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RESEARCH ARTICLE

# Role of Stem Cells in Conjunction with Pathogenesis Related to Head and Neck Region – A Systematic Review

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Abstract: ***Background***: In the last decades, the advancement of biotechnologies has held the promise to disrupt the biomedical field with innovative protocols. These ambitious goals, set in late 1990 with great enthusiasm, seem to have finally become implementable in the dental field, which may be on the verge of attaining important results. Here, the authors wish to recapitulate the most compelling updates dealing with dentistry. Adult stem cells, crucial to tissue engineering, are undifferentiated cells found in nearly all tissues. They can self-renew and develop into various histotypes. Stem cells were first identified in bone marrow (BM), which contains both hematopoietic stem cells (HSCs) and mesenchymal stem cells (MSCs). MSCs are also plentiful in the oral cavity, where they are concentrated in specialized tissues. The first form of dental stem cells was identified from the human pulp tissue of a third molar and dubbed "postnatal dental pulp stem cells" (DPSCs). Later, several types of dental MSCs were defined according to the different sites of isolation: pulp tissue of exfoliated deciduous teeth (SHED); periodontal ligament (PDLSCs); apical papilla of growing teeth (APSCs); dental follicle (DFSCs), gingiva (GFSCs), and buccal fat pad (BFPSCs). ***Material and Methods***: Major databases such as Medline were explored detailed literature search in resulting in a systematic review pertaining to stem cells in oral cavity. ***Results***: Five original research scientific articles dated between 2020 – 2024 pertaining to mentioned topic were highlighted. ***Conclusions***: The oral cavity's homeostasis is determined by the balance of the oral microbiome, the pace of inflammation, and the adaptive bone remodeling of the alveolar bones. When inflammation takes over, irreversible disorders can develop, such as periodontal disease and loss of alveolar bone. MSCs' anti-inflammatory and multi-differentiating characteristics make them suitable for use in regenerative therapy. Nonetheless, because MSCs retain memory of their origin, we feel that using mouth-derived MSCs to treat oral cavity illnesses is appropriate. These cells are found in many locations throughout the oral cavity, and the option of treating patients with autologous MSCs further minimizes the likelihood of unfavorable immunological responses. Detailed information regarding the stem cells in oral cavity is discussed in this systematic review.

Keyword: dental stem cells, regenerative medicine, dental pulp; mesenchymal stem cell; oral cavity; Stem cells; Tissue engineering.

## INTRODUCTION

In the recent decade, stem cells have been proposed for use in regenerative medicine, with mesenchymal stem cells (MSCs) emerging as a prospective treatment alternative in regenerative medicine and tissue engineering due to their regenerative and protective properties. The first therapeutic application of MSCs is a cell-based strategy, where stem cells are delivered directly to the wounded tissue, allowing them to differentiate locally into functional cell types, thereby leading to tissue repair and regeneration. In contrast, the second technique, tissue engineering, involves combining stem cells or differentiated cells with a biodegradable scaffold outside the body to generate a tissue structure that can then be implanted. Most clinical trials have used MSCs obtained from bone marrow.

It is important to note that MSCs obtained from human dental pulp tissue have been employed in clinical studies as a regenerative medicine technique. Several studies and patents now suggest that cells produced from the mouth cavity could be valuable sources of cellular therapies for tissue regeneration, such as wound healing and epithelial restoration. The oral cavity has numerous abundant sources of stem cells, including the mucosal soft tissues, the periodontal ligament (PDL), and the dental pulp, which is the vascularized and innervated tissue located deep within each tooth. The ability of these cells to regenerate tissue has been investigated for dental and other tissues.

Stem cells in the dental pulp are increasingly gaining recognition as pluripotent cells capable of differentiating into numerous lineages. While the regenerative potential

of pulpal stem cells is only beginning to be realized, patients undergoing dental extractions, including wisdom teeth, can now choose to save and store these cells through commercial companies. Pluripotent stem cells can also be extracted from the pulp of shed deciduous (baby) teeth, which may be regarded as an ideal source due to their ease of access.

Given the relatively unknown therapeutic applications and cost, critics may properly question if current pulpal stem cell preservation should be avoided until more is known. Others, of course, believe that storing dental pulp cells is both forward-thinking and appropriate. Pulpal stem cells have been studied for their bioengineering and regenerative properties, both in the oral cavity and beyond. Stem cells from dental pulp may be effective for regenerating soft tissue components such as those found in the pulp itself, as well as mineralized structures such as dentin and bone.

# MATERIALS AND METHODS

"Stem cell" AND "regeneration" AND "oral cavity" were the words used in MEDLINE database using advance search strategy targeting different article categories between 2020 to 2024. The result was 58 articles, out of which we selected 5 articles based in the inclusion criteria. Inclusion criteria was of case studies and scientific literature between 2020-2024. Exclusion criteria was of scientific literature irrelevant to the specific search. This systematic review was conducted to determine importance of stem cells in oral cavity following the guidelines of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses). PubMed, Lilacs, Embase, Scopus, and Web of Science were the source of electronic databases. The search strategy used Boolean operators (AND and OR): [ALL ("stem") AND (cell OR oral OR tissue OR pulp OR mesenchymal) AND (regeneration)]. The following data were collected: first author, year, country of study, type of study and outcome. The quality of studies was assessed using the STROBE (Strengthening the Reporting of Observational Studies) checklist.

# RESULTS

Five articles were included in this systematic review based on the selection criteria. We analyzed and mentioned in the five articles reviewed. This included only relevant research articles and excluded articles pertaining to nonspecific search terms.

**Table 1 – An overview**

| Author | Title | Journal | Outcome |
|---|---|---|---|
| Ilaria Roato, Giorgia Chinigò, Tullio Genova, Luca Munaron, Federico Mussano | Oral Cavity as a Source of Mesenchymal Stem Cells Useful for Regenerative Medicine in Dentistry | Roato I, Chinigò G, Genova T, Munaron L, Mussano F. Oral cavity as a source of mesenchymal stem cells useful for regenerative medicine in dentistry. Biomedicines. 2021 Aug 25;9(9):1085.doi: 10.3390/biomedicines9091085 . | MSCs can be direct, by using cells as components of the tissue to be regenerated |
| Mark Bartold, Saso Ivanovski | Stem Cell Applications in Periodontal Regeneration | Bartold M, Ivanovski S. Stem cell applications in periodontal regeneration. Dental Clinics. 2022 Jan 1;66(1):53-74. doi: 10.1016/j.cden.2021.06.002. | These advances involve identifying dental- and nondental-derived stem cells with the capacity to modulate periodontal regeneration |
| Anami Ahuja, Pankaj Kumar Tyagi, Manoj Kumar, Naveen Sharma, Suraj Prakash, Radha, Deepak Chandran, Sangram Dhumal, Nadeem Rais, Surinder Singh, Abhijit Dey, Marisennayya Senapathy, Lejaniya Abdul Kalam Saleena, Arjun Shanavas, Pran Mohankumar, Sureshkumar Rajalingam, Yasodha | Botanicals and Oral Stem Cell Mediated Regeneration: A Paradigm Shift from Artificial to Biological Replacement | Ahuja A, Tyagi PK, Kumar M, Sharma N, Prakash S, Radha, Chandran D, Dhumal S, Rais N, Singh S, Dey A. Botanicals and oral stem cell mediated regeneration: a paradigm shift from artificial to biological replacement. Cells. 2022 Sep 7;11(18):2792.doi: 10.3390/cells11182792 | In recent years studies were mainly focused on the utilization of oral stem cell-mediated regeneration of bone or dental mesenchymal cells. |

| | | | |
|---|---|---|---|
| Murugesan, Marthandan Vishvanathan, Sangeetha Kizhakkumkara Sathyaseelan, Sabareeshwari Viswanathan, Keerthana Krishna Kumar, Suman Natta, Mohamed Mekhemar | | | |
| Jie Zhao, Ying-Hui Zhou, Ya-Qing Zhao, Zheng-Rong Gao, Ze-Yue Ouyang, Qin Ye, Qiong Liu, Yun Chen, Li Tan, hao-Hui Zhang, Yao Feng, Jing Hu, Marie Aimee Dusenge, Yun-Zhi Feng & Yue Guo | Oral cavity-derived stem cells and preclinical models of jaw-bone defects for bone tissue engineering | Zhao J, Zhou YH, Zhao YQ, Gao ZR, Ouyang ZY, Ye Q, Liu Q, Chen Y, Tan L, Zhang SH, Feng Y. Oral cavity-derived stem cells and preclinical models of jaw-bone defects for bone tissue engineering. Stem Cell Research & Therapy. 2023 Mar 16;14(1):39.https://doi.org/10.1186/s13287-023-03265-z | The type of cell and animal model should be selected according to the specific research purpose and disease type. |
| María Eugenia Cabaña-Muñoz, María Jesús Pelaz Fernández, José María Parmigiani-Cabaña, José María Parmigiani-Izquierdo, José Joaquín Merino | Adult Mesenchymal Stem Cells from Oral Cavity and Surrounding Areas: Types and Biomedical Applications | Cabaña-Muñoz ME, Pelaz Fernández MJ, Parmigiani-Cabaña JM, Parmigiani-Izquierdo JM, Merino JJ. Adult mesenchymal stem cells from oral cavity and surrounding areas: types and biomedical applications. Pharmaceutics. 2023 Aug 9;15(8):2109.doi: 10.3390/pharmaceutics15082109. | human person as a unique being facilitates better clinical and personalized therapy, given the higher prevalence of dental and chronic systemic diseases. |

# DISCUSSION

Stem cells are defined as a special group of clonogenic cells that are characterized by the ability for self-renewal and multilineage differentiation. These cells are responsible for normal tissue renewal as well as for healing and regeneration after injuries.[1]

Stem cells can be divided into three main types, embryonic stem cells (ESCs), adult or postnatal stem cells (ASCs), and induced pluripotent stem cells (iPSCs). ESCs are found in the inner cell mass of mammalian blastocysts during the early stages of embryo development.[2]

A new source of pluripotent stem cells, iPSCs, have been innovatively generated from human somatic cells and potentially can provide tremendous opportunities for tissue regeneration and patient-specific therapies.[3]

ASCs have been identified in almost all the postnatal tissues. Because of their easy accessibility and great ability to generate a tissue different to the site from their origin, ASCs have increasing potential to be used for treatment of degenerative diseases.[4]

Mesenchymal stem cells (MSCs) are multipotent progenitor cells present in many tissues throughout the body and have the capacity to differentiate into bone, cartilage, tendon, fat, and muscle.[5]

Developmental potency is reduced with each step, which means that a unipotent stem cell cannot differentiate into as many types of cells as a pluripotent one.[6]

Totipotent stem cells can divide and differentiate into cells of the whole organism. Totipotency has the highest differentiation potential and allows cells to form both embryo and extra-embryonic structures.[7]

Pluripotent stem cells (PSCs) form cells of all germ layers but not extraembryonic structures, such as the placenta. Embryonic stem cells (ESCs) are an example. ESCs are derived from the inner cell mass of preimplantation embryos.[8]

Another example is induced pluripotent stem cells (iPSCs) derived from the epiblast layer of implanted embryos. Their pluripotency is a continuum, starting from completely pluripotent cells such as ESCs and iPSCs and ending on representatives with less potency—multi-, oligo- or unipotent cells.[9]

One of the methods to assess their activity and spectrum is the teratoma formation assay. iPSCs are artificially generated from somatic cells, and they function similarly to PSCs. Their culturing and utilization are very promising for present and future regenerative medicine.[10]

Multipotent stem cells have a narrower spectrum of differentiation than PSCs, but they can specialize in discrete cells of specific cell lineages. One example is a haematopoietic stem cell, which can develop into several types of blood cells.[11]

After differentiation, a haematopoietic stem cell becomes an oligopotent cell. Its differentiation abilities are then restricted to cells of its lineage. However, some multipotent cells are capable of conversion into unrelated cell types, which suggests naming them pluripotent cells.[12]

Unipotent stem cells are characterized by the narrowest differentiation capabilities and a special property of dividing repeatedly. Their latter feature makes them a promising candidate for therapeutic use in regenerative medicine.[13]

Stem cell biology - A blastocyst is formed after the fusion of sperm and ovum fertilization. Its inner wall is lined with short-lived stem cells, namely, embryonic stem cells. Blastocysts are composed of two distinct cell types: the inner cell mass (ICM), which develops into epiblasts and induces the development of a foetus, and the trophectoderm (TE).[14]

Blastocysts are responsible for the regulation of the ICM microenvironment. The TE continues to develop and forms the extraembryonic support structures needed for the successful origin of the embryo, such as the placenta.[15]

Human embryonic stem cells (hESCs) are derived from the ICM. During the process of embryogenesis, cells form aggregations called germ layers: endoderm, mesoderm, and ectoderm, each eventually giving rise to differentiated cells and tissues of the foetus and, later, the adult organism.[16]

After that, pluripotent stem cells occur all over the organism as undifferentiated cells, and their key abilities are proliferation by the formation of the next generation of stem cells and differentiation into specialized cells under certain physiological conditions.[17]

Signals that influence the stem cell specialization process can be divided into external, such as physical contact between cells or chemical secretion by surrounding tissue, and internal, which are signals controlled by genes in DNA.[18]

Stem cell activity depends on the organ in which they are in; for example, in bone marrow, their division is constant, although in organs such as the pancreas, division only occurs under special physiological conditions.[19]

Stem cell functional division - During division, the presence of different stem cells depends on organism development. Somatic stem cell ESCs can be distinguished. Although the derivation of ESCs without separation from the TE is possible, such a combination has growth limits.[20]

ESCs are derived from the inner cell mass of the blastocyst, which is a stage of pre-implantation embryo ca. 4 days after fertilization. These cells can be described as pluripotent because they are able to eventually differentiate into every cell type in the organism.[21]

Since the beginning of their studies, there have been ethical restrictions connected to the medical use of ESCs in therapies. Most embryonic stem cells are developed from eggs that have been fertilized in an in vitro clinic, not from eggs fertilized in vivo.[22]

Somatic or adult stem cells are undifferentiated and found among differentiated cells in the whole body after development. The function of these cells is to enable the healing, growth, and replacement of cells that are lost each day. These cells have a restricted range of differentiation options.[23]

Mesenchymal stem cells are present in many tissues. In bone marrow, these cells differentiate mainly into the bone, cartilage, and fat cells. As stem cells, they are an exception because they act pluripotently and can specialize in the cells of any germ layer.[24]

Neural cells give rise to nerve cells and their supporting cells—oligodendrocytes and astrocytes. Haematopoietic stem cells form all kinds of blood cells: red, white, and platelets. Skin stem cells form, for example, keratinocytes, which form a protective layer of skin.[25]

The proliferation time of somatic stem cells is longer than that of ESCs. It is possible to reprogram adult stem cells back to their pluripotent state. This can be performed by transferring the adult nucleus into the cytoplasm of an oocyte or by fusion with the pluripotent cell. The same technique was used during cloning of the famous Dolly sheep.[26]

Pluripotent cells can be named totipotent if they can additionally form extraembryonic tissues of the embryo. Multipotent cells are restricted in differentiating to each cell type of given tissue. When tissue contains only one lineage of cells, stem cells that form them are called either called oligo- or unipotent.[27]

As an important part of the maxillofacial region, the jaw bone has crucial role in maintaining the stability of the oral system, mastication, and facial appearance. The maxillofacial region consists of the maxilla and mandible. The mandible and maxilla still have some different characteristics.[28]

Cortical bone density in the mandible is higher than that in the maxilla and increased gradually from the incisor area to the retromolar area. According to attachment/non-attachment of teeth, the maxilla and

mandible are divided into alveolar bone and basal bone.[29]

Basal bone is weighty and has a supporting role, and it is denser and less porous than alveolar bone. As the most important part of the skeletal system, the alveolar bone is closely related to the development, eruption, movement, masticatory function, and exfoliation of teeth.[30]

Teeth attached to the jaw are not only organs that perform masticatory functions directly, but also play an important part in assisting pronunciation, speech, and maintaining facial coordination and beauty.[31]

Teeth consist of dental pulp, cementum, enamel, and dentin. As the toughest tissue in the human body, enamel bears direct masticatory pressure. Dentin forms the main body of the tooth, and the dental pulp within it forms dentin.[32]

The cementum located on the tooth root surface attaches the tooth tightly to alveolar bone through collagen fibers contained within it. Periodontal diseases are inflammatory diseases caused by pathogenic bacteria that bring harm to periodontal tissue, which includes bone and soft tissue that supports the teeth.[33]

The periodontal ligament, as a link between alveolar bone and cementum, can resist and regulate the pressure on teeth during mastication. The strength of the gingiva determines the strength and firmness of teeth.[34]

Mesenchymal SCs (MSCs) are at the forefront of new therapeutic approaches because they can differentiate into a variety of cell types and renew themselves. The most used MSCs are bone marrow MSCs (BMSCs), oral-derived SCs, and adipose-derived MSCs (ASCs).[35]

The Committee on Mesenchymal Stem cells and tissue Stem cells of the International Society of Cell Therapy has proposed a minimum standard for the definition of MSCs: When MSCs are cultured under standard culture conditions, it is adherent to the wall.[36]

MSCs express cluster of differentiation (CD)90, CD73, and CD105, but do not express CD11b or CD14, CD19, CD34, CD45, CD79a, and surface molecules of HLA-DR.In vitro, MSCs exhibit plasticity for osteogenesis, chondrogenesis, and adipogenesis.[37]

SCs in the oral cavity include alveolar bone-derived MSCs (ABMSCs), dental follicle progenitor cells (DFSCs), dental pulp SCs (DPSCs), gingiva-derived MSCs (GMSCs), periodontal ligament SCs (PDLSCs), SCs from the apical papilla (SCAPs), SCs from exfoliated deciduous teeth (SHED), and tooth germ progenitor cells (TGPCs).[38]

Compared with BMSCs, oral cavity-derived SCs have a higher proliferation rate, are easier to obtain, and are very promising sources of SCs for alveolar bone regeneration. The alveolar bone marrow, periosteum, dental tissues, and gingival tissue are available SCs sources.[39]

In terms of the means of acquisition, dental tissues can be less invasive compared to BMSCs because they are "medical waste" which makes them less ethically problematic. And these tissue-derived SCs can be easily amplified from human body with minimal discomfort.[40]

PDLSCs were first isolated and amplified in vitro by Seo and colleagues in 2004. PDLSCs express the cell-surface molecules (CD)66, CD146, CD106, CD105, CD90, stage-specific embryonic antigen-4 (SSEA4), and STRO-1, but not CD45, CD34, CD31, or CD14.[41]

PDLSCs were mainly isolated from the human periodontal ligaments. Some studies have also isolated PDLSCs from the periodontal ligament of animals, such as mice, rats, and rabbits. Enzyme digestion is the most common method to obtain PDLSCs.[42]Several studies revealed that, following a 4-week osteogenic induction, immunohistochemistry and western blotting showed that PDLSCs release Alizarin Red S (ARS) staining and alkaline phosphatase (ALP) demonstrated that PDLSCs formed small circular nodules, which indicated calcium deposition.[43]

In situ tissue engineering, whereby the periodontal ligament is implanted into the periodontal defects of rats for 1, 2, 4, and 8 weeks, revealed that PDLSCs regenerated the cementum–ligament–bone complex at the defect site.[44]

PDLSCs not only have a good ability for bone regeneration but also are an important cell source for periodontal tissue regeneration. PDLSCs can form cementum-periodontal ligament complex in vivo and have the potential to form new periodontal attachment and repair periodontal defects.[45]

Tendon regeneration is another application of PDLSCs. Encapsulated PDLSCs, which develop based on transforming growth factor-β3-loaded RGD-coupled alginate microspheres, were subcutaneously implanted into immunocompromised mice for 4 weeks and showed a stronger tendon regeneration ability than BMSCs or GMSCs.[46]

At present, PDLSCs have been primarily used for tissue regeneration in humans. In a clinical trial, autologous PDLSCs cell membrane was used to treat 3 patients with periodontitis, which found that the periodontal tissue was improved and cementum and periodontal ligament formation could be seen around the cell membrane.[47]

DPSCs are a colony of cloned and rapidly proliferating cells isolated from adult dental pulp. They were first extracted from tooth pulp tissues through enzymatic digestion.[48]

Under specific induction conditions, DPSCs can undergo odontogenesis, adipogenesis, and myogenesis. Without pre-induction, DPSCs can also differentiate toward odontogenic and adipogenic pathways.[49]

In most studies, DPSCs were obtained from the pulp tissue of permanent teeth, deciduous teeth, and tooth germ in humans. There are also a few studies obtained DPSC from animals, including mice, rats, and rabbits.[50]

DPSCs are also used for the regeneration of dentin and dental pulp. In tissue immunocompromised mice, DPSCs grafts could produce a dentin-like structure surrounded by human odontoblast-like cells and pulp-like interstitial.[51]

DPSCs were transplanted subcutaneously into immunodeficient mice and could form a dental pulp–dentin complex at 3 weeks. In terms of clinical application, Chu et al. implanted collagen matrix scaffold with DPSCs into the extraction fossa of mandibular wisdom teeth.[52]

The current main source of SCAPs is the apical papilla of human teeth, and only a few studies have isolated them from the apical papilla of rat teeth.[53]

SCAPs also have a key role in the formation of dentin and pulp tissue. In one study, SCAPs treated with epigallocatechin-3-gallate had a higher proliferation rate, mineral deposition, and ALP activity, and higher expression of odontogenic/osteogenic markers, including bone sialoprotein and collagen type-1, than SCAPs without treatment with epigallocatechin-3-gallate.[54]

The main source of GMSCs is the lamina propria gingival tissue in human, and it has also been isolated from mouse gingival tissue. GMSCs are obtained by enzyme digestion. Gingival tissue was washed twice in phosphate-buffered saline.[55]

SHED is a group of SCs isolated obtained from the residual dental pulp of exfoliated deciduous teeth. SHED can be amplified in vitro and can differentiate into odontoblasts, vascular endothelial cells, adipocytes, smooth muscle cells, neural cells, and osteoblasts.[56]

The residual pulp of exfoliated deciduous teeth is the reliable source of SHED, and no research has shown that SHED can be obtained from animals.[57]

The deciduous teeth derived SHED was implanted into mandibular defects of miniature pig. The authors found that the SHED/β-TCP-treated group had faster repair with formation of many new bones than the control group in which only β-TCP scaffolds were implanted at 6 months.[58]

A dental follicle is an ectomesenchymal tissue surrounding the tooth germ in development. The SCs and directed progenitor cells or progenitor cells in dental follicles are called DFSCs.[59]

DFSCs can differentiate into cementoblasts, osteoblasts, and periodontal ligament cells during tooth development and have the potential for osteogenic, chondrogenic, and adipogenic differentiation in vitro.[60]

DFSCs are mainly separated from dental follicle of impacted third molars in humans. DFSCs are easily obtained because third molar extraction is minimally invasive and harmful to healthy dentition.[61]

DFSCs can also be used for regeneration of dentin and roots. DFSCs induced by a dentin matrix (TDM) differentiated into odontoblasts, expressed bone sialoprotein, osteocalcin, osteopontin, collagen type-I, and ALP and could regenerate intact prefabricated dentin in vivo.[62]

ABMSCs are isolated from human alveolar bone marrow. They have the capacity for osteogenesis, adipogenesis, and chondrogenesis. ABMSCs can be acquired during implant surgery.[63]

The karyotypes of ABMSCs are normal up to 30 population doublings, with significant cell senescence beginning after 35 population doublings.[64]

The source of ABMSC can be human, rats, and mice. Since human ABMSC can be isolated from medical waste generated during implantation or surgery, the most common source is still human.[65]

TGPCs are a group pf SCs in the dental mesenchyme of the tooth germ in the third molar at late bell stage. They were separated from the molar mesenchyme by enzymatic digestion.[66]

Under specific conditions, TGPCs can differentiate into adipogenic, neurogenic, and osteogenic cells, odontoblasts, and hepatocytes.[67]

They can be cryopreserved, and the cryopreserved resuscitated cells can form new bones under the skin of immunocompromised rats.[68]

The third molar tooth germs of humans are the source of TGPCs. For preventative reasons, the third molar tooth germs are usually removed and discarded during orthodontic treatment.[69]

APPLICATIONS OF DENTAL PULP REGENERATION: Based on functional characterization and mechanistic investigations of DPSCs, attempts to achieve pulp regeneration by using DPSCs have been extensively tested in preclinical studies.[70]

The regeneration strategies can be categorized into 4 types of applications: DPSCs with scaffolds, DPSCs with

scaffolds and cytokines, DPSCs with cytokines, and DPSC constructs.[71]

Preclinical experiments on dental pulp regeneration started with using scaffolds, because it was anticipated that scaffolds may exert beneficial effects on the seeded stem cells.[72]

Accordingly, DPSC transplantation was applied with either synthetic or organic materials into partial or whole pulpectomized root canals, confirming that pulp-like tissues with morphologic characteristics resembling the normal dental pulp can be generated in subcutaneous and in situ experiments.[73]

One of the representative cytokines is granulocyte-colony stimulating factor (G-CSF), which possesses anti-inflammatory and antiapoptotic effects while inducing neurogenesis and angiogenesis.[74]

Other cytokines include preameloblast-conditioned medium (PA-CM), which contains natural factors for initiation of odontoblastic differentiation68, and stromal cell-derived factor-1 (SDF-1), which promotes cell survival and neovascularization under hypoxic conditions.[75]

Subpopulations of DPSC-SP cells have further been used in pulp regeneration, which include CD31, CD146, or CD105 DPSC-SP cells. All these functional DPSC subsets were delivered with scaffolds and achieved pulplike tissue regeneration.[76]

Transplantation of DPSCs without scaffolds but pretreated with cytokines is further reported, suggesting that beneficial microenvironments for DPSC function are crucial for pulp regeneration.[77]There are also several studies adopting the exogenous cell-free strategy for pulp regeneration with only cytokine treatments, such as using basic fibroblast growth factor, vascular endothelial growth factor, platelet-derived growth factor, nerve growth factor, and BMP, intending to induce autologous stem cell migration.[78]

However, although connective tissues with abundant cells indeed formed, the cytokineonly strategy is hard to interpret because unidentified cells are recruited with unpredictable outcomes.[79]

In view of the findings and limitations of previous preclinical research, recent studies have documented that application of only DPSC constructs, a regeneration strategy without scaffolds or cytokines, might even be more effective.[80]

These approaches aim to take advantage of the self-assembling niche by DPSCs, which can provide plenty of the natural extracellular matrix resembling the physiological niche structure.[81]

As the sixth most prevalent disease in the world, periodontal diseases (PDs) are chronic inflammatory conditions affecting the periodontium, triggered by the microbial biofilm of dental plaque, which contains up to 800 different species.[82]

Researchers have envisaged the use of MSCs to treat periodontal defects with two main approaches: (a) exploiting the immunomodulatory potential of MSCs and (b) renewing the bone–ligament–cementum complex through tissue engineering protocols.[83]

For instance, DPSCs and GMSCs can interfere with the maturation and activation of dendritic cells, reducing their antigen-presenting cell ability. They also promote the anti-inflammatory phenotype of macrophages, increasing prostaglandin-E2 (PGE2), IL-6, and IL-10.[84]

DPSCs inhibit proinflammatory macrophages modulating the TNF-α/IDO axis. A dysregulation of T cells associated with inflammatory conditions concerns the balance between Th17 and T reg; DPSCs, SHED, PDLSCs, and GMSCs suppress Th17 cells and promote Treg, reducing the inflammation.[85]

The administration of MSCs results in several effects, such as differentiation, secretion of numerous cytokines and growth factors, immune-modulation, and angiogenesis, which are all thought to contribute to the regeneration of damaged human tissues.[86]

MSCs can be considered both sensors and regulators of inflammation in a specific tissue; indeed, their action on the surrounding environment is strictly linked to the rate of inflammation.[87]

The regulation of the immune system exerted by MSCs is relevant since silencing the immune response during tissue repair is necessary to induce tissue regeneration.[88]

Moreover, PDLSC-exosomes are involved in the regulation of bone remodeling during periodontal inflammation. A recent work reported an anti-inflammatory action of PDLSC-exosomes during the interaction between PDLSCs and macrophages.[89]

Exosomes derived from SHED resulted more effectively in stimulating the osteogenic potential of PDLSCs since they activate Wnt/β-catenin and BMP signaling pathways. SHED-exosomes regulated the anti-inflammatory immune response in a mouse model of acute lung injury.[90]

Enamel and dentin are dissolved by acid-forming microorganisms during caries formation. In proximity to the pulp, dentin contains odontoblast processes that are capable of perceiving external stimuli.[91]

Moreover, as soon as microorganisms reach dentin, an infection-related immune response is elicited within the pulp, spanning from an initially reversible, local inflammation to irreversible pulpitis.[92]

Therefore, to prevent pulp degeneration, it is mandatory to limit the inflammatory and immune reaction, which can only be achieved if the microbiological insult is timely kept under control through the removal of caries and cavity sealing.[93]

An intact odontoblast layer enables proper healing, while loss of the odontoblast layer, owing to pathologic noxae or pulp exposure, entails their replacement by odontoblast-like cells. These cuboidal cells secrete reparative dentin, subverting the normal histology of the dentin–pulp interface.[94]

Stem cell therapy with autologous CD105+ cells was proposed successfully in dogs. Briefly, after pulpectomy in fully formed teeth, ex vivo expanded progenitor cells were loaded on carriers with stromal cell-derived factor-1 (SDF-1) and transplanted into root canals.[95]

Exosomes derived from DPSCs cultured under odontogenic differentiation conditions triggered dental pulp-like tissue regeneration in a tooth root-slice model, such as increased expression of DMP1, DPP, and active blood vessels.[96]

Similarly, the regeneration of the dentin pulp complex as a whole owing to the interconnection of its components, albeit theoretically feasible, is hardly implementable at a clinical level to date.[97]

# CONCLUSION

The oral cavity's homeostasis is determined by the balance of the oral microbiome, the pace of inflammation, and the adaptive bone remodeling of the alveolar bones. When inflammation takes over, irreversible disorders can develop, such as periodontal disease and loss of alveolar bone. MSCs' anti-inflammatory and Mult differentiating characteristics make them suitable for use in regenerative therapy. Adult MSCs can be collected from a variety of tissues and exhibit a wide range of differentiation potential. Nonetheless, because MSCs retain memory of their origin, we feel that using mouth-derived MSCs to treat oral cavity illnesses is appropriate.

These cells are found in many locations throughout the oral cavity, and the option of treating patients with autologous MSCs further minimizes the likelihood of unfavorable immunological responses. Extracellular vesicles containing the curative potential of MSCs are undeniably exciting, opening up a plethora of therapeutic possibilities. Future challenges include developing clinical protocols based on a standardized preparation of biological products derived from each patient. To that goal, lowering the cost/benefit ratio will help to make clinical procedures more affordable. Similarly, gathering clinical information on the safety and efficacy of innovative protocols will aid in the transition from current to novel treatments.

In most situations, therapy based on oral-cavity-derived MSCs appears to be highly effective; nevertheless, due to the relatively limited data available in the literature, safety concerns may arise, necessitating additional investigation of any potential harm, particularly in terms of long-term observations. One of the few and most recent studies on MSC safety looked at the pulp regeneration potential and transplantation safety of DPSCs in pulpectomized teeth in dogs, and found no toxicity or adverse effects following transplantation. Based on these principles, in vivo investigations on the potential negative effects of these MSCs are required.

**CONFLICT OF INTEREST**

**NIL**

**AUTHOR'S CONTRIBUTIONS**

- Conceptualization, FIRST AUTHOR
- methodology, SECOND AUTHOR
- software, THIRD AUTHOR
- validation, FOURTH AUTHOR
- formal analysis, FIFTH AUTHOR
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