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# *Advances in the Application of Dental Pulp Stem Cells for Repairing Facial Nerve Damage after Orthognathic Surgery*

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***Abstract.*** In orthognathic surgery, sagittal split mandibulectomy is a commonly used procedure for correcting mandibular deformities, however, postoperative nerve injury is relatively common in clinical practice, and is particularly likely to injure the inferior alveolar nerve (IAN), which may cause prolonged or irreversible facial paresthesia in certain individuals. However, current clinical treatment options are limited, primarily consisting of regular follow-up observations, the use of neurotrophic drugs, and minimally invasive nerve repair surgery. However, due to limitations in the rate of nerve self-repair, nerve activity continues to decline after injury, often resulting in incomplete functional recovery and affecting patients' daily life quality. Dental pulp stem cells (DPSCs) originate from the neural crest in terms of histoembryology and share a common origin with neural stem cells. Therefore, in contrast to mesenchymal stem cells harvested from other tissues such as bone marrow or fat, DPSCs exhibit superior neurogenic capabilities, when subjected to specific stimuli, these cells are capable of differentiating into neuron-like cells and expressing neural markers. Furthermore, they facilitate the regeneration of injured nerves via the paracrine release of nerve growth factor, thus presenting novel therapeutic avenues and research targets for managing such nerve damage. This article reviews recent research progress on the role of dental pulp stem cells in promoting the repair of facial nerve injuries following orthognathic surgery, providing a theoretical basis and research directions for the prevention and treatment of such postoperative nerve injuries.

***Keywords:*** Orthognathic procedures, DPSCs, neural regeneration, inferior alveolar nerve (IAN)

## 1. Introduction

Orthognathic surgery is a core procedure for correcting jaw deformities and improving occlusion and facial appearance. Among these procedures, mandibular sagittal split osteotomy is commonly performed, however, its most frequent complication—injury to the inferior alveolar nerve—often leads to facial numbness and decreased sensation, and in some patients, to persistent or irreversible neurological deficits, including reduced lip sensation, speech difficulties, and eating disorders, which substantially impair patients' quality of life and postoperative satisfaction. Currently, no standardized therapeutic regimen exists for postoperative nerve injury, and recovery largely depends on intrinsic regenerative capacity, with neurotrophic drugs serving as adjunctive therapy minimally

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invasive reconstructive surgery. This approach has drawbacks such as a lengthy treatment period, slow recovery, and inconsistent outcomes, and the current state of clinical treatment requires improvement. Dental pulp stem cells (DPSCs) originate from neural crest tissue and possess remarkable differentiation potential, including the ability to self-renew and differentiate in multiple directions. Under specific conditions, they can differentiate directionally into neuron-like cells and secrete various bioactive neurotrophic factors. Through paracrine pathways, they provide key factors for nerve regeneration and microenvironment reconstruction, demonstrating unique advantages and broad prospects in the field of nerve injury repair. However, few systematic reviews have examined the use of dental pulp stem cells to repair facial nerve damage following orthognathic surgery, and the mechanisms underlying stem cell-assisted nerve repair have not yet been fully elucidated. Based on this, this paper systematically reviews the mechanisms of neural differentiation and neurotrophic regulation in dental pulp stem cells and explores the feasibility of their application in the repair of inferior alveolar nerve injury following orthognathic surgery, with the aim of providing new insights and theoretical references for the clinical treatment of such injuries.

## 2. Nerve injury following orthognathic surgery and the limitations of the body's autogenous repair process following injury

IAN damage represents a prevalent complication following orthognathic procedures. Specifically, SSRO is associated with the highest rate of postoperative NSD, with reported incidences varying between 25% and 95% [1, 2], and 11% of patients still experience persistent NSD one year after surgery [2]. The incidence of NSD following isolated chin augmentation surgery ranges from 6.8% to 12% [3]. The majority of patients report sensory disturbances on the affected side, affecting the lower lip, chin, gingiva, and cheek. These symptoms include numbness, anesthesia, hypoesthesia, dysesthesia, and burning pain. Additionally, the duration and prognosis of these symptoms vary considerably among individuals [3, 4]. IAN injury not only results in sustained patient discomfort but also markedly diminishes quality of life. It leads to varying degrees of sensory dysfunction—such as lip and chin numbness, paresthesia, and neuropathic pain—and may further cause psychological and social disturbances [5].

Injuries to the inferior alveolar nerve caused by orthognathic surgery primarily involve compression, traction, or even rupture of nerve fibers. Following such an injury, the body may initiate the self-repair processes specific to peripheral nerves—Wallerian degeneration (WD) and axonal regeneration. During the Wallerian degeneration phase, the distal end of the damaged axon separates from the cell body and begins to degenerate. Myelin Schwann cells then proliferate and migrate, producing cytokines and neurotrophic factors, and participate in the phagocytosis of neural debris, resident macrophages are activated, and recruited macrophages and neutrophils jointly clear myelin and debris. While clearing myelin debris, macrophages produce cytokines that activate Schwann cells and neurotrophic factors that aid in axonal regeneration [6]. After debris is cleared, Schwann cells are rapidly activated by injury signals. On the one hand, they secrete various neurotrophic factors to support the survival of damaged neurons, on the other hand, they proliferate to form the Büngner band, which guides axonal regeneration, allowing the axon to traverse the injury site and reconnect with distal target tissues. Finally, myelinating Schwann cells remyelinate the regenerated axon, thereby restoring neural function. Throughout this process, the progression of Schwann cells—from dedifferentiation and proliferation to redifferentiation into myelin-producing cells—constitutes a central mechanism of peripheral nerve self-repair.

Although the aforementioned autologous repair procedures can achieve a certain degree of regeneration, the repair outcomes are not ideal: nerve recovery is slow, and some patients still

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experience sensory deficits one year after surgery, for injuries involving the inferior alveolar nerve canal, some patients even develop long-term or permanent sensory abnormalities [3]. Current clinical interventions primarily consist of oral neurotrophic agents (such as methylcobalamin and glucocorticoids), physical therapy, and salvage surgery, however, there is no standardized treatment protocol, and the efficacy of these approaches remains controversial [3]. Against this backdrop, stem cell therapy offers a new way to improving the repair of nerve damage following orthognathic surgery. DPSCs can not only directly participate in repair by differentiating into Schwann cells and neuron-like cells, but also promote, accelerate, and support the body's endogenous repair process through mechanisms such as paracrine neurotrophic factors, and thus hold promise for addressing the shortcomings of current treatments.

## 3. Mechanisms by which stem cells promote neural self-repair

### 3.1. Secretion of neurotrophic factors: promoting neuron survival and axon growth

Paracrine signaling is considered one among the core mechanisms mediating the effects of MSCs exert their neuro-regenerative effects, stem cells can release various neurotrophic factors via paracrine mechanisms, directly supporting neuronal survival and guiding axonal growth. MSCs can release various important neurotrophic factors via paracrine mechanisms, including neurotrophin-3 (NT-3), brain-derived neurotrophic factor (BDNF), basic fibroblast growth factor (bFGF), and glial cell-derived neurotrophic factor (GDNF). Their conditioned medium enhances the survival and growth of Schwann cells, upregulates the exhibition of NGF and BDNF within Schwann cells, and promotes neurite outgrowth in dorsal root ganglion explants [7].

These factors bind to specific receptors on the axonal membranes of neurons (such as BDNF binding to TrkB, NGF binding to TrkA, GDNF binding to GFRα1, and NT-3 binding to TrkC), triggering downstream signal transduction, which results in two key neurobiological effects: first, promoting neuronal survival and maintaining the structural stability of the neuronal cell body, second, promoting neurite growth—specifically, axonal extension and nerve fiber maturation—which aid in the reconstruction and repair of neural networks [8]. Taking GDNF as an example, it significantly promotes neuronal survival and regulates axonal growth, for trigeminal neurons, both GDNF and BDNF can significantly increase the tally of trigeminal neurons in culture as a function of dose, thereby supporting the survival of sensory neurons following injury [9]. Furthermore, MSCs can deliver bioactive molecules to target cells via extracellular vesicles such as exosomes, thereby further amplifying their paracrine reparative effects [10].

### 3.2. Modulating schwann cells: inducing dedifferentiation and proliferation, and establishing a microenvironment for axon growth

Schwann cells are key players in the body's self-repair process after a peripheral nerve injury: after nerve injury, Schwann cells at the nerve stump undergo demyelination and adopt a "repair-type" phenotype. Repair-oriented Schwann cells re-enter the cell cycle and proliferate, clearing myelin debris and aligning along the nerve stump to form "Büngner bands" that guide axonal regeneration, thus offering structural support and directional cues for axonal regeneration and creating a permissive microenvironment [11]. Stem cells play a crucial regulatory role in this process. On one side, MSCs have the ability to differentiate into Schwann cells [12], and Schwann cells secrete various master neurotrophic factors—including nerve growth factor, brain-derived neurotrophic factor, ciliary neurotrophic factor, and glial cell-derived neurotrophic factor—which promote the

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repair of nerve damage [13]. On the other side, paracrine factors secreted by stem cells can stimulate the dedifferentiation and proliferation of endogenous Schwann cells [14]. Thus, MSCs can not only directly participate in myelin remyelination by differentiating into Schwann cells themselves, but also regulate the proliferation of endogenous Schwann cells, thereby jointly creating a microenvironment conducive to axonal growth.

### 3.3. Immune inflammatory regulation: suppressing destructive immune responses and preventing excessive damage

Excessive inflammatory responses following nerve injury are key factors leading to secondary nerve damage and hindering regeneration, MSCs possess significant immunomodulatory and anti-inflammatory properties and can suppress excessive, destructive immune responses [15-17]. Studies show that MSCs engage in crosstalk with various immune cells such as T cells, B cells, dendritic cells, macrophages, and natural killer cells by secreting immune-regulating factors for instance IL-10, TGF-β, IDO, and PGE2. They suppress pro-inflammatory M1 macrophages, promote anti-inflammatory M2 macrophage polarization, induce regulatory T cells (Tregs) to form, and at the same time inhibit dendritic cell maturation [18, 19].What is more, MSC-derived exosomes can deliver bioactive molecules such as proteins and miRNAs to immune cells, thereby inhibiting T-cell proliferation, downregulating the expression of pro-inflammatory factors such as TNF-α and IL-6, promoting M2 polarization, and suppressing M1 activation, thus creating an anti-inflammatory immune microenvironment in the damaged area [20-22]. By suppressing excessive inflammatory responses, MSCs indirectly protect damaged nerve cells from secondary injury, creating a relatively stable tissue environment for self-repair. This is an important mechanism by which they support nerve recovery.

### 3.4. Improved blood supply: promotes angiogenesis in the damaged area and improves nutrient supply

An adequate blood supply is essential for providing the oxygen and nutrients necessary for nerve regeneration. Endothelial cells be a central role in the early repair of peripheral nerve injuries, and MSCs mediate the repair of neurovascular coupling by secreting VEGF. Vascular endothelial growth factor (VEGF) is a key cytokine involved in angiogenesis and neovascularization, it not only promotes angiogenesis to improve blood supply to the damaged area but also protects nerves and promotes nerve regeneration [23]. Previous studies have found significantly elevated levels of angiogenic markers such as VEGF and von Willebrand factor (vWF) at sites of nerve injury repair. Increased VEGF expression correlates with improved nerve regeneration, confirming the importance of angiogenesis for peripheral nerve regeneration [24, 25]. By promoting the proliferation of vascular endothelial cells and rebuilding the vascular network in damaged areas, MSCs provide the oxygen and nutrients necessary for nerve regeneration, thereby indirectly supporting and accelerating the body's natural repair process.

In summary, stem cells exert their multifaceted reparative benefits through the synergistic interaction of four mechanisms: first, immune regulation suppresses destructive inflammatory response and establishes a stable microenvironment conducive to restore. This drives neurotrophic factor secretion, which provide the impetus for neuronal survival and axonal growth. Schwann cells then regulate myelin remyelination and axonal guidance, while vascular regeneration ensures a continuous supply of oxygen and nutrients throughout the process. These four mechanisms are

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closely interconnected and build upon one another, ultimately facilitating the completion of the body's own neural repair process.

## 4. Advantages of dental pulp stem cell therapy

However, there are many types of stem cells, and not all sources of stem cells are suitable for recovery of the lower alveolar nerve after orthognathic surgery the repair of the inferior alveolar nerve following orthognathic surgery. Due to their unique embryonic origin and multidimensional regenerative capacity, DPSCs are considered one of the most promising candidate cell types [26]. DPSCs were first isolated from dental pulp tissue by Gronthos et al. in 2000, and they are adult mesenchymal stem cells that originate from the neural crest. DPSCs can be obtained from the pulp tissue of discarded teeth, such as wisdom teeth extracted during routine clinical procedures or teeth removed for orthodontic purposes, this method involves minimal trauma and requires no additional surgery. Additionally, they offer advantages such as abundant sources, simple extraction, low immunogenicity, and a high proliferation rate in vitro [27]. Crucially, during orthognathic surgery, it is often necessary to simultaneously extract impacted third molars (wisdom teeth) or remove healthy teeth located within the osteotomy line. These teeth would otherwise be discarded as medical waste after surgery, however, if these healthy teeth are collected immediately during the procedure, sufficient DPSCs can be isolated and expanded from their dissected pulp tissue. This provides a convenient source of autologous cells near the surgical site without additional trauma.

From the perspective of repair mechanisms, DPSCs, as a type of stem cell, possess all the repair-promoting mechanisms characteristic of stem cells. Studies have confirmed that they can secrete various neurotrophic factors, including nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), glial cell-derived neurotrophic factor (GDNF), and neurotrophin-3 (NT-3). High expression of these factors mediates tissue repair by promoting axonal regeneration and vascular reconstruction at the site of injury [28, 29]. Following specific induction, DPSCs can also enhance the secretion and expression of the aforementioned key neurotrophic factors, further amplifying their neuroprotective effects [29]. GDNF and NT-3 secreted by DPSCs are crucial for the survival and axonal growth of trigeminal neurons. Furthermore, compared to stem cells derived from bone marrow mesenchyme and fat mesenchymal stem cells, DPSCs secrete approximately 3–10 times higher levels of neurotrophic factors, which provides a unique advantage for their application in neural repair [30, 31].

In addition, DPSCs at different stages of development (such as those derived from primary and permanent teeth) exhibit differences in immune modulation, anti-inflammatory effects, expression of neural markers, and angiogenesis, thereby offering a wider range of options for neural repair [32]. From the perspective of clinical feasibility, DPSCs have demonstrated the potential for repair in various models of peripheral nerve and facial nerve injuries: studies have confirmed that TGF-β3-induced dental pulp stem cells can differentiate directionally into neural stem cells, thereby effectively repairing damaged facial nerves, as evidenced by an increase in new nerve fibers, improved myelination, and significant relief of symptoms associated with nerve injury, transplantation of DPSCs into the site of a transected rat spinal cord promotes axonal regeneration, inhibits apoptosis in various types of neurons, and facilitates nerve regeneration, Schwann-like cells derived from dental pulp stem cells have also been shown to promote regeneration following peripheral nerve injury (including alveolar-associated nerves) [32-34]. Together, these studies demonstrate that the use of DPSCs to repair inferior alveolar nerve injury following orthognathic surgery is technically feasible.

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## 5. Challenges in clinical practice

Currently, clinical studies on DPSCs transplantation for nerve injuries are still in the early exploratory stage. While their short-term safety and effectiveness have been initially confirmed, there are still many obstacles to large-scale, standardized clinical applications. In terms of effectiveness, the process of DPSCs differentiating into nerve cells faces challenges such as poor adaptation to the microenvironment, low differentiation efficiency, and limited controllability. Moreover, issues such as the uncontrollable direction of axonal regeneration and difficulty in restoring functional connections still need to be addressed. Besides, when it comes to jaw corrective surgery specifically, there is a practical dilemma about how to fit the timing of collecting autologous DPSCs (before or during surgery), the period for in vitro expansion, and the timing of transplantation into the established surgical workflow [35]. Overall, most of the current evidence comes from in vitro studies and animal models, and whether this translates well to humans in orthognathic surgery and whether it can be standardized still require further evidence-based validation. In terms of quality control and large-scale production, the large-scale production of stem cells for clinical applications faces significant bottlenecks [36]. Fetal bovine serum used in traditional culture media poses safety risks such as viral transmission and allergic reactions, therefore, it is necessary to establish a culture system free of heterologous serum that complies with Good Manufacturing Practices (GMP) to enable large-scale cell production [37].

To this end, establishing standardized cell characterization criteria and a quality release testing system, as well as refining the regulatory framework, are essential prerequisites for advancing the clinical translation of DPSCs. In terms of safety and ethics, stem cell transplantation still faces potential risks like non-specific differentiation and immune rejection. Unlike embryonic stem cells, the collection of dental pulp stem cells does not involve the destruction of embryos, resulting in relatively fewer ethical controversies, however, as a procedure involving the collection and reinfusion of the patient's own biological material, its clinical application must still adhere to strict standards regarding informed consent, standardized sample handling, and biosafety protocols. At the same time, differences in public understanding of stem cell therapies may also affect the acceptance of this technology, which must be gradually improved through standardized clinical guidelines and science communication. In summary, due to their neural crest origin, diverse regenerative mechanisms, and ease of procurement, dental pulp stem cells offer a highly promising therapeutic approach for the repair of inferior alveolar nerve injury following orthognathic surgery, however, their clinical translation must still proceed steadily across multiple dimensions, including efficacy, quality control, and ethical standards.

## 6. Conclusion

Nerve damage after orthognathic surgery is an important complication that can affect patients' quality of life. This article systematically discusses the mechanisms and prospects of dental pulp stem cells (DPSCs) in repairing this type of injury. The following conclusions can be drawn: As adult mesenchymal stem cells derived from the neural crest, DPSCs possess a synergistic, multi-pathway repair capacity. They can differentiate into neuron-like cells, Schwann cells, and glial cells to reconstruct neural structures, and they can also secrete neurotrophic factors such as NGF, BDNF, GDNF, and other neurotrophic factors and immunomodulatory factors, thereby regulating the inflammatory microenvironment and promoting axonal regeneration and vascular reconstruction. Compared to mesenchymal stem cells from other sources, they possess an inherent advantage in terms of neural differentiation potential, most importantly, DPSCs can be directly harvested from the

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pulp tissue of healthy teeth discarded during maxillary surgery, thereby achieving "autologous sourcing, proximity to the surgical site, and no additional trauma." They offer accessibility, low immunogenicity, and minimal ethical controversy, and animal studies have confirmed their regenerative potential in models of facial nerve, mental nerve, and spinal cord injuries. However, their clinical translation still faces multiple challenges, including validation of efficacy, GMP-level standardized quality control, the controllability of axonal regeneration direction, and public acceptance. Furthermore, most of the existing evidence comes from in vitro experiments and animal models, and there is still a lack of high-quality, large-scale randomized controlled clinical trials to support it. Therefore, future research should focus on establishing a GMP-grade large-scale cultivation and quality control system, conducting prospective, multicenter clinical trials on inferior alveolar nerve injury following orthognathic surgery, identifying optimal protocols regarding the timing of tissue harvesting, expansion cycles, and transplantation, deepening research into the mechanisms of controllable axonal regeneration and functional synaptic reconstruction, and refining the long-term follow-up and efficacy evaluation systems. Overall, dental pulp stem cells offer a very promising technological path for repairing the inferior alveolar nerve, but their large-scale clinical use still depends on ongoing research.

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