

REVIEW

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Advances of exosomes in periodontitis treatment

Hongbing Lin¹, Huishan Chen¹, Xuetao Zhao¹, Tong Ding¹, Yawei Wang¹, Zhen Chen², Yue Tian¹, Peipei Zhang¹ and Yuqin Shen^{1,2*}

Abstract

Periodontitis is an inflammatory disease initiated by dysbiosis of the local microbial community. Periodontitis can result in destruction of tooth-supporting tissue; however, overactivation of the host immune response is the main reason for alveolar bone loss. Periodontal tissue cells, immune cells, and even further activated osteoclasts and neutrophils play pro-inflammatory or anti-inflammatory roles. Traditional therapies for periodontitis are effective in reducing the microbial quantities and improving the clinical symptoms of periodontitis. However, these methods are non-selective, and it is still challenging to achieve an ideal treatment effect in clinics using the currently available treatments and approaches. Exosomes have shown promising potential in various preclinical and clinical studies, including in the diagnosis and treatment of periodontitis. Exos can be secreted by almost all types of cells, containing specific substances of cells: RNA, free fatty acids, proteins, surface receptors and cytokines. Exos act as local and systemic intercellular communication medium, play significant roles in various biological functions, and regulate physiological and pathological processes in numerous diseases. Exos-based periodontitis diagnosis and treatment strategies have been reported to obtain the potential to overcome the drawbacks of traditional therapies. This review focuses on the accumulating evidence from the last 5 years, indicating the therapeutic potential of the Exos in preclinical and clinical studies of periodontitis. Recent advances on Exos-based periodontitis diagnosis and treatment strategies, existing challenges, and prospect are summarized as guidance to improve the effectiveness of Exos on periodontitis in clinics.

Keywords: Periodontitis, Exosomes, Immunomodulation, Immune cells, Osteoclast

Background

Periodontitis is an inflammatory disease initiated by dysbiosis of the local microbial community and is characterized by the relative abundance or influence imbalance of microbial species [1]. However, overactivation of the host immune response is the main reason for the direct activation of osteoclast activity and alveolar bone loss [2]. The composition and total number of microbiota change after the colonization of "keystone" pathogen, which

improves the pathogenicity of the whole community. Thus, the immune response is overactivated, resulting in immune cells infiltration, activation of osteoclast activity, and destruction of soft and hard tissues [3]. Pathological immunity of the host to dysbiotic microbes first occurs between the microbiome and host cells, which include periodontal tissue cells and other immune cells, such as mononuclear phagocytes (MNPs), antigen-presenting cells (APCs), and specific T cell subsets. Naive T cells and B cells not only differentiate into mature T cells or plasma cells but also further activate or promote osteoclasts and neutrophils to play a pro-inflammatory or anti-inflammatory role [4] (Fig. 1).

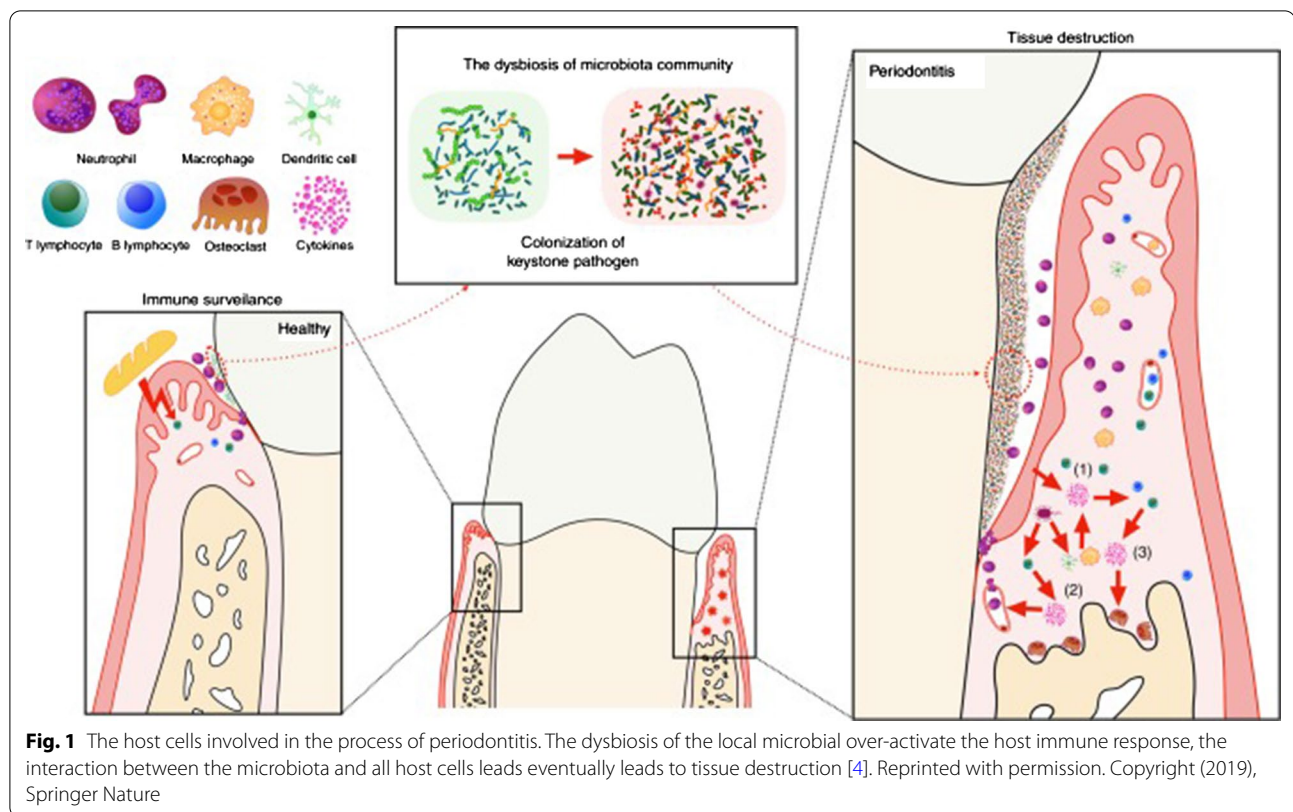
Traditional therapies for periodontitis include scaling and root planning (SRP), systemic and local

*Correspondence: 2020686041@gzhmu.edu.cn

¹ Jilin Provincial Key Laboratory of Tooth Development and Bone Remodeling, Hospital of Stomatology, Jilin University, Changchun, Jilin 130021, People's Republic of China

Full list of author information is available at the end of the article





administration of antibiotics, and oral antiseptics. In the short term, these therapies are usually effective in reducing the microbial quantities in the tissues and blood of periodontitis patients and improving the clinical symptoms of periodontitis. However, these methods are non-selective, and the oral and systemic effects of long-term medication need to be evaluated [5]. It is becoming increasingly clear that new strategies need to be developed to treat periodontitis more effectively.

Exos were discovered in 1987 and have been shown to be important in cell communication [6]. Other studies have confirmed that Exos are a natural nanoparticle delivery method that can treat multiple infectious and immune/inflammatory diseases [7–10]. Thus, in this review, we summarized studies from the last 5 years that have focused on the effect of Exos on periodontitis and host cells.

Exos

The biogenesis of Exos

Exos are secreted by almost all types of cells, including mesenchymal stem cells (MSCs), dendritic cells (DCs), B cells, T cells, and mast cells, and widely exist in many body fluids such as plasma, urine, breast milk, semen, amniotic fluid, and saliva [11]. Exos are among the three major types of extracellular vesicles (EVs). The size of

the Exos is between 50 and 150 nm and the density is between 1.15 and 1.19 g / ml [12]. The biogenesis and release of Exos are different from other of other microbubbles. While other microbubbles are released directly through the plasma membrane, Exos originating from endocytosis [13]. First, the membrane of secretory cells is sunken inward to produce endocytic vesicles. Multiple endocytic vesicles combine to form early nucleosomes, and then miRNA, mRNA and DNA are packaged in the cytoplasm to form late endocytosis vesicles. The late endocytic vesicles germinate inward to form intracavitary vesicles (ILVs). The aggregation of ILVs in late endosomes create multivesicular bodies (MVBs), which are formed by the inward invagination of the endosomal limiting membrane. Finally, some MVBs with low cholesterol were degraded by lysosomes, and some MVBs, rich in cholesterol, release extracellular bodies through the fusion of the cell membrane with itself [13–16]. The active formation of Exos is dependent on the endosomal sorting complex required for transport (ESCRT; ESCRT-0, I, II, III and Vps4) and its accessory proteins (Alix, TSG101, HSC70, and HSP90 β). They recognize ubiquitinated transmembrane proteins and incorporate endosomal proteins into MVBs. [17, 18]. Passive formation of Exos is independent of ESCRT and involves lipids (ceramide), tetrapeptides (CD63) and heat shock proteins

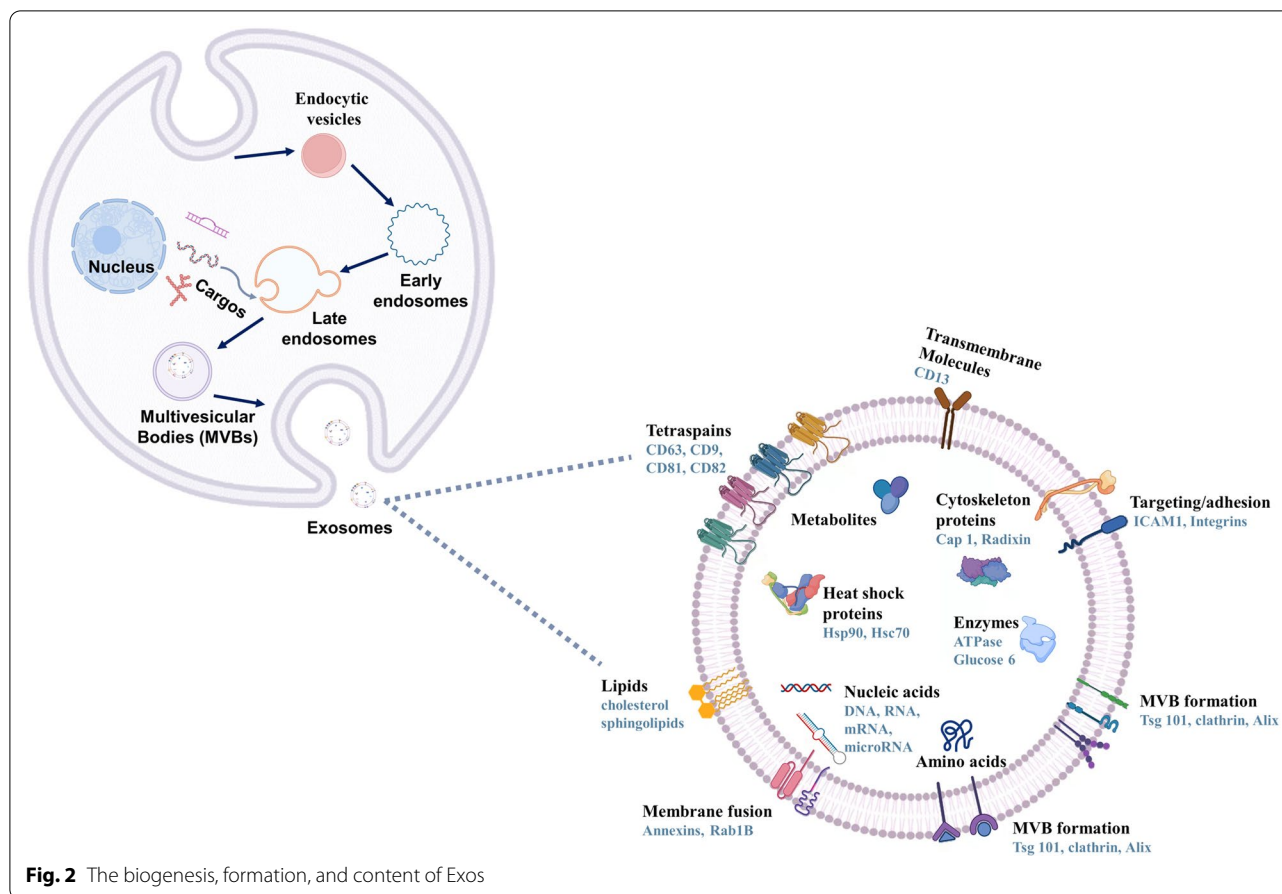


Fig. 2 The biogenesis, formation, and content of Exos

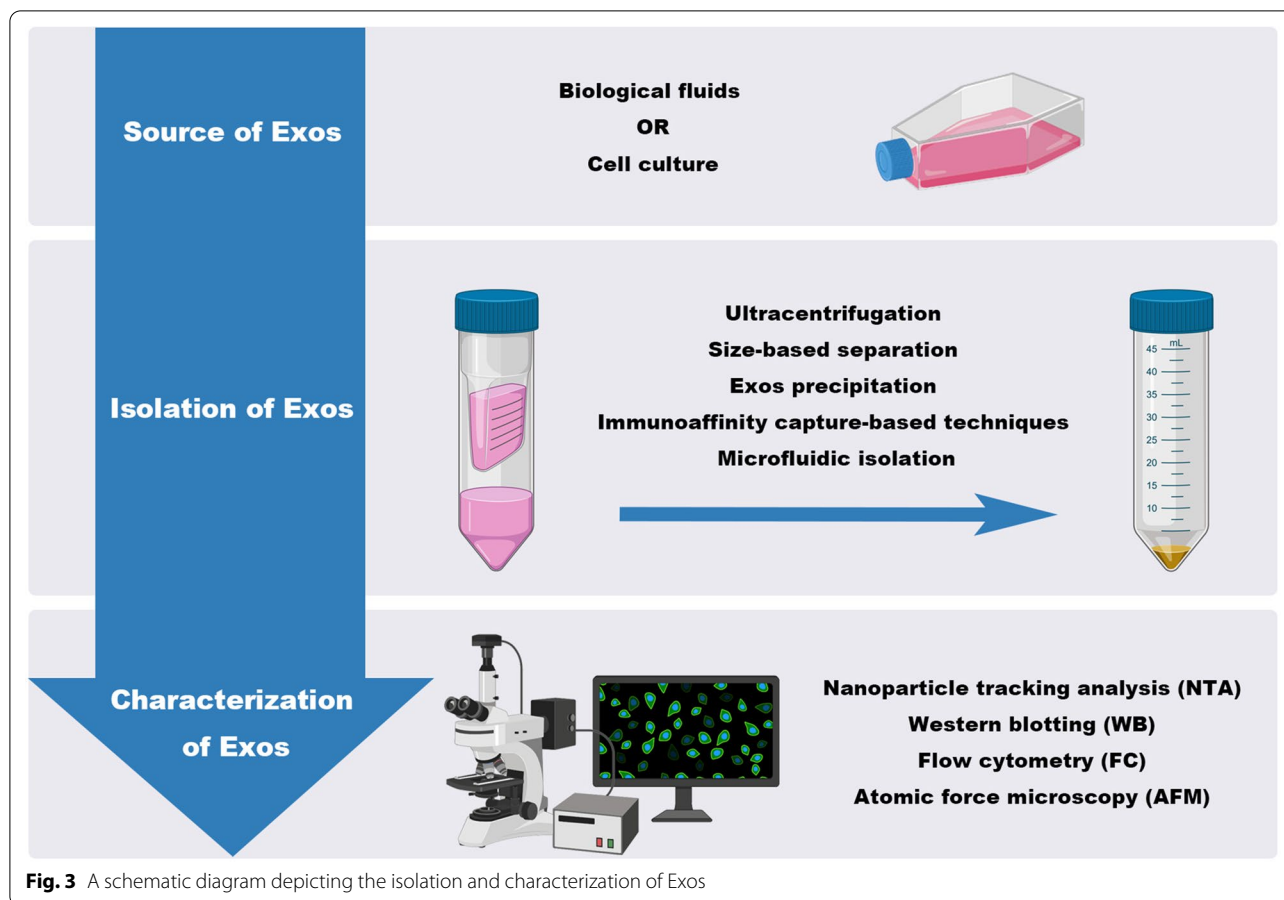
which induce cell membrane budding and promote MVB formation [19, 20]. In addition, certain components, such as four-transmembrane domain proteins and lipid rafts, have been reported to participate in the formation of some exosomes [21, 22]. In addition to the classic pathway, there is a much more immediate route of exosome biogenesis. T cells and erythroleukemia cell lines can release exosomes from the plasma membrane directly, and the Exos produced by these two pathways cannot be distinguished [23, 24]. Furthermore, soluble N-ethylmaleimide-sensitive fusion protein attachment protein receptor (SNARE) proteins and their effectors such as Rab GTPases (Rab27a, Rab27b and Rab35) play a significant role in exosome secretion [14].

The biogenesis of Exos is affected by many external factors, including cell type, serum conditions, cytokines, and growth factors. The heterogeneity of Exos is based on their specific morphology, content, and function [25, 26]. Encapsulated by lipid membranes derived from parental cells, Exos show inherent histocompatibility and tissue orientation mediated by surface molecules such as integrin and glycans [27]. In addition, Exos contain four transmembrane proteins (CD9, CD63, CD81 and CD82), heat

shock proteins, lipoproteins, and some transport-related proteins. These proteins can not only provide markers for Exos identification but also locate Exos in specific target cells [28, 29]. Exos contain substances to mother cells, such as RNA, free fatty acids, proteins, surface receptors, and cytokines, which act as local and systemic intercellular communication media [30, 31]. Owing to these characteristics, Exos play a significant role in various biological functions and regulate many physiological and pathological processes in numerous diseases [32] (Fig. 2).

The isolation and characterization of Exos

The selection and improvement of isolation strategies should be determined according to the kind of biological fluids Exos are isolated from. Effective isolation strategies should be able to concentrate the signals of the Exos to be analyzed and avoid contamination with other molecules, such as lipoproteins, non-vesicular protein aggregates, and other EVs, which are similar to Exos in terms of size and density. At present, there are many techniques for separating and purifying Exos from biological fluids and in vitro cell cultures, including ultracentrifugation, size-based separation, Exos precipitation, immunoaffinity



capture-based techniques, and microfluidic isolation [33–36]. Among these, differential centrifugation is the most widely used and basic method for Exos separation, and it is a feasible strategy to combine two or more methods to improve the yield, purity, and efficiency of Exos extracriion. Various techniques based on biophysical or biological characteristics have been used to verify upstream Exos separation methods and classify Exos subgroups for downstream analysis, such as nanoparticle tracking analysis (NTA), western blotting (WB), flow cytometry (FC), and atomic force microscopy (AFM) [35–37] (Fig. 3).

Exos based periodontitis diagnostic and treatment strategy

Periodontitis is a major public health problem with a high incidence rate worldwide. It could not only cause destruction of the supporting tissues of teeth but also have a negative effect on systematic disease states [38]. Therefore, effective diagnosis and treatment of periodontitis are important to reduce the risk of periodontitis.

Exos-based periodontitis diagnostic strategy

Because the components of Exos can be reprogrammed according to disease status, Exos are increasingly being evaluated as potential diagnostic biomarkers for the diagnosis and prognosis of diseases. These characteristics have made Exos a focus of oral disease research in recent years, including periodontitis [39].

At the gene level, Exos are enriched in specific microRNAs (miRNAs), that can provide disease-specific diagnostic signatures [40]. When compared to healthy controls, plasma-derived exosomal miRs (miR-1304-3p and miR-200c-3p) and snoRs (SNORD57 and SNODB1771) from periodontitis patients are differentially expressed and could be the valuable biomarkers for periodontitis diagnosis [41]. In addition, the level of programmed death-ligand 1 (PD-L1) mRNA in salivary Exos may have the potential to diagnose periodontitis and is relative to the severity of periodontitis [42].

At the protein level, detection and analysis of salivary exosomal proteins in young adults with severe periodontitis (SP) suggested that C6 proteins, which participate in the immune response during the development of periodontitis, were expressed only in the SP group [43].

In addition, levels of CD9 and CD81 Exos in periodontitis patients were significantly lower than those in the healthy controls. Because the concentration of CD9/CD81 Exos in saliva is significantly and negatively correlated with clinical measurements, it may be of great significance in the pathogenesis of periodontal disease [44]. Other advances in salivary Exos in the diagnosis of periodontitis are well-reviewed in the literature [45].

Exos-based periodontitis treatment strategy

Exos have been reported to provide a novel perspective and potential therapeutic approach for treating periodontitis and improving alveolar resorption. Exos derived from 3D-cultured MSCs restored not only the Th17 cell/Treg balance through the miR-1246/Nfat5 axis, but also the immune responses in the inflamed periodontium [46]. Dental pulp stem cell-Exo (DPSC-Exos) can facilitate the conversion of macrophages from a pro-inflammatory phenotype (M1) to an anti-inflammatory phenotype (M2) and promote the healing of alveolar bone in mice with periodontitis, the mechanism of which could be associated with miR-1246 in DPSC-Exos [47]. Exos purified from human leukocyte antigen haplotype homo dental pulp cell lines (HHH-DPCs) stimulated the migration of human DPCs and mouse osteoblastic and significantly suppressed osteoclast formation in vitro [48]. Exos secreted from healthy periodontal ligament stem cells (PDLSCs) promote osteogenic differentiation of PDLSCs derived from periodontitis tissue. Healthy PDLSC-Exos (h-PDLSC-Exos) treatment resulted in accelerated bone formation in alveolar bone defects in rat models of periodontitis. Mechanistically, h-PDLSC-Exos suppressed the overactivation of canonical Wnt signaling to recover the osteogenic differentiation capacity of inflammatory PDLSCs [49]. Exos derived from TNF- α -preconditioned gingival mesenchymal stem cells (GMSCs) could significantly regulate inflammation and osteoclastogenesis, which could provide a therapeutic approach for periodontitis [50]. Human exfoliated deciduous teeth (SHED)-derived Exos (SHED-Exos) restored bone loss in mouse periodontitis model and promoted bone marrow stromal cells (BMSCs) osteogenesis, differentiation, and bone formation [51]. SHED-Exos contribute to periodontal bone regeneration by promoting neovascularization and new bone formation, possibly through the AMPK signaling pathway [52]. Exos from reparative M2 macrophages reduced alveolar bone resorption in mice with periodontitis via the IL-10/IL-10R pathway [53]. Exos derived from adipose-derived stem cells (ADSC-Exos) represent a promising adjunctive treatment to SRP in rats [54]. Exosomal miR-25-3p in saliva contributes to the development and progression of diabetes-associated periodontitis. The discovery of other miR-25-3p targets may

provide critical insights into the development of drugs to treat periodontitis by regulating $\gamma\delta$ T cell-mediated local inflammation [55]. The in vivo effects of Exos on periodontitis are summarized in Table 1.

Possible mechanism of Exos on host cells during periodontitis

Overactivation of the host immune response is caused by the interaction between the dysbiosis of local microbes and host cells, eventually leading to periodontal tissue destruction. The host cells include periodontal tissue cells and other immune cells, which play pro-inflammatory or anti-inflammatory roles [4]. Exos retain proteins, miRNA, mRNA, DNA, and lipids, and can transfer that cargo to distant target cells and modify the target cells. Reports have revealed the biological activities of Exos in modifying host cells (Fig. 4). Modification of host cells with Exos from different sources plays an important role in the treatment of periodontitis.

Effects of Exos on neutrophils

Neutrophils are short-lived cells in the innate immune system. They play an important role in pathogen resistance by producing reactive oxygen species (ROS). Therefore, effective strategies to improve the viability and function of neutrophils may be beneficial for treating infections and immune deficiency diseases. MSC-Exos have a protective effect on neutrophil function and lifespan [56], and could significantly reduce the terminal complement activation complex C5b-9 to inhibit neutrophils accumulation [57]. Exos isolated from ADSCs (ADSC-Exos) can decrease neutrophil apoptosis and increase phagocytosis [58]. Exos isolated from LPS-treated macrophages can induce cytokine production and neutrophils migration [59].

Effects of Exos on macrophages

MSC-Exos can modify the polarization of the pro-inflammatory phenotype (M1 macrophages) to the anti-inflammatory phenotype (M2 macrophages) via shuttling miR-182 [60]. Exos derived from BMSCs (BMSC-Exos) can increase M2 macrophages [61], and BMSC-Exos have been reported to inhibit M1 macrophages and promote M2 macrophages in a murine alveolar macrophage cell line by inhibiting cellular glycolysis [62]. FNDC5 pre-conditioned BMSC-Exos have also been confirmed to play an anti-inflammatory role and promote M2 macrophages via NF- κ B signaling pathway and the Nrf2/HO-1 axis [63]. Exos from human umbilical cord mesenchymal stem cells (hUCMSC-Exos) facilitated CD163+ M2 macrophages [64] and promoted M2 macrophages in LPS-stimulated RAW 264.7 via tumor necrosis factor receptor-associated

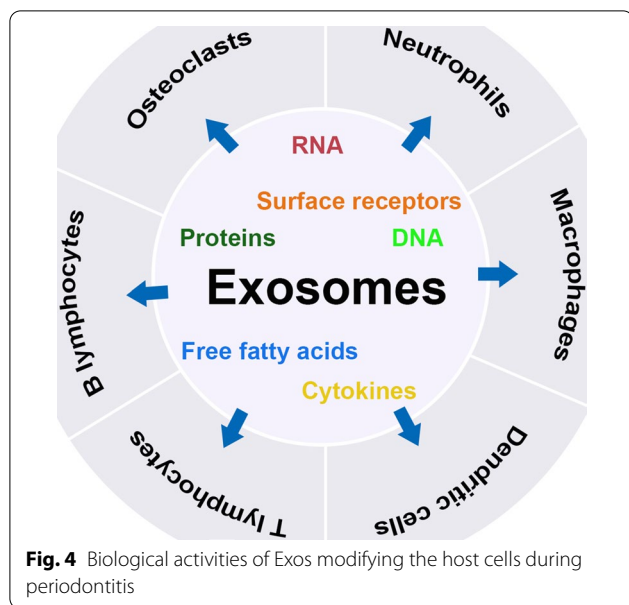
Table 1 Summary of in vivo results showing the Exos-based periodontitis treatment strategy used over the past 5 years

Source of Exos	Study model	Route of delivery	Dose	Duration	Outcomes	References
MSCs	Mouse experimental periodontitis model	Locally injection	50 µg per mouse	14 days	Improve the treatment by restoring the Th17 cell/Treg balance through the miR-1246/Nfat5 axis	[46]
DPSCs	Mouse experimental periodontitis model	Incorporated chitosan hydrogel	50 µg	4 weeks	Facilitate macrophages from M1 to M2 phenotype and promote alveolar bone healing	[47]
HHH-DPSCs	Mouse experimental periodontitis model	Directly applied onto the silk ligature	5 µL containing 7.5×10^8 particles	7 days	Promote the migration of both DPCs and osteoblastic cells; suppress osteoclast formation	[48]
PDLSCs	Rat periodontal bone defect model	Mixed with Matrigel	Exos (225 µg/µL): Matrigel = 2:1 (v/v)	4 weeks	Suppress overactivation Wnt signaling, recover osteogenic differentiation capacity of inflammatory PDLSCs	[49]
TNF-α-treated human GMSCs	Mouse experimental periodontitis model	Locally injection	20 µg per mouse	7 days	Regulate inflammation and osteoclastogenesis	[50]
SHED	Mouse experimental periodontitis model	Locally injection	20 µg	2 weeks	Restore bone loss, promote BMSCs osteogenesis, differentiation, and bone formation	[51]
SHED	Rat periodontal defect models	h β-TCP scaffolds loaded with Exos	2 µg/µL Exos in 100 µL PBS	4 weeks	Contribute to periodontal bone regeneration through the AMPK signaling pathway	[52]
induced M2-like macrophages	Mouse experimental periodontitis model	Locally injection	30 µL (500 ng/ml)	2 weeks	Reduce alveolar bone resorption in mice with periodontitis via IL-10/IL-10R pathway	[53]
ADSCs	Rat experimental periodontitis model	Locally injection	80–150 µg in 200 µL PBS	4 weeks	Represent a promising adjunctive treatment to SRP	[54]
salivary Exos	Insulin resistance-associated mouse experimental periodontitis model	Locally injection	miR-25-3p inhibitors (100 µl of 8 nM)	9 days	Exosomal miR-25-3p in saliva contribute to development and progression of diabetes-associated periodontitis	[55]

factor 1 (TRAF1) [65]. ADSC-Exos can significantly upregulate the mRNA expression of M2 macrophages [66], induce M2 macrophages through the transactivation of Arg-1 by Exos-carried active STAT3 [67], and alleviate LPS induced inflammation by regulating Nrf2/HO-1 expression [68]. Exos from GMSCs (GMSC-Exos) and dental pulp stem cells (DPSC-Exos) can promote the transformation of macrophages from M1 to M2 [47, 69]. TNF-α stimulated GMSC-Exos have also been reported to induce anti-inflammatory M2 macrophage polarization [47, 50].

Effects of Exos on DCs

MSC-Exos decreased DC surface marker expression in cells treated with LPS and decreased lymphocyte proliferation in the presence of MSC-Exos treated DCs, suggesting that MSC-Exos may play a key role in DC-induced immune responses [70]. hUCMSC-Exos suppressed the maturation and activation of DC and decreased the expression of IL-23, which is particularly important for promoting the pathogenicity of Th17 cells [71]. Exos from RegDC (RegDC-Exos) suppress the maturation of DCs and promote the recruitment of Treg cells, resulting in the inhibition of bone resorptive cytokines and reduction in osteoclastic bone loss [72]. Exos from lymphatic



endothelial cells (LEC-Exos) promote the directional migration of human DCs in complex tissue environments in a CX3CL1/fractalkine-dependent fashion [73].

Effects of Exos on T lymphocytes

MSC-Exos decreased T lymphocyte proliferation and the percentage of CD4⁺ and CD8⁺ T cell subsets in a dose-dependent manner while increasing Treg cell populations [74]. MSC-Exos promote the proliferation and immune-suppression capacity of Tregs by upregulating IL-10 and TGF- β 1 [75], and inhibit the differentiation of Th2 cells by regulating the miR-146a-5p/SERPINB2 pathway [76]. PDLSC-Exos alleviated inflammatory microenvironment and maintained Th17/Treg balance via the Th17/Treg/miR-155-5p/SIRT1 regulatory network [77]. CD137-modified endothelial cell-Exos (EC-Exos) promote Th17 cell differentiation via the NF- κ B pathway by regulating IL-6 expression [78].

Effects of Exos on B lymphocytes

MSC-Exos had the beneficial effect of reducing plasma-blasts and increasing Breg-like cells in lymph nodes [74].

Effects of Exos on osteoclasts

Exosomal miR-1260b of TNF- α -preconditioned GMSC-Exos was found to inhibit osteoclastogenic activity by targeting the Wnt5a-mediated RANKL pathway [50]. RegDC-Exos inhibit the production of bone resorptive cytokines and bone loss in osteoclasts [72]. Cyclic mechanical stretch (CMS)-treated BMSC-Exos can impair osteoclast differentiation by inhibiting the RANKL-NF- κ B signaling pathway [79]. ADSC-Exos can

reduce bone resorption and recover bone loss by suppressing NLRP3 inflammasome activation in osteoclasts [80] and by antagonizing osteocyte-mediated osteoclastogenesis [81]. ADSC-Exos combined with microRNA-146a (miR-146a-Exo) were reported to restrain bone resorption by inhibiting pro-inflammatory cytokine production in high glucose-treated osteoclasts [82]. Exos derived from osteoblasts can inhibit osteoclast differentiation via the miR-503-3p/Hpse axis [83]. Exos from endothelial progenitor cells (EPC-Exos) can promote bone repair by enhancing the recruitment and differentiation of osteoclast precursors via LncRNA-MALAT1 [84].

The effects of Exos on the host cells involved in periodontitis are summarized in Table 2.

Summary and prospects

Exos can be secreted by almost all cell types and are the main contributor to cells efficacy. They are natural carriers of functional small RNA and proteins [85], and the constituents can be reprogrammed depending on the disease state [39]. Therefore, potential applications of Exos in the diagnosis and treatment of diseases are becoming increasingly popular. Exos derived from MSCs, with or without biomaterials, have broad application prospects in the treatment of periodontitis, especially in the cell-free treatment of tissue regeneration. Among them, Exos derived from oral stem cells are easier to collect and may show excellent characteristics of immune regulation, repair, and regeneration as well as less ethical, moral, or safety limits [12, 86]. In this review, we summarized the novel strategies using Exos in periodontitis over the last 5 years and analyze the possible mechanism of Exos in the treatment of periodontitis by summarizing the effect of Exos on host cells involved in the process of periodontitis.

Although the applications of Exos in periodontitis has been proved to be useful in animal models of preclinical research, much work needs to be done to apply it to clinics. Originally, Exos in clinical trials had to comply with good manufacturing practice (GMP), which includes the upstream of the cell culture process, the downstream of the purification process, and the quality control of Exos. The content carried by Exos varies from cell type to culture conditions and batch, which causes differences in biological functions. Therefore, it is necessary to explore more convenient and efficient technologies for the separation, purification, and storage of Exos to improve their homogeneity, purity, and repeatability. Furthermore, the corresponding role and mechanism of Exos in the diagnosis and treatment of periodontitis need to be explored more comprehensively. The critical range of differential expression of exosomes in periodontal tissue under

Table 2 Summary of the effects of Exos on host cells

No	Source of Exos	Biological activity	References
Neutrophil			
1	MSCs	Have protective effects on neutrophil function and lifespan	[56]
2	MSCs	Reduce terminal complement activation complex C5b-9 to inhibit neutrophils accumulation	[57]
3	ADSCs	Decrease neutrophils apoptosis and increased their phagocytosis capacity	[58]
4	LPS-treated macrophages	Induce cytokine production and neutrophil migration	[59]
Macrophage			
1	DPSCs	Facilitate macrophages to convert from M1 phenotype to M2 phenotype	[47]
2	TNF- α induced GMSCs	Induce anti-inflammatory M2 macrophage polarization	[50]
3	MSCs	Modify the polarization of M1 macrophages to M2 macrophages via shuttling miR-182	[60]
4	BMSCs	Increase M2 macrophage polarization	[61]
5	BMSCs	Inhibit M1 polarization and promotes M2 polarization in a murine alveolar macrophage cell line by inhibiting cellular glycolysis	[62]
6	FNDC5 pre-conditioned BMSCs	Play anti-inflammation effects and promote M2 macrophage polarization via NF- κ B signaling pathway and Nrf2/HO-1 axis	[63]
7	hUCMSCs	Facilitate CD163 + M2 macrophage polarization, reduced inflammation, and increases anti-inflammatory responses	[64]
8	hUCMSCs	Inhibit M1 polarization and promoted M2 polarization through tumor necrosis factor receptor-associated factor 1 (TRAF1)	[65]
9	ADSCs	Upregulate mRNA expression of M2 macrophages	[66]
10	ADSCs	Induce anti-inflammatory M2 phenotypes through the transactivation of arginase-1 by Exo-carried active STAT3	[67]
11	ADSCs	Polarize macrophage to an anti-inflammatory phenotype via regulating the Nrf2/HO-1 expression	[68]
12	GMSCs	Facilitate macrophages to convert from M1 phenotype to M2 phenotype	[69]
Dendritic cell			
1	MSCs	Decrease DC surface marker expression and modulates DC-induced immune responses	[70]
2	hUCMSCs	Suppress maturation and activation of DCs, and decreases the expression level of IL-23	[71]
3	regDCs	Suppress maturation of recipient DCs resulting in inhibition of bone resorptive cytokines	[72]
4	LECs	Promote the directional migratory in a CX3CL1/fractalkine-dependent fashion	[73]
T lymphocyte			
1	MSCs	Increase Treg cell populations, inhibit T lymphocyte proliferation in a dose-dependent manner and decreases the percentage of CD4 + and CD8 + T cell subsets	[74]
2	MSCs	Upregulate IL-10 and TGF- β 1 to promote proliferation and immune-suppression capacity of Tregs	[75]
3	MSCs	Inhibit the differentiation of Th2 cells via the regulation of the miR-146a-5p/SERPIN2 pathway	[76]
4	PDLSCs	Alleviate inflammatory microenvironment and keep Th17/Treg balance via Th17/Treg/miR-155-5p/SIRT1 regulatory network	[77]
5	CD137-modified ECs	Promote Th17 cell differentiation via NF- κ B pathway mediated IL-6 expression	[78]
B lymphocyte			
1	MSCs	Upregulate Breg-like cells in lymph nodes	[74]
Osteoclast			
1	TNF- α -preconditioned GMSCs	Inhibit osteoclastogenic activity via exosomal miR-1260b to target Wnt5a-mediated RANKL pathway and	[50]
2	regDC	Result in inhibition of bone resorptive cytokines and reduces in osteoclastic bone loss	[72]
3	CMS-treated BMSCs	Impair osteoclast differentiation via inhibiting the RANKL-induced nuclear factor kappa-B (NF- κ B) signaling pathway	[79]
4	ADSCs	Suppress NLRP3 inflammasome activation in osteoclasts and reduces bone resorption and recover bone loss	[80]
5	ADSCs	Antagonize osteocyte-mediated osteoclastogenesis	[81]
6	ADSCs	Inhibit pro-inflammatory cytokines production in high glucose-treated osteoclasts and restrains bone resorption	[82]
7	osteoblast	Inhibit the osteoclast differentiation via miR-503-3p/Hpse axis	[83]
8	EPCs	Promote bone repair by enhancing recruitment and differentiation of osteoclast precursors through LncRNA-MALAT1	[84]

healthy and inflammatory conditions for diagnosis and the amount and duration of safe and effective treatment need to be defined. Ultimately, the mechanisms of interaction between Exos and host cells are not clear, which makes it impossible for Exos to accurately regulate the target cells and functions. However, there is no doubt that Exos have the potential to provide personalized medical strategies for the prevention and treatment of periodontitis.

Conclusions

Exos contain specific substances in their cells and play a significant role in the diagnosis and treatment of numerous diseases, including periodontitis. Exos-based periodontitis treatment strategies have been reported to obtain the potential to overcome the drawbacks of traditional therapies and have tremendous prospect for bench-to-bed translation.

Abbreviations

MNPs: mononuclear phagocytes; APCs: antigen-presenting cells; SRP: scaling and root planning; MSCs: mesenchymal stem cells; DCs: dendritic cells; EVs: extracellular vesicles; SNARE: soluble N-ethylmaleimide-sensitive fusion protein attachment protein receptor; ILVs: intracavitary vesicles; MVBs: multivesicular bodies; NTA: nanoparticle tracking analysis; WB: western blotting; FC: flow cytometry; AFM: atomic force microscopy; miRNAs: microRNAs; PD-L1: programmed death-ligand 1; SP: severe periodontitis; DPSCs: dental pulp stem cells; HHH-DPCs: haplotype homo dental pulp cell lines; PDLSCs: periodontal ligament stem cells; GMSCs: gingival mesenchymal stem cells; SHED: human exfoliated deciduous teeth; BMSCs: bone marrow stromal cells; ADSCs: adipose-derived stem cells; ROS: reactive oxygen species; hUCMSCs: human umbilical cord mesenchymal stem cells; TRAF1: tumor necrosis factor receptor-associated factor 1; LECs: lymphatic endothelial cells; ECs: endothelial cells; CMS: cyclic mechanical stretch; EPCs: endothelial progenitor cells; GMP: good manufacturing practice.

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Author contributions

HL conceived the study and drafted the manuscript. YS revised the manuscript. HC, XZ, TD, YW, ZC, YT and PZ searched for relevant literatures and provided the comments. All authors read and approved the final manuscript.

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Availability of data and materials

Not applicable.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author details

¹Jilin Provincial Key Laboratory of Tooth Development and Bone Remodeling, Hospital of Stomatology, Jilin University, Changchun, Jilin 130021, People's Republic of China. ²Department of Periodontics, Affiliated Stomatology Hospital of Guangzhou Medical University, Guangzhou Key Laboratory of Basic and Applied Research of Oral Regenerative Medicine, Guangzhou, Guangdong 510182, People's Republic of China.

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