

DENTAL PULP STEM CELLS AND MAXILLOMANDIBULAR REGENERATION: CURRENT EVIDENCE, MECHANISMS, AND FUTURE PERSPECTIVES - A NARRATIVE REVIEW

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ABSTRACT:

Reconstruction of maxillomandibular defects arising from trauma, tumour resection, congenital anomalies, and periodontal disease remains a major challenge in oral and maxillofacial surgery, as conventional autografts, allografts, and xenografts are limited by donor site morbidity, restricted graft supply, and unpredictable integration. Dental pulp stem cells (DPSCs), a population of neural crest-derived mesenchymal stem cells isolated from the dental pulp of extracted teeth, have emerged as a promising cell source for craniofacial tissue regeneration owing to their high proliferative capacity, multilineage differentiation potential, low immunogenicity, and accessibility from routinely discarded teeth. This narrative review summarises the biology, classification, isolation, and characterisation of DPSCs; the cellular and molecular mechanisms by which they contribute to osteogenesis, neurogenesis, immunomodulation, and angiogenesis; and the tissue engineering strategies, including natural and synthetic scaffolds, growth factor delivery, and three-dimensional bioprinting, used to translate their regenerative potential into clinically applicable constructs. Clinical applications in alveolar bone regeneration, mandibular reconstruction, maxillary sinus augmentation, periodontal regeneration, and nerve repair are discussed alongside a comparison of DPSCs with other dental- and non-dental-derived stem cell sources. Despite encouraging preclinical and early clinical evidence, translation of DPSC-based therapies is limited by poor post-transplantation cell survival, lack of standardised isolation and culture protocols, scarcity of long-term controlled clinical trials, and regulatory and infrastructural barriers. Emerging strategies such as DPSC-derived extracellular vesicles, genetic and epigenetic modification, smart biomaterials, and artificial intelligence-guided scaffold design offer promising avenues to overcome these limitations. Continued interdisciplinary research will be essential to establish DPSC-based therapeutics as a predictable, evidence-based option for maxillomandibular regeneration.

KEYWORDS: Dental pulp stem cells; Maxillomandibular regeneration; Tissue engineering; Oral and maxillofacial surgery; Mesenchymal stem cells; Bone regeneration; Regenerative medicine

INTRODUCTION:

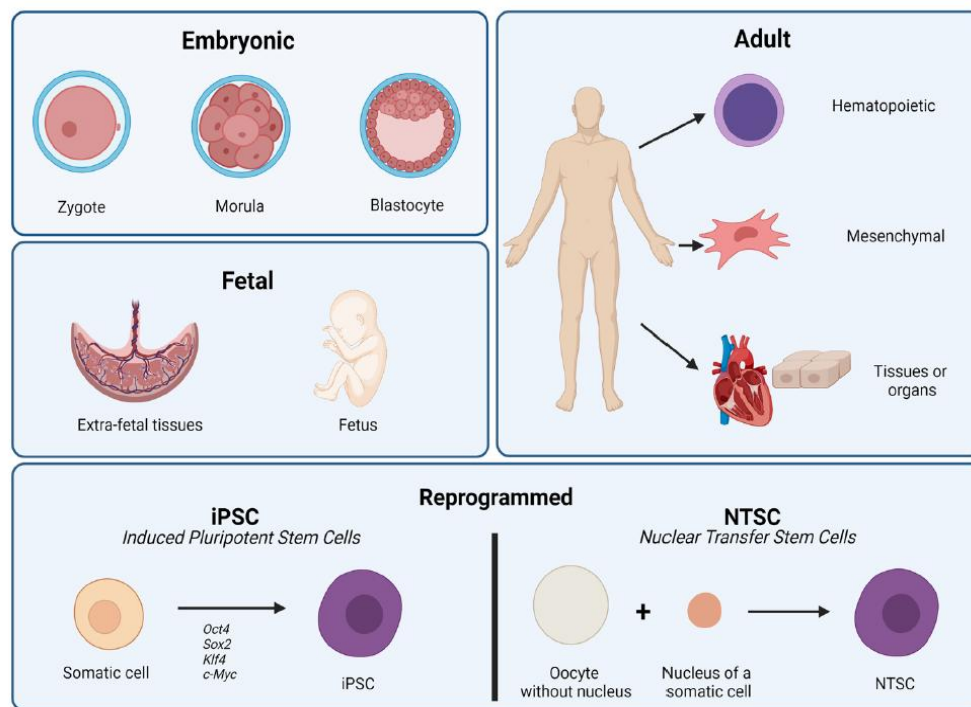
Oral and maxillofacial surgery is a field dealing with complex anatomical structure and functional importance of the craniofacial skeleton which continues to pose a significant challenge in reconstruction of maxillomandibular defects. Despite advances in surgical techniques, predicting and achieving the outcome and long-lasting regeneration of these tissues remains challenging. In recognition of its osteogenic, Osteoinductive and osteoconductive qualities, autogenous bone translation has been regarded as the best option for maxillomandibular regeneration. However considerable donor site morbidity, restricted graft supply, extended surgical time and varying rates of graft resorption are often linked to the clinical usage of autografts. Allografts and xenografts are alternatives to minimise donor site challenge, but they are restricted by immunologic issues, minimal regeneration potential, and delayed integration. The hunt for biologically based methods that can restore native tissue shape and function has been stimulated by these inadequacies.

Tissue engineering and regenerative medicine are currently viable approaches that are meant to repair damaged tissues rather than replace them with the artificial ones. The usage of stem cells, which have an ability to self-renew, differentiate in different cell lineages, and create bioactive substances that aid in tissue healing, is essential to these procedures. Many of the drawbacks of traditional graft-based repair may be addressed by stem cell-based treatments, which have demonstrated promising outcomes in craniofacial bone regeneration.

In the context of maxillomandibular regeneration, dental pulp stem cells have drawn significant attention among the several stem cell populations studied. Dental pulp stem cells are produced from neural crest-derived ectomesenchyme, which have strong osteogenic and neurogenic potential, high proliferative ability, and advantageous immunomodulatory qualities. Their clinical appeal has been further enhanced by their reduced

donor site morbidity and simplicity of access from regularly removed teeth. Their capacity to aid in bone formation, vascularization, and nerve healing inside craniofacial tissues has been shown in experimental and preliminary clinical investigations.[1,2]

Stem Cells



✚ Biology and Characteristics of Dental Pulp Stem Cells

Stem Cell Properties Relevant to Maxillomandibular Regeneration

Stem cell properties include the ability to self-renew, which is essential for extensive proliferation, and the capacity to maintain an undifferentiated state, allowing the generation of sufficient cells for large maxillary and mandibular defects. Another critical characteristic is their ability to differentiate into multiple tissue types, including bone, nerve, cartilage, and soft tissues, which is necessary for effective tissue integration during maxillomandibular regeneration.[1,3]

Along with other craniofacial-derived stem cell populations, dental pulp stem cells (DPSCs) possess distinctive biological characteristics that make them particularly suitable for periodontal ligament and soft tissue regeneration in oral surgery. Unlike other mesenchymal stem cells, DPSCs support axonal regeneration, which is beneficial for alveolar nerve repair and sensory recovery of the mental nerve following trauma. These properties make DPSCs an optimal cell source for oral and maxillofacial applications.[2,4]

Additionally, DPSCs exhibit moderate expression of major histocompatibility complex class I (MHC-I) molecules and low expression of MHC-II, reducing the risk of immune rejection, particularly in immunocompromised patients. For effective maxillomandibular regeneration, stem cells should also enhance vascularization and reduce inflammation through the secretion of growth factors and cytokines. When combined with scaffolds in clinical settings, stem cells should demonstrate strong adhesion and high survival rates. Furthermore, low immunogenicity is advantageous in maxillofacial trauma cases, where rapid and predictable healing is essential.[5]

✚ Classification and Types of Stem Cells

3.1 Classification Based on Potency

Based on their potency, stem cells are classified into five categories: totipotent, pluripotent, multipotent, oligopotent, and unipotent stem cells. Pluripotent stem cells are further categorized into embryonic stem cells and induced pluripotent stem cells.

3.2 Classification Based on Source

Stem cells are also categorized according to their source, including adult (somatic) stem cells, embryonic stem cells (ESCs), dental/oral-derived stem cells, perinatal stem cells, and induced pluripotent stem cells (iPSCs).[6,7] Adult (somatic) stem cells are further classified into peripheral blood stem cells, bone marrow-derived mesenchymal stem cells (BM-MSCs), and adipose-derived stem cells (ADSCs). Perinatal stem cells include umbilical cord-derived mesenchymal stem cells and amniotic fluid stem cells. Dental and oral-derived stem cells are classified as dental pulp stem cells (DPSCs), stem cells from human exfoliated deciduous teeth (SHED), periodontal ligament stem cells (PDLSCs), stem cells from the apical papilla (SCAP), gingival mesenchymal stem cells, and alveolar bone-derived mesenchymal stem cells.[6,8,9,10,11]

Category	Type of Stem Cell	Clinical Source
Dental	DPSCs Dental pulp stem cells[1]	Dental pulp of extracted permanent teeth
	SHED Stem Cells from Human Exfoliated Deciduous Teeth[8]	Exfoliated deciduous teeth
	PDLSCs Periodontal Ligament Stem Cells[9]	PDL of extracted teeth
	SCAP Apical Papilla Stem Cells[10]	Apical papilla
	GMSCs Gingival Mesenchymal Stem Cells[11]	Gingival tissue
	DFSCs Dental Follicle Stem Cells[12]	Dental follicle
	AB-MSCs Alveolar Bone-Derived Mesenchymal Stem Cells	Alveolar bone samples
Adult Nondental	BM-MSCs Bone marrow -derived MSCs[6]	Iliac crest
	ADSCs Adipose Tissue-Derived Stem Cells	Liposuction fat
	PBSCs Peripheral Blood Stem Cells	Peripheral blood
Perinatal	Cord MSCs Umbilical Cord Stem Cells	Umbilical cord
	Amniotic MSCs Amniotic Membrane-Derived MSCs	Amniotic membrane
	Placental MSCs Placenta-Derived Stem Cells	Placenta

3.3 Stem Cells Relevant to Maxillomandibular Regeneration

The stem cell populations most relevant to maxillomandibular regeneration include:

1. **Dental Pulp Stem Cells (DPSCs)[1]** – optimal for bone, nerve, and dentin regeneration
2. **Stem Cells from Human Exfoliated Deciduous Teeth (SHED)[8]** – high proliferative capacity and angiogenic potential
3. **Bone Marrow-Derived Mesenchymal Stem Cells (BM-MSCs)[6]** – gold standard for bone regeneration
4. **Adipose-Derived Stem Cells (ADSCs)** – soft tissue and cartilage repair, including temporomandibular joint applications
5. **Periodontal Ligament Stem Cells (PDLSCs)[9]** – periodontal and peri-implant regeneration
6. **Stem Cells from the Apical Papilla (SCAP)[10]** – root development and mineralization

4. Sources, Isolation, and Characterization of DPSCs

Stem cells originate from three primary biological sources. Embryonic stem cells are derived from early-stage embryos and include totipotent and pluripotent cells with the highest differentiation potential, capable of generating all tissue types. Adult stem cells are present in postnatal tissues throughout life, including bone marrow, adipose tissue, peripheral blood, skin, muscle, liver, and gastrointestinal tissues. These stem cells play a crucial role in tissue maintenance and repair and are widely utilized in clinical regenerative medicine. The third source includes induced pluripotent stem cells (iPSCs), which are artificially generated through genetic reprogramming of somatic cells and possess pluripotent differentiation capabilities.[6,7]

✚ Mechanisms of DPSCs in Maxillomandibular Regeneration

Maxillomandibular regeneration occur through multiple, interrelated biological mechanisms rather than simple cell replacement alone through Dental pulp stem cells. The regeneration capacity is mediated by direct differentiation, paracrine signaling, immunomodulation, angiogenesis and nerve regeneration, all of which play a critical role in restoring the complex structure and function of craniofacial tissues.

The primary mechanism by which DPSCs facilitate regeneration is through osteogenic differentiation. Under appropriate microenvironmental conditions, DPSCs differentiate into osteoblast- like- cells which have capable of producing bone matrixes along with promoting mineralization. These DPSCs have potential osteogenic

potential which a key role in the repair of alveolar bone defects, mandibular discontinuities and maxillary deficiencies. the ability of DPSCs to form mineralized tissue closely resemble native bone and makes them particularly suitable for regeneration in maxillomandibular defects.[1,5]

Dental pulp stem cells (DPSCs) are especially useful for nerve repair in maxillomandibular regeneration in view of their neural crest origin, that gives them a capacity for neurogenic differentiation and axonal development. Through both direct differentiation and paracrine secretion of neurotrophic factors that promote neuronal survival and regeneration, DPSCs aid in neural recovery.[2,13,14]

Additionally, DPSCs contain minimal immunogenicity and immunomodulatory qualities that control immune responses and reduce excessive inflammation. This restricts fibrotic healing and encourages regeneration tissue repair, which is particularly advantageous in maxillofacial regions that have been traumatized or contaminated.[11]

By producing cytokines, growth factors, and extracellular vesicles that promote angiogenesis, attract endogenous progenitor cells, improve matrix remodeling, and coordinate healing responses, DPSCs have powerful paracrine effects that go beyond direct differentiation. Effective tissue regeneration may be largely dependent on these paracrine processes.[15]

The complex biological requirements of maxillomandibular regeneration are addressed by the osteogenic, angiogenic, neuroregenerative, immunomodulatory, and paracrine characteristics of DPSCs taken together, indicating their increasing therapeutic importance in oral and maxillofacial reconstructive techniques.

🌟 Tissue Engineering Strategies Involving DPSCs

Transforming the regenerative potential of dental pulp stem cells (DPSCs) into clinically feasible methods for maxillomandibular restoration requires tissue engineering. The synergistic interaction of DPSCs with scaffolds and bioactive signaling molecules is necessary for effective regeneration; biomaterials offer structural support and biochemical signals for tissue creation, while DPSCs function as the cellular component.[16]

DPSCs have been effectively integrated with both synthetic and natural scaffolds to promote osteogenesis and vascularization. Recent developments in bioprinting, injectable constructs, and three-dimensional culture systems have further improved defect conformity and minimally invasive delivery, making DPSC-based tissue engineering especially appropriate for uses like maxillary sinus augmentation and alveolar bone regeneration.[16,17]

Component	Examples	Key Functions	Clinical Relevance
Stem cells	Dental pulp stem cells (DPSCs)	Osteogenic, angiogenic, neurogenic differentiation; paracrine signaling	Bone, nerve, and soft tissue regeneration
Natural scaffolds	Collagen, fibrin, chitosan	Biocompatibility, cell adhesion, bioactivity	Soft tissue support, early healing
Synthetic scaffolds	Hydroxyapatite, β -TCP, bioactive glass	Mechanical stability, osteoconductivity	Load-bearing craniofacial defects
Growth factors	Osteogenic & angiogenic factors	Promote differentiation, vascularization	Enhanced bone integration
Advanced strategies	3D constructs, bioprinting, injectable hydrogels	ECM mimicry, defect conformity, minimally invasive delivery	Alveolar defects, sinus augmentation

🌟 Clinical Applications of DPSCs in Oral and Maxillofacial Surgery

Due to their capacity for osteogenic, angiogenic, and neurogenic development as well as their therapeutic immunomodulatory characteristics, dental pulp stem cells (DPSCs) show great translational potential in oral and maxillofacial surgery. DPSCs are a promising source of regenerative cells since preclinical and early clinical research demonstrates their efficacy in rebuilding complicated maxillomandibular tissues.[18,19,20]

DPSCs have been studied in clinical settings for neuroregeneration, periodontal and peri-implant regeneration, maxillary sinus augmentation, mandibular defect restoration, and alveolar bone regeneration. DPSCs enable applications including implant site development and craniofacial reconstruction by promoting bone growth, vascularization, and soft tissue healing when paired with osteoconductive scaffolds. When taken as a whole, these uses demonstrate the potential of DPSCs to handle a variety of reconstructive issues in maxillomandibular regeneration; nonetheless, more controlled clinical research is needed to develop standardized procedures.[21,13]

Clinical Application	Regenerative Role of DPSCs	Clinical Relevance
Alveolar bone defects	Osteogenesis, angiogenesis	Implant site development

Clinical Application	Regenerative Role of DPSCs	Clinical Relevance
Mandibular defects	Bone regeneration	Trauma, tumor resection
Maxillary sinus lift	Enhanced bone formation	Posterior maxilla implants
Periodontal regeneration	PDL and bone regeneration	Periodontitis management
Nerve repair	Neurotrophic support	Sensory recovery
Craniofacial defects	Bone and soft tissue repair	Congenital anomalies

✚ Comparison of DPSCs with Other Stem Cell Sources

Although dental pulp stem cells (DPSCs) have attracted increasing attention for maxillomandibular regeneration, they represent only one of several mesenchymal stem cell populations under investigation for craniofacial tissue engineering. Bone marrow-derived mesenchymal stem cells (BM-MSCs) remain the most extensively studied and clinically validated source, having been used in randomized controlled trials of craniofacial bone regeneration[19,20], and are often regarded as the benchmark against which other stem cell populations are compared[6]. However, their collection from the iliac crest is more invasive than harvesting DPSCs from routinely extracted teeth[1].

Direct, donor-matched comparisons of dental-derived stem cell populations indicate that osteogenic capacity varies by tissue of origin: alveolar bone-derived and periodontal ligament-derived mesenchymal stem cells have demonstrated the highest osteogenic differentiation potential, followed by DPSCs, with dental follicle progenitor cells showing the lowest[22]. This finding tempers a straightforward hierarchy in which DPSCs are assumed to be superior for bone regeneration, and suggests that PDLSCs and alveolar bone-derived MSCs may be preferable seed cells for some bone tissue engineering applications[22]. Stem cells from human exfoliated deciduous teeth (SHED) exhibit a higher proliferative rate than both DPSCs and BM-MSCs[8], making them an attractive alternative where rapid cell expansion is required, while stem cells from the apical papilla (SCAP) are particularly suited to dentin-pulp complex and root regeneration[10].

Where DPSCs distinguish themselves is in neurogenic potential: their neural crest origin confers a capacity for functional neuronal differentiation and axonal support that is not shared by mesoderm-derived populations such as BM-MSCs and adipose-derived stem cells (ADSCs)[1,3]. This property, combined with the low immunogenicity common to mesenchymal stem cell populations meeting the minimal criteria for MSC identity[6], makes DPSCs particularly well suited to applications requiring combined bone and nerve regeneration, such as inferior alveolar and mental nerve repair following maxillofacial trauma. Overall, the choice of stem cell source for a given maxillomandibular application should be guided by the specific regenerative requirement — bone volume, nerve function, soft tissue support, or a combination — rather than by a single population being universally superior.

Table: Comparative Overview of DPSCs and Other Stem Cell Sources Relevant to Maxillomandibular Regeneration

Stem Cell Source	Accessibility	Relative Osteogenic Potential	Distinctive Advantage
DPSCs	Extracted permanent teeth (minimally invasive, routinely discarded)	Moderate–high	Neural crest origin confers strong neurogenic and angiogenic potential[1,3]
SHED	Exfoliated deciduous teeth	Moderate	Highest proliferative capacity among dental-derived populations[8]
PDLSCs	Periodontal ligament of extracted teeth	High	Among the highest osteogenic potential in donor-matched comparisons; superior PDL regeneration[9,22]
SCAP	Apical papilla of developing (immature) teeth	Moderate	Root development and dentin–pulp complex regeneration[10]
BM-MSCs	Iliac crest aspirate (more invasive)	High	Long-established benchmark; largest clinical trial evidence base for craniofacial bone[6,19,20]
ADSCs	Liposuction fat (moderately invasive)	Moderate	High yield; well suited to soft tissue and cartilage repair

Table : Challenges and Limitations of DPSC-Based Maxillomandibular Regeneration

✚ Current Challenges and Limitations

Dental pulp stem cells (DPSCs) have great regenerative potential, but their routine clinical application in maxillomandibular regeneration is limited by a few biological and technical issues. Poor cell survival and retention at the defect site because of hypoxia, inflammation, and insufficient vascularization is a serious concern, especially in large or damaged lesions. Furthermore, the biological behaviour and regeneration potential of DPSCs are impacted by variations in donor features, separation techniques, culture conditions, and passage number, which makes standardization and reproducibility across studies difficult.[5,22]

Translational challenges also hinder wider clinical implementation. Long-term, well-controlled clinical trials assessing the safety, effectiveness, and stability of DPSC-based therapies are scarce, limiting evidence-based guideline creation. Regulatory regulations for cell processing, storage, and therapeutic usage complicate treatment, raise costs, and need more infrastructure, limiting accessibility in ordinary practice. Furthermore, patient-specific factors such as systemic health, infection, and local tissue abnormalities can have an impact on regeneration outcomes. Addressing these problems is critical to the effective integration of DPSC-based therapies into standard oral and maxillofacial surgery.[5]

S.no	Challenge	Description	Clinical Impact
1.	Cell survival	Low post-transplant viability	Reduced regeneration
2.	Standardization	Variable isolation & culture protocols	Inconsistent outcomes
3.	Clinical evidence	Limited long-term trials	Restricted adoption
4.	Regulatory issues	Strict cell-therapy guidelines	Increased cost & time
5.	Infrastructure	Need for specialized labs	Limited accessibility
6.	Patient factors	Systemic & local conditions	Variable success rates

✚ Emerging Research Frontiers in Dental Pulp Stem Cell–Based Maxillomandibular Regeneration

Recent breakthroughs in regenerative medicine have taken dental pulp stem cell (DPSC)-based therapies beyond traditional cell transplantation, with new tactics targeted at improving efficacy, safety, and clinical predictability. Notably, DPSC-derived extracellular vesicles and exosomes have gained popularity as cell-free alternatives that maintain paracrine regenerative benefits while lowering cell survival, immunogenicity, and regulatory burden. In parallel, genetic and epigenetic manipulation of DPSCs is being investigated to improve lineage-specific differentiation, although clinical translation necessitates careful safety and ethical consideration.[15,4]

Advancements in biomaterials, smart scaffolds, and three-dimensional bioprinting have accelerated DPSC-based regeneration. Responsive scaffolds that can transmit dynamic biochemical and mechanical cues, as well as patient-specific bioprinted constructions, allow for the accurate restoration of complex maxillomandibular abnormalities.[17,16]

Furthermore, the combination of artificial intelligence and computational modeling opens up new possibilities for optimizing scaffold design and personalizing regenerative techniques. Collectively, these advancements represent a shift toward more refined, customized, and less invasive methods to maxillomandibular regeneration with DPSC.

✚ CONCLUSION

Maxillomandibular regeneration is still a significant problem in oral and maxillofacial surgery due to the functional and cosmetic demands of the craniofacial region. Dental pulp stem cells have emerged as a potentially regenerative cell source due to their neural crest origin, high proliferative ability, multilineage differentiation potential, and immunomodulatory capabilities. While preclinical and early clinical research show promising results in bone, vascular, and neurological regeneration, issues with standardization, regulatory compliance, and long-term evidence remain. Continued interdisciplinary research and technology developments are required to ensure the predictable clinical translation of DPSC-based therapeutics.

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