Exosomes in Cell-free Regenerative therapies: Mechanistic Promise, Clinical Silence

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Abstract*—Regenerating a fully functional periodontium is one of the central challenges in periodontology, requiring the simultaneous, coordinated restoration of alveolar bone, periodontal ligament, cementum, and a stable connective-tissue attachment — all within a wound environment that remains chronically inflamed. Exosomes which are a subset of small extracellular vesicles of endosomal origin, have attracted attention as cell-free therapeutic tools capable of transferring proteins, lipids, and regulatory RNA between cells and reproducing the paracrine effects of mesenchymal stem/stromal cells without the risks associated with transplanting living cells. Dental stem cells — including periodontal ligament stem cells, dental pulp stem cells, stem cells from human exfoliated deciduous teeth, stem cells from the apical papilla, dental follicle progenitors, and gingival mesenchymal stem cells — serve as biologically relevant sources of such exosomes. In periodontal research, exosomes have been shown to support periodontal ligament cell migration and proliferation, osteogenesis, angiogenesis, fibroblast regulation, and immune modulation, and can be incorporated into hydrogels or three-dimensional scaffolds for delivery to intrabony or furcation defects. Despite this preclinical enthusiasm, evidence in humans remains almost entirely absent: to date, no completed clinical trial has evaluated exosomes-based therapy for periodontal regeneration, and only isolated case reports and early-phase or ongoing trial registrations exist. Clinical translation is further constrained by variability in exosomes source and isolation methodology, non-standardised dosing, storage and stability limitations, incomplete potency testing, unresolved safety and manufacturing/scale-up concerns, and questionable cost-effectiveness relative to established regenerative techniques such as guided tissue regeneration. This review covers the biology and isolation of exosomes; their classification among extracellular vesicles, with reference to MISEV reporting guidelines; their mechanisms of action; present and future applications in periodontal regeneration and related periodontal therapies; the reasons underlying the current gap in clinical translation; and the developmental milestones exosomes-based therapies must reach to approach the level of clinical adoption achieved by cell-based therapeutics.

***Index Terms*—exosomes; extracellular vesicles; periodontal regeneration; cell-free therapy; periodontal ligament stem cells; guided tissue regeneration; enamel matrix derivative; platelet-rich fibrin**

I. INTRODUCTION

Periodontitis is a chronic inflammatory disease of the periodontium, which results in destruction of the tooth-supporting structures, and thus, the reconstruction of the periodontium after recovery from the disease is a key challenge for periodontology since true regeneration necessitates the spatially organised formation of alveolar bone, PDL, containing Sharpey's fibers of proper orientation, cementum and new connective tissue attachment, within an inflamed and biofilm-colonised wound site [1]. Currently available regenerative methods – guided tissue regeneration (GTR) using barrier membranes, enamel matrix derivative (EMD), platelet concentrates, and their combinations, proved to provide promising but variable and procedure-dependent outcomes, hence the interest in bioactive additives [1].

MSC-based therapies were considered to be the logical next stage of development of materials used for periodontium regeneration based on the ability of transplanted cells to engraft and form periodontal tissues. However, accumulating evidence suggests that the regenerative effect of MSCs is mostly achieved via paracrine signalling rather than direct differentiation, and that a significant part of the paracrine signalling is provided by exosomes – nano-sized extracellular vesicles of endosomal origin, released due to the fusion of multivesicular bodies with the cell surface

[2,3]. Exosomes provide many of the trophic, immunomodulatory, and regenerative properties of their parental cells without need for live and thus immunogenic or even oncogenic cells to be transplanted, therefore they may serve as a safer and easier-to-manage cell-free approach to stem cell therapy [2,3].

II. HISTORY

The term 'exosome' was first introduced by Trams et al. (1981) to describe shed plasma membrane vesicles, though this early contribution was unrecognised at the time, The name was later anchored to its modern biological meaning in 1987, when Rose Johnstone applied "exosome" specifically to vesicles arising from exocytosis of multivesicular endosomes, following the 1983 discovery that maturing reticulocytes release transferrin-receptor-carrying vesicles. Since then, the term has become firmly embedded in cell biology to describe this distinct class of extracellular vesicles [4].

III. DEFINITION OF EXOSOMES

Exosomes are typically defined as nano-sized (~30–150 nm) extracellular vesicles of endosomal origin, formed by inward budding of the endosomal membrane to create multivesicular bodies, which then fuse with the plasma membrane to release their contents extracellularly [2,3].

The MISEV guidelines, developed by the International Society for Extracellular Vesicles, shifted considerably from this definition. Because assigning a vesicle to a specific biogenesis pathway (endosomal vs. plasma membrane) is difficult in practice, MISEV recommends "extracellular vesicle" (EV) as the generic, operational term for any particle released from a cell, delimited by a lipid bilayer, and incapable of replicating (i.e., lacking a functional nucleus).
Under MISEV2018 and the updated MISEV2023, "exosome" is treated as an operational subtype label rather than a strict definitional category. Unless sub-cellular endosomal origin is specifically demonstrated (e.g., via biogenesis-related markers), a preparation is considered to represent a broader EV population, not exosomes in the strict sense [5].

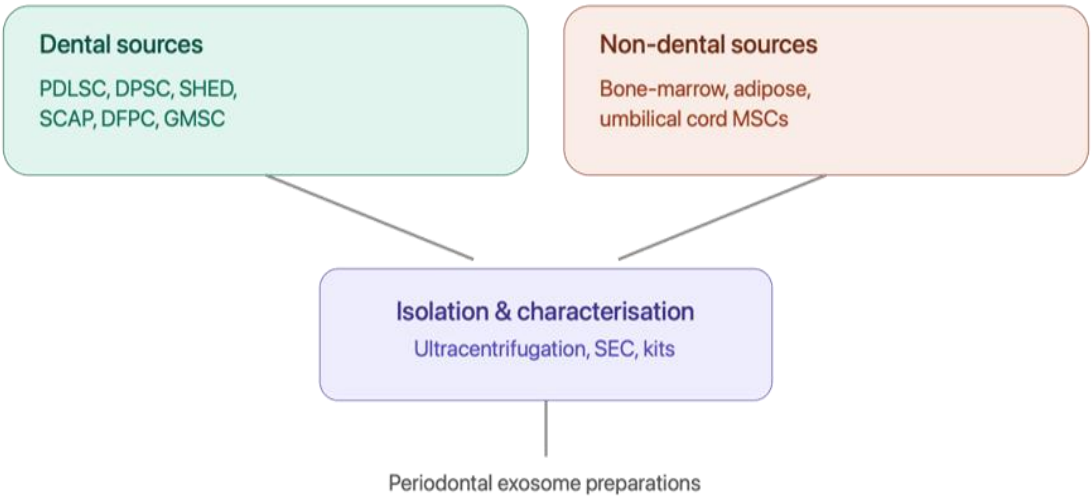
IV. CELLULAR SOURCES OF PERIODONTALLY RELEVANT EXOSOMES

Sources of exosomes
Most periodontal exosome research uses dental-tissue MSCs, based on the (not yet proven) assumption that tissue-matched exosomes are mechanistically/immunologically favourable.
Dental sources: Periodontal Ligament Stem Cells (PDLSC), Dental Papilla Stem Cells (DPSCs), Stem Cells from Human Exfoliated Deciduous Teeth (SHED), Stem Cells from Apical Papilla (SCAPs), Dental Follicle Progenitor Cells (DFPCs), and Gingiva derived Mesenchymal Stem Cells GMSCs [6].
Non-dental sources: bone-marrow and adipose-derived mesenchymal stem cells (MSCs), and umbilical cord MSCs — used experimentally, with a few human case reports [7].

PDLSC-derived exosomes (PDLSC-Exos) — the best-characterised source
Enhance cellular proliferation, osteoblastic differentiation, and modulate inflammation in bone/periodontal models, via specific microRNAs and canonical signalling pathways [3].

A broader review across dental sources confirms support for hard/soft-tissue regeneration, angiogenesis, and immune modulation — but notes no source has been shown superior to the others [6].
Evidence base is still small: an earlier systematic review found only 16 eligible preclinical studies meeting PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) criteria [8].
Isolation workflow

Culture parent cells → collect conditioned medium → concentrate/purify vesicles → characterise and test.
Common isolation methods: differential ultracentrifugation, density gradient separation, ultrafiltration, size-exclusion chromatography, precipitation, immunoaffinity isolation, and microfluidic techniques.



(A) 5ml venous blood transferred to GFC tube, (B) Primary centrifugation (3500 RPM for 10 mins.), (C - D) Prepared supernatant liquid collected for secondary centrifugation, (E - F) Primary centrifugation 1000 RPM for 5 mins. and 4000 RPM for 5 mins. (G) Ultrafiltration done using exposure filtrate (H) Blood derived exosomes obtained

V. CLASSIFICATION OF EXTRACELLULAR VESICLES AND POSITION OF EXOSOMES

Extracellular vesicles (EVs) are membrane-bound vesicles that are released by the cell into its extracellular environment. EVs include a number of vesicles differing in their origin, formation mechanism, size, composition, and functions. Currently, exosomes, microvesicles (ectosomes) and apoptotic bodies are among the major types discussed in scientific literature. Nevertheless, due to the size similarity of some vesicles and non-confirmation of the vesicle formation pathway based on the available experimental methods, modern research in the field of extracellular vesicles pay more attention to operational definition and characterisation of vesicles rather than to their size classification.

Reporting standards are also an important issue in this context. MISEV guidelines provide recommendations on the information about vesicle size distribution, the presence of specific surface markers, and morphology that should be included in publications on exosomes and EVs in general to allow comparability across studies and, consequently, regulatory assessment. Recent reviews on the biology of exosomes focused on dentistry include discussion of classification and characterisation of exosomes derived from dental stem cells according to MISEV guidelines, and compliance with these recommendations is increasingly used as an index of methodological quality when assessing preclinical studies [9,10].

Beyond this vesicle-level classification, it is also useful to situate exosomes within the broader evolutionary trajectory of platelet-derived regenerative products, which are commonly classified into three generations based on their biological activity and mode of preparation [11,12].

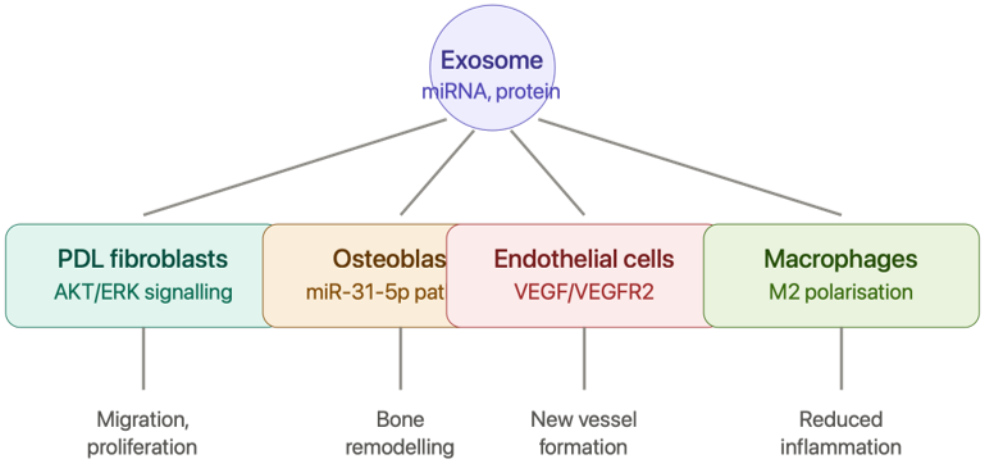
Nonetheless, this third generation still faces unresolved challenges around isolation efficiency, regulatory classification, and standardisation of preparation protocols, which parallel—and compound—the vesicle-level characterisation issues raised by the MISEV guidelines above [11]..

GENERAT-ION	*PRODUCTS*	*PREPARATION*	*KEY CHARACTERISTICS*	*CLINICAL RELEVANCE/ OUTCOMES*
1st Gen	Platelet-rich Plasma (PRP), Platelet-rich Growth factor plasma (PRGF) [11]	Simple centrifugation to concentrate platelets in a liquid formulation [11]	Lacks a fibrin scaffold; limited by rapid growth factor depletion. [11]	-
2nd Gen	Platelet-Rich Fibrin (PRF), Concentrated Growth Factor (CGF); modifications: Advanced-PRF (A-PRF), Injectable-PRF (i-PRF), Titanium-PRF (T-PRF). [11,12]	Low-speed centrifugation protocols generating a natural fibrin matrix. [11,12]	Sustained cytokine release; improved handling properties for periodontal regenerative procedures. [11,12]	Most established platelet-derived biomaterials in periodontal regeneration; PRF-based approaches show favourable outcomes in intrabony defect fill, clinical attachment gain, and alveolar ridge preservation. [12]
3rd Gen	Platelet-Derived Exosomes (PLEXOs). [11]	Isolation of extracellular vesicles rather than whole platelets or fibrin-entrapped cellular material. [11]	Nanoscale vesicles carrying growth factors, miRNAs, and lipids; mediate targeted intercellular signalling, immune regulation, and regenerative processes	Reported greater therapeutic efficacy than 1st- and 2nd-generation concentrates across preclinical contexts. [11]

VI. BIOLOGICAL RATIONALE: COMPOSITION AND MECHANISTIC BASIS OF EXOSOME ACTIVITY

- Exosomes contain a payload of proteins, lipids, mRNAs and other regulatory non-coding RNAs, such as microRNAs, that get transferred to target cells to potentially reprogram their transcription and signalling pathways [2].
- Within the periodontal setting, the payload has been shown to function mechanistically in connection with several discrete cell biological events essential for the regeneration process: migration and proliferation of PDL fibroblasts via AKT/ERK signalling induced by CD73-dependent adenosine receptor stimulation [13].
- Osteoblastic differentiation and osteoclast regulation, such as the action of exosome-derived microRNAs, like miR-31-5p that regulate osteoclastogenesis in diabetic periodontitis models [14].
- Angiogenesis, via exosome-induced upregulation of VEGF/VEGFR2 signalling [3].
- Polarisation of macrophages into anti-inflammatory M2 phenotype, pertinent to the fact that uncontrolled inflammation itself impedes regeneration [3,15].

These actions are focused on tissue compartments damaged during periodontitis, bone, PDL, cementum, and gingival epithelium. Therefore, exosomes have been characterised as multifunctional rather than pathway-specific therapeutic agents in comparison to single-growth-factor biologics, like EMD [1,3].



VII. PRECLINICAL EVIDENCE FOR EXOSOME MEDIATED PERIODONTAL REGENERATION

The preclinical literature forms the predominant body of research on exosome therapy in periodontology. In a 2024-2025 meta-analysis of seventeen preclinical investigations into the effect of MSC-derived exosome therapy for periodontal regeneration, using SYRCLE's risk-of-bias tool, it was found that the effect of MSC-exosomes on periodontal regeneration outcome was statistically significantly positive, although it was noted that the animal defect models used may not completely reflect the pathophysiologic condition of periodontitis and that measures of success mostly relate to bone regeneration rather than cementum or PDL regeneration [16].The use of large animals for experiments on periodontal regeneration, although not exosome specific, shows both the potential and

precarious nature of biological adjuvants in surgically created defects: in a 2025 study in beagle dogs using liquid PRF and volume-stable collagen matrix in one-wall intrabony defects, it was shown that the combination produced the largest amount of cementum and bone formation of all test groups, although the differences measured by micro-CT analysis did not reach statistical significance, which proves how the choice of outcome measure and defect model affects the size of the effect from the biologic [17]. The same applies to the exosome literature, where large-animal, exosome-specific data on intrabony defects is essentially absent.

VIII. CURRENT CLINICAL EVIDENCE: A CRITICAL APPRAISAL OF THE TRANSLATIONAL GAP

One can point out the total lack of human clinical studies in exosome research in periodontology as the most significant characteristic of the scientific field. According to one review about exosome-based therapy for osseous regeneration in dentistry and maxillofacial surgery of 2026, there have been no clinical trials evaluating the regenerative effects of exosomes in human dental applications despite the rapid growth of evidence in preclinical studies [18]. This observation is confirmed by another review where the mechanistic evaluation of PDLSC-Exos revealed just one clinical trial registration in relation to the treatment of periodontitis at Stage III-IV and noted that the results of this trial were not published anywhere. Moreover, there are no other clinical trials registered in this area [3]. In turn, there is an early-phase clinical trial registration that investigates the use of adipose-derived stem cells' exosomes as a supplemental method to scaling and root planing of periodontitis but its results have not been publicly shared [19].

As for other branches of dentistry outside periodontology, there are some case reports about application of dental exosomes to humans — for instance, using umbilical cord MSC-exosomes for a pulpectomized tooth and exosome-functionalized PRF for gingival recession coverage — however, all of these observations relate to individual patients or small patient series and not to clinical trials; moreover, there is no information related to intrabony and furcation periodontal regeneration [7].

IX. DELIVERY SYSTEMS AND SCAFFOLD BASED EXOSOME ENGINEERING

Free exosomes introduced intravenously or topically dissipate quickly from the site of surgery, thus stimulating investigation into exosome use with hydrogels or three-dimensional matrices to ensure the sustained and localised release of exosomes within the intrabony and furcation defect models. The review of exosomes and exosome composites used in periodontal tissue engineering provides an overview of different strategies involving the use of collagen membrane loaded with engineered exosomes for stimulating angiogenesis and bone regeneration in periodontal defect models and proves that scaffold-loaded exosomes usually demonstrate better performance than free exosomes in terms of the release and osteogenic potential of exosomes [20]. There are multiple characteristics of mucoadhesive hydrogels that make them an efficient system for the delivery of exosomes to the periodontal site. First of all, the adhesive property of hydrogels ensures the retention of exosomes at the target site, which helps to avoid quick removal of exosomes through gingival crevicular fluid. The three-dimensional polymeric structure of the hydrogel protects exosomes from degradation and allows their controlled diffusion. The release rate of exosomes may be adjusted depending on such parameters of hydrogels as composition of the polymer, degree of cross-linking, swelling behaviour, and degradation rate for the provision of the sustained and localised release of exosomes rather than burst release. Hydrogels can also demonstrate high biocompatibility and biodegradation rate ensuring tissue healing after the degradation of hydrogel. All these features make mucoadhesive hydrogels more effective for the retention, protection, and delivery of exosomes. This way, anti-inflammatory and regenerative capacity of exosomes would be increased [21]. The analogous research that has been conducted outside the periodontal defect model, such as the combination of exosomes and three-dimensional-printed composite scaffolds for stimulation of angiogenesis and alveolar bone repair, proves the necessity of the scaffold co-delivery of exosomes rather than only exosomes' delivery for efficient spatially limited regeneration [22].

X. EXOSOMES VERSUS CONVENTIONAL REGENRATIVE METHODS

Any potential use of exosomes for periodontal therapy would require comparison to existing techniques with decades of human clinical research behind them. EMD has been used in human practice for three decades and has extensive evidence from numerous randomised controlled trials and longitudinal cohorts of its efficiency in intrabony and, to a lesser degree, furcation defects. The biological mechanism of action of this technique is known and is based on modelling of the normal development of root and periodontium [23]. Autologous platelet concentrates (PRF and its modifications) present an inexpensive, autologous and basically risk-free solution; in several randomised clinical trials comparing PRF to EMD in intrabony defects both have been found equally effective with EMD showing superiority in percentage of defects resolved and no significant differences in clinical attachment gain [24,25]. Randomised controlled case series study comparing advanced PRF, EMD and open flap debridement alone in treatment of molar furcation defects has demonstrated higher probability of obtaining periodontal regeneration using EMD. However, this trial was compromised due to early termination caused by the onset of COVID-19 pandemic [26]. In general, systematic reviews of the literature on PRF in intrabony defects find a clinical benefit of PRF compared to open flap debridement alone, though heterogeneity in PRF preparation protocols makes direct comparison difficult [27].

Against this backdrop, the human comparative clinical evidence for exosomes is lacking. While exosomes are unlikely to surpass other methods in effectiveness, where they could potentially offer a real advantage is in logistic properties. Unlike PRF, exosomes could be produced, standardised and stockpiled outside of the autologous point-of-care model. Unlike EMD (single-defined biological material produced from porcine tooth germs), exosome cargo is multifunctional and could theoretically be engineered. It remains to be seen if any of these hypothetical benefits translate into clinical advantages.

XI. CHALLENGES AND LIMITATIONS TO CLINICAL TRANSLATION

Several overlapping obstacles account for the lack of progress made on human trials of exosome therapy in periodontology at a rate that would match the existing pre-clinical literature. These include first biological and manufacturing variability – exosome yields, contents, and potency vary by cell source, donor, passage number, and culture conditions, and there is no established assay for potency of exosome preparations in periodontology [28,29]. Secondly isolation and storage – standard methods of isolation (ultracentrifugation, size-exclusion chromatography, precipitation kits) result in variable quality preparations that are hard to scale in Good Manufacturing Practice (GMP) conditions, and the long-term stability of exosome preparations is still not well established [29]. Thirdly regulatory issues – the exosome based products cannot be straightforwardly categorised either as biologics, as drugs or as medical devices, and currently no regulatory authority approved any exosome-based product for periodontal or general dental use, which in turn discourages the large financial investment necessary for funding of key human trials [18,30]. And finally the issue of cost-efficiency – the autologous or allogeneic exosome preparations are likely to be much more expensive compared to the GTR membranes, EMD, and autologous PRF preparations, and this cost advantage has been specifically mentioned as one of the obstacles to adoption even in case of eventual efficacy demonstration [30]. The review article summarising the existing translational medicine literature on exosomes lists all of the above bottlenecks as common to the entire exosome preparation process [28].

XII. FUTURE DIRECTIONS AND THE PATH TO CLINICAL PARITY WITH CELL-BASED THERAPEUTICS

While cell-based MSC treatments themselves are not yet a regular component of periodontal care, they are further along the translational timeline than exosome-based therapies and have more registered and completed human studies in periodontal regeneration and adjacent bone regeneration indications. In order to achieve a similar degree of clinical use in the near future, several concrete steps appear to be needed,

according to the gaps described above. These include: setting up of a standardised, preferably MISEV-conformant, characterisation and potency testing protocol tailored specifically for exosomes used in periodontics [9,10]; completion of human clinical trials (of early-phase safety/feasibility type) on periodontal intrabony or furcation defects, such as the current ones that are registered but not yet completed [3,19]; direct comparative trials to EMD and PRF in regard to clinical endpoints (probing depth reduction, clinical attachment gain, radiographic bone fill) rather than in preclinical animal models [24,25]; development of a specific regulatory pathway (biologic, combination product or advanced therapy medicinal product) for periodontal exosome therapy [18,30]; and establishment of cost-effectiveness or superiority in efficacy to justify a higher price point compared to current regenerative techniques [30]. The approaches to engineering that have already been developed in other research domains will undoubtedly influence the future of achieving these milestones. Genetic and surface engineering of parent cells in order to increase the proportion of therapeutically active exosomal cargo, functionalisation of exosome surfaces by adding targeting ligands, and combination with three-dimensional printed or MISEV-characterised scaffolds have been suggested as a way of improving potency, targeting, and manufacturability [31,22]. Whether these engineering methods, coupled with the clinical infrastructure mentioned above, can allow exosome-based periodontal therapy to catch up to cell-based and traditional biologics remains an open question at present.

XIII.CONCLUSION

Exosomes derived from dental and other mesenchymal stem cell sources have a well-supported preclinical mechanistic case for use in periodontal regeneration, acting on PDL cell migration and proliferation, osteogenesis, angiogenesis, and immune modulation. However, this preclinical promise has not yet been matched by human clinical evidence: no completed clinical trial has evaluated exosome therapy for periodontal regeneration, and translation is further constrained by unresolved issues of manufacturing standardisation, storage, regulatory classification, and cost-effectiveness relative to established therapies such as GTR, EMD, and PRF. Closing this gap will require standardised characterisation frameworks, completed early-phase human trials, and direct comparative studies against existing regenerative modalities.

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