor.12839
- Huang, C. C., Narayanan, R., Alapati, S., and Ravindran, S. (2016). Exosomes as biomimetic tools for stem cell differentiation: applications in dental pulp tissue regeneration. *Bio Mater.* 111, 103–115. doi:10.1016/j.biomaterials.2016.09.029
- Hwan, K. K., and Woo, H. L. (2022). Clinical potential of dental pulp stem cells in pulp regeneration: current endodontic progress and future perspectives. *Front. Cell Dev. Biol.*, 10857066–857066. doi:10.3389/fcell.2022.857066
- Imanishi, Y., Hata, M., Matsukawa, R., Aoyagi, A., Omi, M., Mizutani, M., et al. (2021). Efficacy of extracellular vesicles from dental pulp stem cells for bone regeneration in rat calvarial bone defects. *Inflamm. Regen.* 41, 12. doi:10.1186/s41232-021-00163-w
- Jarmalavičiūtė, A., Tunaitis, V., Pivoraitė, U., Venalis, A., and Pivoriūnas, A. (2015). Exosomes from dental pulp stem cells rescue human dopaminergic neurons from 6-hydroxy-dopamine-induced apoptosis. *Cytotherapy* 17 (7), 932–939. doi:10.1016/j.jcyt.2014.07.013
- Jing, X., Wang, S., Tang, H., Li, D., Zhou, F., Xin, L., et al. (2022). Dynamically bioresponsive DNA hydrogel incorporated with dual-functional stem cells from apical papilla-derived exosomes promotes diabetic bone regeneration. *ACS Appl. Mater. and Interfaces* 14 (14), 16082–16099. doi:10.1021/acami.2c02278
- Joo, K., Song, J., Kim, S., Lee, H. S., and Jeon, M. (2018). Cytokine expression of stem cells originating from the apical complex and coronal pulp of immature teeth. *J. Endod.* 44 (1), 87–92. doi:10.1016/j.joen.2017.08.018
- Karamzadeh, R., Baghaban Eslaminejad, M., and Sharifi-Zarchi, A. (2017). Comparative in vitro evaluation of human dental pulp and follicle stem cell commitment. *Cell J.* 18 (4), 609–618. doi:10.22074/cellj.2016.4727
- Khaseb, S., Orooji, M., Pour, M. G., Safavi, S. M., Eghbal, M. J., and Rezai Rad, M. (2021). Dental stem cell banking: techniques and protocols. *Cell Biol. Int.* 45 (9), 1851–1865. doi:10.1002/cbin.11626
- Kotova, A. V., Lobov, A. A., Dombrovskaya, J. A., Sannikova, V. Y., Ryumina, N. A., Klausen, P., et al. (2021). Comparative analysis of dental pulp and periodontal stem cells: differences in morphology, functionality, osteogenic differentiation and proteome. *Biomedicine* 9 (11), 1606. doi:10.3390/biomedicine9111606
- Kunwong, N., Tangjit, N., Rattanapinyopituk, K., Dechkunakorn, S., Anuwongnukroh, N., Arayapit, T., et al. (2021). Optimization of poly (lactic-co-glycolic acid)-bioactive glass composite scaffold for bone tissue engineering using stem cells from human exfoliated deciduous teeth. *Archives oral Biol.* 123, 105041. doi:10.1016/j.archoralbio.2021.105041
- Kwack, K. H., Lee, J. M., Park, S. H., and Lee, H. W. (2017). Human dental pulp stem cells suppress alloantigen-induced immunity by stimulating T cells to release transforming growth factor beta. *J. Endod.* 43 (1), 100–108. doi:10.1016/j.joen.2016.09.005
- Li, C., Wang, X., Tan, J., Wang, T., and Wang, Q. (2014). The immunomodulatory properties of periodontal ligament stem cells isolated from inflamed periodontal granulation. *Cells Tissues Organs* 199 (4), 256–265. doi:10.1159/000367986
- Li, G., Han, N., Zhang, X., Yang, H., Cao, Y., Wang, S., et al. (2018). Local injection of allogeneic stem cells from apical papilla enhanced periodontal tissue regeneration in minipig model of periodontitis. *Biomed Res. Int.* 2018, 1–8. doi:10.1155/2018/3960798
- Li, J., Wu, Z., Zhao, L., Liu, Y., Su, Y., Gong, X., et al. (2023). The heterogeneity of mesenchymal stem cells: an important issue to be addressed in cell therapy. *Stem Cell Res. and Ther.* 14 (1), 381. doi:10.1186/s13287-023-03587-y
- Linglu, J., Yunpeng, Z., Dongfang, L., Zhang, W., Zhang, D., and Xu, X. (2021). Analyses of key mRNAs and lncRNAs for different osteo-differentiation potentials of periodontal ligament stem cell and gingival mesenchymal stem cell. *J. Cell. Mol. Med.* 25 (13), 6217–6231. doi:10.1111/jcmm.16571
- Liu, D., Xu, J., Liu, O., Fan, Z., Liu, Y., Wang, F., et al. (2012). Mesenchymal stem cells derived from inflamed periodontal ligaments exhibit impaired immunomodulation. *J. Clin. Periodontol.* 39 (12), 1174–1182. doi:10.1111/jcpe.12009
- Lu, G., Ying, L., Dixin, C., Yue, P., Liwei, Z., and Mian, W. (2020). Dental tissue-derived human mesenchymal stem cells and their potential in therapeutic application. *Stem Cells Int.* doi:10.1155/2020/8864572
- Lu, H., Zheng, Y., and Wei, Z. (2024). The mechanism of action of dental mesenchymal stem cell exosomes in pulp regeneration. *Int. J. Stomatology* 51 (04), 467–474. doi:10.7518/gjkq.2024064
- Mao, J. J., Robey, P. G., and Prockop, D. J. (2012). Stem cells in the face: tooth regeneration and beyond. *Cell Stem Cell* 11 (3), 291–301. doi:10.1016/j.stem.2012.08.010
- Mason, S., Tarle, S. A., Osibin, W., Kinfu, Y., and Kaigler, D. (2014). Standardization and safety of alveolar bone-derived stem cell isolation. *J. Dent. Res.* 93 (1), 55–61. doi:10.1177/0022034513510530
- Meng, Z., Liu, J., Feng, Z., Guo, S., Wang, M., Wang, Z., et al. (2022). N-acetylcysteine regulates dental follicle stem cell osteogenesis and alveolar bone repair via ROS scavenging. *Stem Cell Res. and Ther.* 13 (1), 466. doi:10.1186/s13287-022-03161-y
- Miura, M., Gronthos, S., Zhao, M., Lu, B., Fisher, L. W., Robey, P. G., et al. (2003). SHED: stem cells from human exfoliated deciduous teeth. *Proc. Natl. Acad. Sci.* 100 (10), 5807–5812. doi:10.1073/pnas.0937635100
- Nör, J. (2006). Buonocore memorial lecture: tooth regeneration in operative dentistry. *Oper. Dent.* 31, 633–642. doi:10.2341/06-000
- Nowwarote, N., Manokwinchoke, J., Kanjana, K., Fournier, B. P., Sukarawan, W., and Osathanon, T. (2020). Transcriptome analysis of basic fibroblast growth factor treated stem cells isolated from human exfoliated deciduous teeth. *Heliyon* 6 (6), e04246. doi:10.1016/j.heliyon.2020.e04246
- Omi, M., Hata, M., Nakamura, N., Miyabe, M., Kobayashi, Y., Kamiya, H., et al. (2016). Transplantation of dental pulp stem cells suppressed inflammation in sciatic nerves by promoting macrophage polarization towards anti-inflammation phenotypes and ameliorated diabetic polyneuropathy. *J. Diabetes Investig.* 7 (4), 485–496. doi:10.1111/jdi.12452
- Pan, J., Deng, J., Yu, L., Wang, Y., Zhang, W., Han, X., et al. (2020). Investigating the repair of alveolar bone defects by gelatin methacrylate hydrogels-encapsulated human periodontal ligament stem cells. *J. Mater. Sci. Mater. Med.* 31, 3–12. doi:10.1007/s10856-019-6333-8
- Qiu, J., Wang, X., Zhou, H., Zhang, C., Wang, Y., Huang, J., et al. (2020). Enhancement of periodontal tissue regeneration by conditioned media from gingiva-derived or periodontal ligament-derived mesenchymal stem cells: a comparative study in rats. *Stem Cell Res. and Ther.* 11 (1), 42. doi:10.1186/s13287-019-1546-9
- Queiroz, A., Albuquerque-Souza, E., Gasparoni, L. M., França, B. N. d., Pelissari, C., Trieverler, M., et al. (2021). Therapeutic potential of periodontal ligament stem cells. *World J. stem cells* 13 (6), 605–618. doi:10.4252/wjsc.v13.i6.605
- Ramírez, D. G., Inostroza, C., Rouabhi, M., Rodríguez, C. A., Gómez, L. A., Losada, M., et al. (2024). Osteogenic potential of apical papilla stem cells mediated by platelet-rich fibrin and low-level laser. *Odontology* 112 (2), 399–407. doi:10.1007/s10266-023-00851-8
- Ribeiro, M. F., Zhu, H. Y., Millard, R. W., and Fan, G. C. (2013). Exosomes function in pro- and anti-angiogenesis. *Curr. An giogenes* 2 (1), 54–59. doi:10.2174/22115528113020020001

- Roato, I., Orrico, C., Meinardi, S., Pedraza, R., Mosca Balma, A., Baima, G., et al. (2025). The pro-angiogenic potential of periodontal ligament stem cells and dental pulp stem cells: a comparative analysis. *Cells* 14 (12), 864. doi:10.3390/cells14120864
- Rufas, P., Jeanneau, C., Rombouts, C., Laurent, P., and About, I. (2016). Complement C3a mobilizes dental pulp stem cells and specifically guides pulp fibroblast recruitment. *J. Endod.* 42 (9), 1377–1384. doi:10.1016/j.joen.2016.06.011
- Ruth, A., Hye-Lim, L., Christine, H., and Wang, C. Y. (2015). Single CD271 marker isolates mesenchymal stem cells from human dental pulp. *Int. J. oral Sci.* 7 (4), 205–212. doi:10.1038/ijos.2015.29
- Sabbagh, J., Ghassibe-Sabbagh, M., Fayyad-Kazan, M., Al-Nemer, F., Fahed, J. C., Berberi, A., et al. (2020). Differences in osteogenic and odontogenic differentiation potential of DPSCs and SHED. *J. Dent.* 101, 103413. doi:10.1016/j.jdent.2020.103413
- Sattary, M., Kefayat, A., Bigham, A., and Rafienia, M. (2022). Polycaprolactone/Gelatin/Hydroxyapatite nanocomposite scaffold seeded with Stem cells from human exfoliated deciduous teeth to enhance bone repair: *in vitro* and *in vivo* studies. *Mater. Technol.* 37 (5), 302–315. doi:10.1080/10667857.2020.1837488
- Seo, B. M., Miura, M., Gronthos, S., Mark Bartold, P., Batouli, S., Brahimi, J., et al. (2004). Investigation of multipotent postnatal stem cells from human periodontal ligament. *Lancet* 364 (9429), 149–155. doi:10.1016/s0140-6736(04)16627-0
- Shin, C., Kim, M., Han, J. A., Choi, B., Hwang, D., Do, Y., et al. (2017). Human periodontal ligament stem cells suppress T-cell proliferation via down-regulation of non-classical major histocompatibility complex-like glycoprotein CD1b on dendritic cells. *J. Periodontol. Res.* 52 (1), 135–146. doi:10.1111/jre.12378
- Sonoyama, W., Liu, Y., Fang, D., Yamaza, T., Seo, B. M., Zhang, C., et al. (2006). Mesenchymal stem cell-mediated functional tooth regeneration in swine. *PloS one* 1 (1), e79. doi:10.1371/journal.pone.0000079
- Sun, W., Wang, Z., Xu, Q., Sun, H., Liu, X., Yang, J., et al. (2019). The treatment of systematically transplanted gingival mesenchymal stem cells in periodontitis in mice. *Exp. And Ther. Med.* 17 (3), 2199–2205. doi:10.3892/etm.2019.7165
- Taoran, Z., Hou, W., and Wang, M. (2024). Therapeutic potential and application risks of mesenchymal stem cells derived from induced pluripotent stem cells. *Chin. J. Biochem. Mol. Biol.* 40 (05), 656–663. doi:10.13865/j.cnki.cjbmb.2024.04.1015
- Tsutsui, T. W. (2020). Dental pulp stem cells: advances to applications. *Stem cells cloning Adv. Appl.* 13, 33–42. doi:10.2147/sccaa.s166759
- Wang, J., Wang, X., Sun, Z., Wang, X., Yang, H., Shi, S., et al. (2010). Stem cells from human-exfoliated deciduous teeth can differentiate into dopaminergic neuron-like cells. *Stem Cells Dev.* 19, 1375–1383. doi:10.1089/scd.2009.0258
- Wang, Z., Xiaolan, L., and Liu, J. (2020). How to apply the immunomodulatory characteristics of dental mesenchymal stem cells in the treatment of oral diseases. *Chin. J. Tissue Eng. Res.* 24 (25), 4060–4067. doi:10.3969/j.issn.2095-4344.2100
- Wu, L., Xue, K., Hu, G., Du, H., Gan, K., Zhu, J., et al. (2021). Effects of iRoot SP on osteogenic differentiation of human stem cells from apical papilla. *BMC Oral Health* 21, 407–410. doi:10.1186/s12903-021-01769-9
- Wu, M., Liu, X., Li, Z., Huang, X., Guo, H., Guo, X., et al. (2021). SHED aggregate exosomes shuttled miR-26a promote angiogenesis in pulp regeneration via TGF- $\beta$ /SMAD2/3 signalling. *Cell Prolif.* 54 (7), e13074. doi:10.1111/cpr.13074
- Wu, J., Li, Y., Hu, X., Huang, S., and Xiang, D. X. (2021). Preservation of small extracellular vesicles for functional analysis and therapeutic applications: a comparative evaluation of storage conditions. *Drug Deliv.* 28 (1), 162–170. doi:10.1080/10717544.2020.1869866
- Yamaza, T., Kentaro, A., Chen, C., Liu, Y., Shi, Y., Gronthos, S., et al. (2010). Immunomodulatory properties of stem cells from human exfoliated deciduous teeth. *Stem Cell Res. Ther.* 1 (1), 5. doi:10.1186/scrt5
- Yao, S., Pan, F., Prpic, V., and Wise, G. (2008). Differentiation of stem cells in the dental follicle. *J. Dent. Res.* 87, 767–771. doi:10.1177/154405910808700801
- You, J., Zhang, Q., Qian, L., Shi, Z., Wang, X., Jia, L., et al. (2024). Antibacterial periodontal ligament stem cells enhance periodontal regeneration and regulate the oral microbiome. *Stem Cell Res. and Ther.* 15 (1), 334. doi:10.1186/s13287-024-03939-2
- Yu, Z., Gauthier, P., Tran, Q. T., El-Ayachi, I., Bhatti, F. U., Bahabri, R., et al. (2015). Differential properties of human ALP<sup>+</sup> periodontal ligament stem cells vs their ALP<sup>+</sup> counterparts. *J. Stem Cell Res. Ther.* 5 (7), 292. doi:10.4172/2157-7633.1000292
- Zhang, W., Walboomers, X. F., Shi, S., Fan, M., and Jansen, J. A. (2006). Multilineage differentiation potential of stem cells derived from human dental pulp after cryopreservation. *Tissue Eng.* 12, 2813–2823. doi:10.1089/ten.2006.12.2813
- Zhang, Q., Shi, S., Liu, Y., Uyanne, J., Shi, Y., Shi, S., et al. (2009). Mesenchymal stem cells derived from human gingiva are capable of immunomodulatory functions and ameliorate inflammation-related tissue destruction in experimental colitis. *J. Immunol.* 183 (12), 7787–7798. doi:10.4049/jimmunol.0902318
- Zhang, X. M., Ouyang, Y. J., Yu, B. Q., Li, W., Yu, M. Y., Li, J. Y., et al. (2021). Therapeutic potential of dental pulp stem cell transplantation in a rat model of Alzheimer's disease. *Neural Regen. Res.* 16 (5), 893–898. doi:10.4103/1673-5374.297088
- Zhang, Z., Chen, O., and Bai, M. (2025). Therapeutic potential of bioactive substances secreted by dental mesenchymal stem cells for bone repair. *Chin. J. Tissue Eng. Res.* doi:10.12307/2025.571
- Zhao, Y., Wang, L., Jin, Y., and Shi, S. (2012). Fas ligand regulates the immunomodulatory properties of dental pulp stem cells. *J. Dent. Res.* 91 (10), 948–954. doi:10.1177/0022034512458690
- Zhao, B., Chen, J., Zhao, L., Deng, J., and Li, Q. (2020). A simvastatin-releasing scaffold with periodontal ligament stem cell sheets for periodontal regeneration. *J. of Appl. Biomaterials and Funct. Mater.* 18, 2280800019900094. doi:10.1177/2280800019900094
- Zhao, Y., Gong, Y., Liu, X., He, J., and Zheng, B. (2022). The experimental study of periodontal ligament stem cells derived exosomes with hydrogel accelerating bone regeneration on alveolar bone defect. *Pharmaceutics* 14 (10), 2189. doi:10.3390/pharmaceutics14102189

## Glossary

|                 |                                                              |             |                                 |
|-----------------|--------------------------------------------------------------|-------------|---------------------------------|
| <b>DMSCs</b>    | Dental mesenchymal stem cells                                | <b>PEG</b>  | Polyethylene glycol             |
| <b>MSCs</b>     | Mesenchymal stem cells                                       | <b>PPD</b>  | Probing pocket depth            |
| <b>DPSCs</b>    | Dental pulp stem cells                                       | <b>GR</b>   | Gingival recession              |
| <b>PDLSCs</b>   | Periodontal ligament stem cells                              | <b>AL</b>   | Adhesion loss                   |
| <b>SHEDs</b>    | Stem cells populations from human exfoliated deciduous teeth | <b>PDGF</b> | Platelet-derived growth factor  |
| <b>GMSCs</b>    | Gingival mesenchymal stem cells                              | <b>NF</b>   | Neurofilament                   |
| <b>DFSCs</b>    | Dental follicle stem cells                                   | <b>CCM</b>  | Concentrated conditioned medium |
| <b>DFPCs</b>    | Dental follicle progenitor cells                             |             |                                 |
| <b>ABMSCs</b>   | Alveolar bone mesenchymal stem cells                         |             |                                 |
| <b>SCAPs</b>    | Stem cells from apical papilla                               |             |                                 |
| <b>DPCs</b>     | Dental pulp cells                                            |             |                                 |
| <b>FBS</b>      | Fetal bovine serum                                           |             |                                 |
| <b>FACS</b>     | Fluorescence-activated cell sorting                          |             |                                 |
| <b>OIM</b>      | Odontogenic induction medium                                 |             |                                 |
| <b>ALP</b>      | Alkaline phosphatase                                         |             |                                 |
| <b>HGF</b>      | Hepatocyte growth factor                                     |             |                                 |
| <b>NCAM-1</b>   | Neural cell adhesion molecule 1                              |             |                                 |
| <b>OM</b>       | Osteogenic medium                                            |             |                                 |
| <b>EV</b>       | Extracellular vesicles                                       |             |                                 |
| <b>COL</b>      | Collagen                                                     |             |                                 |
| <b>β-TCP</b>    | β-Tricalcium phosphate                                       |             |                                 |
| <b>HA</b>       | Hydroxyapatite                                               |             |                                 |
| <b>ECM</b>      | Extracellular matrix                                         |             |                                 |
| <b>CM</b>       | Conditioned medium                                           |             |                                 |
| <b>PGH</b>      | Polycaprolactone/gelatin/hydroxyapatite Nanoparticles        |             |                                 |
| <b>PLGA</b>     | Poly(lactic-co-glycolic acid)                                |             |                                 |
| <b>BBR</b>      | Berberin                                                     |             |                                 |
| <b>iRoot SP</b> | Injectable root canal sealer                                 |             |                                 |
| <b>PRF</b>      | Platelet-rich fibrin                                         |             |                                 |
| <b>LLLT</b>     | Low-level laser therapy                                      |             |                                 |
| <b>OCN</b>      | Osteocalcin                                                  |             |                                 |
| <b>OPN</b>      | Osteopontin                                                  |             |                                 |
| <b>GelMA-</b>   | Methacrylated Gelatin                                        |             |                                 |
| <b>MSM</b>      | Methylsulfonylmethane                                        |             |                                 |
| <b>Exos</b>     | Exosomes                                                     |             |                                 |
| <b>Gel-Alg</b>  | GelMA-Alginate                                               |             |                                 |
| <b>BMSCs</b>    | Bone marrow mesenchymal stem cells                           |             |                                 |
| <b>NAC</b>      | N-acetylcysteine                                             |             |                                 |
| <b>ROS</b>      | Reactive oxygen species                                      |             |                                 |
| <b>SIM</b>      | Simvastatin                                                  |             |                                 |
| <b>PCL</b>      | Polycaprolactone                                             |             |                                 |
| <b>DM</b>       | Diabetes mellitus                                            |             |                                 |