International Journal of Nanomedicine

Dovepress
Taylor & Francis Group

Open Access Full Text Article

REVIEW

Exosomes in Systemic Autoimmune Diseases: Recent Advances in Diagnostic Biomarkers and Therapeutic Applications

Xinchen Lv, Wendong Liu, Xue Zhou, Yu Yang, Wangqian Zhao, Linfeng Meng, Fenghuoyi Mu, Zhixiang Zhang, Shaohua Zhu, Shuai Zhang, Ying Wang

Department of Forensic Medicine, School of Basic Medical Sciences, Soochow University, Suzhou, 215123, People's Republic of China

Correspondence: Ying Wang; Shuai Zhang, Department of Forensic Medicine, School of Basic Medical Sciences, Soochow University, Suzhou, 215123, People's Republic of China, Email yingwang1111@suda.edu.cn; 15225377016@163.com

Abstract: Systemic autoimmune diseases (SADs) encompass a spectrum of organ involvement, clinical heterogeneity, and therapeutic challenges meriting significant research. These conditions involve the immune system mistakenly attacking and damaging multiple body tissues and organs, leading to chronic inflammation and damage. Exosomes are nanoscale extracellular vesicles secreted by cells that modulate intercellular communication and immunity. Accumulating evidence indicates that exosomes have multifaceted roles in the pathogenesis of SADs through processes like cellular signaling, immune modulation, antigen presentation, and inflammatory response. The cargo of exosomes, such as proteins, miRNAs, and lipids, are vital determinants of cellular and humoral immunity. This review examines key signaling pathways in four common SADs, rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, and Sjögren's syndrome, and explores exosome as non-invasive biomarkers for diagnosis, disease monitoring, and therapeutic response prediction. Additionally, the therapeutic potential of mesenchymal stromal cells (MSCs) or various type of mesenchymal stem cells derived exosomes as cell-free immunotherapies for SADs is highlighted. Engineered exosomes, with enhanced targeting, bioavailability, low toxicity, are emerging as promising drug delivery vehicles. However, challenges such as high production costs, technical complexity, and inefficiency, along with the lack of standardized protocols, limit clinical implementation in SADs. A deeper understanding of exosome roles in SADs pathogenesis and innovative immunotherapies may provide valuable theoretical support for the diagnosis and treatment of these challenging conditions.

Keywords: exosomes, systemic autoimmune diseases, immunoregulation, biomarkers, MSC-therapy

Introduction

Autoimmune diseases (ADs) are a group of conditions in which the immune system mistakenly targets and attacks normal tissues, leading to immune regulatory disorders.[1–3] Affecting approximately 10% of the global population, ADs present a significant healthcare challenge due to the increasing number of patients.[4] These diseases are often characterized by the presence of autoreactive lymphocytes and abnormal antibodies, which attack and destroy healthy cells and tissues, causing tissue damage.[5] The causes of ADs are often the result of the interaction of multiple factors, including environmental factors, genetic susceptibility, and immune system status, all contributing to immune abnormalities. Lifestyle factors such as diet, smoking habits, and infections can also affect disease progression.[6,7] ADs are classified based on clinical manifestations into organ-specific ADs and systemic ADs (SADs). SADs exhibit extensive lesions across multiple systems and organs, typically feature more intricate pathological mechanisms and diverse clinical manifestations, thereby posing greater challenges in diagnosis and treatment. Genome-wide association studies (GWAS) have identified numerous genomic loci and variations associated with autoimmunity, which are increasingly used in polygenic scores to predict disease susceptibility.[8–10] For example, integrating GWAS data with protein quantitative trait loci (pQTL) information facilitated identifying

Received: 21 November 2024
Accepted: 2 April 2025
Published: 21 April 2025

proteins targets for multiple sclerosis treatment.[11] Besides pQTL, regions of methylation and expression of quantitative trait loci (mQTL and eQTL) in the genome often undergo mutations, affecting disease susceptibility.[12,13] However, there is still a long way to go in uncovering the specific functional effects of these mutations and linking genetic variations with the molecular mechanisms of diseases. At present, the treatments for SADs are limited and tend to focus on conservative symptomatic relief or systemic immunosuppressive therapy, which often show poor efficacy and serious side effects, lacking precise targeted therapeutic approaches.[14] Therefore, it is urgent to understand the initiation and progression of SADs at refined molecular levels to provide new ideas for the etiology, pathogenesis, and treatment.

A growing body of research indicates that exosomes are involved in the communication between immune cells and the regulation of immune responses. These nanoscale vesicles possess strong immune regulatory properties that are essential for maintaining cellular homeostasis. They mediate immune tolerance and regulation, enabling the body to fight against foreign pathogens.[15] The interaction mechanisms between immune cells include direct contact, the release of soluble immune regulatory factors, and signaling mediated by extracellular vesicles (EVs). The molecular cargos of exosomes, including immune regulatory factors, miRNAs, and lipids, are pivotal in both cellular and humoral immunity. By transferring these components, exosomes modulate gene expression and molecular pathways critical to immune regulation.[2,16] In addition to these natural functions, engineered exosomes produced through genetic modification and the alteration of parental cells using bioengineering techniques have shown great potential as drug delivery vehicles.[17] Compared to natural exosomes, engineered exosomes exhibit higher drug loading efficiency, improved targeting capability, and have been widely studied in the treatment of tumors, neurodegenerative diseases, and immunotherapy.[18] The ability to modify exosomes for specific therapeutic purpose further enhances their role in SADs, where exosomes facilitates intercellular communication and transport bioactive molecules like proteins, lipids, and RNAs that influence the pathogenesis and progression of SADs.[19,20] Exosome can modulate immune responses, disrupt immune homeostasis, and promote inflammation, all of which are central to the development and exacerbation of SADs.[21,22] In systemic lupus erythematosus, exosomes are involved in platelet activation and systemic endothelial activation pathways.[23,24] Exosomes exhibit immunomodulatory effects through functionally transferring endogenous miRNAs to receptor cells.[25] Numerous studies also demonstrate the immunomodulatory function of mesenchymal stromal cells (MSCs) or various type of mesenchymal stem cells derived exosomes in rheumatoid arthritis.[26–28] Furthermore, exosomes have been explored as potential biomarkers for diagnosis and therapeutic agents in SADs.[29,30] Especially in lupus nephritis-associated renal damage, exosomes show promise as non-invasive diagnostic biomarkers.[22,31] These potential applications suggest that exosome can serve not only as feasible diagnostic tools for SADs, but also as a new cell-free immunotherapy.

As exosome regulates the immune system, mediates inflammation and angiogenesis processes, and drives cellular functional disorders, which are key pathological factors in SADs, exploring the relationship between exosomes and SADs may contribute to the timely diagnosis and early prevention of these conditions. This review elaborates on the latest progress in the application of exosomes in SADs, focusing on four common conditions: rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), systemic sclerosis (SSc), and Sjögren's syndrome (SS). From the perspective of exosomes, this review aims to elucidate pathological mechanisms and their potential as disease biomarkers across these conditions. Specifically, current insights are highlighted regarding exosome-mediated effects on immune dysfunction, inflammation, and tissue damage in SADs. Emerging evidence indicates that exosomal miRNA and protein profiles may serve as promising non-invasive diagnostic indicators and surrogate markers for disease assessment over time. Finally, innovative treatment strategies are summarized, including targeted regulation of exosome cargoes in immune cells such as neutrophils, B lymphocytes, or T lymphocytes, which are expected to become new targets for immunotherapy. We also introduced engineered exosomes, modified using bioengineering technologies, which show great potential in the treatment of SADs. In addition, MSC-derived exosome therapy as an emerging therapeutic approach for SADs will be highlighted in this review. With enhanced understanding of exosomes involvement in SADs pathogenesis, opportunities may arise for optimized diagnosis and therapeutic treatment in clinical practice.

The Biological Characteristics of Exosomes

EVs are particles released involuntary from cells, and are a general term for all extracellular lipid bilayer structures. Based on factors such as size, density, biochemical composition, and cell origin, EVs are classified into exosomes, microvesicles, and apoptotic bodies.[32,33] The concept of exosome was first introduced in 1980s to describe small vesicles released during the maturation of sheep reticulocytes, which were subsequently named as "exosomes".[34,35] With advances in separation and extraction technology, mo139re in-depth studies on exosomes have emerged. Specifically, exosomes typically measure 40–160 nm in diameter and feature a phospholipid bilayer membrane structure, originating from the multivesicular endosome. Exosomes contents include nucleic acid, lipids, proteins, amino acids, and other metabolites that can significantly influence immune cell function and autoimmune responses. Many cell surface proteins are distributed on exosomes, including tetraspanins, transporters, signal transduction receptors, and integrins (Figure 1),[33,36] serve as critical mediators of immune cell communication in autoimmune conditions. Lacking a functional nucleus, exosomes are unable to replicate. However, the discovery that exosomes mediate the transmission of their genetic cargo between cells, including mRNA and miRNA,[37] has opened up a new perspective on the understanding of intercellular communication in ADs. This heterogeneity in size and composition directly impacts how exosomes influence autoimmune processes, as different exosome populations can either

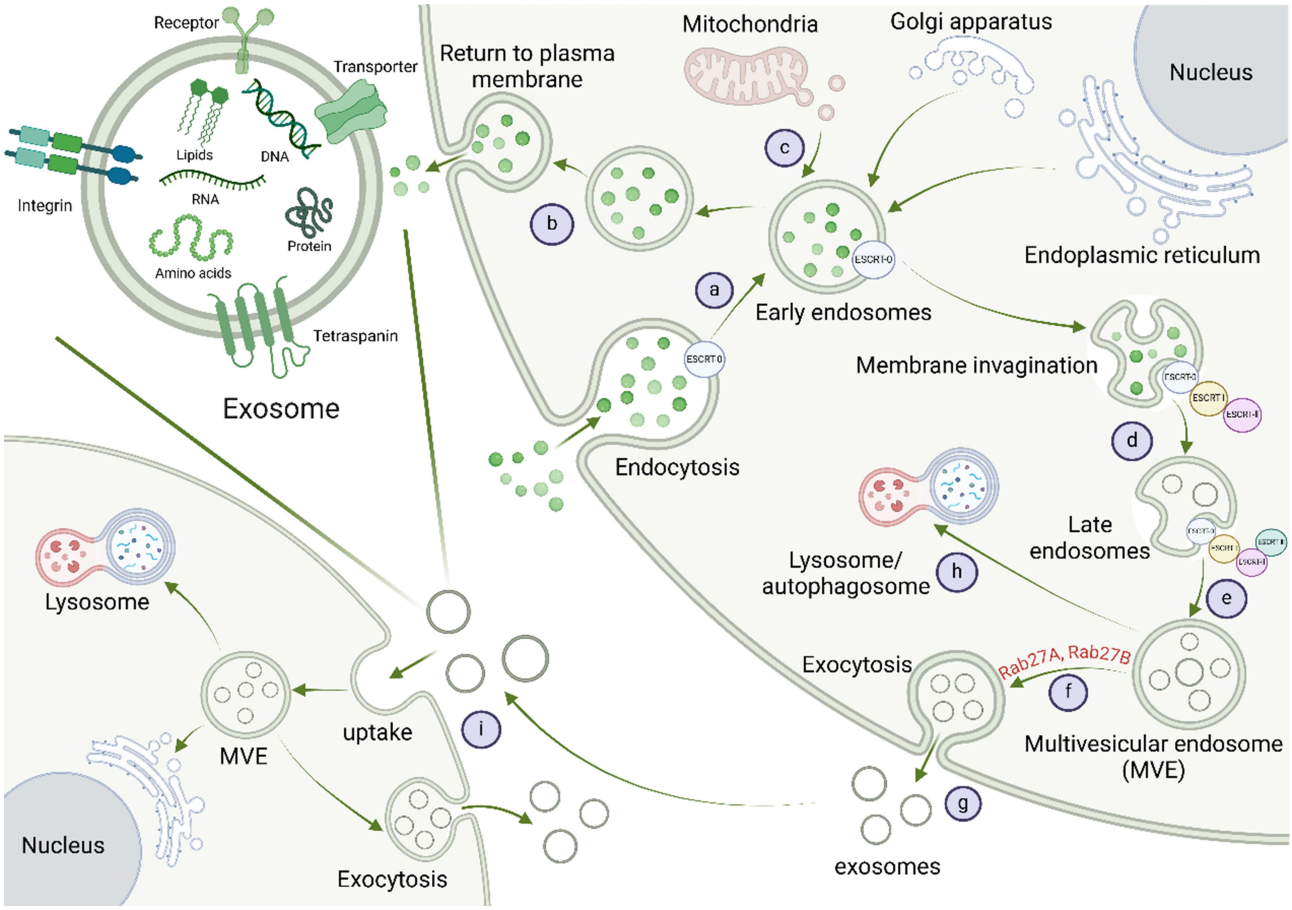

Figure 1 Biogenesis and secretion of exosomes. Exosomes are lipid bilayer vesicles ranging from 40–160 nm in diameter. Their membrane surface contains proteins including tetraspanins, integrins, transporters, and immunomodulatory factors. Exosomal cargos incorporate proteins, DNA, RNA, lipids, amino acids, and metabolites. Exosomes are produced through a series of membrane invaginations and fusion sorting processes involving multiple organelles. The main steps are as follows: (**a**) Initially, the plasma membrane invaginates inward, encapsulating incoming materials to form early endosomes. ESCRT-0 on the cytoplasmic membrane is distributed to the early endosomal membrane and participates in the subsequent membrane invagination. (**b**) Some early endosomes return to the plasma membrane. (**c**) In some cases, vesicles budding from mitochondria, trans-Golgi network or endoplasmic reticulum may also fuse with these early sorting endosomes. (**d**) ESCRT-0 recruits ESCRT-I, ESCRT-II, and ESCRT-III to the endosomal membrane in sequence. They jointly participate in the invagination and shearing of the early endosomal membrane and mature into late endosomes. (**e**) The invagination and fusion of late endosome membranes, coupled with material exchange, leads to the formation of multivesicular endosomes (MVEs). (**f**) Rab27A and Rab27B mediate the movement of MVEs towards the cell periphery. (**g**) MVEs fuse with the plasma membrane, releasing the intraluminal vesicles (ILVs) in the form of exosomes. (**h**) ILVs targeted to lysosomes or autophagosomes are metabolized and degraded. (**i**) Exosomes are taken up by recipient cells through endocytosis or membrane fusion, undergo substance exchanges and signal transduction, or lysosome degradation. Created in BioRender. Lv, X. (2025) https://BioRender.com/m1no9lz.

https://doi.org/10.2147/IJN.S506221

promote inflammation through delivering pro-inflammatory mediators or suppress autoimmunity by transferring immunoregulatory molecules to recipient cells.

Biogenesis of Exosomes

Exosome biogenesis occurs through a highly regulated series of cell membrane invaginations and multiple fusion sorting processes, involving organelles such as the Golgi apparatus and lysosomes. Understanding these mechanisms is important for comprehending how dysregulated exosome production contributes to autoimmune disease pathology. The main stages of exosome formation are as follows: Initially, the plasma membrane invaginates, enfolding incoming material to form early endosomes (Figure 1). In some cases, vesicles sprouting from mitochondria, trans-Golgi network or endoplasmic reticulum may also fuse with these early-sorting endosomes.[33] Subsequently, a portion of the early endosomes returns to the plasma membrane, while another portion matures into late endosomes. Multivesicular endosomes (MVEs) are formed through material exchange as well as the invagination and fusion of the late endosome membrane. After sorting, a subset of MVEs fuse with the plasma membrane with the assistance of Rab27a and Rab27b, and release the intraluminal vesicles (ILVs) as exosomes.[38–40] In autoimmune conditions, this process is often dysregulated, leading to altered exosome composition and release patterns that contribute to immune dysfunction. The remaining ILVs targeted for degradation are transported from MVEs to lysosomes or autophagosomes, where they are ultimately metabolized and degraded. This regulated biogenesis pathway allows selective sorting of cargo into exosomes during biogenesis for extracellular transfer between cells, which is a process that can propagate autoimmune responses through the transfer of autoantigens and inflammatory mediators. Following release, exosomes are taken up by recipient cells through direct or receptor-mediated endocytosis, or membrane fusion. Internalized exosomes then undergo a series of substance exchanges and signal transduction, or lysosomes degradation,[41] which in autoimmune diseases can trigger aberrant immune activation or perpetuate inflammatory cascades.

The formation of MVEs and the generation of ILVs depend critically on the endosomal sorting complex required for transport (ESCRT).[39,40] The ESCRT comprise four functional components (ESCRT-0, -I, -II, and -III), an auxiliary ATPase complex, and several accessory proteins that sorts cargo into endosomes and ultimately packages them into exosomes.[38] In autoimmune conditions, alterations in ESCRT function can lead to improper sorting of immunogenic molecules into exosomes, contributing to disease progression. In the classical ESCRT-dependent pathway, the four ESCRT complexes are sequentially recruited to the endosomal membrane to function.[39] Firstly, ESCRT-0 is recruited to the early endosome by phosphatidylinositol-3-phosphate (PtdIns3P), which is enriched in the nuclear endosomal membrane (Figure 1).[42] ESCRT-0 is responsible for recognizing and binding ubiquitinated proteins to initiate the formation of ILVs.[40] Then, ESCRT-0 recruits ESCRT-I through interaction with the TSG101 subunit.[43,44] At the same time, ESCRT-I also interacts with ESCRT-II, which together participate in the invagination of the endosomal membrane.[45] Finally, ESCRT-II initiates the assembly of ESCRT-III. ESCRT-III involves in membrane shearing and budding ILVs into MVEs.[46] Under Rab27A and Rab27B mediation, MVEs migrate towards the cell periphery, where they fuse with the cell membrane to release ILVs (exosomes).[38,40,47]

The ESCRT machinery not only plays a key role in exosome biogenesis but also influences exosomal protein sorting, directly activating or inhibiting cellular signaling pathways, thereby altering the immunoregulatory microenvironment and affecting autoimmunity.[36,48] For instance, in SLE and RA, altered ESCRT function can lead to increased loading of autoantigens and inflammatory mediators into exosomes. A notable example of this connection is the ESCRT-I associated protein TSG101, which can bind to IQGAP1 to form a complex that facilitates the loading of Gasdermin D and IL-1β into exosomes. In autoimmune inflammatory conditions, stimulation with pathogen-associated molecular patterns like LPS and damage signals such as ATP enhances the interaction between IQGAP1 and ESCRT, promoting the release of IL-1β within exosomes.[49] This mechanism directly contributes to the propagation of inflammatory responses in SADs, including RA and inflammatory bowel disease mediating inflammasome activation and cytokine release. Importantly, targeting the ESCRT machinery can reduce the production of pro-inflammatory exosomes, thereby intervening in the inflammatory progression of SADs at its source.

The Heterogeneity of Exosomes

Exosomes are released by nearly all cells as part of normal physiological processes, yet they exhibit significant "individual differences". The heterogeneity of exosomes is the result of a combination of factors: size, the nature of their progenitor cells, their biogenesis pathways and the ratio and abundance of their contents and functions (Figure 2). Exosomes are endogenous

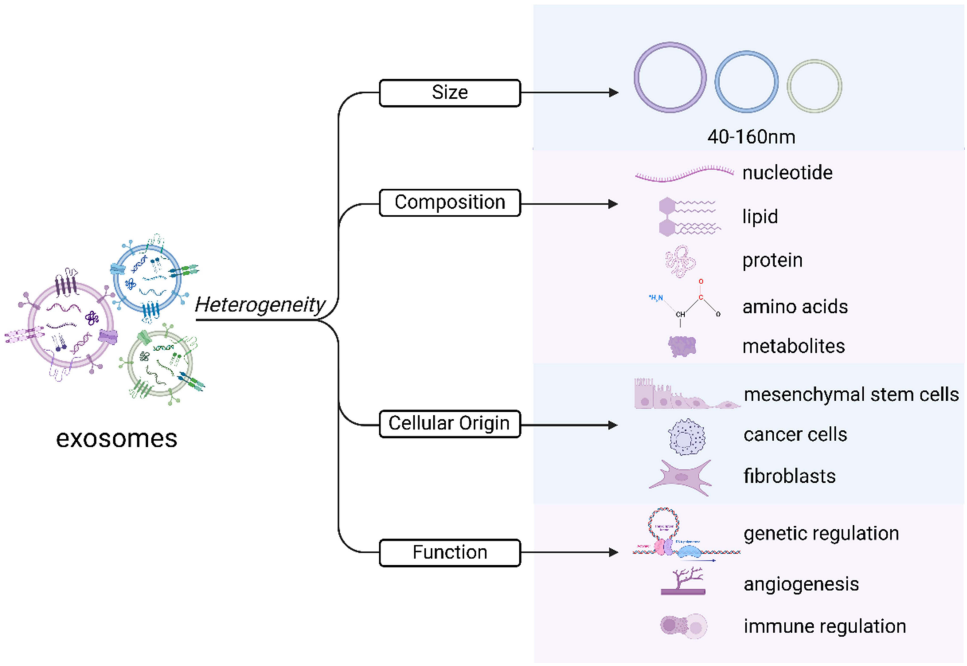

Figure 2 Sources of exosome heterogeneity. Exosomes exhibit variability across four aspects: size, composition, cellular origin, and function. Created in BioRender. Lv, X (2025) https://BioRender.com/k41f012.

nanoparticles in the body that can evade immune clearance and exhibit strong permeability.[50] Their heterogeneity in size, cargoes, and cellular origin means the membrane surface receptors are specific to certain exosome classifications. Consequently, target cells selectively uptake or reject particular exosome subtypes. This targeting specificity underlies the diverse functional specialization of exosomes in intercellular communication and physiological processes. In the context of autoimmune diseases, this heterogeneity contributes to their dual role in either exacerbating pathological immune responses or mediating immunomodulatory effects, depending on their cellular origin and molecular cargo.

Heterogeneity in Composition of Exosomes

The heterogeneity in the constituents of exosome play an important role in both physiological and pathological processes within the body. Exosomes are mainly composed of five types of substances: nucleotide (including RNA), lipid, proteins, amino acids, and metabolites.[33,51,52] RNA and lipids are selectively and actively incorporated into intracavitary vesicles, while the inward budding of the limiting membrane of multivesicular bodies allows for the encapsulation of cytoplasmic proteins and other components.[38] Upon fusion with the cell membrane, these vesicles release their contents into the extracellular space, where they can be taken up by recipient cells, affecting cellular function through substance exchange. Within exosomes, microRNA (miRNA) represents a highly abundant form of nucleic acids. These single-stranded RNA molecules, approximately 22 nucleotides in length, are encoded by endogenous genes and serve as post-transcriptional regulators of gene expression.[37] The bilayer lipid structure of exosomes can protect miRNA from degradation by ribonucleases during transport.[53] Exosomal lipids, such as sphingolipids, sphingomyelin, cholesterol, and phosphatidylserine, provide the requisite conditions for membrane fusion and the recruitment of the ESCRT complex. These lipids are integral to the process of endocytosis and exosomes release and mediates the interaction between exosomes and receptor cells.[54,55]

Proteins within exosomes can be classified based on their localization: surface proteins, transmembrane proteins, and cytoplasmic proteins. Surface and transmembrane proteins, including antigen presenting molecules such as major histocompatibility complex (MHC),[56] tetraspanins like CD63 and CD81,[57,58] adhesion molecules such as integrin-α,[59] membrane transporters like Rab GTPases,[60] glycoproteins,[61] and signal receptors such as tumor necrosis factor receptors.[62] These proteins are critical for exosome targeting, delivery, recognition, and membrane fusion with recipient cells. Cytoplasmic proteins, including components of the ESCRT machinery (Alix, TSG101), cytoskeletal proteins (actin, tubulin), and cytokines (TNF-α, TGF-β), are implicated in the secretion and biogenesis of exosomes, mediating cargo

https://doi.org/10.2147/IJN.S506221

selection and vesicle release.[41] In addition, exosomes contain heat shock proteins (HSP70, HSP90) families, which protect cells against environment stressors and regulate protein homeostasis and synthesis.[63] Metabolomics analyses have revealed that amino acids and metabolites within exosomes can regulate the immune microenvironment, suggesting roles in autoimmune dysfunction.[62,64] High-throughput metabolomic analysis of urine from SLE patients has identified significantly altered metabolic signals, involving pathways such as propionate metabolism, cysteine-methionine metabolism, and branched-chain amino acid metabolism.[65] Screening for differential exosomal contents can help elucidate the pathological mechanisms of SADs and provide new strategies for non-invasive diagnosis. The intricate composition of exosomes is not only crucial for their biogenesis, cargo sorting, and functional delivery, but also instrumental in their targeting and uptake by recipient cells.

Heterogeneity in Sources of Exosomes

Exosomes, originating from a diversity of cellular sources, are integral to the regulations of metabolic processes in both healthy and diseased states through their involvement in cellular communication. Exosomes released from healthy cells not only mediate intercellular interactions, but also participate in the repair mechanisms of injured tissues and cells. For example, exosomes isolated from various types of stem cells, including bone marrow mesenchymal stem cells (BM-MSCs), adipose-derived mesenchymal stem cells (AD-MSCs), human umbilical cord mesenchymal stem cells (hUC-MSCs), and olfactory ecto-mesenchymal stem cells (OE-MSCs), have been shown to regulate immune cells. Compared to traditional mesenchymal stem cell therapy, mesenchymal stem cell-derived exosomes, as cell-free carriers, offer significant advantages in the treatment of SADs.[29] Neuronally derived exosomes support axon growth, differentiation of neural stem cell into neuronal phenotypes, activation of microglia and astrocytes, and maturation of oligodendrocyte progenitor cells. Collectively, these functions contribute to the restoration of the cellular microenvironment at injury site and facilitate recovery of motor function and neuronal regeneration in spinal cord injury models.[66] Similarly, exosomes from MSCs have therapeutic effects in cardiac pathologies, reducing myocardial infarction size and aiding in the preservation of cardiac function.[67] In the context of metabolic regulation, exosome from brown adipose tissue affect liver-targeted metabolic pathways and promote the energy consumption of hepatic cells, thus improving metabolic dysfunctions induced by a high-fat diet.[68] Exosomes derived from antigen-presenting cells (APCs), including B cells, dendritic cells (DCs), and macrophages, are loaded with tumor antigens and various immune-stimulating molecules. In anti-tumor therapy, these exosomes participate in inducing and activating both innate and adaptive immune responses, further enhancing specific anti-tumor immunity.[69]

However, exosomes secreted in pathological states can exacerbate diseases progression. Cancer cell-derived exosomes not only increase the migration and invasion of cancer cells by affecting the surrounding microenvironment, but also induce angiogenesis and promote immune tolerance, accelerating tumor progression.[70,71] In esophageal squamous cell carcinoma, RNA sequencing of EVs revealed that epithelial cells-derived vesicles predominate in malignant tissues, while in benign tissues, vesicles are predominantly derived from endothelial cells and fibroblasts.[72] The same goes for SADs, circRNA in exosomes released by fibroblast-like synoviocytes in RA can promote disease progression.[73] In membranous nephropathy, albumin increases the content of miR-664a-5p in glomerular epithelial cells. This miRNA is then transferred to podocytes via exosomes, where it induces podocyte apoptosis by disrupting autophagy signaling cascade like HIPK2/Calpain1/GSα.[74] Therefore, tracking and analyzing the genetic origins of exosomes can provide valuable insights into disease diagnostics and therapeutics.

Heterogeneity in Functions of Exosome

Exosomes are key intercellular messengers that regulate a spectrum of cellular pathological and physiological functions. Derived from parental cells, they carry a subset of materials that often reflect the functions of their origin. These vesicles are instrumental in genetic regulation, pro-angiogenesis, immune regulation, aging, cell proliferation, and inflammatory response. Exosomes encapsulate genetic materials and characteristic molecules from their parental cells, which are secreted into the extracellular space through exocytosis. This hereditary content, mirroring the characteristics of the parental cells, interacts with the recipient cells, thereby affecting their functions through proteins, miRNAs, and other

components. Recent research highlights that exosomes secreted by RA fibroblast-like synoviocytes are taken up by osteoblasts, delivering miR-486-5p to target and downregulate Tob1 in osteoblasts, thereby regulating osteoblast differentiation and promoting the repair of RA-induced bone destruction.[75] In addition, exosomes significantly improve endothelial function and promote angiogenesis. Pulmonary arterial hypertension (PAH) is one of the most severe complications of SS. Under PAH condition, exosomes have been shown to release miR-224-5p and miR-361-3p to stabilize endothelial function with the aid of SOX17, a key regulatory factor for vascular homeostasis.[76] Furthermore, neuron-derived exosomes transfer miR-132 to endothelial cells. This interaction targets the eukaryotic elongation factor 2 kinase (EEF2K) to regulate the expression of vascular endothelial cadherin, thereby maintaining vascular integrity.[77]

Exosomes are considered as a new mode of cell communication that initiates and maintains adaptive immunity.[78] The process of antigen presentation, a key step in the activation of both innate and adaptive immune responses, was first discovered in exosomes derived from B lymphocyte by Raposo G in 1996.[79] Subsequent research has revealed that exosomes from DCs contain both MHC class-I and -II molecules, which are essential for antigen presentation.[56,80,81] These DC-derived exosomes, when loaded with tumor-specific peptides on MHC-I, can activate tumor-specific cytotoxic T lymphocytes, thereby inhibiting tumor growth.[82] Exosomes derived from non-professional antigen-presenting cells can also perform antigen presentation and pro-inflammatory functions. Exosomes released by thyroid cells stimulated by the inflammatory cytokine IFN-γ have been shown to carry antigen-presenting molecule MHC-II and key autoimmune-related molecules TPO and HSP60, directly inducing $CD4^+$ T cell-mediated adaptive immune responses and contributing to the pathogenesis of autoimmune thyroiditis.[83] This evidence suggests that the exosome-mediated antigen presentation pathway plays a significant role in the occurrence and development of ADs. Conversely, certain exosomes can also exert immunosuppressive effects, depending on their compositions and cellular origin. For instance, exosomes released from Glioblastoma multiforme have been shown to carry the protein LGALS9 ligand. This protein interacts with the TIM3 receptor on DCs in the cerebrospinal fluid, inhibiting the ability of DCs to recognize, process, and present antigens, ultimately compromising cytotoxic T cell-mediated anti-tumor immune responses.[84] This dual immunomodulatory capacity of exosomes shows their complex role in immune regulation and their potential as therapeutic targets in autoimmune conditions.

The Application of Exosomes in Systemic Autoimmune Diseases

Exosomes are closely linked to SADs. Their role in SADs mainly involves the carriage and transmission of specific genetic materials and immune regulatory molecules, which affect and modulate immune responses. Under pathological conditions, exosomes can serve as biomarkers for SADs (Figure 3) and (Table 1). Significant changes occur in the components of exosomes, such as non-coding RNA (ncRNA) and immune related proteins secreted by immune cells into circulation, providing important support for early diagnosis and reflection of disease activity. While current clinical treatments with hormones and immunosuppressants can alleviate the progression of SADs, cure rate remains very low. Thus, developing new therapeutic methods is urgently needed. Due to their low immunogenicity, high efficiency, and controllability, exosomes show great potential in the treatment of SADs (Table 2).

Exosome and Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a common SAD characterized by the progressive destruction of joint cartilage and bones caused by chronic joint inflammation, resulting in deformities, functional impairments, and even permanent disability.[116] The pathogenesis of RA is influenced by genetics, epigenetics, hormone changes, immune abnormality, and external environmental factors.[15,117] Clinical diagnostic methods for RA mainly include medical history, clinical symptoms and signs, imaging examinations, and laboratory examinations. According to standards established by the European Union Against Rheumatology, the main diagnostic indicators for RA include rheumatoid factor (RF) and anti-citrullinated peptide antibody (ACPA).[118] However, RF and ACPA lack specificity and sensitivity, and 20–25% of seronegative cases do not present with typical antibodies.[119] Consequently, an effective and accurate biomarker is urgently needed for the early diagnosis of RA to reduce rates of misdiagnosis and missed diagnosis.

Epigenetic risk factors are mainly involved in the pathogenesis of RA. Under various physiological conditions, miRNA serve as epigenetic regulator, which is essential in the post transcriptional regulation of immune response and other biological processes.[37,120] Exosomes effectively protect internal miRNAs from degradation, reflecting the stability

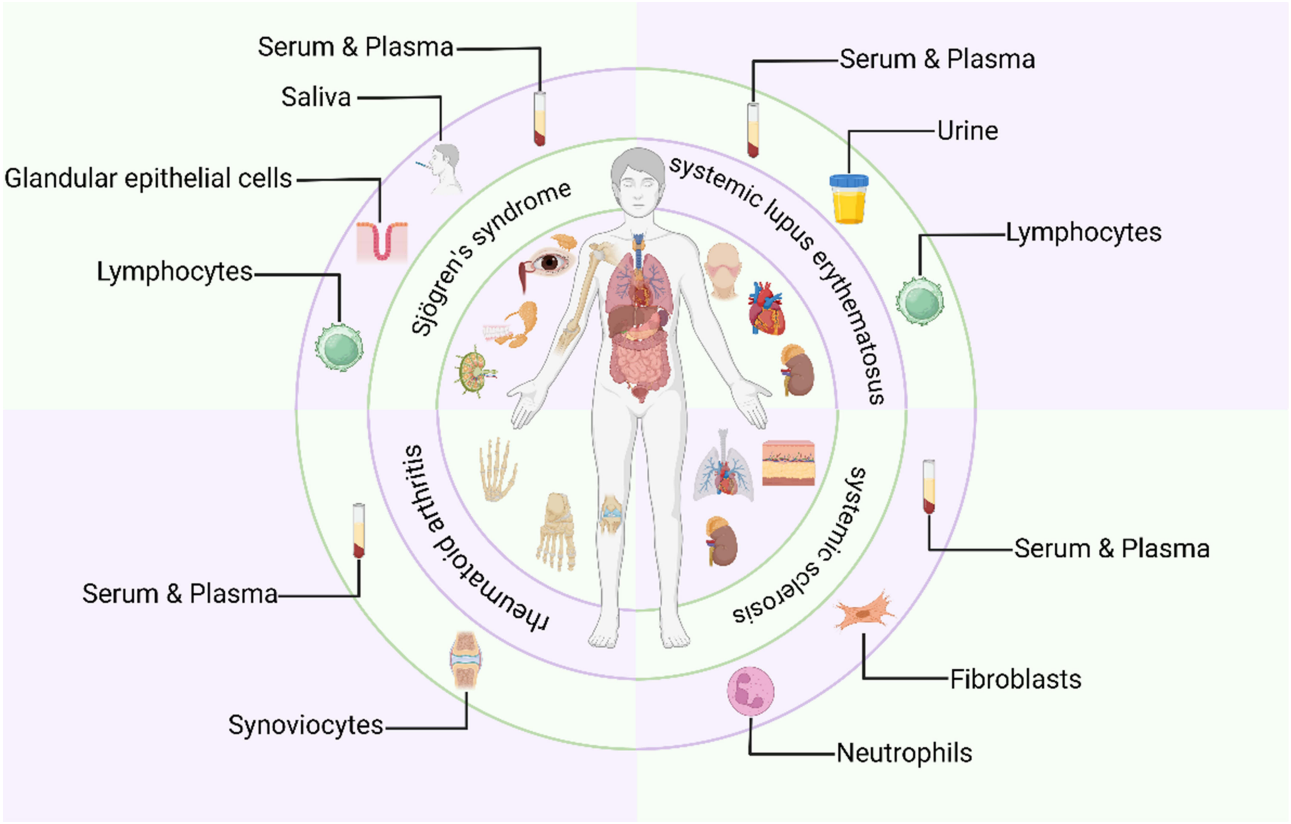

Figure 3 Exosomal roles in organ pathogenesis across four systemic autoimmune diseases. The inner circle represents the primary target organs in rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, and Sjögren's syndrome. The outer circle illustrates the major cellular sources and humoral pathways of exosomes involved in pathophysiological processes for each disease. Created in BioRender. Lv, X (2025) https://BioRender.com/i04t185.

and reliability of exosomal miRNAs.[15] miRNA sequencing has revealed that miR-885-5p, miR-6894-3p, and miR-1268a are significantly upregulated in the serum exosomes of RA patients compared with a healthy control group. Notably, miR-885-5p and miR-6894-3p also show significant expression differences in ACPA-negative RA patients, making them potential biomarkers for this subgroup.[85] RNA microarray analysis has identified significant dysregulation of miR-451a and miR-25-3p in serum exosomes between healthy individuals and early RA patients.[86] Another study found a negative correlation between miRNA-548a-3p in serum exosomes and the severity of RA in patients.[87] These miRNAs mentioned above could facilitate early clinical diagnosis.

Table 1 Exosomes Involved in the Pathogenic Mechanisms of SADs and Their Role as Biomarkers

Disease	Source	Contents	Application	Function	Ref.
RA	Serum	miR-885-5p, miR-6894-3p, miR-1268a	Biomarker	Upregulated in serum exosomes of RA patients	[85]
		miR-451a, miR-25-3p	Biomarker	The combination of miR-451a, miR-25-3p and serum sTWEAK levels outperforms classic ACPA biomarkers in correct diagnosis	[86]
		miR-548a-3p	Biomarker, treatment	Downregulated in serum exosomes of RA patients	[87]
		SNHG6, SNHG31, RPS18P9	Biomarker, treatment	Novel exosomal lncRNAs independently influence clinical indicators related to RA	[88]
	Fibroblast-like synoviocytes	circFTO	Mechanism	Contributes to RA progression by targeting SOX9 in exosomal circFTO derived from Fibroblast-like synoviocytes	[73]

(*Continued*)

Table 1 (Continued).

Disease	Source	Contents	Application	Function	Ref.
SLE	Serum	miR-21, miR-155, miR-146a	Biomarker	Expression of Exosomal miR-21 and miR-155 upregulated, while miR-146a expression downregulated in SLE patients	[89]
		miR-451a	Biomarker, treatment	Downregulated in serum exosomes of SLE patients	[90]
	T cells	BPI	Biomarker	Upregulated in T cells-derived exosomes of SLE patients	[91]
		ECP	Biomarker	Upregulated in T cells-derived exosomes of SLE patients	[92]
LN	Serum	miR-146a	Biomarker	Correlations exist between circulating exosomal miRNA-146a and SLE disease severity	[89]
	Urine	miR-146a	Biomarker	The miR-146a-TRAF6 axis associates with LN renal fibrosis	[93]
		tRF3-Ile-AAT-1, tiRNA5-Lys-CTT-1	Biomarker	Upregulated in urinary exosomes of LN patients	[30]
SSc	Dermal fibroblast	/	Mechanism	Induce macrophage activation in human dermal fibroblast-derived exosomes in SSc	[94]
	Neutrophil	S100A8/A9	Mechanism	The proliferation and migration of HDMECs are possibly inhibited by S100A8/A9 of neutrophil exosomes	[95]
	Serum	ENST00000313807-hsa-miR-29a-3p-*COL1A1* network	Biomarker	The ENST00000313807-hsa-miR-29a-3p-*COL1A1* network in plasma circulating exosomes represents a potential combined biomarker for the clinical diagnosis and treatment of SSc.	[96]
SS	Plasma	Ceruloplasmin, transferrin	Mechanism	Downregulated in plasma exosomes of SS patients	[97]
	Serum	miRNA-127-3p, miRNA-409-3p, miRNA-410-3p, miRNA-541-5p, miRNA-540-5p	Biomarker	Upregulated in serum exosomes of NOD mouse	[98]
	T cell	miR-142-3p	Mechanism	T cell activation may directly impair epithelial cell function through secretion of miRNA-containing exosomes	[99]

Abbreviations: ACPA, anti-citrullinated peptide antibody; BPI, bactericidal/permeability-increasing protein; ECP, eosinophil cationic protein; HDMECs, human dermal microvascular endothelial cells; NOD mouse: a model of early-intermediate SS;

Table 2 Therapeutic Applications of MSCs-Derived Exosomes in SADs

Disease	Source	Contents	Function	Ref.
RA	hUCMSC	miR-451a	Inhibits RA SFs biological traits and improves arthritis in a CIA rat model by inhibiting ATF2	[100]
	OE-MSC	PD-L1	Suppresses the polarization of T follicular helper cells, reduces the differentiation of germinal center B cells into plasma cells, and alleviates synovial inflammation and joint destruction	[101]
	ADSC	Dermatan sulfate	Induces the polarization of M1 macrophage, regulates the M1-M2 balance, and inhibits joint inflammation	[102]
SLE	UC-BSC	miR-19b	Regulates the Th17/Treg cell balance and inflammatory factor expression in SLE patients through miR-19b/KLF13 pathway in UC-BSC exosomes	[103]
	BM-MSC	miR-16, miR-21	Promotes the anti-inflammatory polarization of macrophages in BMMSCs exosomes	[104]
LN	ADSC	miR-20a	Prevents LN development and ameliorates established disease through miR-20a in ADSC transplantation	[105]

(*Continued*)

https://doi.org/10.2147/IJN.S506221

Table 2 (Continued).

Disease	Source	Contents	Function	Ref.
SSc	MSC	miR-29a-3p	Targets and downregulates the expression of pro-fibrotic, remodeling, anti-apoptotic factors, and methyltransferase via the miR-29a-3p of MSCs exosomes	[106]
		miR-196b-5p	Suppresses collagen type I alpha 2 expression through overexpression of miR-196b-5p in fibroblasts	[107]
		/	Improves the therapeutic effect of MSC-EVs preferentially in the lungs of SSc mice with IFNγ-pre-activation	[108]
SS	hUCMSC	/	Exerts an immunomodulatory effect on the CD4 T cells through UCMSC-Exos	[109]
	LGMSC	/	Ameliorates murine SS by modulating the Treg and Th17 cells balance in LGMSCs and their exosomes	[110]
		miR-125b	Attenuates experimental SS by targeting PRDM1 and suppressing plasma cells via LGMSC derived exosomes-mediated miRNA-125b	[111]
	DPSC	/	Revitalizes salivary gland epithelial cell function during SS via the GPER-mediated cAMP/PKA/CREB pathway with DPSC-Exos	[112]
	SHED	/	Promotes saliva secretion by suppressing p-ERK1/2-mediated apoptosis in glandular cells with SHED-exos	[113]
		/	Ameliorates SS-induced hyposalivation by increasing paracellular permeability of glandular epithelial cells through the Akt/GSK-3β/Slug pathway-mediated ZO-1 expression in SHED-exos	[114]
	OE-MSC	IL-6, S100A4	Ameliorates murine SS by modulating myeloid-derived suppressor cells function in OE-MSC-exosomes	[115]

Abbreviations: hUCMSC, human umbilical cord mesenchymal stem cell; OE-MSC, olfactory ecto-mesenchymal stem cell; ADSC, adipose-derived stem cell; UC-BSC, umbilical cord blood mesenchymal stem cell; BM-MSC, bone marrow-derived mesenchymal stem cell; MSC, mesenchymal stromal cell; LGMSC, Labial gland-derived MSCs; DPSC, dental pulp stem cell; SHED, stem cells from human exfoliated deciduous teeth.

In addition to miRNA serving as a biomarker for clinical diagnosis of RA, long non-coding RNA (lncRNA) and mRNA also serve as important markers and therapeutic targets in SADs. The regulation by lncRNAs involves immune response, and the function of lncRNAs specifically expressed in serum exosomes of RA patients relates to cell proliferation, metabolism, and communication. It is notable that inflammation-related markers such as CCL5-mRNA and MPIG6B-mRNA in serum exosomes of RA patients are inversely correlated with RA disease activity.[88,118] Moreover, circRNAs secreted by exosomes also affect the pathological mechanism of RA.[121] For example, the expression of circFTO is increased in exosomes released by fibroblast-like synoviocytes in RA. SOX9, a key transcription factor for cartilage development and regeneration, is targeted by circFTO, which inhibits chondrocyte proliferation, migration, and synthesis metabolism, thus promoting the progression of RA.[73] Both lncRNA and circRNA interact with miRNA, promoting the expression and function of target mRNA, thereby forming a network of lncRNA/circRNA-miRNA-mRNA ceRNAs (competitive endogenous RNA) involved in the pathogenesis of RA.[122]

Beyond their utility as biomarkers, exosomes demonstrate the therapeutic potential for treating RA. MSC transplantation has been shown to mitigate joint inflammation, synovial hyperplasia and bone destruction in RA patients by modulating immune cells like DCs, natural killer cells, and macrophages that are regulated by MSCs.[26,123] Exosomes secreted by MSCs, DCs, and macrophages can also affect the biological functions of immune cells and joint cells, suggesting exosomes may replicate some of the reparative effects of MSC therapy.[116] Human umbilical cord mesenchymal stem cells (hUCMSC)-derived exosomes carry miRNA-451a, which inhibits the proliferation and invasion of synovial fibroblasts by downregulating the expression of ATF2, improving arthritis in a collagen-induced arthritis (CIA) model rats.[100] Exosomes derived from olfactory ectomesenchymal stem cells (OE-MSCs) highly express the immune checkpoint protein PD-L1. PD-L1 downregulates CXCR5 by inhibiting the PI3K/AKT pathway, suppressing the

polarization of T follicular helper cells (Tfh), which in turn reduces the differentiation of germinal center B cells into plasma cells, ultimately alleviating synovial inflammation and joint destruction in the CIA model mice.[101] Furthermore, engineering exosomes as drug delivery carriers have shown promising therapeutic prospects. Exosomes released by anti-inflammatory (M2) macrophages, modified with both oligolysine and matrix metalloproteinase (MMP)-cleavable polyethylene glycol, can remove cell-free DNA (cfDNA) from RA synovial samples, effectively alleviating RA disease activity.[124] Through metabolic glycoengineering and click chemistry techniques, dermatan sulfate (DS) was introduced onto the surface of adipose-derived stem cells (ADSCs), enabling their secreted exosomes (DS-EXOs) to specifically target activated macrophages in inflamed joints. DS-EXOs can also deliver anti-inflammatory miRNAs to regulate the JAK-STAT signaling pathway, thereby inducing the polarization of M1 macrophage, regulating the M1-M2 balance, and inhibiting joint inflammation.[102] Additionally, the delivery of super-repressor IκB (NF-κB inhibitor) via exosome can alleviate joint inflammation and injury in RA.[125] Biomimetic exosomes can also encapsulate and deliver glucocorticoids (GC) directly to inflamed joint tissues, enhancing GC accumulation at the inflammatory site and reducing systemic side effect caused by long-term GC administration.[126] To sum up, these studies demonstrate the potential of exosomes as novel treatments for RA.

Exosomes and Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is an SAD characterized by heterogeneous lesions that can affect multiple organs and tissue throughout the body. The pathological of SLE involves the deposition of immune complexes on vascular wall, which activates complement and immune cells, leading to tissue damage. Symptoms of SLE are complex and vary from person to person, including skin damage, muscle and joint pain, and in severe cases, effects on the blood system, central nervous system, and multiple organs. Cardiovascular complications and lupus nephritis (LN) are the major causes of death in SLE patients.[127] Due to the diversity and high heterogeneity of SLE related autoantibodies, extensive research has been conducted on identification of specific biomarkers, but there is still no definitive biomarker in clinical practice. At the same time, the origins of antigen and pathogenic mechanisms in SLE remain to be fully explored. Serological biomarkers are important for diagnosis and prognosis, and emerging studies suggest that exosomal miRNAs could serve as diagnostic markers and therapeutic targets.[25] The related signaling pathways and proteins targeted by exosomal miRNAs in SLE are expected to elucidate new pathological mechanisms, providing feasible solutions for clinical diagnosis and treatment.

The utility of exosomes as biomarkers for SLE has been increasing validated. SLE is a complex autoimmune condition that can affect multiple organs, with one of its most severe complications being LN, characterized by glomerulonephritis. Currently, the gold standard for diagnosing LN is renal biopsy, an invasive procedure that not only causes trauma to the kidney but also lacks the capability for dynamic monitoring.[30] Exosomes offer a non-invasive alternative for the early diagnosis and monitoring of SLE and LN. Studies have shown that miRNA-21, miRNA-155, and miRNA-451a in serum exosomes correlate positively with disease activity and renal injury in SLE, while miRNA-146a is down-regulated in circulating exosomes of SLE patients.[89,90] However, a study focusing on juvenile proliferative lupus nephritis found that circulating exosomes-derived miRNA-146a is increased and negatively correlates with the pro-inflammatory gene TRAF6 mRNA level.[93] Another study demonstrated that miRNA-146a, enriched in the urinary exosomes of SLE patients, ameliorates the inflammatory response of podocytes by inhibiting the IRAK1/TRAF6/LPS inflammatory pathway.[128] In the diagnosis of renal inflammatory diseases, urine testing is superior to blood testing. In addition to miRNA, small non-coding RNAs derived from tRNA (tsRNAs) in urinary exosomes also serve as non-invasive biomarkers for diagnosing LN. The levels of tRF3-lle-AAT-1 and tiRNA5-Lys-CTT-1 in urinary exosomes are upregulated compared to those in SLE patients without LN, and their expression levels increase with disease activity.[30] T cells, by inducing autoantibody production and inflammatory response, promote the progression of SAD. Research has shown that the expression of bactericidal/permeability-increasing protein (BPI) and eosinophil cationic protein (ECP) is increased in exosomes secreted by T cells in SLE patients. Overexpression of BPI in T cells induces inflammation by inhibiting Treg and releasing exosomes containing BPI. These exosomes can target multiple tissues, induce serum IL-1β, and promote autoimmune reactions.[91] Similarly, T cell-derived exosomes containing ECP can induce arthritis, hepatitis, and nephritis in mice by inducing T cell overactivation and pro-inflammatory cytokine production.[92] Thus, exosomes in

the blood circulation not only serve as biomarkers for diagnosing SLE, but the detection of exosomes in urine also provides a more convenient and effective non-invasive approach for assessing disease activity and prognosis.

Exosomes derived from mesenchymal stem cells exhibit potential therapeutic effects on SLE.[29] Exosomes from umbilical cord blood mesenchymal stem cells (UC-BSCs) possess immunomodulatory functions. These exosomes target the KLF13 gene by increasing miR-19b expression, which balance Th17/Treg cell ratios in SLE patients and inhibit the production of inflammatory cytokines. Th17 and Treg cell are associated with the secretion of inflammatory cytokines, and regulating these cells helps manage inflammation in SLE patients.[103] Exosomes from bone marrow mesenchymal stem cells (BM-MSCs) promote macrophage polarization by delivering miR-16 and miR-21, which efficiently clear apoptotic debris and inducing Treg cell recruitment, counteracting the pro-inflammatory effects of Th17 cells and alleviating inflammatory response in SLE.[104] Moreover, exosomes overexpressing miR-20a from adipose-derived mesenchymal stem cells (miR-20a-ADSCs) increase autophagy levels by targeting the mTOR pathway, which is associated with autophagy. This mechanism reduces podocytes damage, thereby achieving therapeutic effects in LN patients.[105] Exosomes derived from macrophages also show potential as therapeutic targets for LN. In LN patients, the level of miR-181d-5p in exosomes secreted by M0 macrophages is increased. This miRNA targets BCL-2 to promote the inflammatory response and proptosis in human renal mesangial cells. Inhibiting miR-181d-5p in these exosomes can effectively reverse these effects and alleviate renal injury in LN patients.[129] Furthermore, a genetically engineered exosome specifically designed to express CD40 can influence B cell activation. Loading mycophenolate mofetil into CD40-expressing exosomes has been shown to effectively alleviate the autoimmune response in SLE and LN.[130] Overall, exosomes carried by mesenchymal stem cells and immune cells play a beneficial role in modulating the inflammatory response and improving prognosis in SLE and LN patients.

Exosome and Systemic Sclerosis

Systemic sclerosis (SSc), also known as scleroderma, is a rare and highly fatal autoimmune connective tissue disease. The primary pathogenesis of SSc involves vasculopathy and immune system disturbance, which ultimately leads to progressive fibrosis of the skin and internal organs.[131] This condition mainly affects the skin, lungs, kidneys, gastrointestinal tract[132,133] with the causes of death including interstitial lung disease, pulmonary hypertension, renal crisis, and heart disease.[133] Autoantibody profile can predict the extent of organ involvement and disease progression in SSc. Serological testing reveals that 95% of SSc patients exhibit nonspecific positive antinuclear antibodies. In addition, patients with different clinical manifestations show specific autoantibodies related to SSc, such as anti-centromere antibody (ACA), anti-topoisomerase 1 (anti-SCL70), anti-RNA polymerase (RNAP), anti-U1 ribonucleoprotein, and anti-U3 ribonucleoprotein. These autoantibodies help to predict early organ involvement and risk stratification. However, these specific antibodies are not present in every SSc patient, and those with negative SSc-specific autoantibodies often experience rapid disease progression and higher mortality rates.[132–135] Besides autoantibodies, some traditional biomarkers have prognostic value. For example, elevated levels of C-reactive protein in SSc patients are associated with the severity of lung, skin, and joint involvement.[132,136] Most SSc patients exhibit increased expression and activation of type 1 interferon regulatory genes, which can be used to determine the severity of organ lesion and predict immune therapy response.[137] However, such biomarkers lack specificity and cannot provide more precise therapeutic targets for clinical diagnosis and treatment. There remains a significant need for effective treatment of SSc, as symptomatic treatment and immunosuppressive drugs have shown limited success in improving patient survival rates.[138,139]

Similar to other SADs, exosomes have been shown to fulfill a role in the pathogenesis of SSc, including immune response, vascular inflammation, and fibrosis.[140] Recent studies have highlighted the pivotal role of different cell-derived exosomes in SSc pathogenesis. For instance, exosomes from dermal fibroblasts in SSc patients activate macrophages, inducing pro-fibrotic and inflammatory cytokine responses via internalization by macrophages. These activated macrophages, in turn, activate the production of collagen and fibronectin in fibroblasts, promoting inflammation and fibrosis of SSc skin through exosomes.[94] Proteomic analysis has made significant progress in identifying SSc biomarkers in the serum of SSc patients.[141,142] Exosomes serve as carriers of pro-fibrotic signals.[143] Aptamer proteomics analysis on serum exosomes from patients with antinuclear antibodies (ANA) positive and primary Raynaud's phenomenon has revealed differential proteins related to inflammation and immunity, such as apolipoprotein A-1, mannose-binding protein, and BPI. These proteins may be closely related to the pathogenesis of SSc and have potential as early biomarkers for monitoring high-risk patients transitioning from ANA positive and Raynaud's phenomenon to SSc.[144] Previous studies

have shown that exosomes promote angiogenesis.[77] However, in the pathological process of fibrosis and inflammation in SSc patients, exosomes released by neutrophils have an inhibitory effect on angiogenesis. The levels of S100A8/A9 located on the vesicle surface are higher in SSc patients than in the healthy population. S100A8 and S100A9 are calcium binding proteins, mainly present in the form of heterodimeric complexes of S100A8/A9. Early studies have elucidated that the S100A8/A9 complex induces endothelial cell apoptosis and necrosis, leading to endothelial damage in vasculitis and other inflammatory diseases.[145] Neutrophil exosomes in SSc patients inhibit the proliferation and migration of endothelial cells by carrying S100A8/A9.[95] Apart from destructive proteins, a systematic analysis of gene expression profiles of miRNA and lncRNA in exosomes from peripheral blood neutrophils in SSc patients has identified abnormal signaling pathways, including Wnt, AMPK, IL-23, and NOTCH signaling pathways.[146] Similarly, constructing an lncRNA-miRNA-mRNA network in circulating exosomes can also aid in early clinical diagnosis of SSc. For example, the ENST000000313807-has-miR-29a-3p-COL1A1 network is a promising united biomarkers for the clinical diagnosis and treatment of SSc.[96] These dysregulated gene pairs are potential biomarkers and therapeutic targets for SSc.

SSc has a high mortality rate. For multi organ fibrosis, clinical practice currently relies on palliative symptomatic support combined with immunosuppressive therapy. High risk patients meeting strict conditions may undergo organ transplantation or hematopoietic stem cell transplantation, but these procedures carry the risk of serious side effects.[147,148] MSC-based therapy has shown therapeutic effects in SSc animal models.[149] Specifically, MSCs regulate fibrosis in SSc by releasing exosomes. The miR-29a-3p in exosomes of MSCs targets and downregulates the expression of pro-fibrotic, remodeling, anti-apoptotic factors, and methyltransferase.[106] Coincidentally, miR-196b-5p inhibit type I collagen and TGF-β levels.[107] These studies suggest that MSC-derived exosomes carry abundant anti-fibrotic miRNAs that regulate organ fibrosis through multiple pathways. Interestingly, IFNγ pre-activation can improve MSC-EVs-based therapy. Pretreating MSCs with IFNγ generates small size EVs (ssEVs) enriched in exosomes and large size EVs (lsEVs) enriched in microvesicles. Among them, ssEVs enriched in exosomes exhibit functions including the upregulation of anti-inflammatory factors (such as iNOS, IL-1ra and IL-6), improvement of pulmonary fibrosis, remodeling, and serving as inflammatory markers in SSc animal models.[108] As carriers of cellular information, exosomes from dermal fibroblasts in SSc patients interfere between fibroblasts and macrophages, leading to sustained macrophages activation, promoting fibrosis and inflammation, and activating fibroblasts causing skin fibrosis.[94] From the perspective of pathological mechanisms, exosomes mediating the mutual activation of fibroblasts and immunocytes may be potential therapeutic targets for alleviating fibrosis.

Exosomes and Sjögren's Syndrome

Sjögren's syndrome (SS) is an SAD characterized by lymphocyte infiltration into exocrine glands such as the lacrimal and salivary glands.[150,151] Women account for 90% of diagnosed cases. SS is divided into primary and secondary types: primary SS (pSS) only affects exocrine glands, while secondary SS (sSS) often occur after autoimmune diseases such as RA and SLE. The clinical manifestations of SS mainly include dry eyes and dry mouth, which can occur from mild to severe symptoms. Severe cases can lead to a decreased quality of life and a high risk of complications such as malignant lymphoma.[150,152] The pathogenesis of SS results from the interaction between genetic susceptibility and environmental triggers leading to autoimmune reactions.[153,154] Exocrine gland epithelial cells (EGECs) directly participate in the enhancement of the innate immune system in pSS and are also targets of autoimmune responses.[154] Although SS patients accounts for only 0.06% of the world's population,[155] the subtle onset of the disease and the lack of specificity of typical symptoms such as dry eyes and dry mouth often lead to doctors overlooking potential SS cases. In addition, there is no reliable screening method to identify "ordinary" patients who need clinical evaluation for SS, resulting in a high rate of missed diagnosis in clinical practice.[150,155]

According to the diagnostic criteria for pSS established by the American College of Rheumatology/European League Against Rheumatism in 2016,[156] the scoring items include a biopsy of labial salivary gland, detection of autoantibodies (anti-SSA/SSB), ocular staining score, Schirmer's test, and saliva flow rate. However, saliva flow rate and ocular condition examinations are often overlooked by dentists and ophthalmologists due to their time-consuming nature and limited use.[157] The sensitivity of autoantibody-related serological markers is poor, and they may not be detected in the early stages of the disease.[158] Although a lip gland biopsy is considered the gold standard for SS diagnosis, it is invasive, and patients often experience more severe symptoms when abnormalities are detected.[156] Thus, there is an urgent need for non-invasive, sensitive, and specific diagnostic tools for the early detection of SS to reduce the number of patients

who experience delays due to missed diagnoses. In 2005, autoantibodies such as anti-SSA, anti-SSB, and Sm were first detected in exosomes derived from salivary gland epithelial cells (SGECs), revealing the pathway through which exosomes participate in the presentation of intracellular self-antigens to autoreactive lymphocytes in the immune system.[159] Subsequently, through the detection of exosome contents in saliva and plasma, an increasing number of differential miRNAs and proteins have been identified,[98,160,161] providing evidence for the exploration of the pathogenesis of SS. In addition, microRNAs in saliva and plasma exosomes have also become the most promising specific markers for the early detection of SS.

Plasma exosomes contain molecular information that can reflect the pathological state of primitive cells, making them valuable for studying the pathogenesis of diseases.[33] Proteomic analysis of plasma exosomes from patients with pSS revealed differentially expressed proteins (DEPs) associated with ferroptosis processes and signaling pathways, mainly including ceruloplasmin (CP) and transferrin (TF).[97] Ferroptosis is a novel cell death process caused by iron-dependent lipid peroxidation, distinct from programmed cell death.[162] Further research found that plasma exosomes containing ferroptosis-related DEPs may be related from diseased SGECs, suggesting a potential mechanism of ferroptosis damaging SGECs in pSS patients. Notably, compared to healthy participants, there is no significant difference in the expression levels of CP and TF in the plasma of patients with pSS, sSS, and non-autoimmune sicca syndrome (nSS). This suggests that the changes in ferroptosis-related proteins content in exosomes are more indicative of the pathological state of SGECs than in plasma, highlighting the advantages of exosomes as biomarkers.[97] In a study using traditional Chinese medicine (Modified Zengye Decoction, MZD) to treat pSS, 12 down-regulated DEPs were identified through proteomic analysis of plasma exosomes before and after treatment. Gene Ontology (GO) analysis found that these DEPs were mainly involved in insulin response, infection-related Gram-negative bacteria, and protein-polysaccharide binding defense responses. Kyoto Encyclopedia of Genes (KEGG) enrichment analysis showed that down-regulated DEPs were mainly involved in porphyrin metabolism, NF-κB and TLR4 pathways, elucidating the mechanism of action of MZD in treating SS from the perspective of exosomes.[163] circRNA and miRNA in plasma exosomes from patients with pSS have also been confirmed as diagnostic biomarkers.[98,164] Compared to non-pSS subjects, the expression of circ-IQGAP2 and circ-ZC3H6 in plasma exosomes from SS subjects was significantly increased. The expression levels of circ-IQGAP2 and circ-ZC3H6 are significantly correlated with serum IgG levels and focus score. Notably, one of the target miRNAs of circ-IQGAP2 is has-miR-142-3p. Studies have found that has-miR-142-3p expression is abnormal in $CD4^+$ T cells from SLE and multiple sclerosis patients, suggesting that has-miR-142-3p may play a key role in mediating autoimmune activity.[165,166] Recent studies have revealed that miR-142-3p in T cell exosomes is involved in the immunopathogenesis of SS. Adenoid inflammation causes activated T cells to secrete exosomes containing miR-142-3p, which are then taken up by SGECs. miR-142-3p targets intracellular Ca^{2+} signaling pathways and inhibits cAMP production, reducing protein production in salivary gland cells, ultimately damaging the function of gland epithelial cells.[99] Similarly, changes in the levels of some miRNAs in serum exosomes are expected to predict the state of the disease. For instance, differentially expressed miR-127-3p, miR-329-5p, miR-409-3p, miR-410-3p, and miR-541-5p have been screened from serum exosomes of NOD mice (an animal model of SS clinical stage).[98] However, further research is needed to determine the potential mechanisms of these differentially expressed miRNAs in the dysregulation of inflammatory pathways and the pathogenesis of SS in human cohorts, while evaluating their potential as biomarkers for SS and exploring their utility in monitoring disease progression.

Exosomes are also extensively studied as a potential therapy for SS.[151] Among them, exosomes derived from stem cells are the most widely researched for the treatment of SS. Exosomes from human umbilical cord mesenchymal stem cells (UCMSC-Exos) have immunomodulatory effects on $CD4^+$ T cells. UCMSC-Exos regulate the over-proliferation and apoptosis of $CD4^+$ T cells through the autophagy pathway, inhibit the differentiation of Th17 cells, and increase the proportion of Treg cells, thereby restoring the Th17/Treg balance in patients with pSS.[109] Similar to the effects of UCMSC-Exos, exosomes derived from labial gland mesenchymal stem cells (LGMSC-Exos) also play a positive role in balancing Th17/Treg cells and reducing inflammatory infiltration in the salivary glands of NOD mice.[110] LGMSC-Exos exert regulatory effects on B cell subsets of NOD mice, significantly reducing the proportion of CD19CD20CD27CD38 plasma cells in peripheral blood mononuclear cells. Further research found that miR-125b within LGMSC-Exos inhibits plasma cell differentiation in pSS by directly binding to the target gene PRDM1 (PR domain zinc finger protein 1).[111]

Exosomes derived from dental pulp stem cells (DPSC-Exos) have anti-inflammatory, antioxidant, immunomodulatory, and tissue function restoration effects. DPSC-Exos restore the function of SGECs in SS patients by regulating the GPER-mediated cAMP/PKA/CREB pathway, which in NOD mice manifests as increased saliva flow, reduced gland inflammation, and increased AQP5 expression.[112] Exosomes obtained from stem cells of human exfoliated deciduous teeth (SHED-Exos) improve the paracellular permeability of glandular epithelial cells mediated by ZO-1 through the Akt/GSK-3β/Slug pathway, and can inhibit inflammation-induced apoptosis of SGECs by suppressing the p-ERK1/2 activation pathway, thereby increasing saliva secretion.[113,114] Intravenous injection of olfactory epithelial-derived mesenchymal stem cell exosomes (OE-MSC-Exos) can restore the immune suppressive function of myeloid-derived suppressor cells (MDSCs), and inhibit Tfh cell differentiation and autoantibody production through high PD-L1 expression, significantly alleviating the disease progression of mice with experimental Sjögren's syndrome.[115] MSC-Exos are more safe, stable, and convenient for transportation and storage than MSCs themselves, considering their small size and low immunogenicity. The clinical treatment of SS currently mainly includes local treatment, systemic treatment, and biological therapy.[167] Local treatment focuses on relieving dry eyes and dry mouth, while systemic treatment involves the administration of immunomodulators and immunosuppressants, though these drugs have unavoidable side effects. Several biological agents are being explored for targeted treatment of SS. Based on the existing research, exosomes derived from various stem cells become one of the most promising therapeutic approaches for SS.

Summary and Prospect

Exosome have demonstrated considerable potential in the diagnosis and treatment of SADs, particularly as biomarkers,[20] drug delivery carriers,[168,169] and immunotherapy targets.[26,29] While recent reviews have extensively explored the role of exosomes in cancer,[69,170–172] cardiovascular diseases,[173,174] and neurological disorders,[175,176] the specific mechanisms through which exosomes contribute to systemic autoimmune pathology remain less examined. Unlike cancer-focused studies that primarily investigate tumor-derived exosomes and their role in promoting immune responses within the tumor microenvironment, exosomes in SADs function through fundamentally different immunological pathways. While cancer involves immune suppression, SADs feature an overactive immune system with distinct exosome-mediated pathways involving immune dysregulation, aberrant antigen presentation, and inflammatory cascade amplification. Beyond their role in disease pathogenesis, exosomes hold promise as therapeutic agent in autoimmunity. In particular, engineered exosomes derived from MSCs and immune cells offer precision-based alternatives to conventional broad-spectrum immunosuppressants. This therapeutic approach addresses a critical need in autoimmune diseases management, which has not been systematically examined in previous reviews. Although the clinical application of exosomes in SADs remains in early stages and no completed clinical trials have been reported, the review of current evidence provides a specialized framework that contextualizes their emerging relevance in SADs.

Exosomes mediate various pathological processes associated with SADs, including genetic regulation, inflammatory response, immune response, apoptosis, and autophagy. Their functions as intercellular communication vehicles enable the targeted delivery of aberrantly expressed biomolecules, leading to the occurrence and development of SADs. In terms of diagnostic potential, exosome, particular those containing differentially expressed miRNAs and proteins, offer significant advantages over conventional diagnostic methods. The differential expression of specific substances in exosomes derived from various body fluids, such as plasma, urine, and saliva, provides a non-invasive and highly sensitive approach of disease diagnosis and monitoring. Moreover, their ability to accurately reflect the pathological state of SADs enhances their diagnostic precision, positioning exosome as promising candidates for early disease detection, monitoring, and the development of personalized therapeutic strategies (Figure 4).

From a therapeutic perspective, exosomes offer unique advantages over traditional immunosuppressants, which exert broad-spectrum effects on the entire body. Unlike conventional treatments, exosomes can selectively target specific cells and tissues, providing more precise and manageable therapeutic options (Figure 4). Notably, exosomes are particularly effective as highly delivery vehicles for miRNAs due to their low toxicity, weak immunogenicity, and enhanced permeability. The lipid bilayer membrane of exosomes protects miRNAs, ensuring their stability and reducing susceptibility to enzymatic degradation. Exosomes derived from immune cells and MSCs offer additional therapeutic potential for SADs. MSCs are well known for their anti-inflammatory properties, tissue repair capabilities, and immunomodulatory

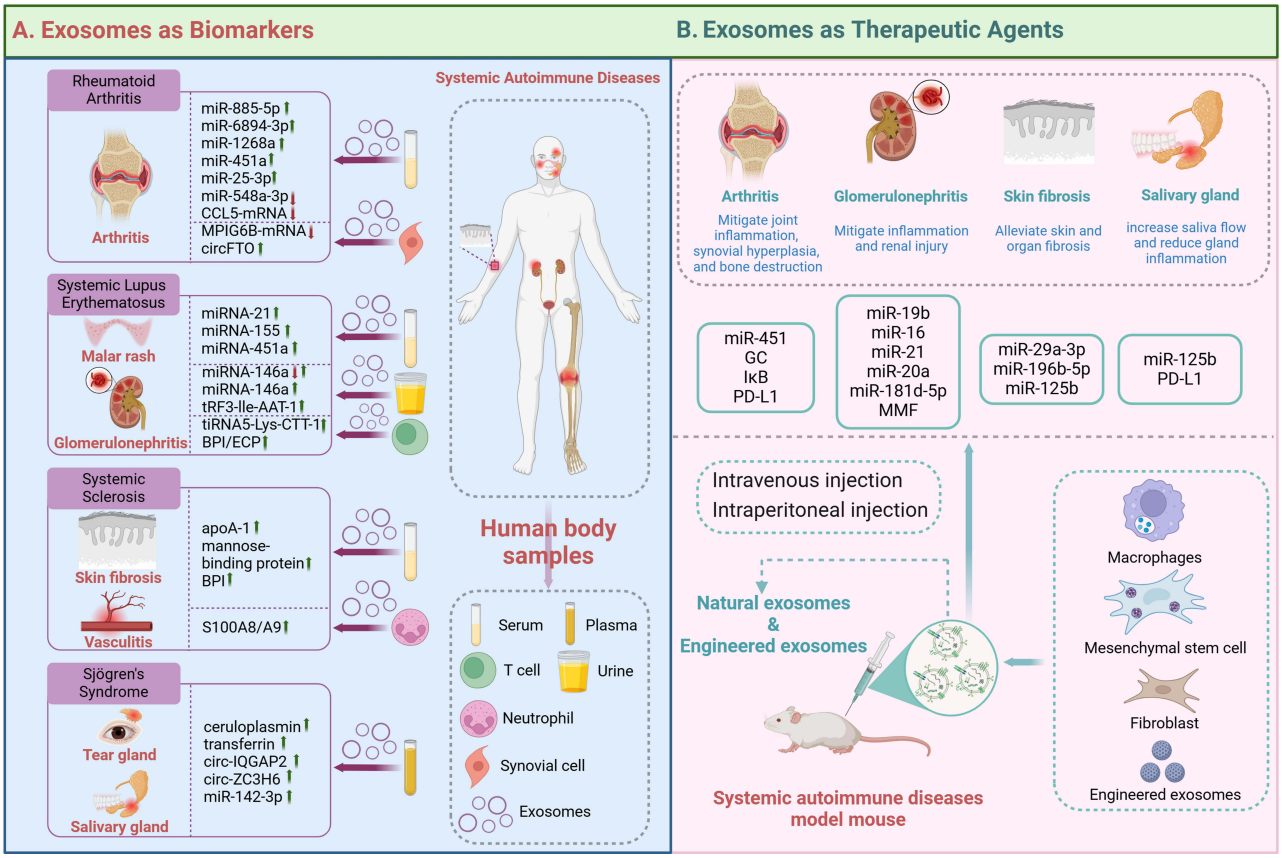

Figure 4 Overview of the role of exosomes in SADs. (**A**) Diagnostic applications: Exosome isolated from various body fluids including serum, plasma, and urine, as well as cellular sources such as neutrophils, macrophages, and synovial cells in patients with rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, and Sjögren's syndrome exhibit differentially expressed molecular components. These distinct exosomal components contribute to disease pathogenesis and represent potential as biomarkers that may facilitate more accurate and earlier disease diagnosis. (**B**) Therapeutic applications: In mouse model of SADs, exosomes derived from various cellular sources, including stem cells, macrophages, fibroblasts, and engineered exosomes are administered through intravenous or intraperitoneal injection. These natural or engineered exosomes, loaded with specific miRNAs or therapeutic agents, demonstrate efficacy in alleviating disease manifestations and slowing disease progression in experimental models, suggesting promising translational potential for exosome-based therapies in clinical applications. Created in BioRender. Lv, X (2025) https://BioRender.com/p10s133.

effects, making them highly suitable for SADs treatment. Compared to MSCs, MSC-Exos provide several advantages, including fewer side effects, a non-immunogenic nature, and easier storage and transport feasibility due to their cell-free composition. These features make MSC-Exos as a potentially more practical therapeutic strategy for SADs. Research has demonstrated that MSC-Exos can significantly alleviate disease symptoms and slow disease progression. Beyond MSCs, exosomes secreted by immune cells such as macrophages, T cells, and DCs are also involved in the pathophysiological of SADs. These immune cell-derived exosomes can exacerbate inflammatory responses, making them as potential targets for therapeutic interventions. Strategic modification of their secretion patterns, molecular composition, or biological activity may offer novel approaches for mitigating the inflammatory processes associated with SADs.

Through genetic engineering and chemical modification,[177] engineered exosomes offer an opportunity to enhance exosome targeting capabilities and prolong circulation half-life. Compared to conventional exogenous nanocarriers such as liposomes, solid lipid nanoparticles, dendritic polymers, and inorganic materials, engineered exosomes are emerging as one of the most promising drug delivery vehicles due to their high bioavailability, low toxicity, drug-protective effects, and precise targeting capabilities.[172] The therapeutic potential of engineering exosome in SADs largely stem from their efficient drug-loading capacity and their unique interaction with immune cells. By purifying naturally isolated exosomes from bodily fluids, loading them with therapeutic agents, and modifying their surface properties to enhance targeting specificity, engineered exosomes can deliver therapeutic payloads more efficiently to affected tissue.[17] This targeted approach represents a significant advancement over conventional immunosuppressive therapies, potentially reducing systemic side effects while improving therapeutic outcomes in SADs.

One area of active research is exosomal PD-L1, an immune checkpoint protein that inhibits T cell activation through the PD-L1/PD-1 signaling pathway. PD-L1 expressing exosomes protect tumor cells from immune surveillance, promoting tumor progression. Studies have shown that tumor-derived exosomes carrying PD-L1 contribute significantly to angiogenesis, tumor formation, migration, and immune evasion.[170,178,179] Beyond tumor cells, exosomal PD-L1 may also originate from immune cells such as macrophages, DCs, and MDSCs. Given its significant role in immune regulation and homeostasis, exosomal PD-L1presents a new perspective for the diagnosis and treatment of SADs. A notable study developed PD-L1 high-expressing EVs from bone marrow MSCs through lentiviral transfection and applied them to mouse autoimmune disease models of ulcerative colitis and psoriasis. The results revealed that these MSC-EVs effectively targeted inflammatory sites, reshaping the local immune microenvironment via the PD-L1/PD-1 pathway. This interaction modulated immune cell function and alleviated symptoms of SADs,[180] highlighting the therapeutic potential of exosomal PD-L1/PD-1 in treating SADs. However, it is important to consider the dual role of exosomal PD-L1 in immune regulation. Due to its co-stimulatory effects on immune cells, targeting tumor-derived exosomal PD-L1 may inadvertently increase the risk of SADs.[181] Similarly, when exploring exosomal PD-L1-based immunotherapy for SADs, potential effects on the tumor microenvironment and associated cancer risks must be carefully evaluated. The complex interplay between exosomal immune checkpoints within both immunoregulatory and tumor microenvironments necessitates further in-depth, multi-layered research to fully elucidate their therapeutic potential and associated risks.

Despite significant progress, major hurdles remain in the clinical translation of exosome-based therapies. The application of exosomal miRNAs as biomarkers for SADs is still limited by challenges in exosome isolation and purification technologies. Current methods, including ultracentrifugation, ultrafiltration, precipitation, density gradient centrifugation, immunomagnetic bead separation, and size-exclusion chromatography, struggle to achieve both high yield and high purity.[17,182] For instance, while ultracentrifugation can isolate a large quantity of exosomes, it has low extraction efficiency and often results in contamination with impurities that interfere with miRNA detection. Similarly, size-exclusion chromatography can compromise the integrity of exosomal membranes. Moreover, these techniques require complex instrumentation, are costly, and lack standardized protocols, further restricting their clinical applicability. Correspondingly, the clinical translation of MSC is still in the early exploratory stages. MSC-Exos derived from different tissues sources, including bone marrow, adipose, umbilical cord, exhibit significant variations in their miRNA and protein profiles, leading to inconsistent therapeutic effects. Additionally, MSC-Exos regulate multiple pathways, including Th17/Treg balance, macrophage polarization, and B cell activation, making it difficult to determine the predominant mechanism of action. The specific immune regulatory pathways influenced by the miRNAs, proteins, and other bioactive cargoes within MSC-Exos remain unclear. One of the primary challenges lies in purifying exosomes in bulk from stem cells while maintaining homogeneity. Although various methods exist for loading immunosuppressive drugs or miRNAs into exosomes, the complexity of exosome preparation, along with issues related to storage, transport, and stability, continues to pose significant obstacles. Moreover, SADs often affect multiple organ systems, and the specificity of target organ microenvironment, as well as the diversity of MSCs sources, must be considered when selecting appropriate carriers and packaging for exosome formulations. Another major challenge is the short biological half-life of exosomes following systemic administration, as they tend to accumulate in the liver and spleen, leading to rapid clearance.[183] Despite these challenges, advance in the development of engineered exosomes hold great promise. To facilitate clinical translation, there is an urgent need to establish standardized exosome preparation protocols, optimize drug-loading strategies, and develop robust evolution systems to assess key parameters such as drug-loading capacity, release kinetics, pharmacokinetics, tissue distribution, and half-life in vivo. More importantly, comprehensive safety assessments of exosome-based formulations are necessary to ensure their clinical viability. Given the technical limitations, high costs, lack of standardized exosome preparation strategies, and unresolved safety and stability concerns, both endogenous exosome-targeted therapies and exogenous exosome infusion remain in the early stages of research. Although the growing body of research highlights the therapeutic potential of exosomes, most studies are currently limited to small-scale animal experiments. Larger-scale investigations are needed to advance exosome-based drug formulations for clinical application.

The pathogenesis of SADs is often influenced by a combination of genetic and environmental factors, with emerging evidence suggesting that ethnicity, gender, and aging may modulate exosome cargo levels.[184] Further research is needed to elucidate how these variables impact exosomal composition and function in the context of SADs. In the future, screening for SAD-related biomarkers in circulating exosomes or other body fluids from susceptible populations could facilitate early

disease detection, risk assessment, and preventive interventions in high-risk populations. In conclusion, while exosome-based therapies for SADs hold immense promise, overcoming technical and logistical barriers is essential for their successful clinical implementation. Continued research and well-designed clinical trials will be crucial in refining exosome-based drug delivery systems and optimizing their therapeutic applications for SADs. At present, no clinical trials have been conducted specifically investigating exosomes-based therapies for SADs. However, clinical studies in the field of medical aesthetics have explored the use of exosome-containing solutions derived from human adipose tissue stem cells for applications such as skin rejuvenation and acne scar treatment.[185] These investigations provide a foundational framework that may pave the way for future exosome-based therapeutic strategies for SADs. Regarding the use of exosome as biomarkers, although they are not yet integrated into routine clinical diagnostics, numerous studies analyzing exosome content in clinical patient samples and healthy individuals indicate their potential for disease monitoring and prognostic evaluation. Further validation through large-scale clinical studies will be necessary to establish standardized protocols for exosome-based biomarkers detection and to facilitate their eventual clinical implementation.

Acknowledgments

This work was supported by the National Natural Science Foundation of China (Grant No. 82171871), the Youth Fund Project of the Jiangsu Province Basic Research Program (Natural Science Foundation) (Grant No. BK20230488), and the Priority Academic Program Development of Jiangsu Higher Education Institutions (PAPD).

Disclosure

The authors declare no conflicts of interest in this work.

References

1. Pisetsky DS. Pathogenesis of autoimmune disease. *Nat Rev Nephrol*. 2023;19(8):509–524. doi:10.1038/s41581-023-00720-1
2. Aloi N, Drago G, Ruggieri S, Cibella F, Colombo P, Longo V. Extracellular vesicles and immunity: at the crossroads of cell communication. *Int J Mol Sci*. 2024;25(2):1205. doi:10.3390/IJMS25021205
3. Shakerian L, Kolahdooz H, Garousi M, et al. IL-33/ST2 axis in autoimmune disease. *Cytokine*. 2022;158:156015. doi:10.1016/J.CYTO.2022.156015.
4. Wen X, Li B. A population-based study on autoimmune disease. *Lancet*. 2023;401(10391):1829–1831. doi:10.1016/S0140-6736(23)00621-9
5. Zhao Q, Chen G. Role of IL-33 and its receptor in T cell-mediated autoimmune diseases. *Biomed Res Int*. 2014;2014:587376. doi:10.1155/2014/587376.
6. Bieber K, Hundt JE, Yu X, et al. Autoimmune pre-disease. *Autoimmun Rev*. 2023;22(2):103236. doi:10.1016/J.AUTREV.2022.103236
7. Conrad N, Misra S, Verbakel JY, et al. Incidence, prevalence, and co-occurrence of autoimmune disorders over time and by age, sex, and socioeconomic status: a population-based cohort study of 22 million individuals in the UK. *Lancet*. 2023;401(10391):1878–1890. doi:10.1016/S0140-6736(23)00457-9
8. Harroud A, Hafler DA. Common genetic factors among autoimmune diseases. *Science*. 2023;380(6644):485–90. doi:10.1126/SCIENCE.ADG2992
9. Gupta A, Weinand K, Nathan A, et al. Dynamic regulatory elements in single-cell multimodal data implicate key immune cell states enriched for autoimmune disease heritability. *Nat Genet*. 2023;55(12):2200–2210. doi:10.1038/S41588-023-01577-7
10. Saurabh R, Fouodo CJK, König IR, Busch H, Wohlers I. A survey of genome-wide association studies, polygenic scores and UK Biobank highlights resources for autoimmune disease genetics. *Front Immunol*. 2022;13:972107. doi:10.3389/FIMMU.2022.972107/PDF
11. Lin J, Zhou J, Xu Y. Potential drug targets for multiple sclerosis identified through Mendelian randomization analysis. *Brain*. 2023;146(8):3364–3372. doi:10.1093/BRAIN/AWAD070
12. Ellinghaus D. How genetic risk contributes to autoimmune liver disease. *Semin Immunopathol*. 2022;44(4):397–410. doi:10.1007/S00281-022-00950-8
13. Cordell HJ, Fryett JJ, Ueno K, et al. An international genome-wide meta-analysis of primary biliary cholangitis: novel risk loci and candidate drugs. *J Hepatol*. 2021;75(3):572–581. doi:10.1016/J.JHEP.2021.04.055
14. Yang S, Zhao M, Jia S. Macrophage: key player in the pathogenesis of autoimmune diseases. *Front Immunol*. 2023;14:1080310. doi:10.3389/FIMMU.2023.1080310/PDF
15. Zakeri Z, Salmaninejad A, Hosseini N, et al. MicroRNA and exosome: key players in rheumatoid arthritis. *J Cell Biochem*. 2019;120(7):10930–10944. doi:10.1002/JCB.28499
16. Veerman RE, Güçlüler Akpinar G, Eldh M, Gabrielsson S. Immune cell-derived extracellular vesicles - functions and therapeutic applications. *Trends Mol Med*. 2019;25(5):382–394. doi:10.1016/J.MOLMED.2019.02.003
17. Chen Z, Xiong M, Tian J, Song D, Duan S, Zhang L. Encapsulation and assessment of therapeutic cargo in engineered exosomes: a systematic review. *J Nanobiotechnol*. 2024;22(1):18. doi:10.1186/S12951-023-02259-6
18. Tian J, Han Z, Song D, et al. Engineered exosome for drug delivery: recent development and clinical applications. *Int J Nanomed*. 2023;18:7923–7940. doi:10.2147/IJN.S444582

19. Turpin D, Truchetet ME, Faustin B, et al. Role of extracellular vesicles in autoimmune diseases. *Autoimmun Rev*. 2016;15(2):174–183. doi:10.1016/J.AUTREV.2015.11.004
20. Fang Y, Ni J, Wang YS, et al. Exosomes as biomarkers and therapeutic delivery for autoimmune diseases: opportunities and challenges. *Autoimmun Rev*. 2023;22(3). doi:10.1016/J.AUTREV.2022.103260
21. Tavasolian F, Moghaddam AS, Rohani F, et al. Exosomes: effectual players in rheumatoid arthritis. *Autoimmun Rev*. 2020;19(6). doi:10.1016/J.AUTREV.2020.102511
22. Wang W, Yue C, Gao S, et al. Promising roles of exosomal microRNAs in systemic lupus erythematosus. *Front Immunol*. 2021:12. doi:10.3389/FIMMU.2021.757096/PDF.
23. Chen YM, Tang KT, Liu HJ, Huang ST, Liao TL. tRF-His-GTG-1 enhances NETs formation and interferon-α production in lupus by extracellular vesicle. *Cell Commun Signal*. 2024;22(1). doi:10.1186/S12964-024-01730-7
24. Juillard S, Karakeussian-Rimbaud A, Normand MH, et al. Vascular injury derived apoptotic exosome-like vesicles trigger autoimmunity. *J Transl Autoimmun*. 2024:9. doi:10.1016/J.JTAUTO.2024.100250.
25. Song W, Li C, Qiu J, Dong J, Liu D, Dai Y. Differential expression of exosomal miRNAs and proteins in the plasma of systemic lupus erythematous patients. *Heliyon*. 2023;9(2). doi:10.1016/J.HELIYON.2023.E13345
26. Liu H, Li R, Liu T, Yang L, Yin G, Xie Q. Immunomodulatory effects of mesenchymal stem cells and mesenchymal stem cell-derived extracellular vesicles in rheumatoid arthritis. *Front Immunol*. 2020;11. doi:10.3389/FIMMU.2020.01912/PDF
27. Chen Z, Wang H, Xia Y, Yan F, Lu Y. Therapeutic potential of mesenchymal cell-derived miRNA-150-5p-expressing exosomes in rheumatoid arthritis mediated by the modulation of MMP14 and VEGF. *J Immunol*. 2018;201(8):2472–2482. doi:10.4049/JIMMUNOL.1800304
28. Zheng J, Zhu L, In II, Chen Y, Jia N, Zhu W. Retraction notice to "Bone marrow-derived mesenchymal stem cells-secreted exosomal microRNA-192-5p delays inflammatory response in rheumatoid arthritis" [Int. Immunopharmacol. 78 (2020) 105985]. *Int Immunopharmacol*. 2023;116. doi:10.1016/J.INTIMP.2023.109873
29. Shen Z, Huang W, Liu J, Tian J, Wang S, Rui K. Effects of mesenchymal stem cell-derived exosomes on autoimmune diseases. *Front Immunol*. 2021;12. doi:10.3389/FIMMU.2021.749192/PDF
30. Chen S, Zhang X, Meng K, et al. Urinary exosome tsRNAs as novel markers for diagnosis and prediction of lupus nephritis. *Front Immunol*. 2023:14. doi:10.3389/FIMMU.2023.1077645/PDF.
31. Mazzariol M, Camussi G, Brizzi MF. Extracellular vesicles tune the immune system in renal disease: a focus on systemic lupus erythematosus, antiphospholipid syndrome, thrombotic microangiopathy and ANCA-vasculitis. *Int J Mol Sci*. 2021;22(8). doi:10.3390/IJMS22084194
32. Théry C, Witwer KW, Aikawa E, et al. Minimal information for studies of extracellular vesicles 2018 (MISEV2018): a position statement of the international society for extracellular vesicles and update of the MISEV2014 guidelines. *J Extracell Vesicles*. 2018;7(1). doi:10.1080/20013078.2018.1535750
33. Kalluri R, LeBleu VS. The biology, function, and biomedical applications of exosomes. *Science*. 2020;367(6478). doi:10.1126/SCIENCE.AAU6977
34. Pan BT, Teng K, Wu C, Adam M, Johnstone RM. Electron microscopic evidence for externalization of the transferrin receptor in vesicular form in sheep reticulocytes. *J Cell Biol*. 1985;101(3):942–948. doi:10.1083/JCB.101.3.942
35. Johnstone RM, Adam M, Hammond JR, Orr L, Turbide C. Vesicle formation during reticulocyte maturation. Association of plasma membrane activities with released vesicles (exosomes). *J Biol Chem*. 1987;262(19):9412–9420. doi:10.1016/S0021-9258(18)48095-7
36. Liu J, Ren L, Li S, et al. The biology, function, and applications of exosomes in cancer. *Acta Pharm Sin B*. 2021;11(9):2783–2797. doi:10.1016/J.APSB.2021.01.001
37. Valadi H, Ekström K, Bossios A, Sjöstrand M, Lee JJ, Lötvall JO. Exosome-mediated transfer of mRNAs and microRNAs is a novel mechanism of genetic exchange between cells. *Nat Cell Biol*. 2007;9(6):654–659. doi:10.1038/NCB1596
38. Van Niel G, D'Angelo G, Raposo G. Shedding light on the cell biology of extracellular vesicles. *Nat Rev Mol Cell Biol*. 2018;19(4):213–228. doi:10.1038/NRM.2017.125
39. Teng F, Fussenegger M. Shedding light on extracellular vesicle biogenesis and bioengineering. *Adv Sci*. 2020;8(1). doi:10.1002/ADVS.202003505
40. Mashouri L, Yousefi H, Aref AR, Ahadi AM, Molaei F, Alahari SK. Exosomes: composition, biogenesis, and mechanisms in cancer metastasis and drug resistance. *Mol Cancer*. 2019;18(1). doi:10.1186/S12943-019-0991-5
41. Gurung S, Perocheau D, Touramanidou L, Baruteau J. The exosome journey: from biogenesis to uptake and intracellular signalling. *Cell Commun Signal*. 2021;19(1). doi:10.1186/S12964-021-00730-1
42. Raiborg C, Bremnes B, Mehlum A, et al. FYVE and coiled-coil domains determine the specific localisation of Hrs to early endosomes. *J Cell Sci*. 2001;114(Pt 12):2255–2263. doi:10.1242/JCS.114.12.2255
43. Lu Q, Hope LW, Brasch M, Reinhard C, Cohen SN. TSG101 interaction with HRS mediates endosomal trafficking and receptor down-regulation. *Proc Natl Acad Sci U S A*. 2003;100(13):7626–7631. doi:10.1073/PNAS.0932599100
44. Bache KG, Brech A, Mehlum A, Stenmark H. Hrs regulates multivesicular body formation via ESCRT recruitment to endosomes. *J Cell Biol*. 2003;162(3):435–442. doi:10.1083/JCB.200302131
45. Wollert T, Hurley JH. Molecular mechanism of multivesicular body biogenesis by ESCRT complexes. *Nature*. 2010;464(7290):864–869. doi:10.1038/NATURE08849
46. Wollert T, Wunder C, Lippincott-Schwartz J, Hurley JH. Membrane scission by the ESCRT-III complex. *Nature*. 2009;458(7235):172–177. doi:10.1038/NATURE07836
47. Ostrowski M, Carmo NB, Krumeich S, et al. Rab27a and Rab27b control different steps of the exosome secretion pathway. *Nat Cell Biol*. 2010;12(1):19–30. doi:10.1038/NCB2000
48. Lee YJ, Shin KJ, Jang HJ, et al. GPR143 controls ESCRT-dependent exosome biogenesis and promotes cancer metastasis. *Dev Cell*. 2023;58(4):320–334.e8. doi:10.1016/J.DEVCEL.2023.01.006
49. Liao Y, Chen X, Miller-Little W, et al. The Ras GTPase-activating-like protein IQGAP1 bridges Gasdermin D to the ESCRT system to promote IL-1β release via exosomes. *EMBO J*. 2023;42(1). doi:10.15252/EMBJ.2022110780
50. Salunkhe S, Dheeraj, Basak M, Chitkara D, Mittal A. Surface functionalization of exosomes for target-specific delivery and in vivo imaging & tracking: strategies and significance. *J Control Release*. 2020;326:599–614. doi:10.1016/J.JCONREL.2020.07.042

51. Zaborowski MP, Balaj L, Breakefield XO, Lai CP. Extracellular vesicles: composition, biological relevance, and methods of study. *Bioscience*. 2015;65(8):783–797. doi:10.1093/BIOSCI/BIV084
52. Baietti MF, Zhang Z, Mortier E, et al. Syndecan-syntenin-ALIX regulates the biogenesis of exosomes. *Nat Cell Biol*. 2012;14(7):677–685. doi:10.1038/NCB2502
53. Cheng L, Sharples RA, Scicluna BJ, Hill AF. Exosomes provide a protective and enriched source of miRNA for biomarker profiling compared to intracellular and cell-free blood. *J Extracell Vesicles*. 2014;3(1). doi:10.3402/JEV.V3.23743
54. Donoso-Quezada J, Ayala-Mar S, González-Valdez J. The role of lipids in exosome biology and intercellular communication: function, analytics and applications. *Traffic*. 2021;22(7):204–220. doi:10.1111/TRA.12803
55. Skotland T, Ekroos K, Kauhanen D, et al. Molecular lipid species in urinary exosomes as potential prostate cancer biomarkers. *Eur J Cancer*. 2017;70:122–132. doi:10.1016/J.EJCA.2016.10.011
56. Pitt JM, André F, Amigorena S, et al. Dendritic cell-derived exosomes for cancer therapy. *J Clin Invest*. 2016;126(4):1224–1232. doi:10.1172/JCI81137
57. Pols MS, Klumperman J. Trafficking and function of the tetraspanin CD63. *Exp Cell Res*. 2009;315(9):1584–1592. doi:10.1016/J.YEXCR.2008.09.020
58. Toh WS, Lai RC, Zhang B, Lim SK. MSC exosome works through a protein-based mechanism of action. *Biochem Soc Trans*. 2018;46(4):843–853. doi:10.1042/BST20180079
59. Wubbolts R, Leckie RS, Veenhuizen PTM, et al. Proteomic and biochemical analyses of human B cell-derived exosomes. Potential implications for their function and multivesicular body formation. *J Biol Chem*. 2003;278(13):10963–10972. doi:10.1074/JBC.M207550200
60. Blanc L, Vidal M. New insights into the function of Rab GTPases in the context of exosomal secretion. *Small GTPases*. 2018;9(1–2):95–106. doi:10.1080/21541248.2016.1264352
61. Berenguer J, Lagerweij T, Zhao XW, et al. Glycosylated extracellular vesicles released by glioblastoma cells are decorated by CCL18 allowing for cellular uptake via chemokine receptor CCR8. *J Extracell Vesicles*. 2018;7(1). doi:10.1080/20013078.2018.1446660
62. Zhao H, Yang L, Baddour J, et al. Tumor microenvironment derived exosomes pleiotropically modulate cancer cell metabolism. *Elife*. 2016;5(FEBRUARY2016). doi:10.7554/ELIFE.10250
63. Regimbeau M, Abrey J, Vautrot V, Causse S, Gobbo J, Garrido C. Heat shock proteins and exosomes in cancer theranostics. *Semin Cancer Biol*. 2022;86(Pt 1):46–57. doi:10.1016/J.SEMCANCER.2021.07.014
64. Clos-Garcia M, Loizaga-Iriarte A, Zuñiga-Garcia P, et al. Metabolic alterations in urine extracellular vesicles are associated to prostate cancer pathogenesis and progression. *J Extracell Vesicles*. 2018;7(1). doi:10.1080/20013078.2018.1470442
65. Yan S, Huang Z, Chen X, et al. Metabolic profiling of urinary exosomes for systemic lupus erythematosus discrimination based on HPL-SEC/MALDI-TOF MS. *Anal Bioanal Chem*. 2023;415(26):6411–6420. doi:10.1007/S00216-023-04916-Z
66. Xu Y, huan ZZ, Xu X, et al. Neuron-derived exosomes promote the recovery of spinal cord injury by modulating nerve cells in the cellular microenvironment of the lesion area. *Mol Neurobiol*. 2023;60(8):4502–4516. doi:10.1007/S12035-023-03341-8
67. Charles CJ, Li RR, Yeung T, et al. Systemic mesenchymal stem cell-derived exosomes reduce myocardial infarct size: characterization with MRI in a porcine model. *Front Cardiovasc Med*. 2020:7. doi:10.3389/FCVM.2020.601990/PDF.
68. Zhou X, Li Z, Qi M, et al. Brown adipose tissue-derived exosomes mitigate the metabolic syndrome in high fat diet mice. *Theranostics*. 2020;10(18). doi:10.7150/thno.43968
69. Gehrmann U, Näslund TI, Hiltbrunner S, Larssen P, Gabrielsson S. Harnessing the exosome-induced immune response for cancer immunotherapy. *Semin Cancer Biol*. 2014;28:58–67. doi:10.1016/J.SEMCANCER.2014.05.003
70. Hamzah RN, Alghazali KM, Biris AS, Griffin RJ. Exosome traceability and cell source dependence on composition and cell-cell cross talk. *Int J Mol Sci*. 2021;22(10). doi:10.3390/IJMS22105346
71. Hellwinkel JE, Redzic JS, Harland TA, Gunaydin D, Anchordoquy TJ, Graner MW. Glioma-derived extracellular vesicles selectively suppress immune responses. *Neuro Oncol*. 2016;18(4):497–506. doi:10.1093/NEUONC/NOV170
72. Zhou B, Guo W, Guo L, et al. Single-cell RNA-sequencing data reveals the genetic source of extracellular vesicles in esophageal squamous cell carcinoma. *Pharmacol Res*. 2023:192. doi:10.1016/J.PHRS.2023.106800.
73. Li G, Fang Y, Xu N, Ding Y, Liu D. Fibroblast-like synoviocytes-derived exosomal circFTO deteriorates rheumatoid arthritis by enhancing N6-methyladenosine modification of SOX9 in chondrocytes. *Arthritis Res Ther*. 2024;26(1). doi:10.1186/S13075-024-03290-0
74. Shan Z, Zhuang Z, Ren P, et al. miR-664a-5p promotes experimental membranous nephropathy progression through HIPK2/Calpain1/GSα-mediated autophagy inhibition. *J Cell Mol Med*. 2024;28(3). doi:10.1111/JCMM.18074
75. Chen J, Liu M, Luo X, et al. Exosomal miRNA-486-5p derived from rheumatoid arthritis fibroblast-like synoviocytes induces osteoblast differentiation through the Tob1/BMP/Smad pathway. *Biomater Sci*. 2020;8(12):3430–3442. doi:10.1039/C9BM01761E
76. Zou X, Liu T, Huang Z, et al. SOX17 is a critical factor in maintaining endothelial function in pulmonary hypertension by an exosome-mediated autocrine manner. *Adv Sci*. 2023;10(14). doi:10.1002/ADVS.202206139
77. Magill ST, Cambronne XA, Luikart BW, et al. microRNA-132 regulates dendritic growth and arborization of newborn neurons in the adult hippocampus. *Proc Natl Acad Sci U S A*. 2010;107(47):20382–20387. doi:10.1073/PNAS.1015691107
78. Lindenbergh MFS, Stoorvogel W. Antigen presentation by extracellular vesicles from professional antigen-presenting cells. *Annu Rev Immunol*. 2018;36:435–459. doi:10.1146/ANNUREV-IMMUNOL-041015-055700
79. Raposo G, Nijman HW, Stoorvogel W, et al. B lymphocytes secrete antigen-presenting vesicles. *J Exp Med*. 1996;183(3):1161–1172. doi:10.1084/JEM.183.3.1161
80. Robbins PD, Morelli AE. Regulation of immune responses by extracellular vesicles. *Nat Rev Immunol*. 2014;14(3):195–208. doi:10.1038/NRI3622
81. Théry C, Duban L, Segura E, Véron P, Lantz O, Amigorena S. Indirect activation of naïve CD4+ T cells by dendritic cell-derived exosomes. *Nat Immunol*. 2002;3(12):1156–1162. doi:10.1038/NI854
82. Qin S, Cao J, Ma X. Function and clinical application of exosome—how to improve tumor immunotherapy? *Front Cell Dev Biol*. 2023;11. doi:10.3389/FCELL.2023.1228624/PDF
83. Cui X, Wang S, Zhao N, et al. Thyrocyte-derived exosome-targeted dendritic cells stimulate strong CD4+ T lymphocyte responses. *Mol Cell Endocrinol*. 2020:506. doi:10.1016/J.MCE.2020.110756.

84. Isaac R, Reis FCG, Ying W, Olefsky JM. Exosomes as mediators of intercellular crosstalk in metabolism. *Cell Metab*. 2021;33(9):1744–1762. doi:10.1016/J.CMET.2021.08.006
85. Gong J, Zhang X, Khan A, et al. Identification of serum exosomal miRNA biomarkers for diagnosis of rheumatoid arthritis. *Int Immunopharmacol*. 2024:129. doi:10.1016/J.INTIMP.2024.111604.
86. Rodríguez-Muguruza S, Altuna-Coy A, Castro-Oreiro S, Poveda-Elices MJ, Fontova-Garrofé R, Chacón MR. A serum biomarker panel of exomiR-451a, exomiR-25-3p and soluble TWEAK for early diagnosis of rheumatoid arthritis. *Front Immunol*. 2021;12. doi:10.3389/FIMMU.2021.790880/PDF.
87. Wang Y, Zheng F, Gao G, et al. MiR-548a-3p regulates inflammatory response via TLR4/NF-κB signaling pathway in rheumatoid arthritis. *J Cell Biochem*. 2019;120(2):1133–1140. doi:10.1002/JCB.26659
88. Shuai ZQ, Wang ZX, Le RJ, Yang XK, Xu B. Differential expressions and potential clinical values of lncRNAs in the plasma exosomes of rheumatoid arthritis. *Int Immunopharmacol*. 2024;128. doi:10.1016/J.INTIMP.2024.111511.
89. Li W, Liu S, Chen Y, et al. Circulating exosomal microRNAs as biomarkers of systemic lupus erythematosus. *Clinics*. 2020;75:1–6. doi:10.6061/CLINICS/2020/E1528
90. Tan L, Zhao M, Wu H, et al. Downregulated serum exosomal miR-451a expression correlates with renal damage and its intercellular communication role in systemic lupus erythematosus. *Front Immunol*. 2021;12. doi:10.3389/FIMMU.2021.630112
91. Chuang HC, Chen MH, Chen YM, et al. BPI overexpression suppresses Treg differentiation and induces exosome-mediated inflammation in systemic lupus erythematosus. *Theranostics*. 2021;11(20):9953–9966. doi:10.7150/THNO.63743
92. Chuang HC, Chen MH, Chen YM, et al. Induction of interferon-γ and tissue inflammation by overexpression of eosinophil cationic protein in T cells and exosomes. *Arthritis Rheumatol*. 2022;74(1):92–104. doi:10.1002/ART.41920
93. Somparn P, Srichaimongkol A, Jungjing S, et al. Potential involvement of circulating exosomal miRNA-146a in disease activity and TRAF6 gene expression in juvenile proliferative lupus nephritis. *Lupus Sci Med*. 2024;11(1). doi:10.1136/LUPUS-2023-001078
94. Bhandari R, Yang H, Kosarek NN, et al. Human dermal fibroblast-derived exosomes induce macrophage activation in systemic sclerosis. *Rheumatology*. 2023;62(SI):SI114–SI124. doi:10.1093/RHEUMATOLOGY/KEAC453
95. Li L, Zuo X, Xiao Y, Liu D, Luo H, Zhu H. Neutrophil-derived exosome from systemic sclerosis inhibits the proliferation and migration of endothelial cells. *Biochem Biophys Res Commun*. 2020;526(2):334–340. doi:10.1016/J.BBRC.2020.03.088
96. Sun X, Ding T, Wang B, et al. Identification of lncRNA–miRNA–mRNA networks in circulating exosomes as potential biomarkers for systemic sclerosis. *Front Med Lausanne*. 2023;10. doi:10.3389/FMED.2023.1111812/PDF
97. Peng X, Hou L, Wu X, et al. The plasma exosomes from patients with primary Sjögren's syndrome contain epithelial cell-derived proteins involved in ferroptosis. *J Mol Med*. 2023;101(10):1289–1304. doi:10.1007/S00109-023-02361-0
98. Kakan SS, Janga SR, Cooperman B, et al. Small RNA deep sequencing identifies a unique miRNA signature released in serum exosomes in a mouse model of Sjögren's syndrome. *Front Immunol*. 2020;11. doi:10.3389/FIMMU.2020.01475/PDF
99. Cortes-Troncoso J, Jang SI, Perez P, et al. T cell exosome-derived miR-142-3p impairs glandular cell function in Sjögren's syndrome. *JCI Insight*. 2020;5(9). doi:10.1172/JCI.INSIGHT.133497
100. Mi L, Gao J, Li N, et al. Human umbilical cord mesenchymal stem cell-derived exosomes loaded miR-451a targets ATF2 to improve rheumatoid arthritis. *Int Immunopharmacol*. 2024;127. doi:10.1016/J.INTIMP.2023.111365
101. Rui K, Tang X, Shen Z, et al. Exosome inspired photo-triggered gelation hydrogel composite on modulating immune pathogenesis for treating rheumatoid arthritis. *J Nanobiotechnol*. 2023;21(1). doi:10.1186/S12951-023-01865-8
102. You DG, Lim GT, Kwon S, et al. Metabolically engineered stem cell-derived exosomes to regulate macrophage heterogeneity in rheumatoid arthritis. *Sci Adv*. 2021;7(23). doi:10.1126/SCIADV.ABE0083
103. Tu J, Zheng N, Mao C, Liu S, Zhang H, Sun L. UC-BSCs exosomes regulate Th17/Treg balance in patients with systemic lupus erythematosus via miR-19b/KLF13. *Cells*. 2022;11(24). doi:10.3390/CELLS11244123
104. Zhang M, Johnson-Stephenson TK, Wang W, et al. Mesenchymal stem cell-derived exosome-educated macrophages alleviate systemic lupus erythematosus by promoting efferocytosis and recruitment of IL-17+ regulatory T cell. *Stem Cell Res Ther*. 2022;13(1). doi:10.1186/S13287-022-03174-7
105. Wei S, Zhang Z, Yan L, et al. miR-20a overexpression in adipose-derived mesenchymal stem cells promotes therapeutic efficacy in murine lupus nephritis by regulating autophagy. *Stem Cells Int*. 2021;2021. doi:10.1155/2021/3746335
106. Rozier P, Maumus M, Maria ATJ, et al. Mesenchymal stromal cells-derived extracellular vesicles alleviate systemic sclerosis via miR-29a-3p. *J Autoimmun*. 2021;121. doi:10.1016/J.JAUT.2021.102660
107. Baral H, Uchiyama A, Yokoyama Y, et al. Antifibrotic effects and mechanisms of mesenchymal stem cell-derived exosomes in a systemic sclerosis mouse model: possible contribution of miR-196b-5p. *J Dermatol Sci*. 2021;104(1):39–47. doi:10.1016/J.JDERMSCI.2021.08.006
108. Rozier P, Maumus M, Maria ATJ, et al. Lung fibrosis is improved by extracellular vesicles from IFNγ-primed mesenchymal stromal cells in murine systemic sclerosis. *Cells*. 2021;10(10). doi:10.3390/CELLS10102727
109. Ma D, Wu Z, Zhao X, et al. Immunomodulatory effects of umbilical mesenchymal stem cell-derived exosomes on CD4+ T cells in patients with primary Sjögren's syndrome. *Inflammopharmacology*. 2023;31(4):1823–1838. doi:10.1007/S10787-023-01189-X
110. Li B, Xing Y, Gan Y, He J, Hua H. Labial gland-derived mesenchymal stem cells and their exosomes ameliorate murine Sjögren's syndrome by modulating the balance of Treg and Th17 cells. *Stem Cell Res Ther*. 2021;12(1). doi:10.1186/S13287-021-02541-0
111. Xing Y, Li B, He J, Hua H. Labial gland mesenchymal stem cell derived exosomes-mediated miRNA-125b attenuates experimental Sjogren's syndrome by targeting PRDM1 and suppressing plasma cells. *Front Immunol*. 2022;13. doi:10.3389/FIMMU.2022.871096/PDF.
112. Hu S, Chen B, Zhou J, et al. Dental pulp stem cell-derived exosomes revitalize salivary gland epithelial cell function in NOD mice via the GPER-mediated cAMP/PKA/CREB signaling pathway. *J Transl Med*. 2023;21(1). doi:10.1186/S12967-023-04198-0
113. Chu WX, Ding C, Du ZH, et al. SHED-exos promote saliva secretion by suppressing p-ERK1/2-mediated apoptosis in glandular cells. *Oral Dis*. 2023. doi:10.1111/ODI.14776
114. Du Z, Wei P, Jiang N, Wu L, Ding C, Yu G. SHED-derived exosomes ameliorate hyposalivation caused by Sjögren's syndrome via Akt/GSK-3β/Slug-mediated ZO-1 expression. *Chin Med J*. 2023;136(21):2596–2608. doi:10.1097/CM9.0000000000002610
115. Rui K, Hong Y, Zhu Q, et al. Olfactory ecto-mesenchymal stem cell-derived exosomes ameliorate murine Sjögren's syndrome by modulating the function of myeloid-derived suppressor cells. *Cell mol Immunol*. 2021;18(2):440–451. doi:10.1038/S41423-020-00587-3

116. Zhang S, Duan Z, Liu F, Wu Q, Sun X, Ma H. The impact of exosomes derived from distinct sources on rheumatoid arthritis. *Front Immunol*. 2023;14. doi:10.3389/FIMMU.2023.1240747/PDF
117. Ogunsanya ME, Cho SK, Hudson A, Chong BF. Validation and reliability of a disease-specific quality-of-life measure in patients with cutaneous lupus erythematosus. *Br J Dermatol*. 2019;180(6):1430–1437. doi:10.1111/BJD.17636
118. Xue L, Wang B, Li X, et al. Comprehensive analysis of serum exosome-derived lncRNAs and mRNAs from patients with rheumatoid arthritis. *Arthritis Res Ther*. 2023;25(1). doi:10.1186/S13075-023-03174-9
119. Coffey CM, Crowson CS, Myasoedova E, Matteson EL, Davis JM. Evidence of diagnostic and treatment delay in seronegative rheumatoid arthritis: missing the window of opportunity. *Mayo Clin Proc*. 2019;94(11):2241–2248. doi:10.1016/J.MAYOCP.2019.05.023
120. Huang RY, Wu JQ, Liu ZH, Sun SL. MicroRNAs in rheumatoid arthritis: what is the latest with regards to diagnostics? *Expert Rev mol Diagn*. 2019;19(5):363–366. doi:10.1080/14737159.2019.1599716
121. Wang Y, Huang Y, Cheng C, et al. Dysregulation of circRNAs in rheumatoid arthritis, with special emphasis on circRNAs secreted by exosomes and the crosstalk between circRNAs and RNA methylations. *Int Immunopharmacol*. 2023;122. doi:10.1016/J.INTIMP.2023.110549
122. Wang J, Yan S, Yang J, Lu H, Xu D, Wang Z. Non-coding RNAs in rheumatoid arthritis: from bench to bedside. *Front Immunol*. 2020;10. doi:10.3389/FIMMU.2019.03129.
123. Gowhari Shabgah A, Shariati-Sarabi Z, Tavakkol-Afshari J, Ghasemi A, Ghoryani M, Mohammadi M. A significant decrease of BAFF, April, and BAFF receptors following mesenchymal stem cell transplantation in patients with refractory rheumatoid arthritis. *Gene*. 2020;732. doi:10.1016/J.GENE.2020.144336.
124. Wang Z, Zhang C, Meng J, et al. A targeted exosome therapeutic confers both CfDNA scavenging and macrophage polarization for ameliorating rheumatoid arthritis. *Adv Mater*. 2023;35(48). doi:10.1002/ADMA.202302503
125. Lee HI, Ahn MJ, Yoo JK, et al. Exosome-mediated delivery of super-repressor IκBα alleviates inflammation and joint damages in rheumatoid arthritis. *Arthritis Res Ther*. 2024;26(1). doi:10.1186/S13075-023-03225-1
126. Yan F, Zhong Z, Wang Y, et al. Exosome-based biomimetic nanoparticles targeted to inflamed joints for enhanced treatment of rheumatoid arthritis. *J Nanobiotechnol*. 2020;18(1). doi:10.1186/S12951-020-00675-6
127. Mohamed A, Chen Y, Wu H, Liao J, Cheng B, Lu Q. Therapeutic advances in the treatment of SLE. *Int Immunopharmacol*. 2019;72:218–223. doi:10.1016/J.INTIMP.2019.03.010
128. Perez-Hernandez J, Martinez-Arroyo O, Ortega A, et al. Urinary exosomal miR-146a as a marker of albuminuria, activity changes and disease flares in lupus nephritis. *J Nephrol*. 2021;34(4):1157–1167. doi:10.1007/S40620-020-00832-Y
129. Chai F, Chang X, Lin Y, et al. Effect of M0 macrophage-derived exosome miR-181d-5p targeting BCL-2 to regulate NLRP3/caspase-1/GSDMD pathway on human renal mesangial cells pyroptosis. *Gene*. 2024;908. doi:10.1016/J.GENE.2024.148289
130. Fang T, Li B, Li M, et al. Engineered cell membrane vesicles expressing CD40 alleviate system lupus nephritis by intervening B cell activation. *Small Methods*. 2023;7(3). doi:10.1002/SMTD.202200925
131. Denton CP, Khanna D. Systemic sclerosis. *Lancet*. 2017;390(10103):1685–1699. doi:10.1016/S0140-6736(17)30933-9
132. Volkmann ER, Andréasson K, Smith V. Systemic sclerosis. *Lancet*. 2023;401(10373):304–318. doi:10.1016/S0140-6736(22)01692-0
133. Jerjen R, Nikpour M, Krieg T, Denton CP, Saracino AM. Systemic sclerosis in adults. Part I: clinical features and pathogenesis. *J Am Acad Dermatol*. 2022;87(5):937–954. doi:10.1016/J.JAAD.2021.10.065
134. Nihtyanova SI, Sari A, Harvey JC, et al. Using autoantibodies and cutaneous subset to develop outcome-based disease classification in systemic sclerosis. *Arthritis Rheumatol*. 2020;72(3):465–476. doi:10.1002/ART.41153
135. Cavazzana I, Vojinovic T, Airo' P, et al. Systemic sclerosis-specific antibodies: novel and classical biomarkers. *Clin Rev Allergy Immunol*. 2023;64(3):412–430. doi:10.1007/S12016-022-08946-W
136. Liu X, Mayes MD, Pedroza C, et al. Does C-reactive protein predict the long-term progression of interstitial lung disease and survival in patients with early systemic sclerosis? *Arthritis Care Res*. 2013;65(8):1375–1380. doi:10.1002/ACR.21968
137. Kakkar V, Assassi S, Allanore Y, et al. Type 1 interferon activation in systemic sclerosis: a biomarker, a target or the culprit. *Curr Opin Rheumatol*. 2022;34(6):357–364. doi:10.1097/BOR.0000000000000907
138. Farge D, Loisel S, Lansiaux P, Tarte K. Mesenchymal stromal cells for systemic sclerosis treatment. *Autoimmun Rev*. 2021;20(3). doi:10.1016/J.AUTREV.2021.102755
139. Herrick AL, Pan X, Peytrignet S, et al. Treatment outcome in early diffuse cutaneous systemic sclerosis: the European scleroderma observational study (ESOS). *Ann Rheum Dis*. 2017;76(7):1207–1218. doi:10.1136/ANNRHEUMDIS-2016-210503
140. Colletti M, Galardi A, De Santis M, et al. Exosomes in systemic sclerosis: messengers between immune, vascular and fibrotic components? *Int J Mol Sci*. 2019;20(18). doi:10.3390/IJMS20184337
141. Sanges S, Rice L, Tu L, et al. Biomarkers of haemodynamic severity of systemic sclerosis-associated pulmonary arterial hypertension by serum proteome analysis. *Ann Rheum Dis*. 2023;82(3):365–373. doi:10.1136/ARD-2022-223237
142. Bălănescu P, Lădaru A, Bălănescu E, Băicuș C, Dan GA. Systemic sclerosis biomarkers discovered using mass-spectrometry-based proteomics: a systematic review. *Biomarkers*. 2014;19(5):345–355. doi:10.3109/1354750X.2014.920046
143. Li M, Jiang M, Meng J, Tao L. Exosomes: carriers of pro-fibrotic signals and therapeutic targets in fibrosis. *Curr Pharm Des*. 2019;25(42):4496–4509. doi:10.2174/1381612825666191209161443
144. Piera-Velazquez S, Dillon ST, Gu X, Libermann TA, Jimenez SA. Aptamer proteomics of serum exosomes from patients with primary Raynaud's and patients with Raynaud's at risk of evolving into systemic sclerosis. *PLoS One*. 2022;17(12). doi:10.1371/JOURNAL.PONE.0279461
145. Viemann D, Barczyk K, Vogl T, et al. MRP8/MRP14 impairs endothelial integrity and induces a caspase-dependent and -independent cell death program. *Blood*. 2007;109(6):2453–2460. doi:10.1182/BLOOD-2006-08-040444
146. Li L, Zuo X, Liu D, Luo H, Zhu H. The profiles of miRNAs and lncRNAs in peripheral blood neutrophils exosomes of diffuse cutaneous systemic sclerosis. *J Dermatol Sci*. 2020;98(2):88–97. doi:10.1016/J.JDERMSCI.2020.02.009
147. Tyndall A. Hematopoietic stem cell transplantation for systemic sclerosis: review of current status. *BioDrugs*. 2019;33(4):401–409. doi:10.1007/S40259-019-00364-3
148. Zanatta E, Codullo V, Avouac J, Allanore Y. Systemic sclerosis: recent insight in clinical management. *Joint Bone Spine*. 2020;87(4):293–299. doi:10.1016/J.JBSPIN.2019.09.015

149. Rozier P, Maria A, Goulabchand R, Jorgensen C, Guilpain P, Noël D. Mesenchymal stem cells in systemic sclerosis: allogenic or autologous approaches for therapeutic use? *Front Immunol*. 2018;9. doi:10.3389/FIMMU.2018.02938/PDF.
150. Wu KY, Serhan O, Faucher A, Tran SD. Advances in Sjögren's syndrome dry eye diagnostics: biomarkers and biomolecules beyond clinical symptoms. *Biomolecules*. 2024;14(1). doi:10.3390/BIOM14010080
151. Zhao J, An Q, Zhu X, et al. Research status and future prospects of extracellular vesicles in primary Sjögren's syndrome. *Stem Cell Res Ther*. 2022;13(1). doi:10.1186/S13287-022-02912-1
152. Akpek EK, Bunya VY, Saldanha IJ. Sjögren's syndrome: more than just dry eye. *Cornea*. 2019;38(5):658–661. doi:10.1097/ICO.0000000000001865
153. Nair JJ, Singh TP. Sjogren's syndrome: review of the aetiology, pathophysiology & potential therapeutic interventions. *J Clin Exp Dent*. 2017;9(4):e584–e589. doi:10.4317/JCED.53605
154. Wu KY, Kulbay M, Tanasescu C, Jiao B, Nguyen BH, Tran SD. An overview of the dry eye disease in Sjögren's syndrome using our current molecular understanding. *Int J Mol Sci*. 2023;24(2). doi:10.3390/IJMS24021580
155. Qin B, Wang J, Yang Z, et al. Epidemiology of primary Sjögren's syndrome: a systematic review and meta-analysis. *Ann Rheum Dis*. 2015;74(11):1983–1989. doi:10.1136/ANNRHEUMDIS-2014-205375
156. Shiboski CH, Shiboski SC, Seror R, et al. 2016 American college of rheumatology/European league against rheumatism classification criteria for primary Sjögren's syndrome: a consensus and data-driven methodology involving three international patient cohorts. *Arthritis Rheumatol*. 2017;69(1):35–45. doi:10.1002/ART.39859
157. Caban M, Omulecki W, Latecka-Krajewska B. Dry eye in Sjögren's syndrome - characteristics and therapy. *Eur J Ophthalmol*. 2022;32(6):3174–3184. doi:10.1177/11206721221091375
158. Veenbergen S, Kozmar A, van Daele PLA, Schreurs MWJ. Autoantibodies in Sjögren's syndrome and its classification criteria. *J Transl Autoimmun*. 2021;5. doi:10.1016/J.JTAUTO.2021.100138
159. Kapsogeorgou EK, Abu-Helu RF, Moutsopoulos HM, Manoussakis MN. Salivary gland epithelial cell exosomes: a source of autoantigenic ribonucleoproteins. *Arthritis Rheum*. 2005;52(5):1517–1521. doi:10.1002/ART.21005
160. Michael A, Bajracharya SD, Yuen PST, et al. Exosomes from human saliva as a source of microRNA biomarkers. *Oral Dis*. 2010;16(1):34–38. doi:10.1111/J.1601-0825.2009.01604.X
161. Aqrawi LA, Galtung HK, Guerreiro EM, et al. Proteomic and histopathological characterisation of sicca subjects and primary Sjögren's syndrome patients reveals promising tear, saliva and extracellular vesicle disease biomarkers. *Arthritis Res Ther*. 2019;21(1). doi:10.1186/S13075-019-1961-4
162. Jiang X, Stockwell BR, Conrad M. Ferroptosis: mechanisms, biology and role in disease. *Nat Rev Mol Cell Biol*. 2021;22(4):266–282. doi:10.1038/S41580-020-00324-8
163. Zeng Y, Peng X, Wang Y, Hou L, Ma W, Yang P. Therapeutic effect of modified zengye decoction on primary Sjogren's syndrome and its effect on plasma exosomal proteins. *Front Pharmacol*. 2022;13. doi:10.3389/FPHAR.2022.930638/PDF.
164. Li F, Liu Z, Zhang B, et al. Circular RNA sequencing indicates circ-IQGAP2 and circ-ZC3H6 as noninvasive biomarkers of primary Sjögren's syndrome. *Rheumatology*. 2020;59(9):2603–2615. doi:10.1093/RHEUMATOLOGY/KEAA163
165. Arruda LCM, Lorenzi JCC, Sousa APA, et al. Autologous hematopoietic SCT normalizes miR-16, −155 and −142-3p expression in multiple sclerosis patients. *Bone Marrow Transplant*. 2015;50(3):380–389. doi:10.1038/BMT.2014.277
166. Ding S, Liang Y, Zhao M, et al. Decreased microRNA-142-3p/5p expression causes CD4+ T cell activation and B cell hyperstimulation in systemic lupus erythematosus. *Arthritis Rheum*. 2012;64(9):2953–2963. doi:10.1002/ART.34505
167. André F, Böckle BC. Sjögren's syndrome. *J Dtsch Dermatol Ges*. 2022;20(7):980–1002. doi:10.1111/DDG.14823
168. Ji Y, Mi L, Zhao M, et al. Innovative diagnosis and therapeutic modalities: engineered exosomes in autoimmune disease. *Int J Nanomed*. 2024;19:3943–3956. doi:10.2147/IJN.S452184
169. Zhang E, Phan P, Zhao Z. Cellular nanovesicles for therapeutic immunomodulation: a perspective on engineering strategies and new advances. *Acta Pharm Sin B*. 2023;13(5):1789–1827. doi:10.1016/J.APSB.2022.08.020
170. Khan NA, Asim M, Biswas KH, et al. Exosome nanovesicles as potential biomarkers and immune checkpoint signaling modulators in lung cancer microenvironment: recent advances and emerging concepts. *J Exp Clin Cancer Res*. 2023;42(1). doi:10.1186/S13046-023-02753-7
171. Lee D, Cho M, Kim E, Seo Y, Cha JH. PD-L1: from cancer immunotherapy to therapeutic implications in multiple disorders. *Mol Ther*. 2024;32(12). doi:10.1016/J.YMTHE.2024.09.026
172. Hao X, Wang S, Wang L, Li J, Li Y, Liu J. Exosomes as drug delivery systems in glioma immunotherapy. *J Nanobiotechnol*. 2024;22(1). doi:10.1186/S12951-024-02611-4
173. Zhang S, Yang Y, Lv X, et al. Unraveling the intricate roles of exosomes in cardiovascular diseases: a comprehensive review of physiological significance and pathological implications. *Int J Mol Sci*. 2023;24(21). doi:10.3390/IJMS242115677
174. Zhang Z, Zou Y, Song C, et al. Advances in the study of exosomes in cardiovascular diseases. *J Adv Res*. 2024;66. doi:10.1016/J.JARE.2023.12.014.
175. Jiang S, Hu L, Zhou H, et al. Novel therapeutic mechanisms and strategies for intracerebral hemorrhage: focusing on exosomes. *Int J Nanomed*. 2024;19:8987–9007. doi:10.2147/IJN.S473611
176. Zhang S, Yang Y, Lv X, et al. Exosome cargo in neurodegenerative diseases: leveraging their intercellular communication capabilities for biomarker discovery and therapeutic delivery. *Brain Sci*. 2024;14(11). doi:10.3390/BRAINSCI14111049
177. Richardson JJ, Ejima H. Surface engineering of extracellular vesicles through chemical and biological strategies †. *Chem Mater*. 2019;31(7):2191–2201. doi:10.1021/ACS.CHEMMATER.9B00050/ASSET/IMAGES/LARGE/CM-2019-000502_0011.JPEG
178. Lu MM, Yang Y. Exosomal PD-L1 in cancer and other fields: recent advances and perspectives. *Front Immunol*. 2024;15. doi:10.3389/FIMMU.2024.1395332/PDF
179. Niu M, Liu Y, Yi M, Jiao D, Wu K. Biological characteristics and clinical significance of soluble PD-1/PD-L1 and exosomal PD-L1 in cancer. *Front Immunol*. 2022;13. doi:10.3389/FIMMU.2022.827921/PDF
180. Xu F, Fei Z, Dai H, et al. Mesenchymal stem cell-derived extracellular vesicles with high PD-L1 expression for autoimmune diseases treatment. *Adv Mater*. 2022;34(1). doi:10.1002/ADMA.202106265

181. Akiyama M, Ohtsuki S, Berry GJ, Liang DH, Goronzy JJ, Weyand CM. Innate and adaptive immunity in giant cell arteritis. *Front Immunol*. 2021;11. doi:10.3389/FIMMU.2020.621098/PDF.
182. Lai JJ, Chau ZL, Chen SY, et al. Exosome processing and characterization approaches for research and technology development. *Adv Sci*. 2022;9(15). doi:10.1002/ADVS.202103222
183. Lai CP, Mardini O, Ericsson M, et al. Dynamic biodistribution of extracellular vesicles in vivo using a multimodal imaging reporter. *ACS Nano*. 2014;8(1):483–494. doi:10.1021/NN404945R
184. Wang L, Wang FS, Gershwin ME. Human autoimmune diseases: a comprehensive update. *J Intern Med*. 2015;278(4):369–395. doi:10.1111/JOIM.12395
185. Park GH, Kwon HH, Seok J, et al. Efficacy of combined treatment with human adipose tissue stem cell-derived exosome-containing solution and microneedling for facial skin aging: a 12-week prospective, randomized, split-face study. *J Cosmet Dermatol*. 2023;22(12):3418–3426. doi:10.1111/JOCD.15872