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Exosomes In Periodontal Regeneration– A Comprehensive Review

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Abstract
Periodontitis is an inflammatory disease of the periodontium which is characterized by a progressive destruction of the tissues supporting the tooth. Subgingival dental biofilm elicits a host inflammatory and immune response, ultimately leading to irreversible destruction of the periodontium (i.e. alveolar bone and periodontal ligament) in a susceptible host. The ultimate goal of periodontal therapy is the regeneration of the tissues destroyed as a result of periodontal disease. Periodontal regeneration is the restoration of lost or diminished periodontal tissues including cementum, periodontal ligament, and alveolar bone. Some of the techniques for regeneration involves Free gingival graft, guided tissue regeneration, guided bone regeneration, Enamel matrix derivative, bone grafts, root bio modification, tissue engineering, cell sheet engineering, stem cells. Exosomes generated from stem cells are now a promising alternative to stem cell therapy, with therapeutic results comparable to those of their blast cells. It has great potential in regulating immune function, inflammation, microbiota, and tissue regeneration and has shown good effects in periodontal tissue regeneration.

Keywords: *Exosomes, Periodontitis, Periodontal regeneration, Extracellular vesicles(EV's), Multivesicular bodies, Stem cells.*

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I. Introduction

The complex structure known as the periodontium is made up of both soft and hard tissues. The soft tissues are made up of gingiva and periodontal ligament, while the hard tissues are made up of dental cementum and alveolar bone. The hard and soft tissues work together to evenly distribute and withstand the forces produced during mastication[3].A complex illness known as periodontitis is the disruption of the subgingival microbiota that causes the degeneration of periodontal tissues. The early stage of periodontitis is known as gingivitis; if the bacteria that are forming plaque, calculus, and dental biofilm are completely eradicated, the condition will not proceed to periodontitis; if the microbiota is not restored, periodontitis will continue[1][2]. Scaling and root planing are used as the first treatment. The replication or restoration of a missing or injured portion to restore the form and function of lost structures is known as periodontal regeneration[4].Free gingival grafts, guided bone and tissue regeneration, enamel matrix derivatives, bone grafts, root biomodification, tissue engineering, cell sheet engineering, and stem cells are a few of the cutting-edge methods for periodontal regeneration. In GTR, a barrier membrane is utilised to encourage the selective repopulation of the periodontal defect by periodontal ligament-derived cells, at the expense of gingival cells. The application of Enamel Matrix Derivative is justified biologically by recapitulating developmental pathways, in which it is hypothesised that enamel matrix proteins are essential for promoting cementogenesis.[5]

Using periodontal cell sheets created in vitro and then transplanted into periodontal deficiencies is known as periodontal tissue engineering; Through gene therapy, growth factor genes can be inserted into the local cell population to enable longer-term local delivery of growth factors; The patient's habits and dental hygiene, the tooth's endodontic condition and mobility, the anatomy of the periodontal defect, and other factors all have an impact on the clinical result of regenerative surgery[4].Exosomes are now the most studied subjects in regenerative medicine. Different exosomes made from stem cells have been shown to be effective in reducing inflammation of periodontal tissue and encouraging the repair of alveolar bone. [5]

The phrase "platelet dust" was used more than 50 years ago to describe extracellular vesicles (EVs). In 1983, the field of exosomes, two research groups were recognised for their contributions. Labelled transferrin receptors (TfRs) were tracked in these investigations, as they entered developing reticulocytes from the plasma membrane and once transferrin receptors reach their target cells, they internalise and repackage into extremely small (50 nm) vesicles. Contrary to earlier theories, the scientists discovered that mature blood reticulocytes discharged vesicles into the extracellular space, where they were ultimately given the name exosomes because of their vesicular escape from the cell[5].

Exosomes, the tiniest extracellular vesicles, are present in most body fluids and range in size from 30 to 150 nm[6]. Exosomes are widely present in many bodily fluids, including plasma, urine, breast milk, semen, amniotic fluid, and saliva. They are released by nearly all cell types, including mesenchymal stem cells (MSCs), dendritic cells (DCs), B cells, T cells, and mast cells[7]. They carry signalling chemicals that are involved in many biological processes, such as immune responses, tumour metastasis, and other cellular functions, as well as cell signalling. Less risky and more efficient than mesenchymal stem cells are exosomes. They are able to move useful miRNAs. They are able to cross the blood-brain barrier (BBB) and control inflammation due to their low immunogenicity and high transport efficiency[6].

II. Extracellular Vesicles

Extracellular vesicles (EVs) are one of the particles that mesenchymal stem cells produce. The International Society for Extracellular Vesicles (ISEV) has authorised the term "EV" for non-replicable bilayer lipid membrane vesicles that contain a variety of signalling molecules, proteins, lipids, and nucleic acids. EVs are secreted by the majority of eukaryotic cells and play vital functions in intercellular interactions. They transport active signals that can affect nearby or far-off recipient cells' activities. It has been proposed that EVs, growth factors, and survival signals all regulate the paracrine function of MSCs[8].

Extracellular vesicles can be broadly categorised into three groups according to where they come from:
1) The lysosome and plasma membrane create ***exosomes***, which are 50–150 nm in size.
2) ***microvesicles,*** which are 0.1–1 μm in diameter and directly come from the plasma membrane;
3) ***apoptotic bodies***, which are 1–5 μm in diameter and are generated by dead cells[3].

III. Biogenesis of exosomes

1.Origination of exosomes from endocytosis.
2.Endocytic vesicles are formed by the inward
sunkening of membrane of secretory cells.
3.Early nucleosomes are formed by the combination
of Multiple endocytic vesicles.
4.Formation of late endocytosis vesicle.
5.Formation of intracavitary vesicles. (ILVs)
(inward gemination of late endocytic vesicle)
6.Formation of multivesicular bodies (MVBs) by aggregation of ILVs.
7.Fusion of multivesicular bodies to the cell membrane
8.Formation of extra cellular vesicle outside the cell
9.Formation of exosomes, micro vesicles, apoptotic bodies.

Exosomes can develop in two different ways: passively and actively. The endosomal sorting complex required for transport (ESCRT; ESCRT-0, I, II, III, and Vps4) and its auxiliary proteins (Alix, TSG101, HSC70, and HSP90β) are necessary for the **active production** of exosomes. They integrate endosomal proteins into MVBs and are able to identify ubiquitinated transmembrane proteins. Heat shock proteins, tetrapeptides (CD63), and lipids (ceramide) are involved in the **passive** creation of exosomes, which occurs independently of ESCRT and promotes the formation of MVBs by inducing cell membrane budding.[7]

Ceramide and other transmembrane proteins are involved in the development of multivesicular structures when ESCRT is reduced. Furthermore, it has been revealed that specific constituents, including lipid rafts and proteins with four transmembrane domains, are involved in the production of certain exosomes. Apart from the conventional mechanism, exosome biogenesis can also occur via a considerably faster route. Exosomes can be directly released from the plasma membrane by T cells and erythroleukemia cell lines. It is impossible to distinguish between the exosomes generated by these two processes. Moreover, exosome secretion is significantly influenced by soluble N-ethylmaleimide-sensitive fusion protein attachment protein receptor (SNARE) proteins and their effectors, including Rab GTPases Rab27a, Rab27b, and Rab35 [7].

IV. Exosome Biology

These are the four general principles of exosome biology,

a. Exosomes are generated by budding from both the plasma membrane and the endosome membrane ;
b. Exosomes can transfer signals and macromolecules to target cells;
c. Exosome biogenesis is a mechanism of protein quality control;
d. Exosome biology plays critical roles in human health and disease.[5]

V. In Target Tissues

Exosomes bind to specific ligands on target cells' receptors to activate them, this process is called L-R binding (L-ligand, R-receptor).Exosomes have the ability to transfer cell surface receptors to the recipient cell through the budding process. Lastly, membrane fusion enables the cytosolic contents of the donor cell to be transferred horizontally to the recipient cell.[5]

VI. Composition

Like other lipid vesicles, exosomes float on sucrose gradients, and their densities vary from 1.13 g/ml (produced from B cells) to 1.19 g/ml (derived from intestinal cells).[3]

Exosomes exhibit a distinctive "saucer-like" morphology when examined with whole-mount electron microscopy. This morphology is characterised by a flattened sphere that is bounded by a lipid bi-layer. Typically, their diameter ranges from 30 to 100 nm, making them too small to be seen by photon microscopy. The most uniformly sized exosomes are formed from B cells, measuring between 60 and 80 nm. Numerous proteins, lipids, RNA, miRNA, and other non-coding RNA are found both within and outside of exosomes. Non-specific and specific proteins make up the majority of the contents of extracellular vesicles, which are made up of proteins.[3]

Specific exosomal proteins normally make up adhesion molecules such as class II molecules, integrins, tetracycline, MHC I on lymphocytes and dendritic cells, and transferrin receptor (TFR) on the surface of reticulocytes. Actin, myosin, the cytoskeleton proteins tubulin, the non-specific proteins Alix, and the membrane fusion and transport proteins Annexin, Flotillin, GTPases, Rab2, Rab7, heat shock protein proteins HSP70, HSP84, and HSP90, as well as transmembrane proteins CD9, CD63, CD59, CD81, and CD82 (JOURNAL OF TRANS MED), mediate the formation of MVB, and are components of exosomes. These general proteins are crucial for the synthesis and release of exosomes.

Exosomes, which are typically rich in cholesterol, glycosphingolipids, ceramide, and phosphatidylserine, also contain substantial amounts of lipids. In addition to providing structural support for exosome membranes, lipids are crucial for the production and release of exosomes into the extracellular milieu[3].

VII. Isolation Of Exosome

Exosomes can be extracted from a variety of materials, including cell culture media, milk, CSF, saliva, urine, serum, and plasma. Various processing techniques may be needed for each type of exosome. Exosomes, microvesicles, apoptotic bodies, plasma proteins, and cell debris are examples of the various constituents of plasma, a complex biological fluid with a wide range of sizes and biochemical properties. pee requires more pee to produce the same amount of exosomes because urine has a lower concentration of exosomes than blood or plasma. Since culture media obtained following cell culture is simple, affordable, and does not need the use of animal or human subjects, it is frequently utilised in exosome mass manufacturing. It is possible that the exosome yield obtained from cell culture media surpasses that of plasma or serum. [3]

VIII. Exosome Isolation Techniques

Size-exclusion chromatography, immunoaffinity capture, precipitation, ultrafiltration, and ultracentrifugation are some of these techniques. Exosomes are produced using these methods in different yield and purity levels[1].

IX. Quantification Of Exosomes

There are currently many different methods being utilised for their quantification due to advancements in technology and devices. These include surface plasmon resonance (SPR), flow cytometry, electron microscopy, dynamic light scattering, surface plasmon resonance (SPR), nanoparticle tracking analysis, tunable resistive pulse sensing, microfluidics-based detection, and single particle interferometric reflectance imaging sensor (SP-IRIS).[3]

X. Exosome Characterization

Using quantitative characterisation techniques, the quantity and purity of biomolecules such as proteins, lipids, and nucleic acids, as well as the overall quality of the separated exosomes, may be assessed. Flow cytometry, electron microscopy (EM), resistive pulse sensing (RPS), dynamic light scattering (DLS), fluorescence

correlation spectroscopy (FCS), and nanoparticle tracking analysis are techniques used to measure total exosomes. Flow cytometry, NTA, and FCS are the most widely utilised techniques. Purity of exosomes may be assessed, in part, by figuring out how much protein (measured in mass) they contain. The percentage of protein mass in relation to the total number of exosome particles can be used to determine a sample's purity. Mass spectrometry and enzyme-linked immunosorbent assays (ELISAs) are used to identify and quantify protein markers. Based on the lipids they carry in their membranes, exosomes can be divided into a number of groups. The percentage of total exosomes that contain a target lipid can be used to determine the purity of targeted exosomes. Sulfo-phospho-vanillin (SPV) tests, fluorescence microscopy, and Fourier transform infrared (FT-IR) spectroscopy are a few techniques used in lipid measurement. Through exosomes, DNA and RNA can be transferred between cells. The ratio of targeted DNA/RNA sequences to the total number of exosomes can also be used to assess the purity of exosomes. For exosome DNA/RNA research, common nucleic acid quantification techniques that may be used include polymerase chain reaction, next-generation sequencing (NGS), and microarrays[3].

XI. Exosome Biogenesis Inhibitors

Pantethine, GW4869, Imipramine, Spiroepoxide, DPTIP (2,6-dimethoxy-4–(5-phenyl-4-thiophen-2-yl-1H- imidazole-2-yl)-phenol), Simvastatin, Glibenclamide (Glyburide), and Indomethacin are a few of the exosome biogenesis inhibitors.[9]

XII. Exosome Release Inhibitors

Calpeptin, Bisindolylmaleimide I, Y-27632, U0126, Manumycin A, Dimethyl amiloride, Tipifarnib, Ketoconazole, Endothelin A receptor antagonist, Cannabidiol, and Ketotifen are among the medications that limit the production of exosomes.[9]

XIII. Functions Of Exosomes

A. Exosomes will never trigger immunological refusal.
B. Exosomes are more user-friendly and more suited for storage.
C. Unlike cells, exosomes are small enough to pass across numerous tiny barriers, including the blood-brain barriers.
D. Exosomes have the ability to reduce inflammation, regulate cell division, and expedite the healing process for damaged tissues.
E. Studies have demonstrated the beneficial effects of exosomes on the immune system, lung, heart, liver, kidney, skin, muscle, and bone, as well as on viral infections.
F. Exosomes' capacity to be used in the identification and treatment of immunological rejection and tumorigenicity related to cell therapy[5].
G. Exosomes are regarded as a potential medicinal delivery method and as a breakthrough in diagnosis[10].
H. Exosomes have attracted a lot of attention from the drug delivery scientific community due to their ability to transport a wide range of compounds, such as proteins, lipids, carbohydrates, and nucleic acids[11].

XIV. Exosomes In General Application

Sl.no	Used in	Conditions
1	Neurodegenerative disorders	Alzheimer's disease, central nervous system, depression, multiple sclerosis, Parkinson's disease, post-traumatic stress disorders, traumatic brain injury, peripheral nerve injury.[6]
2	Damaged organs	Heart, kidney, liver, stroke, myocardial infarctions, myocardial infarctions, ovaries.[6]
3	Degenerative processes	Atherosclerosis, diabetes, hematology disorders, musculoskeletal degeneration, osteoradionecrosis, respiratory disease.[6]
4	Infectious diseases	COVID-19, hepatitis.[6]
5	Regenerative procedures	Antiaging, bone regeneration, cartilage/joint regeneration, osteoarthritis, cutaneous wounds, dental regeneration, dermatology/ skin regeneration, erectile dysfunction, hair regrowth, intervertebral disc repair, spinal cord injury, vascular regeneration.[6]
6	Cancer therapy	Breast, colorectal, gastric cancer and osteosarcomas.[6]
7	Immune function	Allergy, autoimmune disorders, immune regulation, inflammatory diseases, lupus, rheumatoid arthritis.[6]

XV. Role Of Exosomes In Dentistry

In regeneration

Promising therapeutic strategies for the stimulation of angiogenesis in regenerative dentistry include exosomes that are directed towards local endothelial cells from stem cells found in the oral cavity. Exosomes, which have a strong capacity for regeneration, are secreted by the stem cells located in the mouth cavity. A variety of oral cavity tissue types, including the bone and dental cementum, have successfully undergone architectural

replacement thanks to these exosomes, which transmit information between stem cells and other cells. For this type of approach, bone marrow stem cells, dental pulp stem cells, periodontal ligament stem cells, gingival mesenchymal stem cells, and induced pluripotent stem cells are the exosome-secreting stem cells that are used. These cells can be transfected with pro-angiogenic genes, which will cause them to secrete more pro-angiogenic exosomes, or they can be grown under stressful environments like hypoxia. It is possible to separate and modify exosomes in vivo to change their cargo to one that is more pro-angiogenic. Molecular mediators like VEGFs, PDGF, FGF, EGF, ANG1/2, ILGF, TNFα, TGFβ, HIF-1A, CXCR2, MMP2/9, and pro-angiogenic microRNAs like miR-21, miR-23, miR-1246, miR-378, miR-16 family, miR-142, miR-196a, miR-17, miR-2861, miR-210, miR-20a, miR-29a, miR-10a/b, miR-126, miR-19a/b, miR-125a, miR-31, miR-145, miR-221/222, miR-126, miR-320a, and miR-424 should be present in the cargo of these exosomes. Because of the close relationship that exists between EC and stem cells—maintained in particular by exosomes—therapeutic stimulation of angiogenesis in regenerative dentistry should take into account the synchronised treatment of all relevant factors[13].

Exosome in periodontics

Exosomes are suitable drug carriers for periodontal regeneration due to their isolation from every biological fluid, biocompatibility, low toxicity and high concentration of drugs reaching the target tissue. Exosomes obtained from mesenchymal stem cells can be used for periodontal regeneration in periodontal flaps, scaffolds, or periodontal defect areas through biomaterials such as drugs and hydrogels. [14].

XVI. Exosomes In Diagnosing Periodontitis

Exosomes are being considered more and more as possible diagnostic indicators for the diagnosis and prognosis of diseases since their constituent parts can be reprogrammed based on the state of an illness. These features have shifted the focus of research on oral diseases, such as periodontitis, to exosomes in recent years.

Exosomes are enriched in particular microRNAs (miRNAs) at the gene level, which can offer disease-specific diagnostic markers. Plasma-derived exosomal miRs (miR-1304-3p and miR-200c-3p) and SNORDs (SNORD57 and SNODB1771) from individuals with periodontitis are expressed differently from healthy controls and may be useful biomarkers for the diagnosis of periodontitis. Furthermore, the degree of programmed death-ligand 1 (PD-L1) mRNA in salivary exosomes is correlated with the severity of periodontitis and may be used to diagnose the condition.

According to protein analysis and detection of salivary exosomal proteins in young adults with severe periodontitis, only the group with severe periodontitis expressed C6 proteins, which are involved in the immune response during the development of periodontitis.

Furthermore, compared to the healthy controls, periodontitis patients had much reduced quantities of CD9 and CD81 exosomes. Saliva's CD9/CD81 Exosome concentration has a strong negative correlation with clinical measures, suggesting that it plays a major role in the pathophysiology of periodontal disease[7].

XVII. Different Sources Of Exosomes And Its Role

Sl no	Different sources of exosomes	Its role
1	Dental pulp stem cell-Exosomes (DPSC-Exosomes)	Healing of alveolar bone in mice with periodontitis and help convert macrophages from a proinflammatory phenotype (M1) to an anti-inflammatory phenotype (M2) may be linked to miR-1246 in DPSC-Exosomes.[7]
2	Human leukocyte antigen haplotype homo dental pulp cell lines (HHH-DPCs)	Inhibits the development of osteoclasts in vitro while stimulating the migration of human DPCs and mice osteoblastic cells.[7]
3	Healthy Periodontal ligament stem cell (h-PDLSC- Exosome)	Promotes bone growth in alveolar bone deficiencies in rat models.[7]

Exosomes produced from gingival mesenchymal stem cells (GMSCs) conditioned with TNF-α have the potential to greatly control osteoclastogenesis and inflammation, offering a potential treatment for periodontitis. By encouraging neovascularisation and the creation of new bone, SHED-Exosomes may aid in the regeneration of periodontal bone via the AMPK signalling pathway. Through the IL-10/IL-10R pathway, reparative M2 macrophage exosomes decreased alveolar bone resorption in periodontitis-affected rats. Adipose-derived stem cell-derived exosomes, or ADSC-Exos, are a potentially effective supplement to SRP in rats. Diabetes-related periodontitis is facilitated in its onset and progression by exosomal miR-25-3p in saliva. Through the regulation of γδ T cell-mediated local inflammation, the identification of additional miR-25-3p targets may offer crucial insights into the creation of medications to treat periodontitis[7].

Numerous research endeavours have concentrated on augmenting periodontal tissue regeneration by the utilisation of mesenchymal stromal/stem cells (MSCs) in therapeutic approaches. MSC therapy for tissue repair

has recently undergone a paradigm change, moving from a strategy focused on cellular differentiation and replacement to one based on secretion and paracrine signalling. The functions of periodontal ligament cells were enhanced in vitro and periodontal regeneration was promoted in experimental animals by adipose-derived stem cells (ADSCs) and their exosomes, stem cells from human exfoliated deciduous teeth (SHED)-derived conditioned exosomes, sEVs from lipopolysaccharide-preconditioned dental follicle cells, and sEVs derived from bone marrow mesenchymal stem cells[7].

XVIII. Mechanism Of Exosome Mediated Periodontal Tissue Regeneration

Immunoregulation and inflammatory regulation of exosomes

Extracellular vesicles from mesenchymal stem cells have immunomodulatory properties that can aid in bone healing. Exosomes derived from mesenchymal stem cells maintain blood flow, encourage osteogenic differentiation, quicken bone remodelling, and stabilise the bone transplant environment. Exosomes produced from periodontal ligament stem cells (PDLSC-exosomes) have been shown to carry the miR-155-5p to CD4+ T cells, which in turn modifies the Th17/Treg balance in periodontitis and changes the expression of SIRT1 protein. Extracellular vesicles derived from mesenchymal stem cells in bone marrow may be involved in the OPG-RANKL-RANK signalling pathway, which could influence osteoclast activity and hinder the advancement of periodontitis and immune-mediated damage by controlling inflammatory immune responses and macrophage polarisation.

Exosomes produced from gingival mesenchymal stem cells are treated with TNF-α, which upregulates CD73 and miR-1260b. This leads to macrophage polarisation towards the M2 type, which promotes the resolution of inflammation in periodontal tissues and stops additional alveolar bone loss. In periodontitis mice, pulp stem cells form exosomes which cause macrophages to change from pro-inflammatory to anti-inflammatory phenotypes.

Using conditioned medium made from human adipose-derived mesenchymal stem cells dramatically lowers TNF-α, IL-1, and IL-6 mRNA expression levels in lipopolysaccharide-activated macrophages. This suggests that AMSC-CM protects bone by inhibiting the generation of cytokines that promote inflammation. According to Liu et al. (2019), Periodontal ligament stem cells (PDLSC- CM) derived conditioned medium has the ability to stimulate macrophage differentiation towards an anti-inflammatory phenotype by downregulating the expression of tumour necrosis factor-alpha (TNF-α) and upregulating the expression of CD163, interleukin-10, and arginase-1.

SHED generated exosomes have been observed to suppress the expression of pro-inflammatory cytokines, such as TNF-α and IL-6. After periodontal ligament stem cell-derived conditioned medium (PDLSC-CM) is administered, periodontal tissues exhibit a drop in TNF-α mRNA expression level along with a tendency towards lower levels of COX-2, a chemical which is implicated in inflammatory processes. These results suggest that PDLSC-CM may have anti-inflammatory effects on periodontal tissues, which could make it a promising therapeutic agent for the treatment of periodontal diseases.[3]

Exosome-mediated stimulation of endogenous stem cell differentiation and regeneration

In addition to helping mesenchymal stem cells with periodontal defects proliferate and develop into osteoblastic or odontoblastic lineages, exosomes transport growth factors and cytokines that promote periodontal regeneration.

The bone marrow mesenchymal stem cells (MSC-CM) conditioned medium demonstrates a strong osteogenic potential that is facilitated by the combined effects of many growth factors, such as HGF, VEGF, TGF-β1, and IGF-1. Numerous osteogenic processes, including as angiogenesis, cell migration, proliferation, and osteoblastic differentiation, are regulated by these cytokines.

IGF-1 stimulates osteoblast-like cell migration and proliferation in the bone, as well as matrix synthesis and mineralisation during the development of new bone. Furthermore, IGF-1 can promote periodontal regeneration by activating PDL cells through the PI3K pathway.

Vascular endothelial growth factor, or VEGF, is thought to have the ability to directly control angiogenesis in vivo, which aids in osteogenesis. It also supports the survival and development of endothelial cells.

The growth and maintenance of skeletal tissues depend on TGF-β1 (transforming growth factor-β1), which simultaneously influences the osteoblastic and osteoclastic lineages and aids in preserving the dynamic equilibrium between bone formation and resorption. Transforming growth factor-β (TGF-β1) can help promote PDL regeneration and repair by regulating the proliferation, differentiation, and matrix formation of PDL cells.

Another strong angiogenic factor is HGF, which mostly acts directly on endothelial cells to mediate its effects. Therefore, by delivering these cytokines and growth factors, exosomes might encourage osteogenesis.[3]

Exosomes' function in stimulating angiogenesis during the regeneration of periodontal tissue

Bone marrow mesenchymal stem cells (MSC-CM) have conditioned medium that contain growth factors such as TGF-β1, VEGF, and IGF-1. These elements support endogenous stem cell migration, proliferation, and tissue vascularization, all of which aid in the early development and maturation of bone. These results suggest that MSC-CM may be a promising therapeutic approach to enhance bone regeneration and tissue repair in the setting of periodontal disease. Conditioned media made from human umbilical vein endothelial cells and bone marrow-derived mesenchymal stem cells can be used to encourage the osteogenic development of human gingival mesenchymal stem cells. [3]

XIX. Conclusion

In conclusion, this review highlights the significant potential of exosomes in periodontal regeneration. Derived from various sources including mesenchymal stem cells, dental pulp stem cells, and gingival mesenchymal stem cells, exosomes have demonstrated remarkable abilities to promote tissue regeneration, modulate immune responses, and stimulate angiogenesis. Their capacity to influence cell behavior through the transfer of bioactive molecules, including proteins, lipids, and nucleic acids, positions them as powerful tools in regenerative dentistry.

The current body of research suggests that exosome-based therapies could offer several advantages over traditional treatments, including reduced immunogenicity, easier storage and handling, and the potential for cell-free therapies. However, challenges remain in standardizing exosome isolation, characterization, and delivery methods.

With continued research and development, exosome-based therapies may soon offer new hope for patients suffering from periodontal diseases, potentially leading to more effective, less invasive treatments and improved oral health outcomes.

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