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Diagnostic and therapeutic potentials of extracellular vesicles for primary Sjögren's Syndrome: A review

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Abstract

Primary Sjögren syndrome (pSS) is a chronic autoimmune disease mainly affecting salivary and lacrimal glands. The current pSS biomarkers, serum autoantibodies, are negative in many pSS patients diagnosed with histopathology changes, indicating the need of novel biomarkers. The current therapies of pSS are merely short–term symptomatic relief and can't provide effective long–term remedy. Extracellular vehicles (EVs) are nano–sized lipid bilayer–delimited particles spontaneously released by almost all types of cells and carrying various bioactive molecules to mediate inter–cellular communications. Recent studies found that EVs from salivary gland epithelial cells and immune cells play essential roles in pSS pathogenesis. Correspondingly, EVs and their cargos in plasma and saliva are promising candidate biomarkers for pSS diagnosis. Moreover, EVs from mesenchymal stem cells have shown promises to improve pSS treatment by modulating immune responses. This review summarizes recent findings in roles of EVs in pSS pathogenesis, diagnosis, and treatment of pSS, as well as related challenges and future research directions.

Keywords

Primary Sjögren's syndrome; Salivary diagnostics; Extracellular vesicle; MicroRNAs; Mesenchymal stem cells; Immune modulation

1. Overview of primary Sjogren's syndrome

Primary Sjögren's syndrome (pSS) is a chronic autoimmune disease mainly affecting salivary and lacrimal glands with lymphocytic infiltration, B cell hyperactivity, and autoantibody formation [1,2]. The long–term hypofunction of these exocrine glands leads to dry mouth (xerostomia), dry eyes (xerophthalmia), and consequent symptoms such as dental caries, periodontal disease, taste impairment, and difficulties in speech, swallow, and sleep [3,4]. Systematic symptoms of pSS include common fatigue, musculoskeletal pain, fever and lymphadenopathy, as well as less common pulmonary, renal and dermal

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disorders [5–7]. Due to the critical role of saliva in oral health, quantitative and qualitative changes in saliva are associated with discomfort and drop of life quality [8]. Therefore, oral and dental problems are common in pSS patients, including oral mucosa atrophy, oral ulcers, fungal infections, glossitis, halitosis, chemosensory abnormalities, and dentures wearing difficulties [9–11]. Sjögren syndrome (SS) could be consequences of other systemic autoimmune diseases such as systemic sclerosis (SSc), systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). In these cases, SS is defined as secondary SS (sSS) with clinical, serological and pathological features different from pSS [12]. Therefore, this review focuses on pSS.

Serum autoantibodies, anti–Sjögren's–syndrome–related antigen A (anti–SSA/Ro) and anti–SSB/La, can be detected in 50–70 % of pSS patients [13]. The anti–SSA antibodies recognize two cellular proteins with molecular weights of approximately 52 and 60 kD, i.e. Ro52 and Ro60. Ro 52, also known as tripartite motif–containing protein 21 (TRIM21), is a ubiquitin E3 ligase that targets cytosolic virus–antibody complexes for degradation; while Ro60, also known as TROVE2, is a RNA–binding protein. SSB, also known as Lupus La protein, is involved in diverse aspects of RNA metabolism. Anti–SSA and –SSB antibodies are also found in patients with SLE and may be present in patients with other autoimmune diseases, including systemic sclerosis and RA [14]. Therefore, secretory functions of salivary glands and tear glands need to be tested for pSS diagnosis. For pSS patients negative for these autoantibodies, labial salivary gland (LSG) or minor salivary gland biopsy (MSGB) is necessary for diagnosing [14]. Besides serum autoantibodies, the increase of serum Type I interferon (I–IFN) is another remarkable SS manifestation and the sources of I–IFN include DCs, peripheral blood mononuclear cells and CD14+ monocytes [15]. Serum levels of multiple other proinflammatory cytokines such as TNF–α, IL–17A, IL–6 also increased in pSS patients [16–18]. IL–17A is mainly produced by T helper 17 (Th17) cells [19,20], while the increased IL–6 during SS pathogenesis promotes Th17 differentiation and results in differentiation of B cells into plasma and memory cells [21–24]. However, the changes of these pro–inflammatory cytokines are not specific for pSS and found in various autoimmune diseases.

In saliva of pSS patients, S100A proteins related to IL–12 production, proteins vital for innate major histocompatibility complex class I (MHC class I) cellular regulation such as Neutrophil gelatinase–associated lipocalin (NGAL) and T–cell activation (CD44), β–2 macroglobulin (B2M) correlated with lymphocyte infiltration in labial salivary glands, and IgM and IgA autoantibodies against salivary protein 1 (SP–1), parotid secretory protein (PSP) or anti–carbonic anhydrase 6 (CA6) are at significantly higher levels than in non–SS patients [25–27]. Further studies are warranted to determine diagnostic and prognostic value of these salivary biomarkers.

2. Overview of extracellular vesicles

Extracellular vesicles (EVs) are nano–sized lipid bilayer–delimited particles spontaneously released by almost all types of cells and found in almost all tissues and biological fluids [28–30]. Based on their origin, EVs are classified as exosomes formed by the endosomal route, microvesicles (MV) formed by direct outward budding from cell membrane, and apoptotic

bodies released by dying cells [31,32]. Exosomes are the smallest EVs with diameters of 40–100 nm and also termed as small EVs (sEVs); the size of MVs typically range from 100 to 1000 nm in diameter, while apoptotic bodies are with size from 50 to 5000 nm in diameter [33–35].

EVs contain various biomolecules including nucleic acids (ssDNA, genomic DNA, microRNA, tRNA, non–coding RNA, circular RNA), lipids (phosphoglycerides, cholesterol), proteins (integrins, heat shock proteins, Alix, TSG101, tetraspanins, cytokines, and growth factors) [36–38]. The unique characteristics of EVs such as high stability and low immunogenicity make EVs a reliable vehicle to deliver these biomolecules into recipient cells [39,40]. Therefore, EVs play essential roles in various biological activities including intercellular communications, immune modulation, angiogenesis, inflammation, and transportation of genetic signals and biomolecules [41–44]. This review will focus on immune modulatory effects of EVs secreted by immune cells such as T and B cells, macrophages [45], dendritic cells (DCs) [46] and natural killer cells (NKs) [47] and non–immune cells [1,48]. Moreover, we will review recent findings on EVs for the early diagnosis of autoimmune disorders such as SS before autoantibodies including antinuclear antibody (ANA), anti–Ro/SSA and anti–La/SSB [49–51] are detectable in later course of the disease [52,53].

Corresponding to SS, there have been also studies reporting the increasing amount of circulating EVs in different autoimmune diseases such as RA [54], SSc [55] and SLE [56]. The miRNA content of EVs have shown alterations in autoimmune disorders patients and miRNA content of salivary–derived EVs in SS patients is an example for that [57–59]. Hence, the detection of Salivary EVs and their miRNA cargo alterations in SS patients has acquired increasing interest in recent years and therefore, in this review, we will discuss about SS pathogenesis, the role of salivary EVs and derived miRNA in the diagnosis and treatment of this autoimmune disorder.

3. EVs and pSS pathogenesis

Although SS etiology remains unclear, low estrogen levels and dihydrotestosterone defects partially elucidate much higher pSS incidence in women. This hormonal imbalance could result in apoptosis of salivary gland epithelial cells (SGECs) and the release of SS–specific autoantigens such as a–fodrin, SS–A and hy1–RNA [60]. These apoptotic cells and their DNA/RNAs activate multiple toll–like receptors (TLRs) primarily expressed in human epithelial and immune cells [61] to provoke inflammatory responses through type I–IFN pathway induction in the exocrine glands of SS patients [60]. In this process, apoptotic bodies formation and immune tolerance impairment are essential for the emergence of autoinflammation in SS patients [60,61]. Elevated levels of EVs have been identified in multiple autoimmune disorders including pSS [52,62,63]. During the disease progression, emergence of damage–associate molecular patterns (DAMPs) such as DNAs and RNAs activate pattern–recognition receptors (PRRs) such as TLRs to trigger autoinflammation [62,64].

DNAs and RNAs delivered by apoptotic bodies and other types of EVs are processed in endosomes of recipient cells and activate multiple endosomal TLRs [61,62]. During pSS progression, TLR–7/8 signaling is activated by single strand RNA (ssRNA) including GU–rich microRNAs such as miR–21 and let7 miRNAs abundant in EVs [65]. The activation of TLR–7/8 signaling triggers two important inflammatory–related downstream pathways, nuclear factor–κB (NF–κB) and the interferon–regulatory factors (IRFs) that induce type I IFN, IFN–α and IFN–β responses [65,66]. Furthermore, TLR–7 signaling pathway enhances SS progression through MYD–88 pathway positively correlated to *CXCR5, CXCL13, LT–α* and *TNF* expression [67]. In the NOD.B10 mouse model of pSS, TLR–7 agonist Imiquimod administration significantly promoted pSS progression [68]. In SGECs from pSS patients, TLR–7 signaling promoted the presentation of autoantigens Ro52/SS–A and TRIM21 by MHC class I, which likely contributes to the progression of pSS [69]. Secondly, the stimulation of endosomal TLR–3 by double strand RNA (dsRNA) also induces type I interferon (*IFNβ*) and inflammatory cytokines such as *IL–6, IL–1β* and *CCL5* in submandibular gland (SMG) tissues of pSS patients [70–72]. In the NZB/WF1 mouse model of pSS, the administration of TLR–3 agonist accelerated the development of SS–like disease [70–72]. In SGECs from pSS patients, TLR–3 agonist induced apoptosis [73] and enhanced the expression of autoantigens Ro/SS–A and La/SS–B [74].Moreover, exosomes produced from SGECs of pSS patients contain autoantigens Ro/SSA, LA/SSB, and Sm ribonucleoproteins and may mediate the presentation of these autoantigens via surface receptors or antigen–presenting cells (APC) [75]. Plasma exosomes from pSS patients contain epithelial cell–derived proteins involved in ferroptosis, suggesting that ferroptosis may be closely related to SS epithelial cell lesions [76]. Ca^{2+} and cAMP signaling pathways regulate the secretion of enzymes and fluids by salivary glands. Exosomes from B cells of pSS patients can transfer an EBV–specific microRNA (EBV–miR–BART13–3p) to SGECs, which impairs salivary gland function through targeting the Ca^{2+} sensor stromal interaction molecule 1 (STIM1) [77]. Exosomes from T cells of pSS patients can transfer miR–142–3p to SGECs, down–regulate key elements of intracellular Ca^{2+} signaling and cAMP production, and consequently impair the secretory function of SGECs [78].

4. Diagnostic values of plasma and salivary EVs and their cargos for pSS

In diagnosed pSS patients, around 40 % were positive for histopathology but negative for SSA/SSB autoantibodies [79]. The salivary gland biopsy requires trained professionals and its interpretation can be challenging. Therefore, the lack of serological markers in so many pSS patients has encouraged researchers to investigate for novel minimally invasive diagnostic biomarkers [80]. Since EVs and EV–associated miRNAs and proteins play important roles in pSS pathogenesis, they are promising candidates of such early diagnostic biomarkers. In the NOD mouse model of SS, small RNA deep sequencing identified a unique miRNA signature in serum exosomes including miR–127–3p, miR–409–3p, miR–410–3p, miR–541–5p, and miR–540–5p, which dysregulate pathways involved in inflammation [81,82]. In plasma of pSS patients, prothrombinase capture and flow cytometry assays indicated that levels of total platelet and leukocyte microparticles all significantly increased, while the increase of platelet–derived microparticles is accompanied

with the increase of platelet activation markers, sCD40L and sCD62P, highlights platelet activation in pSS [52].

Chronic autoimmune diseases generally cause endothelial damage, while circulating endothelial microparticles ($CD31^{+}CD42^{-}$ microvesicles) greatly increased in pSS patients with respect to healthy controls, which directly correlated with disease duration from symptoms and diagnosis [52,83]. In a more recent study using size exclusion chromatography (SEC) and flow cytometry, specific plasma EV sub-populations derived from neutrophils, endothelial, and epithelial cells were found increased in pSS patients compared to healthy donors and patients with SLE; consistently, plasma EVs from pSS patients showed a proteomic signature featured with neutrophil–, epithelial–, and endothelial–related proteins, such as integrin alpha M (ITGAM), olfactomedin–4 (OLFM4), Ras–related protein RAB10, and CD36 [84].

Isolating EVs from plasma or serum is challenging mainly due to high levels of proteins and lipoproteins associated with EVs [85,86]. The absence of lipoproteins and low level of proteins in saliva make it an attractive source of EVs as biomarkers for various disorders such as autoimmune diseases, cancer and brain injuries [85,87–90]. Moreover, saliva is an easily accessible biological fluid for EV isolation due to convenient, inexpensive, and safe collection method [85,91,92].

Saliva EVs and miRNAs have been isolated from pSS patients and showed significant differences from non–pSS controls [58,80]. In EVs isolated from saliva of pSS patients with SEC, liquid chromatography–mass spectrometry (LC–MS) analysis identified biomarkers critical for activation of the innate immune system (SIRPA and LSP1) and adipocyte differentiation (APMAP) [93]. Reverse transcription–quantitative polymerase chain reaction (RT–qPCR) analyses of whole saliva showed that saliva miRNA profile of pSS patients is different from non–pSS controls with significant downregulation of the miR–17 family; moreover, 9 saliva miRNAs correlated significantly with salivary flow rates and histopathology; therefore, this saliva miRNA signature, especially the simultaneous downregulation of miR–17–5p and upregulation of let–7i–5p, could be considered as specific diagnostic biomarkers of pSS [94]. Since small RNAs including miRNAs are enriched in EVs, Cross et al. isolated EVs from pooled saliva of pSS patients or healthy controls with SEC and then isolated EV–RNAs for microarray analysis. This study revealed that saliva EV tRNAs (transfer RNAs), particularly tRNA–Ile–AAT–2–1, were greatly downregulated in pSS patients, which might be a potential diagnostic biomarker for pSS [95]. This study also identified one miRNA (MIR6870) significantly downregulated in saliva EV of pSS patients.

Since small RNAs are more enriched and more representative of the local environment in saliva EVs compared to whole saliva, the former may provide a superior diagnostic oral liquid biopsy than latter. However, current evidence is still insufficient to show that EVs or EV–miRNAs can be used as reliable markers of pSS. One major challenge is the high cost and low yield of current EV isolation approaches such as ultracentrifugation and SCE. The development of more efficient and affordable EV isolation approaches such as microfluidic technology is promising to overcome this hurdle [96].

5. pSS treatment using EVs

pSS has long been an orphan disorder since no therapy has demonstrated to be really effective, and current therapeutic management for pSS is mainly based on the symptomatic treatment of sicca symptom-atology and a variety of immunosuppressive agents for systemic features [97]. Mesenchymal stem cells (MSCs), multipotent stem cells isolated from various tissues, can modulate immune responses through paracrine effects. In preclinical studies and a few small clinical trials, allogeneic but not autologous MSCs alleviated pSS after systemic infusion [19,98]. However, the clinical application of MSCs is hindered by their high cost, variations, and safety concerns. EVs from MSCs showed similar immune–modulatory properties and appear more feasible for clinical applications than live cells.

EVs from different sources of MSCs showed similar therapeutic effects on pSS but the underlying mechanisms appear different. In an experimental Sjögren syndrome (ESS) mouse model induced by immunization with salivary gland proteins, the intravenous injections of exosomes (Exo) derived from bone marrow MSCs or olfactory ecto–MSCs (OE–MSCs) significantly improved saliva flow rate, and OE–MSC–Exos also significantly decreased serum levels of autoantibodies, which is achieved through the restoration of impaired immunosuppressive function of myeloid–derived suppressor cells (MDSCs) by OE–MSC–Exo–secreted IL–6 [99,100]. Notably, the immunosuppressive function of MDSCs is also mediated by EVs, and the intravenous injection of EVs from tumor–induced functional MDSCs into abovementioned ESS mice significantly attenuated the progression of ESS and markedly reduced the percentage of germinal center B cells, which is likely mediated by targeting Bcl–6 with miR–10a–5p in EVs generated from MDSC [40]. In the NOD mouse model of sSS, intravenously injected exosomes from human labial gland MSCs (LGMSCs) alleviated SS–like symptoms, which is likely mediated by inhibiting the plasma cell response via targeting BLIMP1 with miR–125b delivered by exosomes [101]. In mouse models of both secondary and primary SS (NOD and NOD.B10 mice), intravenously injected EVs from human iPS cell–derived standardized MSCs (iPSC–MSCs) inhibited the onset of SS [3,102]. Further study indicated intravenously injected EVs accumulated mainly in the spleen and taken up by splenic macrophages, which promoted the polarization of splenic macrophages into the anti-–inflammatory M2 phenotype and consequently inhibited the differentiation of Th17 cells [103]. Notably, only EVs from young but not aging iPSC–MSCs inhibited the pSS onset, which is related to the enrichment of multiple immune–modulatory molecules in young EVs such as TGFβ1 protein and miR–21 [102]. Interestingly, EVs from aging iPSC–MSCs are enriched with miR–125b, whereas the transfer of miR–125b inhibitors into aging iPSC–MSCs restored the effect of their EVs in blocking pSS onset [103]. These findings seemingly contradictory to those on LGMSC exosomes [101], suggesting that either miR–125b plays a context–dependent role or other cargos in EVs outweigh the effect of miR–125b in SS progression.

Instead of using EVs/exosome isolated from MSC culture medium, some researchers prefer MSC extracts produced by the repeated freezing and thaw of MSCs, which contain EVs/exosome and other paracrine mediators [104,105]. In the NOD mouse model, intravenously injected extract of mouse bone marrow MSCs preserved both salivary and lacrimal glands function, which is related to the re–establishment of the peripheral tolerance [104].

The increase of Th17 cells and the decrease of Treg cells are essential for pSS progression. In $CD4^+$ *T* cells sorted from blood of pSS patients, treatment with EVs derived from umbilical cord MSCs (UC–MSCs) inhibited Th17 cell differentiation, promoted Treg cell differentiation, and restored the Th17/Treg balance, which is likely through reducing the elevated autophagy levels [106].

For the dry eye symptom of pSS, subconjunctivally injected small extracellular vesicles from human umbilical cord MSCs (hUC–MSC–sEVs) attenuated autoimmune dacryoadenitis in a rabbit model, which is through promoting M2 macrophage polarization and inducing Tregs via miR–100–5p [107]. The dry eye disease associated with Graft–versus–host disease (GVHD) shares many features with that in pSS. In both mice and humans, MSC exosomes administered as eye drops notably alleviate GVHD–associated dry eye disease by suppressing inflammation and improving epithelial recovery, which is related to miR–204–mediated reprogramming of macrophages toward the immunosuppressive M2 phenotype [108]. These findings encourage the research on locally injected EVs for treating dry eye.

Multiple studies proposed various microRNAs as key effectors in MSC EVs for inhibiting pSS progression. However, many other types of immune–modulatory molecules are present in MSC–EVs [109] whereas GU–rich microRNAs such as miR–21 and let7 miRNAs abundance in some MSC–EVs can activate TLR–7/8 signaling pathway that involves in pSS pathogenesis [65]. Therefore, the relative contribution of microRNAs vs. other types of bioactive molecules to the therapeutic effects of MSC EVs still needs to be carefully analyzed.

6. Other salivary diagnostic tests for pSS detection and future prospective

Beside salivary EVs and their cargos, other salivary biomarkers are emerging for SS diagnosis, especially for discriminating SS from Non-–Sjögren's Sicca. Most of these salivary biomarkers are proteins involved in the immune response and inflammation, such as kappa and lambda free light chains (KFLC and LFLC) and IgG [110], tripartite motif containing protein 29 (*TRIM29*) [111], and β–2 microglobulin [112]. Some salivary protein biomarkers are promising to improve diagnosis of pSS in the early stage. One small clinical study showed that salivary levels of tissue–specific autoantibodies, including anti–CA6, anti–SP1, and anti–PSP IgGs, increased significantly in anti–SSA–negative pSS patients compared with healthy controls [113]. However, many protein markers are identified in proteomics studies using expensive methods such as Mass Spectrometry and two–dimensional sodium dodecyl sulfate polyacrylamide gel electrophoresis (2D SDS–PAGE) [114]. When using more clinically feasible methods, inconsistent results have been reported for these putative biomarkers. For instance, salivary levels of LFLC and IgG measured by immunoturbidimetry were significantly different between pSS and healthy controls [115], but salivary levels of LFLC and KFLC measured by commercial immunonephelometry kits are not suitable to distinguish SS patients with neurological involvement and neurological control subjects [116]. Therefore, for the accurate differential diagonisis of SS, these salivary protein markers need to be combined with other biomarkers such as EVs, and more reliable and clinically feasible methods for detecting salivary protein markers need to be developed.

7. Summary

EVs play important roles in the pathogenesis of pSS such as inducing auto–immune responses and impairing the secretory function of gland epithelial cells. The altered sources and cargos of EVs in plasma and saliva make them promising biomarkers for pSS diagnosis. Moreover, EVs from MSCs and other immune–modulatory cells are promising to improve pSS treatment.

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Abbreviations:

ANA
Antinuclear antibody

Anti–carbonic anhydrase 6
CA6

Anti–SSA/Ro
anti–Sjögren's–syndrome–related antigen A

APC
Antigen–presenting cells

B2M
β–2 macroglobulin

DAMPs
Damage–associate molecular patterns

dsRNA
Double strand RNA

ESS
Experimental Sjögren syndrome

EV
Extracellular vesicle

Exo
Exosome

KFLC
Kappa Free light chain

GVHD
Graft–versus–host disease

I–IFN
Type I interferon

iPSC–MSC
iPS cell–derived MSC

IRFs
Interferon–regulatory factors

ITGAM
Integrin alpha M

LC–MS
Liquid chromatography–mass spectrometry

LFLC
Lambda Free light chain

LGMSC
Labial gland MSC

LSG
Labial salivary gland

MDSC
Myeloid–derived suppressor cell

MHC class I
Major histocompatibility complex class I

MSC
Mesenchymal stem cell

MSGB
Minor salivary gland biopsy

MV
Microvesicle

NF–κB
Nuclear factor–κB

NGAL
Neutrophil gelatinase–associated lipocalin

OE–MSC
Olfactory ecto–MSC

OLFM4
Olfactomedin–4

PRRs
Pattern–recognition receptors

pSS
Primary Sjögren syndrome

SP–1
Salivary protein 1

PSP
parotid secretory protein

RA
Rheumatoid arthritis

RT–qPCR
Reverse transcription–quantitative polymerase chain reaction

SEC
Size exclusion chromatography

sEV
Small EV

SGECs
Salivary gland epithelial cells

SGUS
Salivary gland ultrasonography

SLE
Systemic lupus erythematosus

SMG
Submandibular gland

SS
Sjögren syndrome

sSS
Secondary Sjögren syndrome

ssRNA
Single strand RNA

SSc
Systemic sclerosis

STIM1
Stromal interaction molecule 1

Th17
T helper 17

TLRs
Toll–like receptors

TRIM29
Tripartite motif containing protein 29

tRNAs
Transfer RNAs

TRIM21
tripartite motif–containing protein 21

UC–MSC
Umbilical cord MSC

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