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Short Communication

Mesenchymal stem cell exosomes in periodontal regenerations

Ankita Chaudhary[1], Sachit Anand Arora[1], Gunjan Gupta[1]*, Shivesh Mishra[1], Priyanka Tandon[1], Jeevika A Das[1]

[1]Dept. of Periodontics, ITS Dental College, Greater Noida, Uttar Pradesh, India

Abstract

Periodontal diseases are chronic inflammatory conditions affecting the tooth-supporting structures and represent a significant global health burden due to their high prevalence, complex etiology, and the need for long-term treatment and maintenance. While conventional periodontal therapy effectively halts disease progression through mechanotherapy and chemotherapeutic approaches, predictable regeneration of the lost periodontal apparatus remains a major clinical challenge. Various graft materials such as autografts, allografts, and xenografts have been employed with varying degrees of clinical success; however, consistent histological evidence of true periodontal regeneration remains elusive.

Recent advances in regenerative medicine have shifted focus toward biologically driven strategies involving signaling molecules, cells, and scaffolds to promote periodontal regeneration. Among these, mesenchymal stem/stromal cell (MSC)–derived exosomes have emerged as a promising cell-free therapeutic modality. Exosomes are nano-sized extracellular vesicles that mediate intercellular communication and possess potent immunomodulatory, anti-inflammatory, angiogenic, and regenerative properties. MSC-derived exosomes have demonstrated the ability to suppress inflammatory responses and enhance tissue repair through the delivery of bioactive molecules.

Preclinical evidence suggests that MSC exosome–based therapies can enhance periodontal ligament cell function and promote periodontal regeneration. Experimental studies using exosome-loaded collagen scaffolds have shown significant improvements in alveolar bone formation, functional periodontal ligament regeneration, and inhibition of epithelial down-growth in animal models. These findings indicate that transient exposure to MSC-derived exosomes may initiate sustained endogenous regenerative processes.

Although clinical application of MSC exosomes in periodontology is still in its early stages, ongoing clinical trials highlight their translational potential. MSC-derived exosomes represent a novel and promising approach for achieving predictable periodontal regeneration and may overcome the limitations associated with conventional grafting and cell-based therapies.

Keywords: Alveolar bone, Tissue engineering, Cell-free therapy.

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1. Introduction

Periodontal diseases are chronic inflammatory disorders that affect the tooth-supporting structures, including the gingiva, periodontal ligament (PDL), cementum, and alveolar bone. They are among the most prevalent oral diseases worldwide and constitute a major cause of tooth loss in adults. Epidemiological studies indicate that severe periodontitis affects a substantial proportion of the global population, contributing significantly to oral dysfunction, aesthetic compromise, and diminished quality of life. In addition to local effects, periodontal diseases have been associated with several systemic conditions, including diabetes mellitus, cardiovascular diseases, and adverse pregnancy outcomes, further amplifying their public health importance.[1]

The global burden of periodontal disease remains high due to its multifactorial etiology, chronic progressive nature, and the need for lifelong maintenance therapy. Conventional periodontal therapy aims to control the microbial biofilm and suppress inflammation primarily through mechanical debridement, surgical intervention, and adjunctive chemotherapeutic agents. These approaches are effective in halting disease progression and maintaining periodontal stability; however, they fall short of predictably regenerating the lost periodontal tissues.

*Corresponding author: Gunjan Gupta
Email: drgunjan.dntlgn@its.edu.in

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The ultimate goal of periodontal therapy is the regeneration of the periodontal attachment apparatus, defined histologically by the formation of new cementum with inserting collagen fibers, a functionally oriented periodontal ligament, and newly formed alveolar bone. Over the decades, various regenerative techniques such as guided tissue regeneration (GTR), bone grafting, and the use of biologics have been explored to achieve this objective. Autografts, allografts, xenografts, and synthetic bone substitutes have been extensively used with variable clinical outcomes. Despite measurable clinical improvements in probing depth reduction and clinical attachment gain, true periodontal regeneration as evidenced by histological studies remains unpredictable and inconsistent.

In recent years, advances in regenerative medicine and tissue engineering have introduced novel biologically driven strategies that aim to enhance the intrinsic regenerative capacity of periodontal tissues. These approaches involve the coordinated use of signaling molecules, cells, and scaffolds to stimulate endogenous healing processes. Cell-based therapies utilizing mesenchymal stem/stromal cells (MSCs) and adult fibroblasts have demonstrated encouraging results in experimental studies; however, their clinical application is limited by concerns related to immune rejection, tumorigenicity, ethical issues, cost, and regulatory complexities.

Emerging evidence suggests that the regenerative effects of MSCs are primarily mediated through their paracrine activity rather than direct cell differentiation. This paracrine signaling is largely facilitated by extracellular vesicles, particularly exosomes. MSC-derived exosomes have gained increasing attention as a cell-free regenerative therapy due to their ability to modulate inflammation, promote angiogenesis, and enhance tissue regeneration. Consequently, exosome-based therapies, often combined with suitable scaffold systems including nano-scaffolds, represent a promising and innovative approach in periodontal regeneration.

This article reviews the role of mesenchymal stem cell–derived exosomes in periodontal regeneration, focusing on their biological characteristics, mechanisms of action, experimental evidence, and translational potential.

2. MSCs-Exosomes

Stem cells, just like every other cell in the human body, release exosomes to communicate with each other. Exosomes are membrane-bound vesicles with a diameter of about 40–160 nm, which are released from cells by an endosomal pathway.

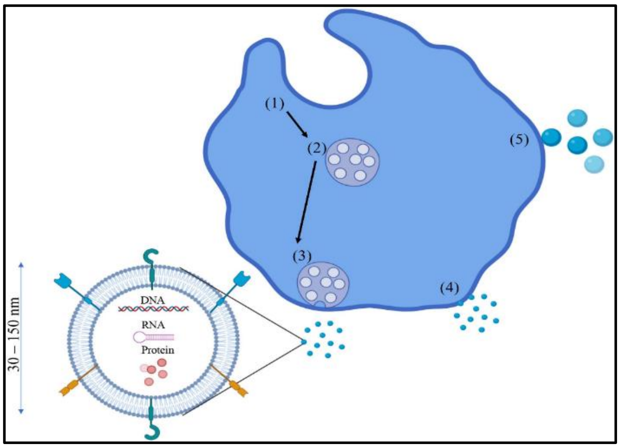

Figure 1: Exosomes: Exosome formation typically begins as endosomes (1) begin to bud inward and form multi-vesicular bodies (MVBs) (2). These MVBs then fuse with the plasma membrane (3) and release the exosomes into the intracellular space. Plasma membrane can also bleb off small extracellular vesicles 30–150 nm in diameter which fall in the same size classification as exosomes, so differentiating the two can be difficult (4). If these plasma membrane blebs are > 150 nm in diameter, they are classified as microvesicles or microparticles (5). Exosomes can contain a number of different molecules as cargo such as proteins/cytokines (free floating and membrane bound), DNA, RNA, and other nucleic acids.

Cholesterol, sphingomyelin, ceramide, and various lipid molecules are found in large quantities on the exosomal membrane (Mashouri et al., 2019).[2] Once the exosomes are released into the intercellular space, they can be taken up by recipient cells by endocytosis, receptor–ligand binding, or through direct binding (Kahroba et al., 2019).[3]

2.1. Potential mechanisms of action

Mesenchymal stem/stromal cells have been shown to suppress inflammation through direct cell-to-cell contact in inflamed tissues and through production of numerous anti-inflammatory molecules such as indoleamine 2,3 dioxygenase (IDO) (Su et al., 2014),[4] nitric oxide (NO) (Su et al., 2014),[4] prostaglandin E2 (PGE2) (Hsu et al., 2013),[5] transforming growth factor (TGF)-β, heme oxygenase 1 (HO1) and hepatocyte growth factor (HGF) among others. These molecules suppress the effect of immune cells such as macrophages Eslani et al., 2018),[6] monocytes, dendritic cells. B-cells, NK cells and T-cells.

In addition to soluble factors, MSCs influence target cells through the secretion of exosomes, which encapsulate and deliver bioactive molecules directly to recipient cells. MSC-derived exosomes have been shown to modulate macrophage polarization, reduce pro-inflammatory cytokine production, and promote a regenerative microenvironment. These properties are particularly relevant in periodontal disease, where chronic inflammation plays a central role in tissue destruction.

Preclinical studies have demonstrated the therapeutic potential of MSC-derived exosomes in a variety of pathological conditions, including wound healing (Fang et al., 2016; Samaeekia et al., 2018),[7] angiogenesis (Huang et al., 2017),[8] ischemic injury, and inflammatory diseases. By delivering microRNAs and proteins that regulate cell proliferation, differentiation, and survival, exosomes can orchestrate complex regenerative processes without the risks associated with live cell transplantation

2.2. Mesenchymal stem cell exosomes enhance periodontal ligament cell functions and promote periodontal regeneration

The application of MSC-derived exosomes in periodontal regeneration has gained increasing attention due to their ability to enhance periodontal ligament cell function and promote tissue repair. One of the most significant studies in this field was conducted by Jacob Ren Jie Chew et al. in 2019,[9] who investigated the regenerative potential of MSC exosome-loaded collagen sponges in an immunocompetent rat periodontal defect model.

In this study, human MSC-derived exosomes were incorporated into collagen sponges and implanted into surgically created periodontal defects. The authors demonstrated that exosome-loaded collagen scaffolds significantly enhanced periodontal regeneration without eliciting any adverse immune reactions. Periodontal regeneration was evaluated using standard parameters, including alveolar bone formation, functional periodontal ligament length, and inhibition of epithelial down-growth.

Collagen sponges were selected as the scaffold material due to their widespread clinical use, biocompatibility, radiolucency, resorbability, and relative inertness compared to bone substitutes such as deproteinized bovine bone mineral. These characteristics made collagen an ideal scaffold for evaluating the regenerative effects of MSC-derived exosomes on periodontal tissues.

The study revealed that a single application of exosome-loaded collagen sponge resulted in significantly enhanced bone regeneration and increased functional periodontal ligament length at four weeks post-implantation. Notably, although exosomes were rapidly released and degraded within the first 48 hours, their regenerative effects persisted for at least four weeks. This finding suggests that transient exposure to MSC-derived exosomes may be sufficient to initiate a sustained regenerative cascade by restoring tissue homeostasis and activating endogenous repair mechanisms.

These observations support the hypothesis that MSC-derived exosomes act as biological triggers that modulate the local microenvironment, reduce inflammation, and promote coordinated tissue regeneration rather than serving as long-term structural components.

3. Clinical Translation and Current Status

Despite promising preclinical evidence, the clinical application of MSC-derived exosomes in periodontology remains in its early stages. To date, no completed human clinical trials specifically evaluating MSC exosome therapy for periodontal regeneration have been published. However, ongoing clinical trials indicate growing interest in translating this technology into clinical practice.

One such study titled "Effect of Adipose-Derived Stem Cell Exosomes as an Adjunctive Therapy to Scaling and Root Planing in the Treatment of Periodontitis" is currently underway. This trial aims to evaluate the safety and efficacy of exosome-based therapy as an adjunct to conventional periodontal treatment. The outcomes of such studies are expected to provide valuable insights into the feasibility, optimal dosage, delivery methods, and long-term effects of MSC-derived exosomes in periodontal therapy.

4. Conclusions

Periodontal regeneration remains one of the most challenging objectives in periodontal therapy due to the complex architecture and functional requirements of the periodontal tissues. While conventional grafting materials and regenerative techniques have demonstrated clinical benefits, predictable and complete regeneration of the periodontal attachment apparatus remains elusive.

Mesenchymal stem/stromal cell–derived exosomes represent a novel and promising cell-free therapeutic approach for periodontal regeneration. Their potent immunomodulatory, anti-inflammatory, and regenerative properties, combined with reduced safety concerns compared to cell-based therapies, make them attractive candidates for future clinical applications. Emerging preclinical evidence suggests that MSC-derived exosomes can enhance periodontal regeneration by modulating the local microenvironment and activating endogenous repair mechanisms.

Although clinical translation is still in its early phases, ongoing research and clinical trials highlight the potential of MSC exosome–based therapies to revolutionize periodontal regeneration. With further investigation into optimal delivery systems, dosage, and long-term outcomes, MSC-derived exosomes may offer a predictable and biologically driven solution for achieving true periodontal regeneration in the future.

5. Source of Funding

None.

6. Conflict of Interest

None.

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