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Review article

A review of the roles of exosomes in salivary gland diseases with an emphasis on primary Sjögren's syndrome

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Abstract Salivary gland diseases encompass a broad range of conditions, including autoimmune, inflammatory, obstructive, and neoplastic disorders, significantly impacting oral health and overall well-being. Recent research has highlighted the crucial role of exosomes, small extracellular vesicles, in these diseases. Exosomes mediate intercellular communication by transferring bioactive molecules such as proteins, microRNAs, and lipids, positioning them as potential diagnostic biomarkers and therapeutic agents. In primary Sjögren's syndrome (pSS), exosomes derived from Epstein—Barr virus-infected B cells and activated T cells transfer key microRNAs that impair calcium signaling, contributing to glandular dysfunction. Exosome-based biomarkers like Ro/SSA and La/SSB, found in saliva, serum, and tears, offer non-invasive diagnostic tools for early disease detection. Furthermore, mesenchymal stem cell-derived exosomes show promise in treating pSS by modulating immune responses and promoting tissue repair. While exosomes hold promise for the diagnosis and treatment of other salivary gland diseases, such as radiation-induced xerostomia and sialolithiasis, their application remains limited, necessitating further research to unlock their full diagnostic and therapeutic

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potential. This review focuses on the role of exosomes in salivary gland diseases, with an emphasis on pSS, and highlights the need for future clinical applications and large-scale trials.

Introduction

The salivary glands play a crucial role in producing and secreting saliva, which is vital for maintaining both oral and overall health.[1] Salivary gland diseases represent a diverse group of conditions, including salivary gland dysfunction, obstructive diseases, inflammatory conditions, and neoplastic lesions.[2] Among these, salivary gland dysfunction is commonly caused by primary Sjögren's Syndrome (pSS), radiotherapy for head and neck cancer, diabetes, menopause, and the use of certain medications. Other etiologies, such as those underlying sialolithiasis and certain neoplasms, also contribute to significant diagnostic and therapeutic challenges. These disorders significantly increase the risk of oral infections, dental caries, and xerostomia, ultimately reducing the patients' quality of life.[3] Consequently, there is a pressing need for the development of new diagnostic and therapeutic strategies.

One promising approach to addressing these challenges is through the study of exosomes—small extracellular vesicles (EVs) that transport bioactive molecules including proteins, lipids, DNA, mRNA, microRNA (miRNA), and long non-coding RNA.[4–10] The lipid bilayer of exosomes protects their cargo from proteolytic degradation, enhancing stability and detectability.[11–13] Consequently, research has shown that measuring exosomal proteins and RNA in plasma or saliva provides a more accurate representation of the physiological and pathological states of the salivary glands, positioning exosomes as promising non-invasive biomarkers for the early detection of salivary gland dysfunction.

Exosomes also play a crucial role in intercellular communication by facilitating the transfer of bioactive molecules between cells.[14,15] Exosomes also offer therapeutic potential by selectively delivering bioactive molecules to target cells through ligand—receptor interactions.[16–20] Exosomes derived from mesenchymal stem cells (MSCs) have garnered particular interest due to their low immunogenicity, stability, and manipulability, emerging as powerful therapeutic tools across a range of diseases.[21–27] Studies have demonstrated that exosomes can suppress inflammation and promote tissue repair in salivary gland diseases, further underscoring their therapeutic potential.

Despite the progress in understanding exosomes, no comprehensive review has yet synthesized their diagnostic and therapeutic roles in salivary gland diseases. This article seeks to address that gap by providing an in-depth review of the current research on the applications of exosomes in these conditions, highlighting their potential as both diagnostic and therapeutic tools.

Narrative methodology and characteristics of selected studies

The search strategy encompassed PubMed, Ovid MEDLINE, Embase, Web of Science, and CENTRAL databases. Our search involved the utilization of various keywords including 'exosome,' 'extracellular vesicle,' 'salivary gland,' 'parotid,' 'submandibular,' 'sublingual,' 'hyposalivation,' and 'xerostomia,' both individually and in combination, restricted to English-language publications. The final search was conducted in August 2024. The review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) 2020 guideline (Fig. 1).[28] A thorough review was carried out, which included research on exosome and/or EV, covering in vivo and in vitro experiments, as well as clinical trials. Our focus was to explore the potential of exosomes in the diagnosis and treatment of salivary gland diseases. XC and LL conducted individual screenings of the records by examining titles, abstracts, and complete texts. Subsequently, XC, CD, and SM extracted the data. Any inconsistencies in evaluations were resolved through constructive discussions with YC.

Data collection was conducted using predesigned data extraction tables, and statistical analysis was performed in R (version 4.1.0). The bibliometrix package (version 4.1.2) was used for bibliometric analysis, following its established protocols.[29]

We retrieved a total of 809 records. After removing duplicates, 772 unique records remained. The titles and abstracts of these 772 records were screened, and 723 were excluded. Full-text analysis was conducted on the remaining 49 records, of which 31 studies were selected for inclusion in the final review (Fig. 1).

The bibliometric analysis of the 31 original research articles highlights key aspects of the research landscape on salivary gland diseases. The articles, published between 2005 and 2024, show increased output after 2017, driven by advancements in molecular techniques and exosome research (Fig. 2A). Kapsogeorgou EK (2005)[30] and Aqrawi LA (2017)[31] are the most cited studies, providing essential insights into pSS and EVs, shaping subsequent research in the field (Fig. 2B). Keyword analysis reveals a focus on "Sjögren's syndrome," "salivary glands," and "extracellular vesicles," with growing interest in mesenchymal stem cell-derived exosomes for PSS treatment, aligning with the focus of this review (Fig. 2C). This analysis provides a concise overview of key contributors and emerging trends, offering a foundation for future research.

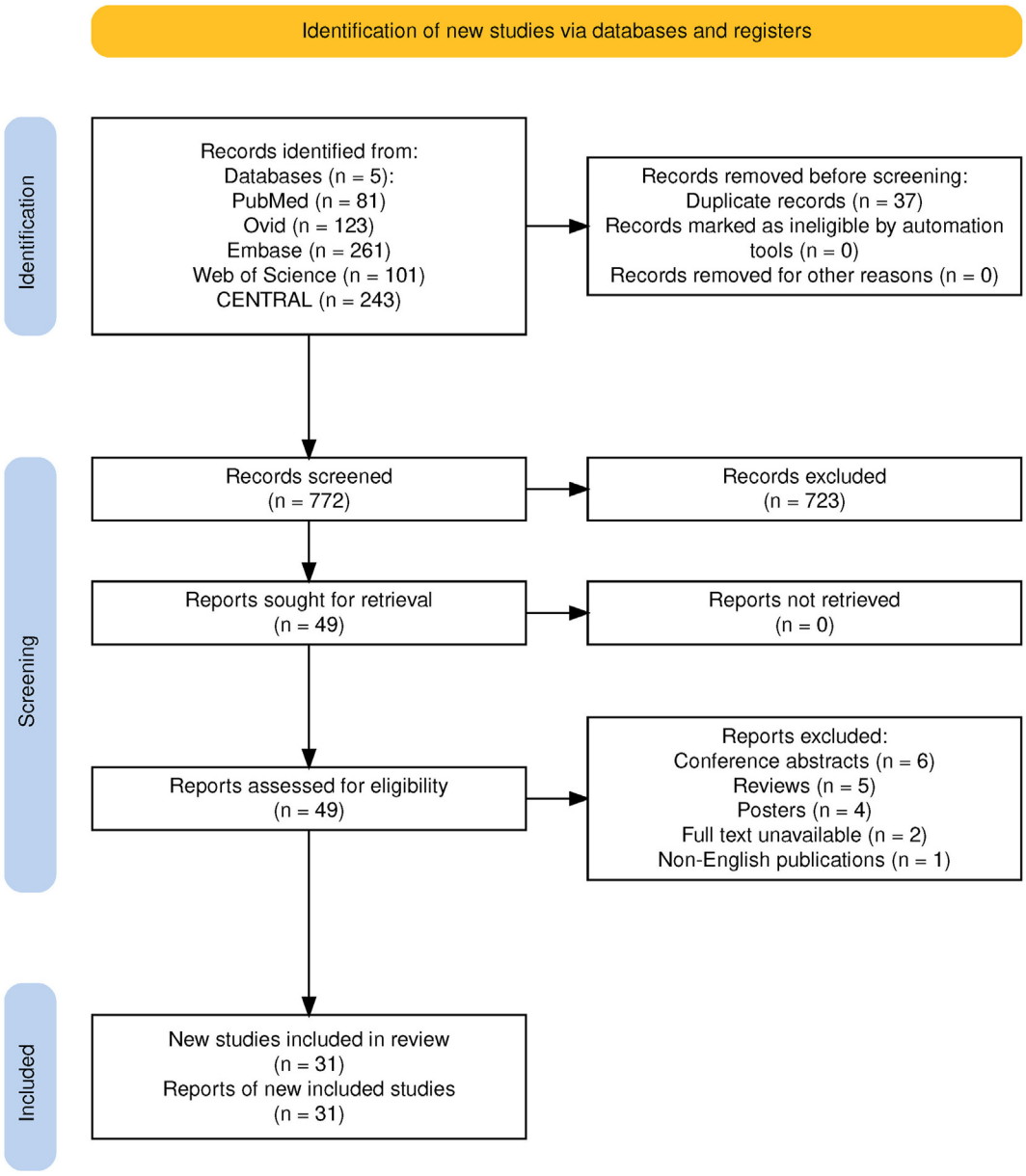

Figure 1 The PRISMA flowchart. This flow diagram provides a visual summary of the screening and selection processes, illustrating the number of articles recorded at each different stage.

The biogenesis of exosomes

Exosomes were first identified as membrane vesicles with 5′-nucleotidase activity.[32] Unlike ectosomes, which bud from the plasma membrane, exosomes originate from the endosomal system through the inward invagination of the endosomal membrane, forming multivesicular bodies (MVBs). These MVBs contain intraluminal vesicles that can either undergo lysosomal degradation or fuse with the plasma membrane to release exosomes, typically ranging from 40 to 160 nm in diameter.[13] The biogenesis of exosomes is regulated by several molecular pathways, with the ESCRT (endosomal sorting complexes required for transport) machinery playing a primary role.[33—35] However, ESCRT-independent mechanisms, such as ceramide production by neutral type II sphingomyelinase and the involvement of tetraspanins, are also crucial in endosomal sorting and exosome release.[34] Rab GTPases, such as Rab27a and Rab27 b, further facilitate this process by regulating the transport of MVBs to the plasma membrane, ensuring proper vesicle formation, cargo sorting, and secretion.[36]

The salivary gland serves both as a source of exosome secretion and as a recipient for exosomes from other tissues. Salivary epithelial and mesenchymal cells can secrete exosomes, which interact with receptor cell membranes via surface molecules and homologous ligands, enabling their entry and subsequent regulation of the recipient cells' biological functions.[37,38] The first detection of exosome secretion by non-tumor salivary epithelial cells occurred in 2005, where exosomes containing ribonucleoproteins were

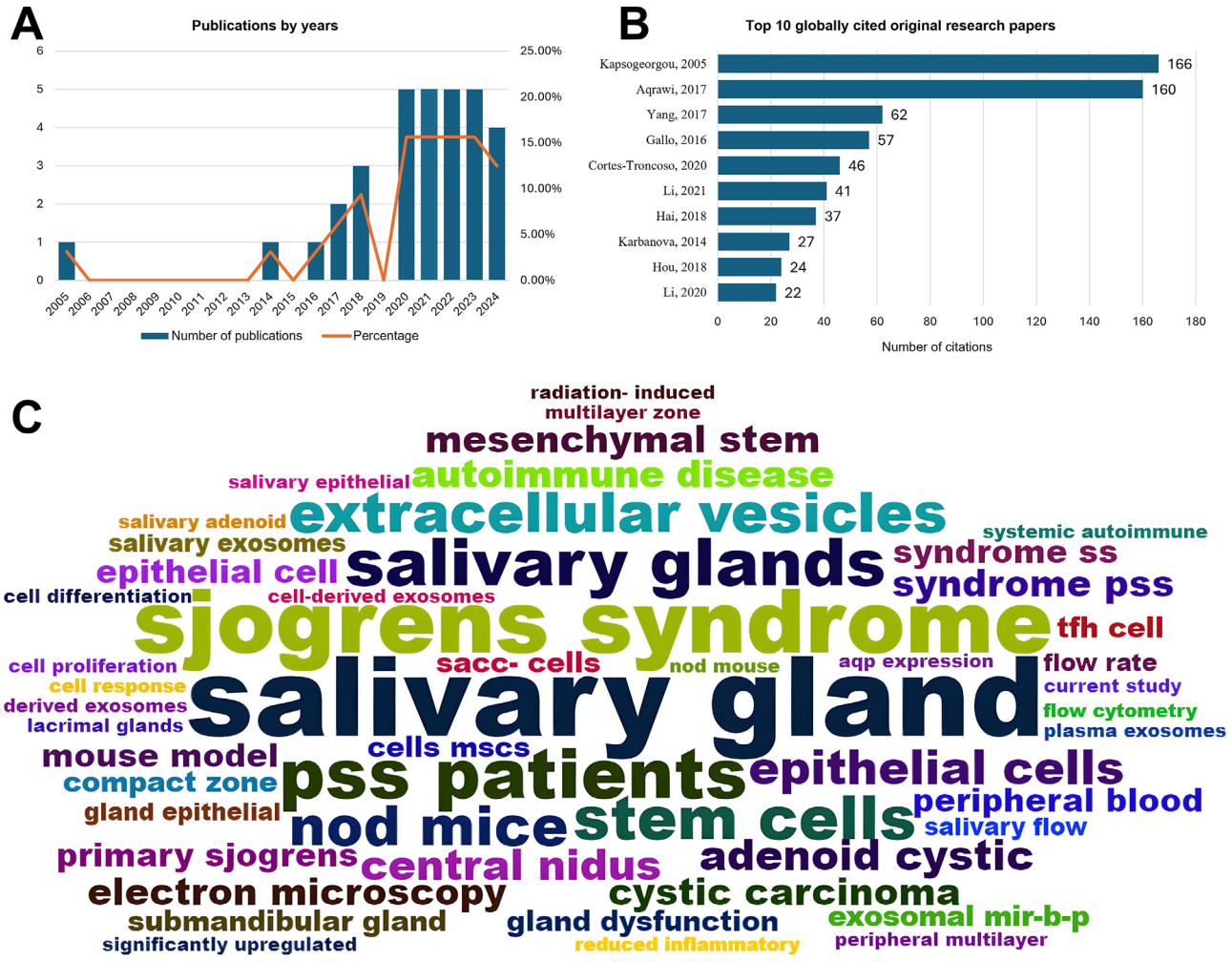

Figure 2 Bibliometric analysis of research trends in exosomes and salivary gland diseases. (A) Annual publication trends from 2006 to 2024, showing an increase in research output on exosomes in salivary gland diseases. The rise in studies post-2017 correlates with advancements in molecular techniques and exosome research. (B) Top 10 most-cited papers in the field, with Kapsogeorgou EK (2005) leading with 166 citations. (C) Word cloud of frequent keywords, highlighting terms like "Sjogren's syndrome," "salivary glands," and "extracellular vesicles."

identified.[30] Later studies using Multidimensional Protein Identification Technology identified numerous proteins in parotid gland-derived exosomes, involved in signal transduction, immune responses, cell adhesion, and antigen presentation.[11]

Furthermore, salivary gland mesenchymal cells secrete exosomes containing miRNA-133 b-3p, which are transferred to the salivary epithelium. This process downregulates DIP2B expression, influencing the proliferation of epithelial progenitor cells and contributing to salivary gland morphogenesis.[39] Salivary epithelial cells can also act as recipient cells for exosomes from other tissues. For instance, breast cancer-derived exosome-like microvesicles have been shown to interact with salivary gland epithelial cells (SGECs), leading to changes in the protein and mRNA composition of the exosomes they secrete.[40]

The salivary gland serves a dual role, both secreting exosomes that regulate recipient cells and acting as a target for exosomes from other tissues, influencing its expression and metabolism. This bidirectional interaction highlights the vital role of exosomes in mediating cellular communication. Given their regulatory functions, exosomes present significant potential for understanding, diagnosing, and developing treatments for salivary gland diseases, offering promising clinical applications.

The role of exosomes in salivary gland diseases

Primary Sjögren's syndrome

pSS is a chronic autoimmune disease characterized by lymphocytic infiltration of the salivary and lachrymal glands, leading to xerostomia and xerophthalmia.[41] Although the exact etiology of pSS remains unclear, recent studies focusing on exosomes and EVs have offered new insights into its underlying pathological mechanisms, particularly in the context of intercellular communication. These findings not only enhance our understanding of disease progression but also provide a foundation for

potential advancements in diagnosis and therapeutic strategies (Fig. 3).

Pathogenesis of primary Sjögren's syndrome

Previous research suggests that environmental triggers, such as Epstein—Barr virus (EBV) infection, may promote the release of Ro/SSA and La/SSB ribonucleoproteins (RNPs), thereby activating the innate immune system and the production of interferons, which play a crucial role in the onset of the disease.[42]

Further studies have identified elevated levels of EBV-specific microRNA (EBV-miRNA-BART13-3p) in the B cells and SGECs of pSS patients. This miRNA can be transferred from B cells to SGECs via exosomes, where it inhibits the expression of crucial proteins like stromal interacting molecule 1 (STIM1) and aquaporin 5 (AQP5). This inhibition may result in the loss of store-operated $Ca2+$ entry (SOCE) and reduced activation of nuclear factor of activated T cells (NFAT), which ultimately contributes to impaired saliva secretion (Table 1).[43]

Additionally, exosomes secreted by activated T cells in pSS patients contain miRNA-142-3p, which can be transferred to glandular cells. This miRNA targets key intracellular signaling elements—such as sarco(endo)plasmic reticulum $Ca2+$ ATPase 2 b (SERCA2B), ryanodine receptor 2 (RyR2), and adenylate cyclase 9 (AC9)—disrupting $Ca2+$ signaling and cAMP production. The resulting decrease in protein production in SGECs may further contribute to epithelial dysfunction.[44] These findings suggest that exosome-mediated transfer of miRNAs from immune cells to epithelial cells plays a pivotal role in pSS pathogenesis by impairing salivary gland function.

Given the understanding of these mechanisms, recent research has turned towards the development of exosome-based biomarkers for the early diagnosis of pSS, driven by the need for more accurate and non-invasive.

Diagnosis of primary Sjögren's syndrome

Recent studies have highlighted the potential of exosome-derived biomarkers in the early diagnosis of pSS, addressing limitations in conventional diagnostic methods. Exosomes, with their protective lipid bilayer, ensure the stability of their contents, such as miRNAs and proteins, making them promising candidates for biomarkers.

In 2005, Kapsogeorgou et al. discovered that exosomes secreted by SGECs in pSS patients contain autoantigenic Ro/SSA, La/SSB, and Sm RNPs, as well as epithelial-specific cytokeratins. This study identified intracellular RNPs in exosomes from SGECs, providing new insights into the potential role of exosomes in antigen presentation mechanisms within the immune system.[30]

Subsequent studies revealed the upregulation of proteins involved in innate immunity (LCN2), cell signaling (CALM), and wound repair (GRN and CALML5) in the saliva of pSS patients, suggesting a distinct exosomal protein signature associated with the disease.[31] Additionally, elevated levels of exosomal circular RNAs (circ-IQGAP2 and circ-ZC3H6) have been found in both minor salivary glands and serum samples from pSS patients.[45] Studies using the Non-Obese Diabetic (NOD) mouse model, a widely accepted model for pSS, also identified five upregulated miRNAs (miRNA-127-3p, miRNA-409-3p, miRNA-410-3p, miRNA-541-5p, and miRNA-540-5p) in serum exosomes.[46]

Furthermore, a comparison of the EV-enriched saliva sub-proteome of pSS patients with the whole saliva proteome revealed 121 differentially expressed proteins.[47] This discovery underscores the potential of exosome-based biomarkers to provide a comprehensive molecular profile of pSS.[47]

Emerging studies have also linked exosome-derived proteins to novel pathological mechanisms in pSS. For instance, differentially expressed proteins related to ferroptosis, such as ceruloplasmin and transferrin, were found to be downregulated in exosomes from the plasma of pSS patients. This was the first study to establish a connection between ferroptosis and epithelial cell damage in pSS, offering new perspectives on disease mechanisms and potential therapeutic targets.[48]

In summary, exosome-based biomarkers, including proteins, circular RNAs, and miRNAs, show great promise for the early detection of pSS. These developments could lead to more timely and accurate diagnoses, ultimately improving patient outcomes.

Treatment of primary Sjögren's syndrome

The treatment of pSS remains a significant challenge, as current therapies are primarily focused on symptom management. Although B-cell-targeted therapies, such as rituximab and belimumab, have been introduced in recent years, their non-selective depletion of B cells offers limited improvement in managing the dry symptoms associated with pSS.[49] At present, mesenchymal stem cell-derived exosomes (MSCs-exos) have shown promise in mimicking the immunomodulatory and tissue repair functions of MSCs.[50]

Recent research underscores the critical role of specific miRNAs encapsulated within exosomes or EVs in treating pSS. For example, exosomes derived from early-passage induced pluripotent stem cells-derived MSCs (iPSC-MSCs) are more effective in suppressing inflammatory responses and regulating immune function compared to late-passage exosomes. This effect is primarily mediated by molecules such as TGF-β1, miRNA-21, and miRNA-125 b.[51] And exosomes derived from lip salivary gland MSCs (LGMSC-exos) contain miRNA-125 b, which targets PRDM1, a key regulator of plasma cell differentiation.[52] Similarly, miRNA-10a-5p in exosomes from myeloid-derived suppressor cells, which effectively inhibits B cell proliferation by targeting Bcl-6.[53] Further emphasizing the therapeutic potential of miRNA-loaded exosomes in modulating immune responses, miRNA-10a-5p within exosomes significantly impacts autoimmune conditions like pSS by altering critical immune cell functions.[53] Additionally, miRNAs in olfactory ecto-MSCs-derived exosomes influence T follicular helper cell responses, adding another dimension to miRNA-mediated regulation in pSS.[54]

Exosomes derived from bone marrow MSCs and iPSCs have been shown to inhibit Th17 cell differentiation while promoting Treg cell expansion, resulting in reduced

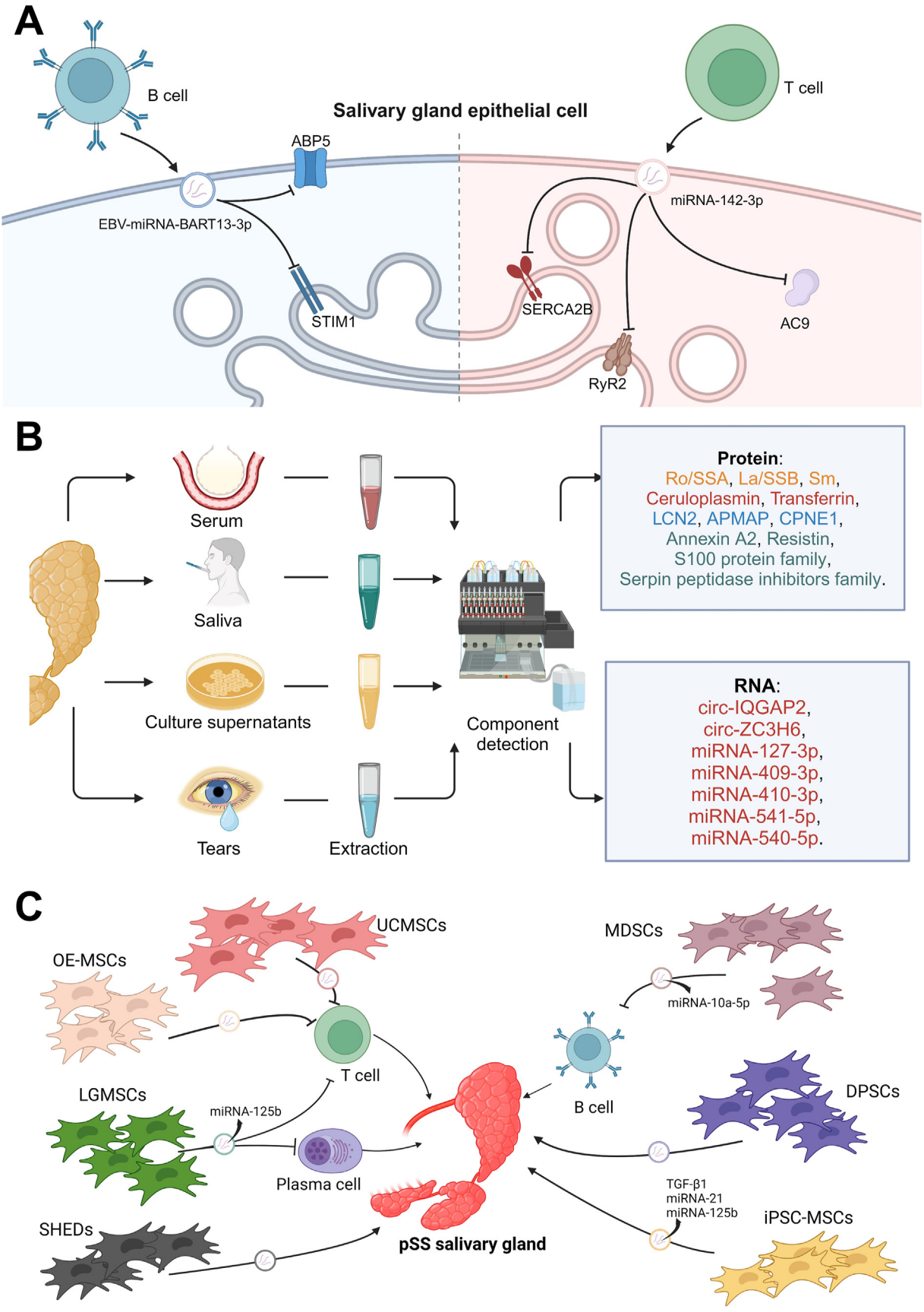

Figure 3 Exosome-mediated mechanisms, diagnostics, and treatment in pSS (A) Mechanism: Exosomes derived from EBV-infected B cells and activated T cells negatively impact salivary gland epithelial cells. Exosomes from B cells transfer EBV-miR-BART13-3p,

lymphocytic infiltration in salivary glands and decreased serum autoantibody levels.[55] Similar effects were observed with exosomes from labial gland-derived MSCs, which play a key role in regulating the Treg/Th17 balance, crucial for controlling inflammatory responses in pSS.[56] Further studies demonstrated that exosomes from human umbilical cord MSCs exhibit immunosuppressive properties, reducing inflammation by modulating the Treg/Th17 balance and improving gut microbiota composition.[57,58] These findings collectively highlight exosomes' capacity to alleviate pSS symptoms by targeting immune regulatory pathways.

In addition to their immunomodulatory effects, exosomes have shown potential in enhancing tissue repair and cellular function. Exosomes from dental pulp stem cells (DPSC-exos) enhance salivary gland epithelial function through the GPER-mediated cAMP/PKA/CREB pathway, underscoring a signaling pathway-driven mechanism.[59] Similarly, that exosomes from human exfoliated deciduous teeth reduce cellular apoptosis and enhance glandular function by suppressing p-ERK1/2-mediated apoptosis.[60]

Collectively, exosomes play a critical role in the pathogenesis, diagnosis, and treatment of pSS. Mechanistically, exosomes from EBV-infected B cells and activated T cells transfer key miRNAs, such as EBV-miRNA-BART13-3p and miRNA-142-3p, to salivary gland epithelial cells, disrupting calcium signaling pathways and reducing saliva secretion. These exosomes contribute to glandular dysfunction by downregulating key proteins like STIM1 and AQP5. Diagnostically, exosomes offer non-invasive biomarkers, with molecules such as Ro/SSA, La/SSB, and circular RNAs (e.g., circ-IQGAP2) found in serum, saliva, and tears, facilitating early detection and disease monitoring. In terms of treatment, MSC-exos demonstrate significant potential by modulating immune responses, balancing Treg and Th17 cells, reducing inflammation, and promoting tissue repair. However, challenges such as exosome heterogeneity, limited standardization in isolation methods, and the need for large-scale clinical trials remain in pSS. Addressing these issues will be crucial for translating exosome-based therapies into clinical practice. Future research should focus on refining exosome-based diagnostics and expanding the clinical use of MSC-exos to restore salivary gland function and improve pSS symptoms.

Radiation-induced salivary gland dysfunction

Exosome-based therapies have shown potential in addressing the underlying causes of salivary gland dysfunction. In particular, radiotherapy-induced xerostomia, a prevalent and severe side effect affecting head and neck cancer survivors, has been a target for innovative therapeutic approaches. For instance, exosomes derived from human dental pulp stem cells have been shown to reduce inflammatory cytokine production and reverse oxidative stress in submandibular gland cells, thereby preventing cellular senescence induced by radiation.[61] Similarly, exosomes from hypoxia-pretreated human urine-derived stem cells have demonstrated the ability to repair radiation-induced salivary gland injuries by activating the Wnt3a/GSK3β pathway.[62] Moreover, exosomes derived from salivary gland organoids assembled through magnetic 3D bioassembly have emerged as a promising strategy for mitigating epithelial damage in irradiated submandibular gland models.[63]

Diabetes-related salivary gland dysfunction

Diabetes is one of the most common metabolic diseases affecting salivary function.[64] More than half of diabetic patients suffer from xerostomia and salivary gland hypofunction.[65] Research has suggested that circulating exosomal miRNAs may be related to insulin resistance. Further experiments demonstrated that bone marrow MSC-derived exosomes can inhibit diabetic sequelae in the salivary glands and its complications by inhibiting TGFβ and its related pathway via Smad 2 and Smad 3 in streptozotocin-induced diabetic rats.[66] Additionally, research indicated that salivary exosomes reduced blood glucose levels and enhanced salivary gland function in diabetic rats.[67]

Menopause-related salivary gland dysfunction

Menopause is often accompanied by physiological and functional changes in the oral cavity.[68] Previous studies have indicated that hormone deficiency post-menopause may lead to reduced salivary gland secretion. Currently,

which downregulates STIM1 and AQP5, crucial for calcium signaling and fluid secretion. T cell-derived exosomes carry miRNA-142-3p, targeting SERCA2B and RyR2, further disrupting calcium and cAMP signaling pathways, leading to gland dysfunction and reduced saliva production. (B) Diagnosis: Exosomes in serum, saliva, and tears contain key biomarkers like Ro/SSA, La/SSB, and circular RNAs (e.g., circ-IQGAP2). These molecules serve as non-invasive diagnostic tools, aiding in the early detection and progression monitoring of pSS through their presence in easily accessible bodily fluids. (C) Treatment: Exosomes derived from MSCs have shown therapeutic potential in pSS. By modulating immune responses, balancing Treg and Th17 cells, and promoting tissue repair, these exosomes enhance salivary gland function and restore saliva secretion, presenting a promising treatment option. Abbreviations: pSS, Primary Sjögren's syndrome; BART13: EBV-miRNA-BART13-3p, Epstein—Barr virus-encoded microRNA BART13-3p; AQP5, Aquaporin 5; STIM1, Stromal interaction molecule 1; SERCA2B, Sarco(Endo)plasmic reticulum calcium ATPase 2 B; AC9: Adenylyl cyclase 9; RyR2: Ryanodine receptor 2; Ro/SSA, Ro/Sjögren's syndrome-related antigen A; La/SSB, La/Sjögren's syndrome-related antigen B; Sm, Smith antigen; LCN2, Lipocalin 2; APMAP, Adipocyte plasma membrane-associated protein; CPNE1, Copine 1; miRNA, microRNA; iPSC-MSCs, Induced pluripotent stem cell-derived mesenchymal stem cells; LGMSCs, Lip salivary gland mesenchymal stem cells; UCMSCs, Umbilical cord mesenchymal stem cells; DPSCs, Dental pulp stem cells; OE-MSCs, Olfactory ecto-mesenchymal stem cells; SHEDs, Stem cells from human exfoliated deciduous teeth; MDSCs, Myeloid-derived suppressor cells; MSCs-exos, Mesenchymal stem cells-derived exosomes.

Table 1 Main conclusions of studies on exosomes in salivary gland diseases.

No.	Author and year	Disease	Exosome role	Origin of exosome/EVs	Main conclusion
1	Gallo et al.[43] (2016)	pSS	Mechanism	EBV-positive B cell line ×50-7	Exosomes from EBV-infected B cells transfer EBV-miRNA-BART13-3p to their own salivary gland epithelial cells, downregulating key molecules like STIM1 and AQP5, impairing calcium signaling and fluid secretion, contributing to gland dysfunction.
2	Cortes-Troncoso et al.[44] (2020)	pSS	Mechanism	Human T cells	Exosomes from activated T cells carry miRNA-142-3p, which targets key molecules like SERCA2B, RyR2, and AC9 in their own salivary gland epithelial cells. This disrupts calcium signaling and cAMP production, impairing glandular secretion.
3	Kapsogeorgou et al.[30] (2005)	pSS	Diagnosis	Non-neoplastic SGEC cell lines	SGECs secrete exosomes containing autoantigenic ribonucleoproteins (Ro/SSA, La/SSB, and Sm), potentially facilitating intracellular autoantigen presentation and contributing to autoimmune mechanisms.
4	Aqrawi et al.[31] (2017)	pSS	Diagnosis	Saliva and tear fluids of patients	EVs from saliva and tears carry biomarkers like LCN2, APMAP, and CPNE1, which are involved in immune response, cell signaling, and tissue repair.
5	Li et al.[45] (2020)	pSS	Diagnosis	Minor salivary gland of patients	Circ-IQGAP2 and circ-ZC3H6 are significantly upregulated in plasma exosomes and minor salivary glands from patients, correlating with clinical markers like serum IgG and focus scores.
6	Kakan et al.[46] (2020)	pSS	Diagnosis	Serum of NOD mice	Serum exosomes contain a distinct miRNA signature, featuring the upregulation of miRNA-127-3p, miRNA-409-3p, miRNA-410-3p, miRNA-541-5p, and miRNA-540-5p, all of which are associated with inflammation-related pathways.
7	Finamore et al.[47] (2021)	pSS	Diagnosis	Saliva of patients	Salivary EVs display a distinct proteomic signature, with 121 differentially expressed proteins primarily linked to the innate immune response, including pathways like neutrophil degranulation and interleukin-12 signaling.
8	Peng et al.[48] (2023)	pSS	Diagnosis	Plasma of patients	Plasma exosomes carry epithelial cell-derived proteins, including ceruloplasmin and transferrin, which are involved in ferroptosis and may contribute to epithelial cell damage by disrupting iron homeostasis.
9	Kim et al.[51] (2021)	pSS	Therapy	Human iPSC-MSCs	Exosomes derived from early-passage iPSC-MSCs are more effective in suppressing inflammatory responses and regulating immune function compared to late-passage exosomes. This effect is primarily mediated by molecules such as TGF-β1, miR-21, and miR-125 b.
10	Xing et al.[52] (2022)	pSS	Therapy	LGMSCs from lip mucoceles patients' normal labial gland tissues	LGMSC-Exos deliver miRNA-125 b, which targets PRDM1 (Blimp 1) to suppress plasma cell differentiation, effectively alleviating the disease in a mouse model.
11	Zhou et al.[53] (2023)	pSS	Therapy	Myeloid-derived suppressor cells from tumor-bearing mouse spleens	Myeloid-derived suppressor cell-derived EVs carrying miRNA-10a-5p suppress germinal center B cells by targeting Bcl-6 in a mouse model.
12	Rui et al.[54] (2022)	pSS	Therapy	Olfactory ecto-MSCs from C57BL/6 mice	Olfactory ecto-MSC-exos alleviate disease in a mouse model by suppressing Tfh cells through PD-L1 expression, reducing autoantibody production and immune response.
13	Hai et al.[55] (2018)	pSS	Therapy	Human iPSC-MSCs	iPSC-MSCs and their EVs (iPSC-MSC-EVs) inhibited the onset of sialadenitis in a mouse modelby suppressing immune activation and reducing

Table 1 (*continued*)

No.	Author and year	Disease	Exosome role	Origin of exosome/EVs	Main conclusion
					lymphocyte infiltration in the salivary glands.
14	Li et al.[56] (2021)	pSS	Therapy	LGMSCs from from lip mucoceles patients' normal labial gland tissues	LGMSCs and their exosomes (LGMSC-exos) restore the Treg/Th17 balance in a mouse model by increasing Treg cells and reducing Th17 cells, thereby decreasing inflammatory cytokines and promoting anti-inflammatory responses.
15	Ma et al.[57] (2023)	pSS	Therapy	Human UCMSCs	UCMSC-exos modulate CD4+ T cells in patients by restoring the Th17/Treg balance, regulating autophagy, and reducing pro-inflammatory cytokines.
16	Zou et al.[58] (2024)	pSS	Therapy	Human UCMSCs	UCMSCs and their exosomes (UCMSCs-exos) improve salivary secretion and reduce inflammation in a NOD mouse model by regulating the gut microbiota and restoring the Treg/Th17 balance.
17	Hu et al.[59] (2023)	pSS	Therapy	Human DPSCs	DPSC-exos restore salivary gland function in a NOD mouse model by activating the GPER-mediated cAMP/PKA/CREB pathway, increasing AQP5 expression and improving salivary secretion.
18	Chu et al.[60] (2023)	pSS	Therapy	Stem cells from human exfoliated deciduous teeth	Exosomes derived from stem cells from human exfoliated deciduous teeth promote saliva secretion in a NOD mouse model by suppressing p-ERK1/2-mediated apoptosis in glandular epithelial cells.
19	Dong et al.[61] (2021)	Radiation-induced dysfunction	Therapy	Human DPSCs	Small EVs derived from DPSCs alleviate irradiation-induced senescence in submandibular glands in a mouse model by reducing oxidative stress and senescence-related gene expression.
20	Xiao et al.[62] (2022)	Radiation-induced dysfunction	Therapy	Human USCs	Exosomes derived from hUSCs repair radiation-induced salivary gland injury in a rat model by activating the Wnt3a/GSK3β pathway, reducing α-SMA, and promoting c-Kit.
21	Charoenlappanit et al.[63] (2022)	Radiation-induced dysfunction	Therapy	Human DPSCs and salivary glands functional organoids	EVs generated via magnetic bioassembly platforms, promote epithelial repair in irradiated salivary glands in a rat model by delivering key proteins like FGF10.
22	AbuBakr et al.[66] (2020)	Diabetes-related dysfunction	Therapy	Bone marrow-derived MSCs from the tibia of white female albino rat	Exosomes derived from bone marrow-derived MSCs restore salivary gland function in a diabetic rat model by inhibiting the TGFβ/Smad 3 pathway, reducing fibrosis and improving glandular architecture.
23	Salem et al.[67] (2021)	Diabetes-related dysfunction	Therapy	Human saliva	Salivary exosomes improve salivary gland dysfunction and xerostomia in a diabetic rat model by lowering blood glucose levels and reducing inflammation through TNFα and NFκB/p65 downregulation.
24	Kim et al.[69] (2022)	Menopause-related dysfunction	Therapy	Human tonsil-derived MSCs	EVs derived from tonsil-derived MSCs prevent submandibular gland dysfunction in a rat model of ovariectomy by reducing inflammation and fibrosis, while enhancing AQP5 and α-amylase expression.
25	Busso et al.[80] (2020)	Sialolithiasis	Mechanism	Human sialolith	In human sialoliths, extracellular exosomes and blood microparticles are key components, with proteins involved in stone formation showing similarities to bone and kidney stones.

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Table 1 (*continued*)

No.	Author and year	Disease	Exosome role	Origin of exosome/EVs	Main conclusion
26	Sodnom-Ish et al.[81] (2023)	Sialolithiasis	Mechanism	Human sialolith	In human sialoliths, inflammatory exosomes and bacteria in the central nidus initiate calcification, while the stone grows through the deposition of salivary epithelial cells in the peripheral multilayer zone and calcium apatite in the intermediate compact zone.
27	Sodnom-Ish et al.[82] (2024)	Sialolithiasis	Mechanism	Human sialolith	In a human case of recurrent sialolithiasis, bacteria, inflammatory exosomes, and salivary epithelial cells drive sialolith formation by initiating calcification and promoting stone growth.
28	Karbanová et al.[89] (2014)	SACC	Mechanism	Non-neoplastic SGEC cell lines	In human salivary gland diseases, prominin-1 (CD133) is released in a ubiquitinated form via EVs and interacts with CEA and MUC1.
29	Yang et al.[90] (2017)	SACC	Mechanism	SACC-83 and SACC-LM cell line	Epiregulin-enriched exosomes promote lung metastasis in a mouse model by inducing EMT, enhancing angiogenesis, and increasing vascular permeability in the pre-metastatic niche.
30	Hou et al.[91] (2017)	SACC	Mechanism	SACC-83 cell line	Tumor-derived exosomes downregulate cell junction proteins such as ZO-1 and Claudin-1 in a human cell model, thereby enhancing endothelial permeability and facilitating tumor cell invasion and metastasis.
31	Hou et al.[92] (2022)	SACC	Mechanism	SACC-83 and SACC-LM cell line	In the in vitro experiments, exosomal miR-23 b-3p from SACC-LM cells showed a stronger effect on promoting endothelial cell migration and tube formation compared to exosomes from SACC-83 cells. In the in vivo experiments, exosomes loaded with miR-23 b-3p from SACC-83 cells significantly promoted tumor growth and increased microvessel formation in mice.

Abbreviations: pSS, Primary Sjögren's syndrome; EBV, Epstein—Barr virus; SGEC, Salivary gland epithelial cells; EV, Extracellular vesicle; NOD, Non-obese diabetic; iPSC-MSCs, Induced pluripotent stem cell-derived mesenchymal stem cells; iPSC-MSC-EVs, Extracellular vesicles derived from induced pluripotent stem cell-derived mesenchymal stem cells; LGMSCs, Lip salivary gland mesenchymal stem cells; LGMSC-exos, Exosomes derived from lip salivary gland mesenchymal stem cells; UCMSCs, Umbilical cord mesenchymal stem cells; UCMSC-exos, Exosomes derived from umbilical cord mesenchymal stem cells; DPSCs, Dental pulp stem cells; DPSC-exos, Exosomes derived from dental pulp stem cells; USCs, urine-derived stem cells; MSCs, mesenchymal stem cells; SACC, Salivary adenoid cystic carcinoma.

there is no standard effective treatment for salivary gland dysfunction occurring after menopause. However, tonsil-MSC-derived EVs alleviated salivary gland dysfunction caused by menopause through anti-inflammatory and anti-fibrosis mechanisms in ovariectomized rats.[69] Further research is needed to identify the specific miRNAs and proteins that play a critical role in post-menopausal salivary gland dysfunction.

Sialolithiasis

Sialolithiasis, or salivary calculi, is characterized by the mechanical obstruction of the salivary glands' excretory ducts due to the partial deposition of calcific materials.[70] It accounts for one-third of all salivary gland disorders, with the majority of calculi occurring in the submandibular glands. The accumulation of salivary stones can lead to recurrent chronic sialadenitis, as the presence of these stones promotes bacterial aggregation, which can cause inflammation and infection.[71] Although the exact mechanisms behind sialolith formation remain unclear, various theories have been proposed. Some suggests that changes in ion concentration in saliva, the presence of bacteria or foreign bodies in the ducts, or mucous plugs may initiate stone formation.[72—74]

The organic core theory posits that the organic components at the center of calcification, such as bacteria, foreign bodies, or desquamated epithelial cells, act as nucleating sites for calculus formation.[75,76] In contrast, some theories suggest that stone formation is secondary to sialadenitis, where the swelling during chronic inflammation leads to salivary stasis and the subsequent formation of a calcium-rich core.[77] Some studies have found no organic components in the central area of the calculus core.[78,79]

However, recent research has provided evidence that exosomes may play a role in the formation and development of sialolithiasis. Using liquid chromatography-mass spectrometry and microscopy, exosomes were confirmed to be present in salivary calculi.[80] Additionally, numerous EVs and degraded cytoplasmic organelles were observed in the central nidus of the stones through transmission electron microscopy.[81] Further examination also revealed the presence of exosomes and bi-layered bacterial cell membranes in the central nidus of a patient with recurrent sialolithiasis.[82] These findings suggest that exosomes might contribute to the pathogenesis of sialolithiasis, although further research is needed to elucidate the exact mechanisms involved.

Salivary adenoid cystic carcinoma

SACC accounts for approximately 1 % of head and neck tumors and 10 % of salivary gland tumors.[83] Due to its proximity to critical anatomical structures, achieving negative surgical margins during treatment is often difficult. This challenge contributes to a high recurrence rate, with nearly 40 % of patients experiencing local recurrence within five years. Additionally, SACC has a significant risk of distant metastasis, ranging from 8 % to 60 %, resulting in a generally poor long-term prognosis.[84]

SACC is primarily characterized by hematogenous metastasis, with the lungs being the most commonly affected site.[85] Exosomes, small vesicles secreted by cancer cells, have been increasingly recognized as playing a crucial role in this metastatic process.[86—88] PROMININ-1 (CD133) is significantly expressed in SACC and is released into saliva through exosomes or EVs.[89] This suggests that exosomes could be involved in both the diagnosis and progression of SACC.

Further supporting the role of exosomes in SACC, the upregulation of epithelial regulatory proteins in SACC cells induces epithelial—mesenchymal transition by modulating the GLI1/E-cadherin axis. This process not only increases the expression of pro-angiogenic factors like VEGFA, bFGF, and IL-8 but also facilitates their transfer via exosomes. These exosomes enhance angiogenesis within the tumor microenvironment and increase vascular permeability in the pre-metastatic lung microenvironment, thereby promoting metastasis.[90] Exosomes from SACC-83 cells further enhance these invasive capabilities by increasing endothelial cell permeability through targeting tight junction proteins such as claudin-1, ZO-1, and β-catenin.[91] Notably, SACC cell-derived exosomes contribute to angiogenesis and local vascular microleakage by transporting miRNA-23 b-3p, suggesting that this miRNA could serve as a potential biomarker for distant metastasis in SACC.[92]

Current challenges in clinical integration of exosomes for salivary gland diseases

Despite their promising potential, several challenges need to be addressed before exosomes can be fully integrated into clinical practice for salivary gland diseases. One major challenge is improving techniques for exosome extraction and purification, particularly from oral fluids or serum, to develop standardized protocols and establish reliable diagnostic standards. Additionally, the heterogeneity of exosomes, due to their diverse origins and cargo, limits their application as biomarkers. Further exploration is needed to understand the mechanisms involved in salivary gland diseases and to identify novel exosome-based biomarkers. Finally, clinical trials involving exosomes in salivary gland diseases remain limited, often relying on small sample sizes. Expanding research to larger-scale population studies is essential for translating basic scientific discoveries into practical clinical applications.

Implications for clinical practice and future research

Exosomes offer substantial potential to improve clinical outcomes in salivary gland diseases, particularly as non-invasive biomarkers and therapeutic tools. In conditions like pSS and sialolithiasis, exosomes can enable earlier and more precise diagnosis due to their molecular stability and specificity. Moreover, exosomes derived from MSCs show promise in modulating immune responses and promoting tissue repair, opening the door to novel therapeutic strategies.

For these potentials to be fully realized, future research must prioritize large-scale clinical trials to validate exosome-based diagnostics and treatments. Further exploration of the mechanisms by which exosomes regulate immune responses and repair damaged tissues will be essential. Additionally, advancements in exosome engineering, such as customizing their cargo for specific therapeutic targets, could transform exosomes into a cornerstone of personalized medicine. Identifying disease-specific biomarkers will also be critical to refining diagnostic precision and enhancing therapeutic interventions.

Conclusion

Exosomes and their cargo play a critical role in intercellular communication, positioning them as promising biomarkers, therapeutic targets, and drug delivery vehicles for salivary gland diseases. However, continued research is necessary to fully realize these possibilities and to integrate exosome-based diagnostics and therapies into routine clinical practice.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

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