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REVIEW

Exosomes in Oral Diseases: Mechanisms and Therapeutic Applications

Qiandai Miao, Shaoqing Li, Weijia Lyu, Jianxia Zhang, Yan Han

Department of Stomatology, China Academy of Chinese Medical Sciences, Xiyuan Hospital, Beijing, 100091, People's Republic of China

Correspondence: Yan Han, Email hy1352111@163.com

Abstract: Exosomes, small extracellular vesicles secreted by various cells, play crucial roles in the pathogenesis and treatment of oral diseases. Recent studies have highlighted their involvement in orthodontics, periodontitis, oral squamous cell carcinoma (OSCC), and hand, foot, and mouth disease (HFMD). Exosomes have a positive effect on the inflammatory environment of the oral cavity, remodeling and regeneration of oral tissues, and offer promising therapeutic options for bone and periodontal tissue restoration. In OSCC tumor-derived exosomes promote cancer progression through cell proliferation, migration, invasion, and angiogenesis, and serve as potential biomarkers for early diagnosis and prognosis. Additionally, engineered exosomes constructed specifically based on exosome properties hold great promise for targeted drug delivery and regenerative therapies such as bone regeneration in orthodontics and periodontal healing. With continued research, exosomes hold great potential for improving diagnosis and treatment in oral diseases, advancing personalized and regenerative therapies.

Keywords: exosomes, orthodontics, periodontitis, treatment, regenerative therapy

Introduction

The mouth consists of the lips, tongue, teeth, cheeks, and palate and serves as the beginning of the digestive tract and is responsible for ingesting, chewing, and swallowing food. The human oral cavity contains at least 700 species of microorganisms and is one of the most complex and important parts of the human body.[1] With the economic and social development of mankind, people are paying more and more attention to their oral health. Oral diseases, such as dental caries, periodontal disease and oral cancer, affect nearly 3.5 billion people globally, especially those who are socio-economically disadvantaged.[2] Because the oral cavity is rich in water, nutrients, and blood vessels, the most common clinical scenario is an infection of the mucous membranes or teeth in the oral cavity by a variety of pathogens. In order to alleviate these burdens, researchers have come up with various types of diagnostic as well as therapeutic novelties.

In recent years, more and more researchers have focused on exosomes. Exosomes are microscopic vesicles that are produced and released by almost all cells and usually contain large amounts of proteins, lipids and nucleic acids.[3] Exosomes can be viewed as one of the pathways by which cells excrete ribonucleic acid and proteins, and are present in almost all kinds of biological fluids.[4–6] In addition, exosomes can act as messengers and carriers for signalling or transporting substances to other cells,[7–9] thereby altering the function of cells in different states.[10,11] It has been demonstrated that exosomes are associated with many diseases. In the field of cancer, exosomes are associated with the progression of cancer disease,[12,13] and some researchers have used exosomes for cancer diagnosis and treatment.[14–17] Su-Kang Shan et al summarised the pathophysiological mechanisms, clinical manifestations and therapeutic effects of exosomes in which they are involved from a bone metabolism-related perspective.[18]

Due to the active role of exosomes in various diseases, researchers are gradually linking them to oral diseases. Exosomes have been found to play a multifaceted role in the treatment of oral diseases in recent studies. Exosomes derived from oral cancer could exacerbate the malignancy of cancer.[19] In addition, exosomes functioned as a kind of message transmitter, sending messages between tumor cells and the rest of the body.[20] It is important to note that exosomes made from oral

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mesenchymal stem cells (MSCs) have been shown to be able to regenerate dental pulp and periodontal tissues in regenerative medicine and orthodontics.[21] This review focuses on the relevance of exosomes to human oral diseases.

Exosome Characterization

In the 1980s, exosomes were described as small vesicles formed during reticulocyte development that contribute to the selective externalisation and clearance of transferrin receptors from erythrocytes.[22,23] A few years later, Johnstone coined the term "exosome".[24] Until recently, it was determined that these vesicles were membrane-bound extracellular vesicles around 100 nm in diameter released by cells after fusion of the cell membrane with intracellular multivesicular bodies (Figure 1).[25,26] Usually electron microscopy imaging is the gold standard for characterising exosomes.[27] Electron microscopy resolution is usually in the range of 1–5 nm, allowing the most intuitive morphological characterisation of exosomes.[28] Nanoparticle tracking analysis is an optical particle tracking method that can be used to characterise the concentration as well as the size of exosome.[29,30] Dynamic light scattering has also been applied to characterise the size distribution of placental exosomes, but particles of different sizes and morphologies affect the accuracy and reliability of the technique's measurements, making it less suitable for analysing heterogeneous populations.[31] Western Blot (WB) is widely used in laboratories to detect specific proteins in mixtures of proteins extracted from biological samples and can be used to demonstrate specific proteins or exosome-cell interactions in exosome lysates.[32,33] Exosome characterisation methods are summarised in the Table 1.[34]

Conventional methods of isolation of exosomes include ultracentrifugation, size filtration, size exclusion chromatography and polymer precipitation.[35] In recent years, immunological methods have been favoured by many researchers due to their high purity of isolation as well as their productivity.[36] In further method improvement, researchers used relevant magnetic nanoparticles to magnetically separate exosomes after surface modification, which greatly enhanced

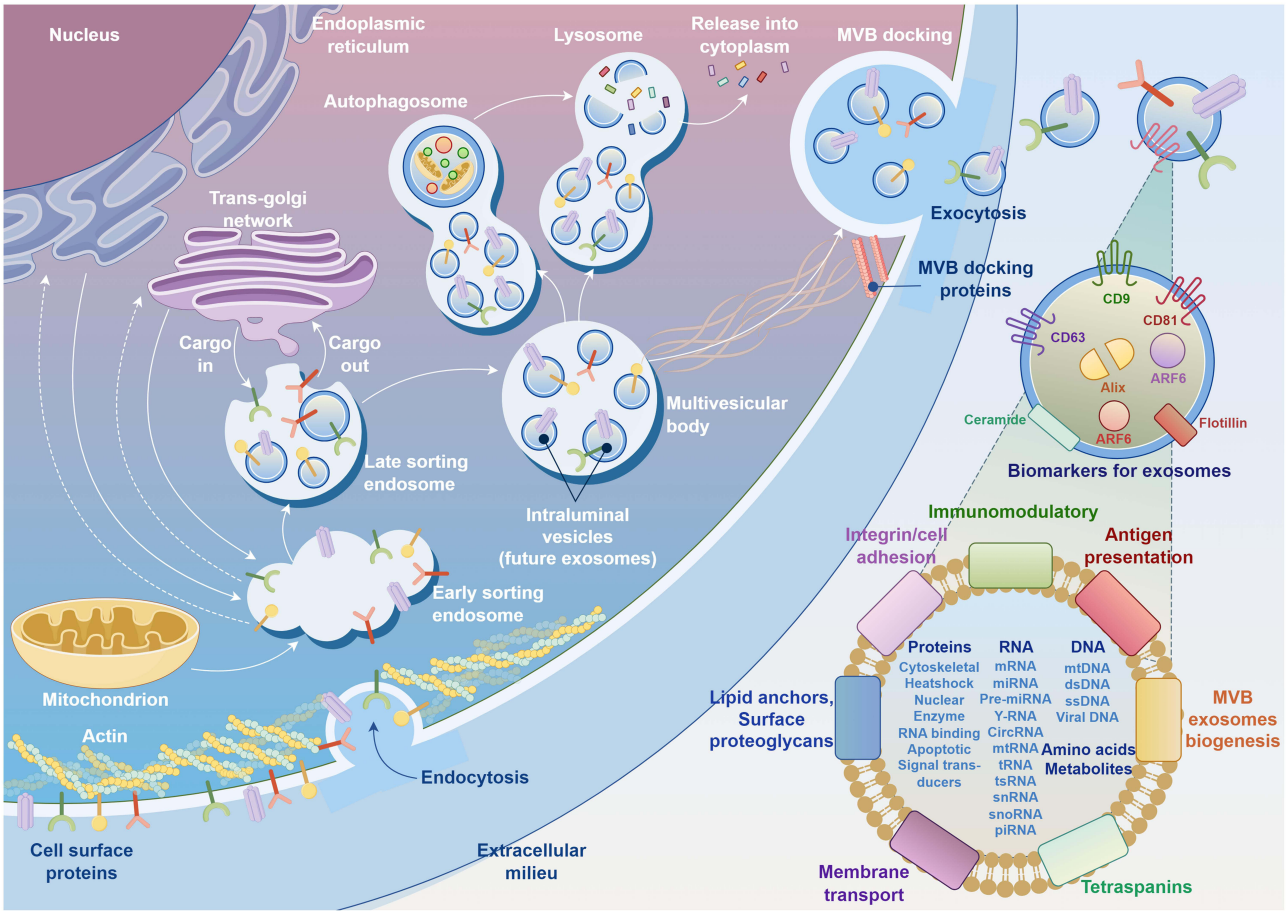

Figure 1 Exosome characterization. By Figdraw.

Table 1 Exosome Characterisation Methods

Method	Type	Characteristic
Electron microscope	Physical	High resolution and intuitive
Nanoparticle tracking	Physical	Characterisation of particles with a wide range of size
Dynamic light scattering techniques	Physical	Determination of the mean hydrodynamic diameter of isolated particles with a relatively uniform size distribution
Western Blot	Biological	Can be used to detect specific proteins in protein mixtures
Test kits	Biological	High sensitivity, convenient

the exosome separation yield, but limited the wide application because of its high cost.[37] With the development of microfluidics focusing on micro- and even nano-sized studies, microfluidics has also been applied to exosome-related studies.[38]

Exosomes and Oral Disease

Recent studies have highlighted the diverse roles of exosomes in oral diseases. This review examines their involvement in orthodontics, periodontitis, oral squamous cell carcinoma (OSCC), and hand, foot, and mouth disease (HFMD). In orthodontics, exosomes regulate bone remodeling during tooth movement, potentially improving treatment outcomes. In periodontitis, they influence inflammation, osteoclastogenesis, and tissue regeneration, offering new therapeutic possibilities. Exosomes in OSCC contribute to tumor progression and can serve as diagnostic tools, while in HFMD, exosomal miRNAs play a role in viral replication and immune response.

Exosomes in Orthodontics

Orthodontic treatment involves applying controlled mechanical forces to move teeth, which triggers bone remodeling in the surrounding alveolar bone.[39] This process requires a coordinated balance between bone resorption and formation, and it is critical for the successful and efficient movement of teeth. Exosomes, small extracellular vesicles secreted by osteoclasts, osteoblasts, and other cells involved in bone metabolism, are gaining recognition as key regulators in bone remodeling during orthodontic tooth movement.[40,41] These vesicles, carrying bioactive molecules such as proteins, lipids, small molecules, and microRNAs, have the potential to modulate both bone resorption and formation, making them an attractive tool to enhance orthodontic therapy.[42]

Studies have shown that exosomes derived from osteoclast precursors are capable of stimulating osteoclastogenesis, the differentiation and activation of osteoclasts, which are essential for bone resorption.[43] In orthodontics, accelerating osteoclastogenesis can be particularly beneficial during the early stages of tooth movement, where resorption of bone on the pressure side of the tooth is necessary for creating space for tooth displacement.[44,45] By enhancing osteoclast function, exosomes from osteoclast precursors could help speed up this process, potentially reducing the duration of orthodontic treatment.[46] On the other hand, exosomes derived from osteoblasts, the cells responsible for bone formation, are likely to play an equally important role in orthodontics. Osteoblast-derived exosomes can carry factors that promote osteoblast differentiation, bone matrix production, and mineralization, all of which are essential for remodeling the bone at the tooth's new position after movement.[47] The presence of these osteoblast-derived exosomes could help facilitate the bone formation necessary for stabilizing the tooth in its new location, ensuring long-term success of the treatment.

Exosomes derived from osteoclasts and osteoblasts can significantly influence bone resorption and formation during orthodontic force application.[48] Specifically, exosomes from osteoclast precursors have been shown to stimulate osteoclastogenesis, which could accelerate the resorption of alveolar bone during the initial stages of tooth movement, thereby facilitating more efficient orthodontic adjustments.[48] Meanwhile, exosomes from osteoblasts play a vital role in promoting bone formation at the site of tension, aiding in the remodeling of bone as the tooth moves to its new position.[49,50] This dual role of exosomes in regulating both bone resorption and formation presents an exciting opportunity to enhance the efficiency of orthodontic treatments.

Exosomes and Periodontitis

Periodontitis is a devastating inflammatory disease that is one of the leading causes of tooth loss in adults.[51] Severe periodontitis can lead to permanent periodontal tissue damage and even lead to bone tissue damage.[52,53] Some researchers now believe that inflammatory factors such as IL-1, TNF-α and IL-17 are responsible for periodontitis.[54,55] Several studies have suggested that exosomes may be closely related to the development and treatment of periodontitis.

Xiao Song et al[56] extracted and characterised exosomes produced by inflammatory macrophages by inducing macrophages in an inflammatory cell state. The uptake of exosomes by bone marrow mesenchymal stem cells (BMSCs) was observed by fluorescence microscopy to study and analyse the effect of exosomes on the inflammatory response and osteogenic differentiation of BMSCs. The findings suggest that exosomes produced by macrophages in periodontitis upregulate the expression levels of interleukin-6 and tumour necrosis factor-α in BMSCs and mediate inflammatory stimuli to inhibit osteogenic differentiation of BMSCs. It was also shown that perhaps interfering with macrophage exosome production could promote bone tissue regeneration in periodontitis. In another study, the researchers collected exosomes released from primary human periodontal ligament fibroblasts (hPDLFs) treated with Porphyromonas gingivalis lipopolysaccharide by collecting them and incorporating them into MG-63 osteoblast cells in the primary hPDLFs.[57] A study on macrophages and periodontal ligament stem cells (PDLSCs) by Yazheng Wang et al[58] demonstrated that exosomes derived from PDLSCs in an inflammatory milieu decrease the polarisation of macrophages to inhibit inflammatory phenotypes and contribute to the conversion of macrophages to pro-inflammatory phenotypes. In addition, the exosome inhibitor GW4869 was shown in the above study to attenuate the inhibitory effects of exosomes released from inflammatory macrophages and hPDLFs on osteoblasts as well as inhibit inflammatory-type transformation of macrophages.

Several studies have shown that exosomes generated from Mesenchymal stem cell (MSC), stem cells from exfoliated deciduous teeth (SHED), and Dental Pulp Stem Cell (DPSC) can promote the repair and regeneration of alveolar bone and periodontal tissues.[59–61] A study by Yuki Nakao et al[62] found that gingival tissue-derived MSCs (GMSCs) pretreated with TNF-α increased the number of exosomes they produced and enhanced the exosome expression of CD73, inducing anti-inflammatory macrophage polarisation. In addition, it was found that exosomes produced by GMSCs inhibited osteoclastogenesis by experiments on periodontitis model mice. The experimental results demonstrated the ability of exosomes produced by TNF-α-treated GMSCs to modulate inflammation and inhibit osteoclastogenesis, exploring new ways to enhance the therapeutic potential of MSCs. Tianliang Yu et al[63] showed that SHED exosomes (SHED-exosomes) are enriched in miR-92a-3p and can enhance the proliferation and differentiation of PDLSCs and have an inhibitory effect on the inflammatory response. Also in further studies, miR-92a-3p was found to alleviate the development of periodontitis by inactivating the KLF4/PI3K/AKT signalling pathway. Exosomes produced by dental pulp stem cells (DPSC-EXO) have been found to be strongly associated with tissue regeneration by researchers because of their similar biological properties to metameric cells.[64] Xin Qiao et al[65] showed that DPSC-EXO promoted the proliferation and osteogenesis of PDLSCs and directly inhibited the expression of inflammatory factors. In periodontitis rats, DPSC-EXO promotes the healing of alveolar bone and periodontal epithelium, and this study suggests that the mechanism is related to the inhibition of the IL-6/JAK2/STAT3 signalling pathway.

The damage to the oral cavity caused by current periodontitis, especially bone destruction, is difficult to recover from. The anti-inflammatory and osteogenic studies related to exosomes and periodontitis all imply potential treatment options for periodontitis.

While exosomes have shown effectiveness in animal models for periodontitis in preclinical studies, further research is necessary for clinical application.[21,66] Initially, exosomes should be subjected to good manufacturing practice (GMP), including the purification processes and quality control. In addition, a more comprehensive investigation of exosomes role as a diagnostic and treatment tool for periodontitis demands further investigation.

Exosomes and Oral Squamous Cell Carcinoma

Oral squamous cell carcinoma (OSCC) is the most common type of head and neck cancer, and the current five-year survival rate for patients with various stages of oral cancer is only about 50%.[67,68] It has been reported that cancer cells can produce more exosomes to contribute to the progression of cancer, and the analysis of exosomes in the tumour

microenvironment can deepen the understanding of tumours and provide assistance in diagnosis, treatment and prognosis of tumours.[69–71]

Tumor cell-derived exosomes (TEXs) affect cancer cell proliferation, migration and invasion, and promote tumour malignancy.[72,73] Studies have shown that exosomal miRNAs, such as miR-24-3p and miR-21-5p, can significantly increase the cell viability and proliferation rate of OSCC cells.[74,75] Tumour growth and metastasis cannot be achieved without a large amount of nutrients, and blood vessels, as the main channel for nutrient transport in the body, have an important role in the process of tumour growth and metastasis. Studies have shown that exosomes in the circulation and tumour tissues of OSCC patients can promote neoangiogenesis by enhancing the ability of vascular endothelial cells to proliferate, migrate, and invade.[76,77] A study by Shufang Li et al[78] found that exosomes extracted from oral leukoplakia and OSCC MSCs enhanced their angiogenic capacity with their high matrix metalloproteinase 1 content compared to exosomes produced by normal mucosal MSCs.

In addition, some researchers believe that exosomes can be used as a means of exploring potential therapeutic targets and as a vehicle for drug delivery.[79] Qian Zhang et al[80] conducted a novel anti-OSCC study with milk exosomes, which synthesised a novel PH-responsive nanoparticle against OSCC using bovine milk-derived exosomes. Sensitive delivery of nanoparticles is stimulated using an acidic environment, combined with photochemotherapy to generate reactive oxygen species for OSCC inhibition. Wei Deng et al[81] demonstrated that exosomes loaded with microRNA-34a were taken up by HN6 OSCC cells in an in vitro environment and could successfully inhibit the proliferation, migration and invasion of HN6. Yuanhe You et al[82] found that blocking IL6 in M1-like tumour-associated macrophages polarised by exosomes from OSCC cells significantly impaired the ability of OSCC cells to form colonies, invade, and migrate. In further cell signalling experiments, it was shown that blocking the activation of the Jak/Stat3 pathway could significantly weaken the viability of OSCC cells, providing a new idea for targeted treatment of OSCC. Studies of Cancer-associated fibroblasts-derived exosomes (CAFs-Exo) by Wei-Zhou Wang et al[83] demonstrated that CAFs-Exo can affect OSCC through immunosuppression-related effects. In addition, it was found that CAFs-Exo may affect OSCC by regulating the expression of PIGR, CD81, UACA, and PTTG1IP in Cal-27, which means that PIGR, CD81, UACA, and PTTG1IP may be effective targets for OSCC treatment in the future. Due to the structural characteristics of exosomes, they can enter most tissue cells without being consumed by macrophages and can serve as an ideal vehicle for in vivo drug delivery.[84] Previous studies have demonstrated that exosomes can act as carriers for chemotherapeutic agents such as curcumin, DOX, and PTX to enhance efficacy.[10,85]

Currently, the most effective tool against cancer is early diagnosis. Early diagnosis can greatly improve the survival rate of cancer patients[86]. It has been shown that salivary and blood derived exosomes in OSCC patients differ in status and expression from those in healthy individuals.[87] The use of simpler and more convenient tests for early diagnosis and prognosis prediction of OSCC brings a broader prospect for OSCC research. Aditi Patel et al[88] showed that miR-1307-5p was expressed at higher levels in tissue and salivary exosomes of OSCC patients than in non-cancer patients, and that high levels of expression of this exosome were associated with low survival, cancer progression, and chemotherapy resistance. The study by Hejia Guo et al[89] first used proteomics to identify differentially expressed proteins in OSCC, and then verified that C-reactive protein (CRP), von Willebrand factor (VWF), and leucine-rich α-2-glycoprotein (LRG) were potential clinically relevant OSCC biomarkers in serum exosomes of OSCC by analysis.

Exosomes and Hand, Foot and Mouth Disease

Hand, foot and mouth disease (HFMD) is caused by human enteroviruses, and about 40 of the more than 100 human enteroviruses reported globally are associated with HFMD.[90,91] HFMD is common in young children under 5 years of age and is characterised by typical manifestations such as oral herpes and rashes on the hands and feet, which are usually not serious but highly contagious.[92] However, HFMD can lead to other serious complications such as viral myocarditis and type I diabetes.[93] The study by Zhihui Ruan et al[94] centred on one of the main pathogens of HFMD, human enterovirus 71 (EV71). There is evidence that EV71 infection significantly increases exosome levels in the serum of patients with HFMD. It has been shown that the interaction of EV71 3A, a non-structural protein of EV71, with vacuolar protein sorting 25 (VPS25) can affect exosome production and thus viral replication. Yan Wang et al[95] showed that miRNA-30a expression was higher than normal in exosomes secreted from oral epithelial cells of EV71-infected patients. Further studies revealed that exosomal miRNA-30a can promote viral replication by inhibiting the type

I interferon response and thereby promoting viral replication after transfer to macrophages. Jing Wu et al[96] showed that the expression level of microRNA-155 increased in exosomes after EV-A71 infection, and microRNA-155 could be directly transferred from infected cells to non-infected cells via exosomes. Another study found that exosomal miRNA-155 could inhibit infection by down-regulating phosphatidylinositol clathrin assembly protein (PICALM) through in vitro and in vivo experiments, and the results showed the antiviral activity of exosomal miRNA-155, which may be a potential therapeutic drug for severe infections.

Exosomes, as carriers of biomass delivery, have different effects on different oral diseases, depending on their source as well as their contents, and the mechanisms of their effects vary. The summary is shown below (Table 2).

Exosomes in Oral Diseases Therapy

Engineered Exosomes

In recent years, research on exosomes has been carried out extensively, and many studies have demonstrated the mechanism of action and therapeutic effects of exosomes in relation to various diseases. However, due to the heterogeneity and complex composition of natural exosomes, their therapeutic efficacy in disease treatment as well as their specificity is greatly reduced, and engineered exosomes were created.[97] Current research on engineered exosomes is mainly focused on the field of cancer, and properly modified engineered exosomes can efficiently and precisely deliver drugs to the tumour site while reducing the occurrence of adverse reactions. The main modification methods of engineered exosomes are, physical modification, chemical modification, biological modification, etc.[37,98]

In a study by Yutaro Kase et al,[99] exosomes from normal fibroblasts transfected with Epstein-Barr virus-inducible-3 (EBI3) cDNA were electroporated with siRNA for lymphocyte cytoplasmic protein 1 (LCP1) in order to develop OSCC-targeting exosomes (octExosomes). The results showed that octExosomes could effectively transform siLCP1 into OSCC cells, down-regulate the expression of LCP1 in OSCC cells, and produce significant anti-tumour effects in both in vitro and in vivo assays. Sushrut Kamerkar et al[100] describe an engineered exosome delivering an antisense oligonucleotide (ASO) targeting STAT6 that inhibits STAT6 expression in immunosuppressive tumour-associated macrophages, thereby remodelling the tumour microenvironment and inducing anti-tumour immunity.

The study by Haotian Luo et al[101] validated the role of the macrophage-associated anti-inflammatory small molecule miR-126 in periodontitis in clinical samples by constructing an exosome of miR-126 overexpressing C-X-C matrix chemokine receptor 4 (CXCR4) (CXCR4-miR126-Exo). It was demonstrated that CXCR4-miR126-Exo could regulate the inflammatory-type polarisation of macrophages. In periodontitis rat experiments, CXCR4-miR126-Exo could effectively inhibit osteoclastogenesis, reduce bone resorption and inhibit periodontitis progression. The anti-inflammatory and osteogenic properties of M2 macrophage exosomes (M2-Exos) were identified in a study by Jiali Shou et al.[102] Bone marrow mesenchymal stem cell-specific aptamers and M2-Exos were combined via 3-way junction (3WJ) RNA nanoparticles to enhance M2-Exos-specific targeting. Also, in comparison experiments with systemic administration of

Table 2 Summary of Exosomes and Oral Diseases

disease	Source	Method	Reference
Orthodontics	Osteoclast precursors	Activation of osteoclasts	[43]
Orthodontics	Osteoblasts	Promote osteoblast differentiation	[47]
Periodontitis	Inflammatory macrophages	Promote inflammation	[56]
Periodontitis	PDLSCs	Inhibit inflammation	[58]
Periodontitis	GMSCs	Inhibit inflammation and osteoclastogenesis	[62]
Periodontitis	SHED	Enhance the proliferation and differentiation of PDLSCs	[63]
Periodontitis	DPSC	Promoted the proliferation and osteogenesis of PDLSCs and inhibit inflammation	[65]
OSCC	Tumor cell	Affect cancer cell proliferation, migration and invasion	[72]
OSCC	Oral leukoplakia and OSCC MSCs	Enhance angiogenic capacity	[78]
OSCC	OSCC cells	Block IL6 in M1-like tumour-associated macrophages polarised	[82]
OSCC	CAFs	Immunosuppression	[83]
HFMD	Oral epithelial cells of EV71-infected patients	Promote viral replication by inhibiting the type I interferon response	[95]

M2-Exos in the M2-Exos femur fracture mouse model, functionalized M2-Exos accumulated predominantly at the fracture site and promoted healing at a significantly higher rate than the M2-Exos effect. It has been shown that macrophage-derived exosomes have a therapeutic effect on periodontitis, and the study of related specific aptamers provides a broad direction to improve the therapeutic effect of exosomes.

In addition to the therapeutic effects described above, engineered exosomes can also serve as novel drug delivery vehicles. In recent years, nanomedicine delivery systems have become an important advancement in the treatment of disease because of multiple advantages over traditional approaches, including reduced drug degradation, improved targeting efficiency, and prolonged drug release time.[103] It is noteworthy that exosomes derived from different types of cells have specific cell tropisms and can target particular tissues or organs.[104] Further, exosomes are more resistant to phagocytosis by mononuclear phagocytes than synthetic nanodrugs, thus acting as a "cloak of invisibility" for incorporated therapeutic compounds.[105] The delivery of siRNA by exosomes to recipient cells has been demonstrated in vitro.[106] Two distinct siRNAs targeting RAD51 and RAD52 were transfected into exosomes for therapeutic delivery, effectively inducing post-transcriptional gene silencing in recipient cells.

The promise of engineered exosomes is exciting, but many challenges remain in the field of engineered exosome applications. Currently, exosome production and purification are time-consuming, costly and difficult to ensure stability, and there is still a lack of consensus on standardized protocols and quality control standards for engineered exosomes. Pharmacokinetics, safety, and efficacy still require more in-depth studies before engineered exosomes can be maturely used in the clinic.

Regenerative Therapy of Mesenchymal Stem Cell-Derived Exosomes

Mesenchymal stem cells (MSCs) are a class of pluripotent stem cells originating from the mesoderm. Unlike hematopoietic stem cells originating from the blood system, MSCs can be found in the perinatal tissues of infants (such as placenta, umbilical cord, etc)., dental pulp, fat, and other parts of the body in adults. In addition, MSCs have five major characteristics: self-replication, low immunogenicity, high activity, inflammatory, and non-tumorigenic.[107] It is increasingly recognized that the use of exosomes derived from MSCs can alleviate tissue injury and promote tissue regeneration in dental treatments (Figure 2).

The secretion of exosomes by MSCs was found to facilitate periodontal regeneration.[108] In rats with periodontal intrabony deficiencies, collagen sponges containing human MSCs-Exosomes more effectively repaired defects, promoted new bone and PDL formation, and increased PCNA+ cell proliferation. In addition, researchers found that exosomes secreted by adipose-derived stem cells (ASCs-Exos) had a greater effect on ligature-induced periodontitis than themselves, which resulted in a greater area of newly formed tissues.[109]

When periodontitis is present, alveolar bone loss is a typical manifestation. One of the key issues in periodontitis management is encouraging bone regeneration and repair. The concept behind periodontitis regenerative treatment is to reduce abnormal inflammatory changes in the periodontal cells and microenvironment.[110] When high lipid levels or TNF-provocation conditions are present, gingival MSC-secreted exosomes inhibited NF- kB signaling and Wnt5a in the periodontal microenvironment and modulated macrophage polarization.[62] Acute periodontitis murine models with newly formed PDLs and alveolar bone showed that ADSCs and DFC exosomes could promote periodontal healing.[109] However, human models do not provide sufficient data on the underlying mechanisms or applications.

Exosomal regenerative therapies are also potential in other oral diseases that are characterized by bone destruction. In temporomandibular joint osteoarthritis, exosomal therapies could reduce inflammation and induce differentiation of chondrocytes.[111] The adenosine activation of the AKT, ERK, and AMPK signaling pathways further enhanced cartilage regeneration in the presence of MSC-derived exosomes.

It is possible for the salivary gland to become dysfunctional in patients with Sjogren's syndrome, menopause, diabetes, or who have had radiotherapy for OSCC. The effects of exosomal therapy on salivary gland regeneration have been studied in vivo in murine models. Through the cAMP/PKA/CREB pathway, DPSC-Exos revived salivary gland epithelial cell function, suggesting their potential therapeutic value in treating Sjogren's syndrome.[112] Similarly, tonsil mesenchymal stem cell exosomes contributed to salivary gland regrowth after ovariectomy, mimicking menopause.[113] In response to hypoxia, urine-derived stem cells secrete exosomes that repair the salivary gland following radiotherapy, via the Wnt3a/GSK3 pathway.[114]

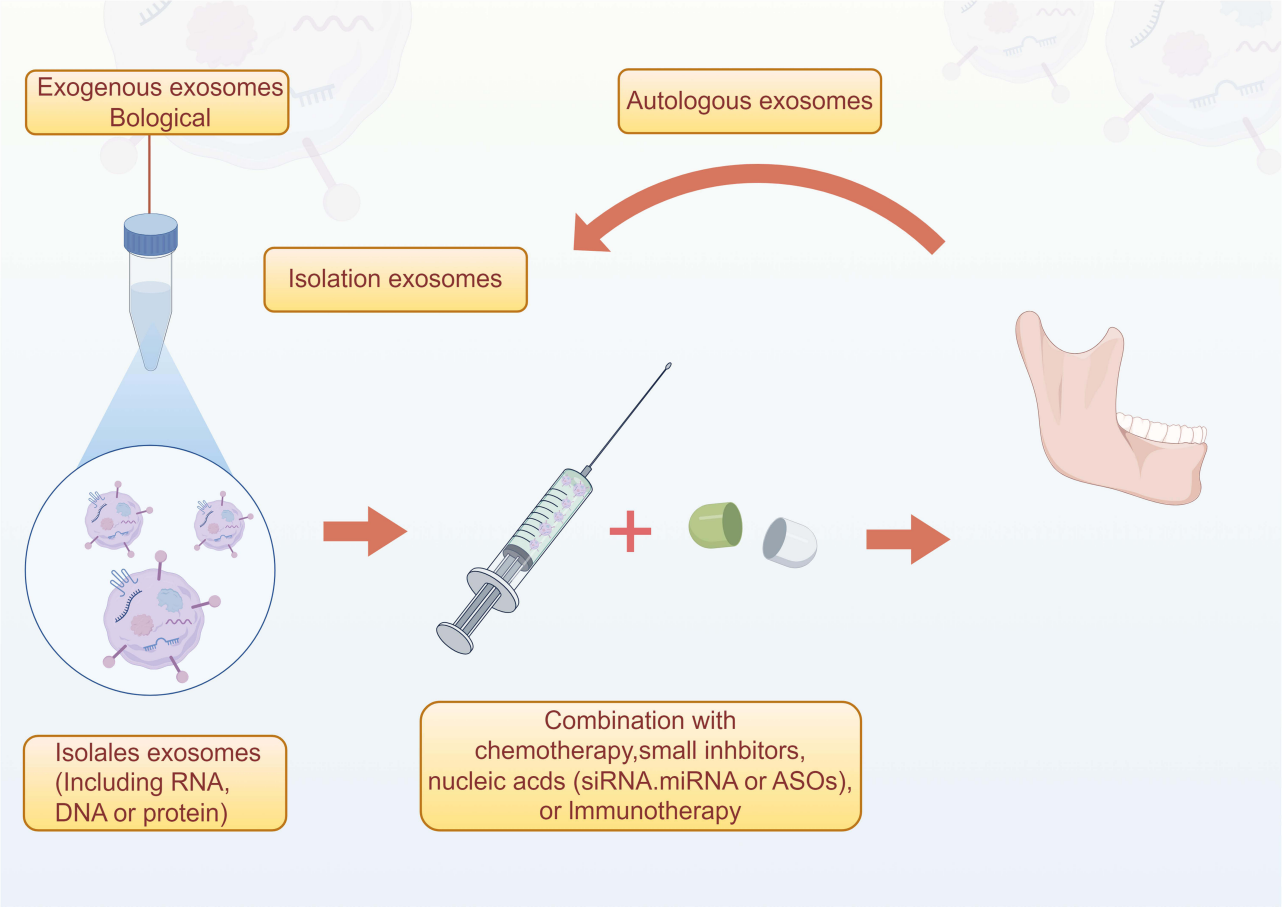

Figure 2 Regenerative therapy of mesenchymal stem cell-derived exosomes in oral diseases. By Figdraw.

Based on the evidence contributes to various oral regenerative therapies, further research is underway. Exosomes derived from other tissues may improve oral therapies, and there should be more emphasis placed on the crosstalk between oral and other diseases. Oral regenerative treatment relies heavily on the application of exosomes. Translating basic research into clinical practice is one of the future focuses.

The therapeutic efficacy of exosomes in related diseases has been supported by considerable evidence, but considerable further work is needed for clinical application. The engineered exosomes and MSCs therapeutic work are shown in Table 3.

Table 3 Exosomes in Oral Diseases Therapy

type	Disease	Method	Reference
Engineered exosomes	OSCC	Transform siLCP1 into OSCC cells and down-regulate the expression of LCP1	[99]
	Tumour	Deliver an ASO targeting STAT6 and induce anti-tumour immunity	[100]
	Periodontitis	Regulate the inflammatory-type polarisation of macrophages and and inhibit periodontitis	[101]
MSCs	Periodontitis	Promote new bone and PDL formation, and increase PCNA+ cell proliferation	[109]
	Periodontitis	Inhibit NF- kB signaling and Wnt5a in the periodontal microenvironment and modulate macrophage polarization	[62]
	Temporomandibular joint osteoarthritis	Reduce inflammation and induce differentiation of chondrocytes	[111]
	Salivary gland dysfunction	Revive salivary gland epithelial cell function by the cAMP/PKA/CREB pathway	[112]

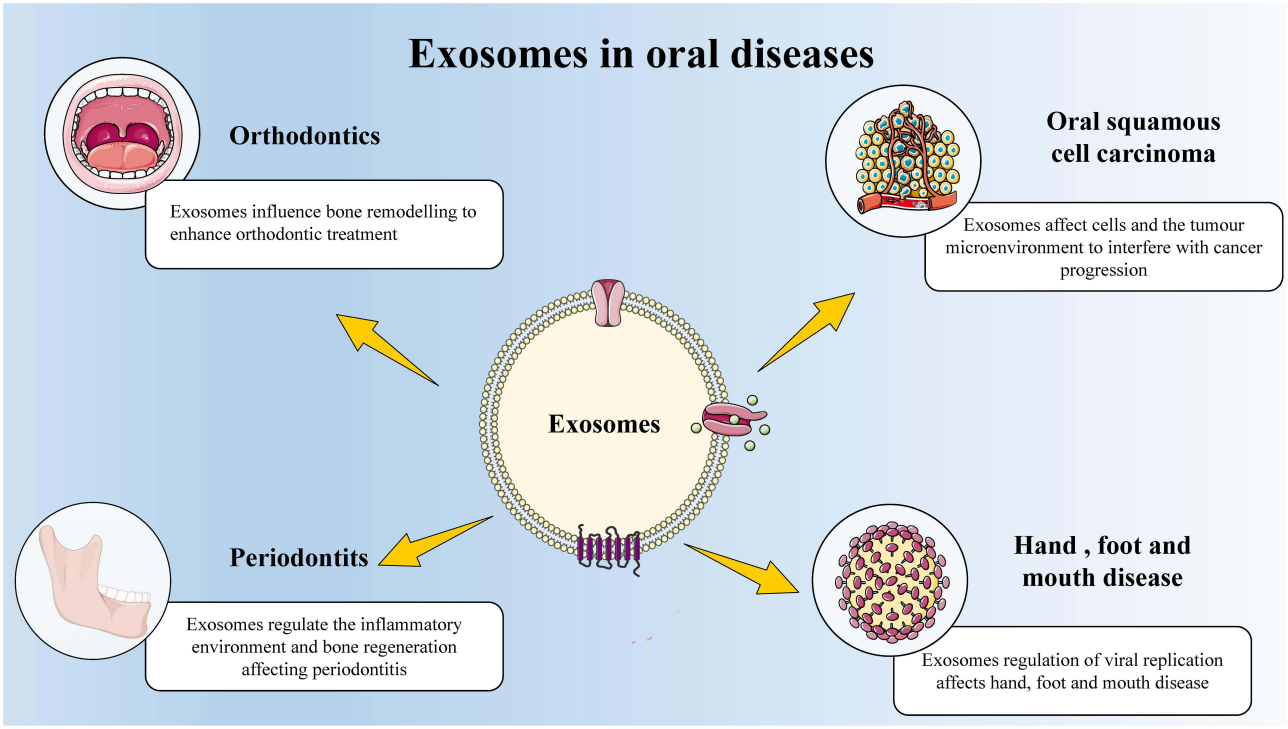

Figure 3 Role of exosomes in orthodontics, periodontitis, oral squamous cell carcinoma and hand, foot and mouth disease.

Conclusion

Exosomes have emerged as critical players in both the pathophysiology and treatment of oral diseases (Figure 3). In orthodontics, they facilitate bone remodeling by balancing osteoclastogenesis and osteoblast differentiation, offering a potential strategy to enhance treatment efficiency. Similarly, in periodontitis, exosomes from MSCs and periodontal cells modulate inflammation, promote osteogenesis, and accelerate tissue regeneration, suggesting their promise for novel regenerative therapies to combat periodontal bone loss.

In OSCC, exosomes contribute to tumor progression, immune modulation, and metastasis, while also serving as potential biomarkers for early detection. Engineered exosomes, capable of delivering targeted therapies, offer a promising approach to enhance cancer treatment specificity. Additionally, in HFMD, exosomes mediate viral replication and immune responses, highlighting their potential as a therapeutic tool for viral infections. Despite the promising advances in exosome-based therapies, their clinical application is still hindered by challenges related to their heterogeneity and complexity. Engineered exosomes, offer a solution by improving targeting and therapeutic payload delivery, making them a promising tool for overcoming these obstacles. However, challenges remain in the clinical application of engineered exosomes, and there is still a lack of consensus on standardized methods to isolate, quantify, and analyze engineered exosomes in the clinical stage from complex tissues. In addition, methods to accurately quantify exosomes and their contents are inconclusive. There is growing evidence of the favorable therapeutic effects of exosomes in oral diseases, and highly specific modifications for different diseases are also in need of research for clinical treatment. Therefore, more in-depth studies are needed to optimize these approaches.

Data Sharing Statement

The current study was based on the results of relevant published studies.

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Figures 1 and 2 were created by Figdraw.

Author Contributions

Qiandai Miao, Jianxia Zhang, and Yan Han contributed to writing and editing of this review. Shaoqing Li1, Weijia Lyu, Yan Han collected the information and created figures. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declared that they have no competing interests in this work.

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