

REVIEW

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Extracellular vesicles as potential biomarkers and therapeutic approaches in autoimmune diseases

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Abstract

Extracellular vesicles are heterogeneous populations of naturally occurring secreted small vesicles. EVs function as signaling platforms to facilitate intracellular communication, which indicates the physiological or pathophysiological conditions of cells or tissues. Considering that EVs can be isolated from most body fluids and that molecular constituents could be reprogrammed according to the physiological status of the secreting cells, EVs are regarded as novel diagnostic and prognostic biomarkers for many diseases. The ability to protect encapsulated molecules from degradation in body fluids suggests the potential of EVs as biological medicines or drug delivery systems. This article focuses on the EV-associated biomarkers and therapeutic approaches in autoimmune diseases.

Keywords: Autoimmunity, Biomarker, Therapy, Extracellular vesicle, Exosomes, MicroRNA

Introduction

Extracellular vesicles (EVs) [1], membrane-encapsulated vesicles released by cells, are characterized by lipid bilayer membranes. EVs contain specific biomolecules, including proteins, microRNAs, mRNAs, long noncoding RNAs, cytokines, growth factors, and bioactive lipids [2]. Some of these biomolecules indicate the vesicle origin, and others involve in targeting cells. According to the biogenesis, morphology and dimensions, EVs are classified into (i) exosomes (30–150 nm); (ii) microparticles (MPs; 100–1000 nm); and (iii) apoptotic bodies (1000–5000 nm) [3]. EVs are released by almost all cell types and present in virtually all body fluids, such as blood, urine, milk, saliva, semen, sweat, bile, cerebrospinal fluid, amniotic fluid, and ascites [4, 5].

Released EVs involve in intercellular communication and cellular function regulation under normal physiological conditions, while reprogrammed EVs cargo can lead to an immune response and contribute to the

development of diseases under pathological conditions [6]. Various cell types, including natural killer cells, monocytes, dendritic cells, and macrophages [7, 8], have been shown to release EVs to mediate immunostimulatory and immunosuppressive effects by transporting antigens to antigen-presenting cells, activating T cells or inhibiting the activation of regulatory T cells [9]. Accumulating evidence suggested that total EVs, EVs constituents, and EVs surface molecules associate with autoimmune diseases, such as primary Sjögren's syndrome (pSS), and systemic lupus erythematosus (SLE), oral lichen planus (OLP) [10–14]. Given that, theoretically, EVs can be released by every cell in the body and may increase in pathological conditions [4, 5, 15], EVs have been suggested as promising novel biomarkers [15, 16]. Compared to traditional biomarkers, biological medicines or drug delivery systems, EVs possess several distinct advantages, including (i) capacity to function as noninvasive biomarkers released by almost all cell types and present in almost all body fluids; (ii) ability to reflect the progress of diseases and the effects of treatments through vesicle origin or cargo; (iii) ability to protect natural cargos from freeze/thaw cycles during long-term

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storage; and (iv) the biodegradability of EVs in body fluids [15, 16].

This review focuses on the EV-associated biomarkers and potential applications of EVs in autoimmune diseases.

EVs as potential biomarkers in autoimmune diseases

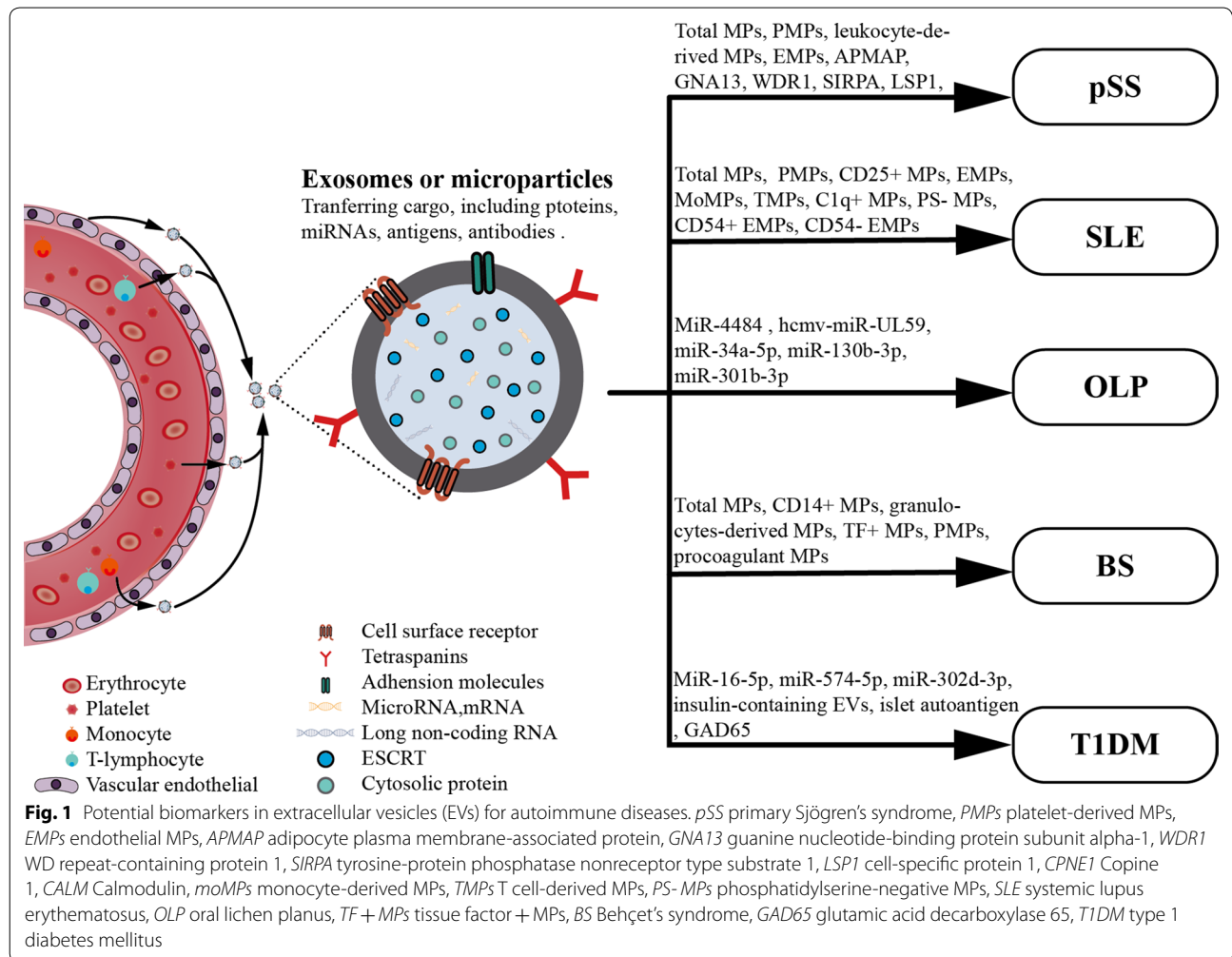
Autoimmune diseases, characterized by self-immune responses, are one of the leading causes of morbidity and mortality among chronic diseases [17]. Imbalance in the activation and regulation of cells can result in dysregulated cell activation, leading to the production of autoantibodies and damage to tissues expressing the target antigen [18]. Considering the increasing number of new cases of autoimmune diseases and the poor understanding of the etiologies of autoimmune diseases that greatly impedes the prevention, diagnosis and treatment of autoimmune diseases, researchers worldwide have been searching for more reliable and convenient biomarkers for autoimmune diseases. Some previous studies have

determined that EVs are involved in immunostimulation or immunosuppression in autoimmune diseases through pro-inflammatory or anti-inflammatory effects induced by their specific constituents [10, 14, 15, 19, 20]. Moreover, studies have suggested increasing total EVs levels and specific EVs constituents as potential diagnostic biomarkers in several autoimmune diseases, such as primary Sjögren’s syndrome, systemic lupus erythematosus, and systemic sclerosis [21] (Fig. 1).

EVs as biomarkers in primary Sjögren’s syndrome

Primary Sjögren’s syndrome, a chronic female-dominant autoimmune disorder influencing approximately 1% of the general population and 3% of people older than 50 years [21], is characterized by keratoconjunctivitis sicca and xerostomia induced by the focal lymphocytic infiltration in exocrine glands and lacrimal gland.

One previous study reported that although the levels of MPs in pSS patients with high or low disease severity were higher than health controls, those in pSS



patients with high disease severity were lower than those in patients with low disease severity (Table 1) [22]. The potential explanations include consumption or confinement of MPs by adhesion in the tissue target of pSS, MPs sequestered in leukocyte-platelet complexes, and MPs destruction induced by phospholipases, especially secretory phospholipase A2, in active disease [22–27]. In addition to increased PMPs levels, increased levels of endothelial microparticles (EMPs), which are significantly correlated with the disease duration from symptom onset and diagnosis, were also found in pSS patients compared with healthy controls [28]. Aqrabi et al. identified thirty-six proteins, including adipocyte plasma membrane-associated protein, which correlates with adipocyte differentiation, and SIRPA and LSP1, which are associated with activation of the innate immune system, upregulated in the EVs from saliva of pSS patients compared to controls. They also revealed increased expressions of Copine 1 and Calmodulin in the tears of pSS patients [24]. Study also suggested hsa-mir-768-3p and hsa-mir-574-3p in the minor salivary glands, which are involved in minor salivary gland inflammation and detectable in salivary EVs, to be promising biomarkers in the minor salivary glands reflecting inflammation and salivary gland dysfunction in pSS [29, 30] Overall, these results revealed increased EVs from different biofluids in pSS, as well as changed expressions of specific proteins and miRNAs in EVs. Levels of EVs and specific components of EVs may be promising diagnosis or prognosis markers and reflect the potential underlying mechanisms of pSS.

EVs in systemic lupus erythematosus

Systemic lupus erythematosus, a systemic autoimmune disease influencing multiple organs simultaneously with poor quality of life and substantial mortality, is characterized by the presence of autoreactive T cells and hyperactive B cells that produce autoantibodies forming immune complex deposits [31, 32].

Proven to increase adhesion molecule expressions, chemokine productions, and structural alterations in macrovascular and microvascular endothelial cells, which can lead to endothelial alterations and tissue leukocyte infiltration [10, 33], MPs in the plasma of SLE patients have been intensively studied as elements in “liquid biopsies” for SLE (Table 2).

Many studies have shown increased total MPs levels in the plasma of SLE patients compared with those of healthy controls [22, 34–38]. López et al. proved that total MPs, CD25 + MPs, EMPs, platelet-derived MPs, monocytes or T cells in the plasma of SLE patients associated with the increased disease duration and higher risk of cardiovascular disease [23]. Scientists have also found increased total MPs and IgG + MPs [37, 38], as well as relatively lower IgM + MPs and C1q + MPs in patients with SLE [39]. Another study showed a positive association between plasmatic CD14 + monocyte-derived MPs and disease activity [40]. A subsequent study showed that phosphatidylserine-negative MPs/MPs was increased in SLE patients compared to healthy controls, especially in females and smokers [36]. Moreover, Fortin et al. revealed a positive correlation between CD41 + MPs harboring IgG and the SLE Disease Activity Index 2000, as well as a positive association between the concentrations of CD41– MP harboring IgG and Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index, and carotid US plaques and intima-media thickness [41]. Moreover, a previous study reported higher CD31 +/annexin V +/CD42b-EMPs levels in SLE patients than in healthy controls and an association between CD31 +/annexin V +/CD42b-EMPs and the median global BILAG-2004 score after treatment [42]. Another study found increased EMPs levels and a lower ratio of CD54(+) EMPs/total EMPs in SLE patients, especially in women with moderate-to-high disease activity, compared to controls [34]. In conclusion, EVs mediates intercellular communication between immune cells, endothelial cells, and platelets with the changes of specific components in the development of SLE and provide potential biomarkers for SLE diagnosis

Table 1 EV-associated biomarkers in primary Sjögren’s syndrome

EVs or constituents	Source	Isolation method	Quantification method	References
Total MPs, PMPs, leukocyte-derived MPs	Plasma	Centrifugation	Functional prothrombinase capture assay and flow cytometry	[22]
EMPs	Plasma	Affinity-based capture	Flow cytometry	[28]
APMAP, GNA13, WDR1, SIRPA, LSP1	Saliva	Size-exclusion chromatography	Flow cytometry	[24]
CPNE1, CALM	Tear	Size-exclusion chromatography	Flow cytometry	[24]

MPs microparticles, PMPs platelet-derived MPs, EMPs endothelial MPs, APMAP adipocyte plasma membrane-associated protein, GNA13 guanine nucleotide-binding protein subunit alpha-1, WDR1 WD repeat-containing protein 1, SIRPA tyrosine-protein phosphatase nonreceptor type substrate 1, LSP1 cell-specific protein 1, CPNE1 Copine 1, CALM Calmodulin

Table 2 EV-associated biomarkers in systemic lupus erythematosus

EVs or cargo in EVs	Source	Isolation method	Quantification method	References
Total MPs	Plasma	Affinity-based capture	Flow cytometry	[35]
Total MPs, PMPs, CD25 + MPs, EMPs, monocyte-derived MPs, and T cell-derived MPs	Plasma	Centrifugation	Flow cytometry	[23]
Total MPs and IgG + MPs	Plasma	Centrifugation	Flow cytometry	[37]
Total MPs, IgM + MPs, and IgG + MPs	Plasma	Centrifugation	Flow cytometry	[38]
IgM + MPs and C1q + MPs	Plasma	Affinity-based capture	Flow cytometry	[11]
CD14 + monocyte-derived MPs	Plasma	Centrifugation	Flow cytometry	[40]
Total MPs and phosphatidylserine-negative MPs	Plasma	Centrifugation	Flow cytometry	[36]
CD41 + MPs harboring IgG and CD41- MP harboring IgG	Plasma	Affinity-based capture	Flow cytometry	[41]
CD31 + /annexin V + /CD42b- EMPs	Plasma	Affinity-based capture	Flow cytometry	[42]
Total EMPs, CD54 + EMPs, CD54- EMPs, and CD54 + EMPs/total EMPs	Plasma	Fluorophore-conjugated mAb staining	Flow cytometry	[34]
Total MPs and PMPs	Plasma	Centrifugation	Flow cytometry and a functional prothrombinase capture assay	[22]

MPs microparticles, PMPs platelet-derived MPs, EMPs endothelial microparticles, PS- MPs phosphatidylserine-negative MPs

and prognosis. These biomarkers may partly implicate the mechanism of SLE and provide new directions for the targeted therapies of SLE.

EVs in other autoimmune diseases

EV-associated biomarkers have been intensively studied in other autoimmune diseases (Table 3). Oral lichen planus, a T cell-mediated chronic autoimmune disease with a prevalence rate of 0.1–4.0% in the adult population [43, 44], is characterized by keratotic or erythematous lesions in the oral mucosa. The symptoms of OLP could be symmetrical, bilateral, or multiple lesions with different patterns of plaque, reticular, papular, bullous, erosive, and atrophic features [45]. A previous study suggested that different expression patterns of miRNAs in

EVs associated with cytokine regulation in OLP patients may contribute to the elucidation of the pathogenesis of OLP [46], and a recent study reported that EVs from the plasma of OLP patients could enhance T cell proliferation and attenuate apoptosis, which might promote the development of OLP [47]. Ding et al. reported increased levels of hcmv-miR-UL59, which is primarily encapsulated in EVs in the plasma, in the plasma of OLP patients [48]. Another study revealed the upregulated expression levels of miR-4484 in salivary EVs from OLP patients and identified this miRNA as a potential biomarker for OLP [45]. In addition, a study reported different expression levels of miR-34a-5p, miR-130b-3p, and miR-301b-3p in circulating EVs in OLP, as well as an association between the level of miR-34a-5p and disease severity [49].

Table 3 EV-associated biomarkers in other autoimmune diseases

EVs or cargo in EVs	Source	Isolation method	Quantification method	Biomarkers	References
MiR-4484	Saliva	Precipitation	MiRNA microarray analysis and flow cytometry	OLP	[45]
MiR-34a-5p, miR-130b-3p and miR-301b-3p	Plasma	Membrane affinity -based capture	MiRNA microarray analysis and flow cytometry	OLP	[49]
Hcmv-miR-UL59	Plasma	Precipitation	RT-qPCR analysis	OLP	[48]
Total MPs, CD14 + MPs, Granulocytes-derived MPs, and tissue factor + MPs	Plasma	Affinity-based capture	Flow cytometry	BS	[59]
PMPs	Whole blood	Unreported	Flow cytometry	BS	[60]
Procoagulant MPs	Plasma	Affinity-based capture	Functional prothrombinase capture assay	BS	[61]
MiR-16-5p, miR-574-5p and miR-302d-3p	Plasma	Ultracentrifugation	RT-qPCR analysis	T1DM	[62]
Insulin-containing exosomes, exosomal islet autoantigen and GAD65	Plasma	Size-based filtration	Affinity-based capture and RT-PCR analyses	T1DM	[63]

OLP oral lichen planus, RT-qPCR Realtime quantitative polymerase chain reaction, BS Behçet's syndrome, TF + MPs tissue factor + MPs, PMPs platelet-derived MPs, T1DM type 1 diabetes mellitus, GAD65 glutamic acid decarboxylase 65

Behçet’s syndrome (BS), a multisystem inflammatory disorder involving venous and arterial vessels [50], is characterized by oral and genital ulceration, mucocutaneous lesions, arthritis, and uveitis [51]. Although the etiopathogenesis of BS is not fully understood, study have suggested an association between BS and activation of the hemostatic system which could be induced by EVs [52]. Studies have shown that clot propagation is affected by tissue factor + MPs, which are also associated with atherosclerosis and venous thromboembolism [53–55], in preclinical models [56–58]. A study reported increased levels of total MPs and tissue factor + MPs in BS patients and a low ratio of TFPI + MPs counts to tissue factor + MPs counts, which associated with clinical thrombosis risk [59]. Furthermore, an increased percentage of platelet-derived MPs and increased procoagulant MPs expressions were found in BS patients [60, 61].

Type 1 diabetes mellitus (T1DM), a disorder caused by an autoimmune response against insulin-producing β cells in the pancreatic islets, is the most severe form of diabetes mellitus. A recent study indicated that EVs play an important role to transfer autoantigen peptides from insulin-producing β cells in the pathogenesis of T1DM [15]. Study had reported upregulated expressions of

miRNAs in EVs, including miR-16-5p, miR-574-5p and miR-302d-3p, in the plasma of T1DM patients compared with those of healthy controls [62]. In addition, Korutla reported that insulin-containing EVs from transplanted islets and the cargos in these EVs, including islet autoantigen and glutamic acid decarboxylase 65, could reflect the destruction of transplanted β cells secondary to recurrent T1DM autoimmunity [63]. In summary, further studies are necessary to explore the potential diagnostic and prognostic EVs biomarkers in autoimmune diseases.

EVs as therapeutic approaches in autoimmune diseases

In addition to the promising use as biomarkers, EVs have been suggested as potential therapeutic approaches which can be divided into four categories: (i) utilizing EVs to transfer the natural cargo of EVs to induce immunosuppressive or immunostimulatory effects, including antimicrobial effects, anti-inflammatory effects, and antitumor effects or utilizing EVs as an alternative to mesenchymal stem cell transplantation; (ii) utilizing bio-engineering techniques to modify EVs as nanocarriers for drug delivery systems to deliver specific nucleic acids (miRNAs, siRNAs, and mRNAs), proteins, and therapeutic agents to target cells or tissues; (iii) utilizing EVs

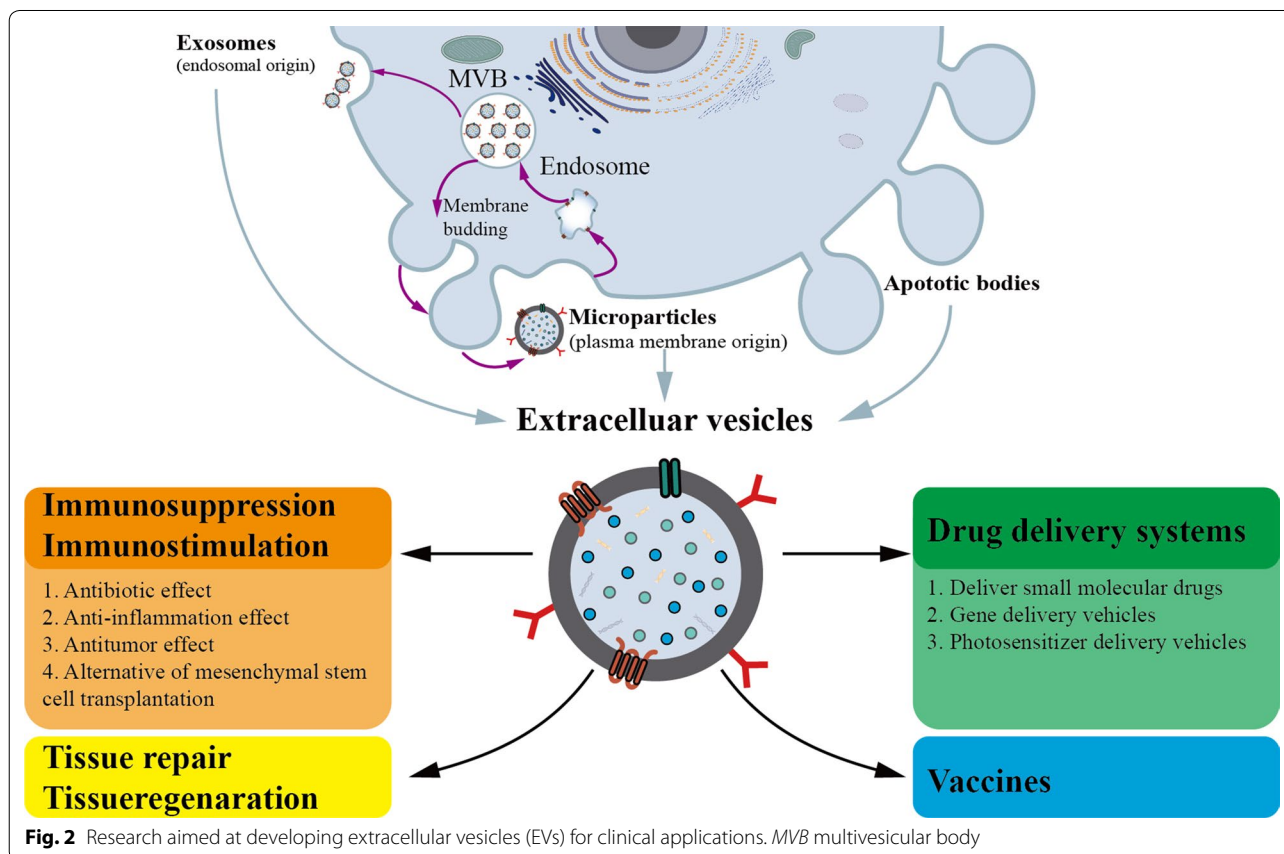


Fig. 2 Research aimed at developing extracellular vesicles (EVs) for clinical applications. *MVB* multivesicular body

to induce tissue regeneration and tissue repair; and (iv) utilizing EVs as novel vaccines in the treatment of tumors or infections (Fig. 2) [20].

Conclusion

Accumulating evidence supports that EVs involve in intercellular communication inducing immunostimulation and immunosuppression, and EVs are promising biomarkers or therapeutic approaches for autoimmune diseases. In this review, we provided evidence for the biomarker potential of EVs in several autoimmune diseases and summarized the potential use of EVs in therapies. However, both basic and applied studies of EVs are still in the early stages, and the poor understanding of the underlying mechanisms hinders the clinical translation of EVs. Obviously, extensive studies of EVs are necessary before application for the clinical diagnosis, prognosis and therapy of autoimmune diseases can be performed, including (i) studies on the separation and purification of EVs; (ii) studies providing an intensive understanding of EVs biogenesis and targeting; (iii) studies providing an intensive understanding of the mechanism by which EVs induce immunostimulation and immunosuppression; (iv) studies assessing the effect and reliability of EVs as nanodrugs or drug delivery systems in vivo; and (v) studies on clinical applications. Despite the challenges and difficulties remaining before EVs can be clinically applied, their biological and physiological characteristics have shown the great potential of EVs as biomarkers and therapeutic tools. In conclusion, intensive study of the biological functions and mechanisms of EVs could help to identify potential biomarkers and facilitate the clinical translation of EVs.

Abbreviations

EVs: Extracellular vesicles; MPs: Microparticles; pSS: Primary Sjögren's syndrome; SLE: Systemic lupus erythematosus; OLP: Oral lichen planus; EMPs: Endothelial microparticles; BS: Behçet's syndrome; T1DM: Type 1 diabetes mellitus.

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Authors' contributions

XK wrote the main manuscript text and prepared tables and figures. LQ, WK wrote the main manuscript. LL, ZM, YH prepared tables and figures. WX and WW reviewed and edited the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The primary data for this study is available from the authors on direct request.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no potential conflicts of interest with respect to the research, authorship, or publication of this article.

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