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Use of Exosomes for Nerve Regeneration after Inferior Alveolar Nerve Injury: A Review

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KEYWORDS

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ABSTRACT:

Introduction: Inferior alveolar nerve (IAN) injury is a frequent complication of dental and maxillofacial surgery, often causing persistent sensory deficits. Conventional treatments achieve limited recovery. Exosomes, nano-sized extracellular vesicles carrying proteins, nucleic acids, and lipids, have emerged as promising cell-free therapies. They can stimulate axonal growth, activate Schwann cells, modulate neuroinflammation, and promote angiogenesis. This review highlights the biological features of exosomes, their mechanisms in nerve repair, and their potential in IAN regeneration.

Methodology:

A literature search was conducted in PubMed, Scopus, and Web of Science using the terms "exosomes," "inferior alveolar nerve injury," "Schwann cells," and "nerve regeneration." Relevant experimental and review studies in English were included, with a focus on exosomes in peripheral nerve repair.

Results:

Preclinical studies demonstrate that exosomes enhance axonal regeneration, stimulate Schwann cell activity, regulate inflammation, and improve vascularization. Their low immunogenicity and non-reliance on donor grafts minimize complications. Key limitations include a lack of standardized isolation methods, uncertainties in dose optimization, and limited clinical trial data.

Conclusion:

Exosomes represent a minimally invasive and effective strategy for IAN repair, supported by encouraging preclinical findings. Future research should prioritize clinical translation,

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protocol standardization, and integration with biomaterials or genetic modification to maximize therapeutic potential.

Introduction

Injury to the inferior alveolar nerve (IAN) is a common and often debilitating complication arising from dental and maxillofacial procedures such as third molar extraction, dental implant placement, orthognathic surgery, and mandibular trauma management. These injuries frequently result in sensory disturbances, including paraesthesia, hypoesthesia, or dysesthesia, significantly impacting patients' quality of life [1]. While peripheral nerves possess some regenerative capacity, the recovery following IAN injury is frequently incomplete. Conventional treatment options, ranging from pharmacological agents to microsurgical repair and autologous nerve grafting, face limitations such as donor site morbidity, scar formation, and variable functional outcomes. In recent years, exosomes have emerged as a promising, cell-free approach in the field of regenerative medicine [2].

These nano-sized extracellular vesicles (approximately 40–160 nm in diameter) are secreted by a variety of cells, including Schwann cells and mesenchymal stem cells. Rich in bioactive molecules such as proteins, mRNAs, and microRNAs, exosomes facilitate intercellular communication and modulate key processes in nerve repair [3]. Their regenerative potential lies in their ability to promote axonal growth, activate Schwann cells, regulate neuroinflammation, and enhance angiogenesis. Unlike traditional grafting techniques, exosome-based therapies offer a minimally invasive alternative with a lower risk of immune rejection or donor site complications [4]. This review aims to provide a comprehensive overview of the biological characteristics of exosomes and their emerging role in peripheral nerve regeneration, with a specific focus on their therapeutic application in inferior alveolar nerve injury.

Exosomes in Nerve Regeneration: Biological Basis

Exosomes are nano-sized extracellular vesicles that originate from multivesicular bodies and are released into the extracellular space through exocytosis. Their composition varies according to the source cell type and its physiological condition, but they typically carry a rich cargo of proteins, lipids, mRNAs, and microRNAs that exert significant regulatory effects on recipient cells. In the context of peripheral nerve regeneration, such as after inferior alveolar nerve injury, exosomes exhibit multiple therapeutic functions [5].

They exert neurotrophic effects by delivering key growth factors like brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), glial cell line-derived neurotrophic factor (GDNF), and neurotrophin-3 (NT-3), which are known to facilitate axonal regeneration and neuronal survival. Furthermore, exosomes contribute to neovascularization at the injury site through pro-angiogenic molecules such as vascular endothelial growth factor (VEGF) and microRNA-126 (miR-126), which support nutrient delivery and tissue repair [6]. Their immunomodulatory properties also play a critical role by influencing macrophage polarization toward the anti-inflammatory M2 phenotype and downregulating pro-inflammatory cytokines, thereby establishing a microenvironment conducive to healing. Additionally, exosomal microRNAs like miR-21 and miR-219 have been shown to stimulate Schwann cell proliferation, differentiation, and remyelination, key processes in effective peripheral nerve repair. Together, these multifaceted mechanisms highlight the potential of exosomes as powerful biological agents for

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promoting functional recovery following nerve injury [7].

Mechanisms of Exosome-Mediated Nerve Regeneration

Axonal Regeneration and Schwann Cell Modulation by Exosomes

Exosomes play a pivotal role in promoting axonal regeneration and modulating Schwann cell (SC) behaviour, both of which are fundamental processes in peripheral nerve repair, including the healing of inferior alveolar nerve injuries. These extracellular vesicles act as delivery vehicles for a variety of bioactive molecules—such as proteins, microRNAs (miRNAs), and messenger RNAs (mRNAs)—that regulate key cellular activities necessary for nerve regeneration (Yu et al., 2021; Supra et al., 2023) [6,7]. One of the critical mechanisms involves the internalization of exosomes by damaged axons and resident Schwann cells. Exosomal cargo can enhance axonal survival, stimulate growth cone dynamics, and encourage axonal elongation by promoting a pro-regenerative phenotype.

Moreover, exosomes significantly influence Schwann cell behaviour by inducing their dedifferentiation and proliferation. This is essential not only for supporting the regeneration process but also for clearing myelin debris a crucial step in creating a permissive environment for axonal sprouting. These activated Schwann cells secrete growth factors and guide regenerating axons through the distal nerve stump, thereby facilitating functional nerve recovery [8]. By orchestrating both direct axonal repair and the supportive functions of glial cells, exosomes offer a sophisticated and coordinated approach to peripheral nerve regeneration, representing a promising therapeutic strategy for clinical application.

Exosome-Mediated Axonal Regrowth and Inflammatory Modulation

Exosomes contribute significantly to axonal regrowth and directional guidance during nerve regeneration by transporting a diverse array of signalling molecules, including specific microRNAs such as miR-21 and various neurotrophic factors. These bioactive components promote neurite outgrowth and axonal elongation by influencing critical intracellular signalling pathways. Notably, exosomes are known to suppress the expression of phosphatase and tensin homolog (PTEN) while simultaneously activating the PI3K/Akt pathway, both of which are essential for enhancing neuronal survival and facilitating axonal regeneration [9]. In addition to their direct effects on axons, exosomes play a crucial immunomodulatory role in the nerve healing process.

Following injury, an orchestrated inflammatory response is necessary for clearing cellular debris; however, excessive or chronic inflammation can impair regeneration by inducing scar formation and impeding axonal progress. Exosomes help fine-tune this response by promoting the polarization of macrophages toward an anti-inflammatory M2 phenotype and downregulating pro-inflammatory cytokines. This regulatory action reduces fibrotic scar formation and creates a microenvironment that is conducive to effective neural repair and functional recovery. Through this dual mechanism, enhancing axonal outgrowth and optimizing the inflammatory milieu, exosomes emerge as powerful therapeutic agents capable of significantly improving outcomes in peripheral nerve injuries [10].

Exosomes in Vascular Regeneration and Immunomodulation for Nerve Repair

Vascular regeneration is a critical component of successful nerve repair, as a well-established blood supply ensures the delivery of oxygen and nutrients

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while facilitating waste removal, conditions essential for supporting regenerating nerve tissues. Exosomes, particularly those derived from mesenchymal stem cells (MSCs), have demonstrated the ability to enhance angiogenesis through the delivery of pro-angiogenic microRNAs, such as miR-126, and growth factors like vascular endothelial growth factor (VEGF) [11]. These vesicles stimulate endothelial cell proliferation and migration, leading to the formation of new capillaries around the injury site, thereby creating a metabolically supportive environment for axonal regeneration and Schwann cell function. In addition to promoting vascularization, exosomes play a vital role in modulating the inflammatory and immune response following nerve injury [12].

They carry anti-inflammatory proteins and regulatory miRNAs that suppress excessive inflammatory cascades and promote immune homeostasis. This is especially important in the oral and maxillofacial region, where inflammation is often heightened due to microbial exposure and surgical trauma. By influencing immune cells such as polarizing macrophages toward a regenerative M2 phenotype, exosomes help limit secondary tissue damage, reduce fibrosis, and support the resolution of inflammation [13]. The combined effects of enhanced vascular regeneration and immune modulation position exosomes as multifaceted agents that not only directly promote neural recovery but also optimize the surrounding tissue environment for effective peripheral nerve regeneration, including applications in inferior alveolar nerve injuries [14].

Cellular Sources and Optimization Strategies for Exosome-Based Nerve Regeneration

The therapeutic potential of exosomes in peripheral nerve repair is heavily influenced by their cellular origin, as different source cells secrete exosomes with distinct molecular cargos and regenerative capabilities. Among the most studied are adipose-derived stem cells (ADSCs), which produce exosomes rich in neurotrophic factors, anti-inflammatory molecules, and angiogenic mediators. These exosomes have demonstrated significant promise in enhancing nerve regeneration. Attempts to further augment their efficacy, such as pre-treating ADSCs with pharmacological agents like FK506 (Tacrolimus), have yielded mixed results; while some studies noted enhanced regenerative potential, others reported negligible improvements in functional outcomes (Rau et al., 2021) [15]. In addition to stem cells, fibroblast- and Schwann cell-derived exosomes have garnered interest due to their content of specialized RNAs and proteins that support axonal growth while concurrently inhibiting fibrotic scar formation, a major barrier to nerve regeneration (Zhou et al., 2023) [16].

Each exosomal source has its advantages and limitations. For instance, mesenchymal stem cell (MSC)-derived exosomes are known for their rich content of growth factors and their ability to modulate immune responses and promote angiogenesis; however, their efficacy can vary depending on donor characteristics and cell passage number. Schwann cell-derived exosomes are highly effective in enhancing remyelination and guiding regenerating axons, but large-scale harvesting remains technically challenging. Neural stem cell (NSC)-derived exosomes offer benefits in promoting neurogenesis and axonal elongation, although their limited availability restricts their broader application. More recently, gingival mesenchymal stem cells (GMSCs) have emerged as a promising and easily accessible source, with early studies indicating strong immunomodulatory properties and minimal risk of immune rejection. While still in the early stages of exploration, GMSC-derived exosomes may represent a practical and scalable option for future clinical use. Collectively, the strategic selection and potential enhancement of exosome-producing cells are critical steps in optimizing cell-free therapies for nerve regeneration [13,14].

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

A growing body of preclinical research highlights the regenerative potential of exosomes in peripheral nerve repair, particularly in models involving sciatic and facial nerve injuries. For example, Li et al. (2020) demonstrated that exosomes derived from human umbilical cord mesenchymal stem cells (MSCs) facilitated sciatic nerve regeneration by activating the PI3K/Akt signalling pathway, which is vital for neuronal survival and axonal growth. Similarly, Zhang et al. (2022) reported that exosomal miR-21 significantly reduced inflammation and promoted Schwann cell proliferation in a rat nerve injury model, suggesting strong anti-inflammatory and neuroregenerative properties. Although direct studies on inferior alveolar nerve injury (IANI) are currently lacking, these findings can be extrapolated due to the shared biological characteristics of peripheral nerves [15]. The application of MSC-derived exosomes in IANI models holds significant promise, particularly in enhancing Schwann cell activity, including proliferation, migration, and myelination, which collectively contribute to improved axonal regeneration and functional muscle reinnervation [16].

Advanced delivery systems are being explored to maximize the therapeutic efficacy of exosomes in such nerve injuries. Localized injection near the injury site offers targeted action, while sustained-release systems, such as exosome-loaded hydrogels made from biocompatible materials like chitosan, fibrin, or collagen, help maintain therapeutic levels over an extended period. Moreover, innovations like 3D-printed nerve conduits embedded with exosomes and scaffold materials provide structural guidance for axonal regrowth across nerve gaps. In addition, stem cells derived from dental tissues such as dental pulp stem cells or periodontal ligament stem cells have shown neurotrophic and immunomodulatory potential, making them highly relevant for treating dental-specific nerve injuries, including those involving the inferior alveolar nerve. These preclinical insights lay the foundation for translating exosome-based therapies into clinical protocols aimed at restoring function after IANI [17].

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

Exosome-based therapies present numerous advantages over traditional approaches such as autologous nerve grafts, particularly in the context of inferior alveolar nerve (IAN) regeneration. One of the most significant benefits is their low immunogenicity, which drastically reduces the risk of immune rejection compared to conventional grafts that may elicit a host response. Moreover, exosomes carry a minimal risk of tumorigenicity, unlike certain stem cell therapies, which can potentially form tumours. Donor site morbidity, a major limitation of autologous graft harvesting, is entirely avoided with exosome therapy, making it a safer and less invasive option [18]. Additionally, exosomes are easier to store, handle, and standardize, offering better logistical feasibility for clinical use. They also enable targeted delivery, allowing localized treatment through controlled release systems or direct injections, which is more challenging with traditional nerve grafts.

Despite these advantages, several challenges remain before exosome therapy can be widely implemented in clinical practice. Standardization is a key issue; optimal source selection, dosage, and delivery methods need to be clearly defined and validated. Importantly, while most existing data are derived from preclinical animal models, well-designed clinical trials (Phase I/II) specifically targeting IANI or trigeminal nerve injuries are essential to evaluate the safety, efficacy, and reproducibility of these treatments in human patients [19]. Looking forward, future directions include the integration of exosomes with

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biomaterials, such as injectable hydrogels and 3D-printed nerve conduits, to achieve site-specific and sustained therapeutic effects. Additionally, advancements in genetic engineering could allow the enhancement of donor cells to secrete exosomes enriched with key regenerative molecules like miR-133b, BDNF, or NT-3. The development of point-of-care autologous exosome production systems, where a patient's own cells are used to produce personalized exosomes, may further reduce immunological risks and improve treatment outcomes. These innovations, combined with robust translational research, hold great promise for positioning exosome therapy as a transformative modality in the management of inferior alveolar nerve injuries [20].

Conclusion

Exosome-based therapies represent a novel and promising approach for promoting nerve regeneration after inferior alveolar nerve injury. By leveraging their capacity to modulate Schwann cell behaviour, stimulate axonal regrowth, and create a pro-regenerative microenvironment, exosomes could overcome many limitations of current treatments. Continued research and clinical validation will be essential to translate these advances into standard care for dental nerve injuries.

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