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Exosomes and Their Potential in Repairing Inferior Alveolar Nerve Injuries: A Review of Current Evidence

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Abstract

Injury to the inferior alveolar nerve (IAN) is a frequent and debilitating complication of dental and maxillofacial procedures, often resulting in sensory deficits that significantly affect quality of life. Conventional treatments, including pharmacological management, microsurgical repair, and autologous nerve grafting, are limited by donor site morbidity, incomplete functional recovery, and variable outcomes. Exosomes, nano-sized extracellular vesicles secreted by various cell types such as mesenchymal stem cells and Schwann cells, have emerged as a promising, cell-free therapeutic approach for peripheral nerve regeneration. These vesicles carry a rich cargo of proteins, mRNAs, and microRNAs, which collectively promote axonal growth, modulate Schwann cell behavior, regulate neuroinflammation, and enhance angiogenesis, creating a favorable microenvironment for nerve repair. Preclinical studies have demonstrated that exosome therapy can stimulate neurite outgrowth, promote Schwann cell proliferation and remyelination, and reduce inflammatory responses through macrophage polarization and suppression of pro-inflammatory cytokines. Advances in delivery systems, including localized injections, hydrogel-based sustained release, and 3D-printed nerve conduits, have further improved their therapeutic potential. While most evidence remains preclinical, exosome-based interventions show superior safety profiles with minimal immunogenicity, tumorigenicity, and donor site complications compared to traditional grafts or stem cell therapies. This review summarizes the biological mechanisms, cellular sources, optimization strategies, and preclinical evidence supporting the application of exosomes in IAN injury. With continued translational research and clinical validation, exosome therapy holds significant promise as a minimally invasive and effective strategy for enhancing functional recovery following inferior alveolar nerve injuries.

Keywords: Inferior alveolar nerve, Nerve regeneration, Exosomes, Schwann cells, Axonal growth

Introduction

Injuries to the inferior alveolar nerve (IAN) are a frequent and often debilitating consequence of various dental and maxillofacial interventions, including third molar extractions, dental implant placement, orthognathic surgeries, and management of mandibular trauma. Such injuries commonly lead to sensory abnormalities like paraesthesia, hypoesthesia, or dysesthesia, which can significantly diminish a patient's quality of life [1]. Although peripheral nerves possess an inherent ability to regenerate, recovery after IAN damage is often partial and unpredictable. Traditional treatment strategies—including pharmacological therapies, microsurgical repair, and autologous nerve grafting—are constrained by challenges such as donor site morbidity, scar formation, and inconsistent functional recovery.

In recent years, exosomes have gained attention as a promising cell-free therapeutic option in regenerative

medicine [2]. These nanoscale extracellular vesicles, typically ranging from 40 to 160 nm in diameter, are secreted by various cell types, including Schwann cells and mesenchymal stem cells. They are enriched with bioactive components such as proteins, messenger RNAs, and microRNAs, which facilitate communication between cells and regulate critical processes involved in nerve repair [3]. Exosomes support regeneration by promoting axonal growth, activating Schwann cells, modulating neuroinflammatory responses, and enhancing angiogenesis. Compared to conventional grafting techniques, exosome-based therapies are minimally invasive and carry a reduced risk of immune rejection or donor site complications [4].

This review aims to provide an in-depth examination of the biological properties of exosomes and highlight their emerging role in peripheral nerve regeneration, with a particular emphasis on their potential therapeutic application in the management of inferior alveolar nerve injuries.

Exosomes in Nerve Regeneration: Biological Basis

Exosomes are small extracellular vesicles, typically ranging from 40 to 160 nm, which originate from multivesicular bodies and are secreted into the extracellular environment via exocytosis. The molecular composition of exosomes varies depending on the type and physiological state of the parent cell, but they generally contain a complex cargo of proteins, lipids, messenger RNAs, and microRNAs that can profoundly influence recipient cells. In the setting of peripheral nerve regeneration, such as after inferior alveolar nerve injury, exosomes demonstrate a range of therapeutic activities [5].

These vesicles exert neurotrophic effects by transporting essential growth factors, including brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), glial cell line-derived neurotrophic factor (GDNF), and neurotrophin-3 (NT-3), all of which support axonal regrowth and enhance neuronal survival. Exosomes also promote angiogenesis at sites of nerve injury by delivering pro-angiogenic molecules such as vascular endothelial growth factor (VEGF) and microRNA-126, improving blood supply and facilitating tissue repair [6].

In addition to their regenerative and vascular effects, exosomes possess immunomodulatory properties. They can induce macrophage polarization toward the anti-inflammatory M2 phenotype while suppressing pro-inflammatory cytokine production, thereby creating a microenvironment favourable for nerve healing. Specific exosome microRNAs, including miR-21 and miR-219, have been shown to enhance Schwann cell proliferation, differentiation, and remyelination, which are critical steps in effective peripheral nerve repair. Through these multifaceted actions—neurotrophic support, angiogenesis, immune modulation, and Schwann cell activation—exosomes emerge as highly promising biological mediators for improving functional recovery after peripheral nerve injury [7].

Axonal Regeneration and Schwann Cell Modulation by Exosomes

Exosomes are key mediators in peripheral nerve repair, particularly in processes such as axonal regeneration and Schwann cell (SC) modulation, which are critical for recovery following inferior alveolar nerve injuries. These extracellular vesicles serve as carriers of a diverse array of bioactive molecules - including proteins, microRNAs (miRNAs), and messenger RNAs (mRNAs) - that regulate essential cellular pathways involved in nerve regeneration (Yu et al., 2021; Supra et al., 2023) [6,7].

A central mechanism of action involves the uptake of exosomes by injured axons and surrounding Schwann cells. The molecular cargo of exosomes supports neuronal survival, enhances growth cone activity, and promotes axonal elongation by inducing a pro-regenerative state in the neurons.

Exosomes also exert a profound influence on Schwann cell function. They stimulate SC dedifferentiation, proliferation, and activation, processes vital for debris clearance and the formation of a microenvironment conducive to axonal growth. Activated Schwann cells, in turn, release neurotrophic factors and form

guiding pathways through the distal nerve stump, facilitating precise axonal navigation and functional recovery [8].By simultaneously promoting direct axonal repair and optimizing the supportive functions of glial cells, exosomes provide a coordinated, multifaceted approach to peripheral nerve regeneration, making them a highly promising candidate for therapeutic applications in clinical settings.

Exosome-Mediated Axonal Regrowth and Inflammatory Modulation

Exosomes play a critical role in promoting axonal regrowth and guiding regenerating nerve fibres by delivering a variety of signalling molecules, including specific microRNAs such as miR-21 and key neurotrophic factors. These bioactive cargos stimulate neurite extension and axonal elongation by modulating intracellular signalling pathways. For example, exosomes can downregulate phosphatase and tension homolog (PTEN) while activating the PI3K/Akt pathway, mechanisms that are vital for neuronal survival and efficient axonal regeneration [9].

Beyond their direct effects on axons, exosomes exert important immunomodulatory actions that facilitate nerve repair. Following nerve injury, a regulated inflammatory response is essential for clearing cellular debris; however, uncontrolled or prolonged inflammation can hinder regeneration, promote scar formation, and obstruct axonal growth. Exosomes help balance this response by inducing macrophage polarization toward the anti-inflammatory M2 phenotype and suppressing pro-inflammatory cytokine production. This modulation minimizes fibrotic scarring and establishes a microenvironment favourable for neuronal repair and functional recovery. By simultaneously enhancing axonal regrowth and shaping a supportive inflammatory milieu, exosomes provide a dual mechanism that positions them as potent therapeutic agents with significant potential to improve outcomes in peripheral nerve injuries [10].

Exosomes in Vascular Regeneration and Immunomodulation for Nerve Repair

Vascular regeneration is essential for effective nerve repair, as an adequate blood supply delivers oxygen and nutrients while removing metabolic waste, thereby supporting the survival and function of regenerating nerve tissue. Exosomes, particularly those derived from mesenchymal stem cells (MSCs), have shown significant potential in promoting angiogenesis. They carry pro-angiogenic molecules, including microRNAs such as miR-126 and growth factors like vascular endothelial growth factor (VEGF), which stimulate endothelial cell proliferation and migration. This leads to the formation of new capillaries at the site of injury, creating a metabolically favourable environment for axonal growth and Schwann cell activity [11].

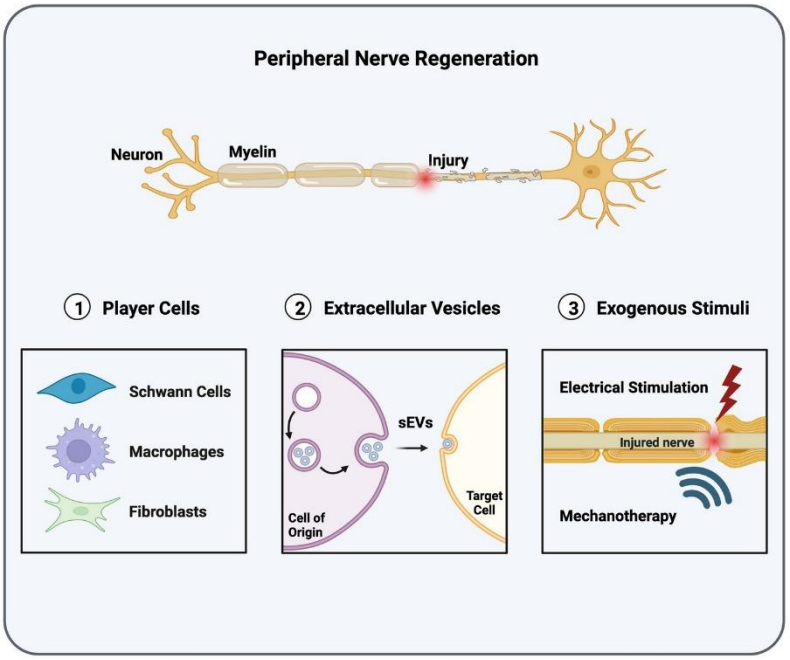

Figure 1: Role of extracellular Vesicles and exogenous stimuli in peripheral nerve regeneration

In addition to their pro-vascular effects, exosomes play a pivotal role in modulating inflammation and immune responses following nerve injury. They transport anti-inflammatory proteins and regulatory microRNAs that help suppress excessive inflammatory signalling and maintain immune homeostasis. This function is particularly important in the oral and maxillofacial region, where surgical trauma and microbial exposure can exacerbate inflammatory responses. By promoting macrophage polarization toward the regenerative M2 phenotype, exosomes help minimize secondary tissue damage, reduce fibrosis, and support timely resolution of inflammation [12,13].

Through the dual actions of enhancing vascularization and regulating immune responses, exosomes act as versatile agents that not only directly facilitate neural repair but also optimize the surrounding tissue environment. This makes them a promising therapeutic strategy for promoting peripheral nerve regeneration, including applications in inferior alveolar nerve injuries [14].

Cellular Sources and Optimization Strategies for Exosome-Based Nerve Regeneration

The regenerative efficacy of exosomes in peripheral nerve repair is closely linked to their cellular origin, as different cell types produce vesicles with unique molecular profiles and functional capacities. Adipose-derived stem cells (ADSCs) are among the most extensively studied sources, generating exosomes enriched with neurotrophic factors, anti-inflammatory molecules, and pro-angiogenic mediators. These vesicles have shown considerable promise in promoting axonal regeneration and functional recovery. Strategies to further enhance their therapeutic potential, such as preconditioning ADSCs with pharmacological agents like FK506 (Tacrolimus), have produced variable outcomes, with some studies reporting improved regenerative effects while others observed limited benefit (Rau et al., 2021) [15].

Beyond ADSCs, exosomes derived from fibroblasts and Schwann cells have attracted attention for their cargo of specialized RNAs and proteins that support axonal growth and simultaneously inhibit fibrotic scar formation, a major impediment to nerve repair (Zhou et al., 2023) [16]. Each cellular source presents distinct advantages and challenges. Mesenchymal stem cell (MSC)-derived exosomes are valued for their rich growth factor content and ability to modulate immune responses and stimulate angiogenesis, although their therapeutic consistency can be influenced by donor variability and cell passage number. Schwann cell-derived exosomes are particularly effective at promoting remyelination and guiding regenerating axons, but large-scale production remains technically demanding. Neural stem cell (NSC)-derived exosomes facilitate neurogenesis and axonal elongation, yet their limited availability restricts widespread clinical use.

Recently, gingival mesenchymal stem cells (GMSCs) have emerged as a promising, accessible source of exosomes, offering potent immunomodulatory effects and minimal risk of immune rejection. Although research is still in early stages, GMSC-derived exosomes may provide a practical and scalable option for future therapeutic applications. Overall, careful selection of the exosome-producing cell type, along with strategies to enhance their regenerative properties, is crucial for developing effective cell-free approaches for nerve repair and functional restoration [13,14].

Preclinical Evidence and Emerging Applications of Exosomes in Inferior Alveolar Nerve Injury

Recent preclinical studies underscore the therapeutic potential of exosomes in peripheral nerve repair, with most research focusing on models of sciatic and facial nerve injuries. For instance, Li et al. (2020) demonstrated that exosomes derived from human umbilical cord mesenchymal stem cells (MSCs) enhanced sciatic nerve regeneration by activating the PI3K/Akt signalling pathway, a critical mediator of neuronal survival and axonal growth. Similarly, Zhang et al. (2022) showed that exosome miR-21 reduced inflammation and stimulated Schwann cell proliferation in a rat model of nerve injury, highlighting both anti-inflammatory and neurodegenerative effects. Although direct investigations in inferior alveolar nerve

injury (IANI) remain limited, these findings can be reasonably extrapolated due to the shared biological mechanisms governing peripheral nerve repair [15]. MSC-derived exosomes in IANI models hold particular promise for enhancing Schwann cell functions, including proliferation, migration, and myelination, which collectively support axonal regeneration and facilitate functional reinnervation of target muscles [16].

To maximize therapeutic outcomes, advanced delivery strategies are being developed. Direct local injection at the injury site provides targeted effects, while sustained-release systems - such as exosome-loaded hydrogels composed of biocompatible materials like chitosan, fibrin, or collagen-help maintain effective concentrations over time. Additionally, innovative approaches like 3D-printed nerve conduits embedded with exosomes offer structural guidance for axonal growth across nerve gaps. Stem cells from dental tissues, including dental pulp stem cells and periodontal ligament stem cells, also exhibit neurotrophic and immunomodulatory properties, making them particularly relevant for dental-specific nerve injuries such as IANI. These preclinical findings provide a strong foundation for developing clinical protocols aimed at restoring function following inferior alveolar nerve injuries [17].

Advantages, Challenges, and Future Directions of Exosome Therapy for IAN Regeneration

Exosome-based therapies offer several notable advantages over traditional approaches such as autologous nerve grafts, particularly for inferior alveolar nerve (IAN) repair. A major benefit is their low immunogenicity, which substantially reduces the risk of immune rejection compared to conventional grafts. Unlike certain stem cell treatments, exosomes also carry minimal tumorigenic potential. Additionally, exosome therapy eliminates donor site morbidity associated with autologous graft harvesting, making it a safer and less invasive option [18]. Exosomes are also easier to handle, store, and standardize, improving logistical feasibility in clinical settings. Their ability to enable localized, targeted delivery-via controlled-release systems or direct injections - further enhances their therapeutic utility, which is often challenging with conventional grafts.

Despite these advantages, several challenges must be addressed before exosome therapy can become a mainstream clinical option. Standardization remains a key concern, as optimal cell sources, dosing regimens, and delivery methods need to be clearly established and validated. Most current evidence comes from preclinical animal models, underscoring the need for well-designed clinical trials (Phase I/II) focusing on IAN or trigeminal nerve injuries to determine safety, efficacy, and reproducibility in human patients [19].

Looking ahead, future strategies may involve combining exosomes with biomaterials, such as injectable hydrogels or 3D-printed nerve conduits, to provide site-specific, sustained therapeutic effects. Advances in genetic engineering could allow donor cells to produce exosomes enriched with critical regenerative molecules like miR-133b, BDNF, or NT-3. The development of point-of-care systems for producing autologous, patient-specific exosomes could further minimize immunological risks and improve clinical outcomes. Collectively, these innovations, coupled with rigorous translational research, position exosome therapy as a promising and potentially transformative approach for the management of inferior alveolar nerve injuries [20].

Discussion on Recent Literatures

Study (Year)	Model / Design	Exosome source	Delivery / Method	Key findings	Main limitations
Yu et al[1]., 2021	In vivo (rat) experimental	Schwann cell-derived	Local implantation / graft containing	Enhanced axonal regeneration and	Limited to animal models

			exosomes	remyelination	
Namini et al[2]., 2023 (review)	Systematic review of preclinical studies	MSC-derived	Multiple delivery strategies summarized (injection, hydrogels, conduits)	Activated PI3K/Akt pathway, improved axonal growth	Donor variability
Xia et al[3]., 2024	Review / translational perspective	PRP + MSC exosomes	Discusses local injection and biomaterial carriers	Combined therapy boosted nerve repair	Complex design
Li et al[6]., 2025 (MDPI)	Preclinical studies summarized	iPSC-derived	Discusses mechanisms (paracrine signalling, PI3K/Akt activation)	Promoted regeneration, safe short-term	Long-term safety unclear
Zhang et al[4]., 2024 (J Control Release)	In vivo / translational study	MSC exosomes + 3D conduit	Local delivery; combined therapy	Sustained release improved repair	Manufacturing challenges
Wang et al[5]., 2025	In vivo (rat sciatic) safety/efficacy	Hypoxia-conditioned MSC	Local injection: safety assessment	Increased pro-regenerative factors	Needs standardization
Yao et al[7]., 2025 / 3D conduit papers	Bioengineering + in vivo tests	Schwann cell-derived	Exosome-loaded hydrogel inside aligned 3D nerve conduits	Enhanced axonal regeneration and remyelination	Limited to animal models
Zeng et al[8]., 2025	Preconditioning study (in vitro / in vivo)	MSC-derived	Preconditioning of parent cells prior to exosome harvest	Activated PI3K/Akt pathway, improved axonal growth	Donor variability

Summary

Injuries to the inferior alveolar nerve (IAN) during dental and maxillofacial procedures can cause sensory disturbances that impair quality of life. Conventional treatments like nerve grafting and microsurgery often yield inconsistent outcomes. Exosomes, nanosized vesicles secreted by various cells, have emerged as a promising cell-free therapy for nerve regeneration. They deliver bioactive molecules that promote axonal growth, Schwann cell activation, angiogenesis, and immune regulation, creating an environment favorable for nerve repair.

Derived from sources such as mesenchymal stem cells (MSCs), Schwann cells, and gingival stem cells, exosomes enhance regeneration through pathways like PI3K/Akt activation and macrophage M2 polarization. They offer several advantages—low immunogenicity, no donor site morbidity, and ease of handling but require further standardization and clinical trials. With advancements in genetic engineering and biomaterial-based delivery systems, exosome therapy holds strong potential as a safe, minimally invasive, and effective approach for inferior alveolar nerve regeneration.

Conclusion

Exosome-based therapy offers a novel and promising strategy for enhancing nerve regeneration following inferior alveolar nerve injury. Through their ability to modulate Schwann cell activity, support axonal

growth, and establish a favourable regenerative microenvironment, exosomes have the potential to address many of the limitations associated with current treatment approaches. Ongoing research, along with carefully designed clinical studies, will be crucial to translating these preclinical advances into effective and standardized therapies for dental nerve injuries.

Conflict of Interest: Nil

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