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Review Article

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Exosomes in Action: Unraveling Their Role in Autoimmune Diseases and Exploring Potential Therapeutic Applications

Shuanglong Zhou [1], **Jialing Huang** [1], **Yi Zhang** [1], **Hongsong Yu** [1,*], **Xin Wang** [2,*]

[1]Department of Immunology, Special Key Laboratory of Gene Detection and Therapy of Guizhou Province, Zunyi Medical University, Guizhou 563002, China
[2]School of Basic Medical Sciences, Zunyi Medical University, Guizhou 563002, China

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***Correspondence to**
Hongsong Yu
Department of Immunology, Special Key Laboratory of Gene Detection and Therapy of Guizhou Province, Zunyi Medical University, 201 Da Lian Lu, Huichuan District, Guizhou 563002, China.
Email: yuhongsong@163.com

Xin Wang
School of Basic Medical Sciences, Zunyi Medical University, 201 Da Lian Lu, Huichuan District, Guizhou 563002, China.
Email: wangxin@zmu.edu.cn

ORCID iDs
Shuanglong Zhou
https://orcid.org/0009-0000-2073-7411
Jialing Huang
https://orcid.org/0009-0004-9118-5203
Yi Zhang
https://orcid.org/0009-0002-2321-8822

ABSTRACT

Exosomes are double phospholipid membrane vesicles that are synthesized and secreted by a variety of cells, including T cells, B cells, dendritic cells, immune cells, are extracellular vesicles. Recent studies have revealed that exosomes can play a significant role in under both physiological and pathological conditions. They have been implicated in regulation of inflammatory responses, immune response, angiogenesis, tissue repair, and antioxidant activities, particularly in modulating immunity in autoimmune diseases (AIDs). Moreover, variations in the expression of exosome-related substances, such as miRNA and proteins, may not only offer valuable perspectives for the early warning, and prognostic assessment of various AIDs, but may also serve as novel markers for disease diagnosis. This article examines the impact of exosomes on the development of AIDs and explores their potential for therapeutic application.

Keywords: Exosomes; Autoimmune disease; Pathogenesis; Therapeutics

INTRODUCTION

Autoimmune diseases (AIDs) are a variety of conditions that cause damage to the body's own tissues due to immune reactions against self-Ags (1). There are over 100 distinct types of AIDs, which can affect almost any part of the body, including the heart, brain, nerves, muscles, skin, eyes, thyroid, and numerous others. Abnormal autoantibodies are often associated with the diagnosis of AIDs, but the majority of autoantibodies have an unknown origin (2,3). Although the specific causes of AIDs are diverse and largely unknown, genetic susceptibility, autoimmune, and environmental factors have been identified as being associated with the progression of AIDs (4). The treatment options for AIDs vary depending on the type of AIDs, the presence or absence of autoantibodies, and the stage of the disease. The prevalent treatment options for such illnesses currently consist of glucocorticoids, anti-inflammatory agents, immunosuppressants, and biologics. Nevertheless, the majority of patients are unable to achieve a complete cure and often require lifelong medication. Due to the need for long-term medication, patients are prone to drug resistance and side effects (5). Although

Hongsong Yu
https://orcid.org/0000-0002-1209-2104
Xin Wang
https://orcid.org/0000-0002-0245-8045

Conflict of Interest

The authors declare no potential conflicts of interest.

Abbreviations

AID, autoimmune disease; AITD, autoimmune thyroid disease; BMMSC, bone marrow mesenchymal stem cell; DC, dendritic cell; EBV, Epstein-Barr virus; ESCRT, endosomal sorting complex; EV, extracellular vesicle; EXO, exosome; GD, Graves' disease; GMG, generalized myasthenia gravis; HT, Hashimoto 's thyroiditis; LGMSC, lip gland mesenchymal stem cell; MG, myasthenia gravis; MOG, myelin oligodendrocyte glycoprotein; MS, multiple sclerosis; MSC, mesenchymal stem cell; MVB, multivesicular body; OMG, ophthalmic myasthenia gravis; pSS, primary Sjogren's syndrome; RA, rheumatoid arthritis; RRMS, relapsing-remitting MS; SLE, systemic lupus erythematosus; SPMS, secondary progressive MS; SS, Sjogren's syndrome; T1DM, type 1 diabetes; UC-BSC, umbilical cord mesenchymal stem cell; UVRAG, UV radiation resistance associated gene.

Author Contributions

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new treatment methods for AIDs have been continuously developed in recent years, these methods are not suitable for all patients, as many patients do not respond to current treatment methods. Therefore, exploring the diagnostic markers, specific pathogenesis and effective treatment options of AIDs are the difficult and hot topics in this field that need to be solved.

Exosomes (EXOs), ranging in size from 40–150 nm, which are secreted by different types of cells like immune cells, epithelial cells, and neuron cells, can be found in various bodily fluids like blood, urine, saliva, milk, and cerebrospinal fluid (6-11). The formation of EXOs begins with the invagination of the plasma membrane to form an early endosome. Under the action of the endosomal sorting complex and related proteins, the early endosome membrane invaginates inward to form a vesicle, which then transforms into a multivesicular body (MVB). The MVB fuses with the cell membrane under the action of RAB enzymes to bud and secrete into the extracellular space, forming EXOs (**Fig. 1**) (12). EXOs can be detected by utilizing specific protein markers such as AliX, TSG101, HSC70, CD63, CD81, and CD9. It is intriguing to note that unhealthy cells produce a higher number of EXOs compared to healthy cells (11,13).

There is a significant correlation between EXOs and AIDs. Firstly, EXOs play a crucial role in the pathogenesis of AIDs, serving as key mediators of protein and lipid exchange between cells. They also facilitate the transfer and regulation of genetic information between cells. Secondly, EXOs serve as valuable biological markers for AIDs. The surface of EXOs contains various immune response molecules and carries important biological messengers like proteins, mRNA, and DNA fragments. These messengers regulate diverse immune response phenomena, such as Ag information exchange between immune cells, immune cell activation, and inhibition. Thirdly, EXOs hold significant therapeutic potential in AIDs. Not only can they serve as targets for treating AIDs, but they can also act as drug delivery vehicles, enabling targeted treatment of these conditions (7,14).

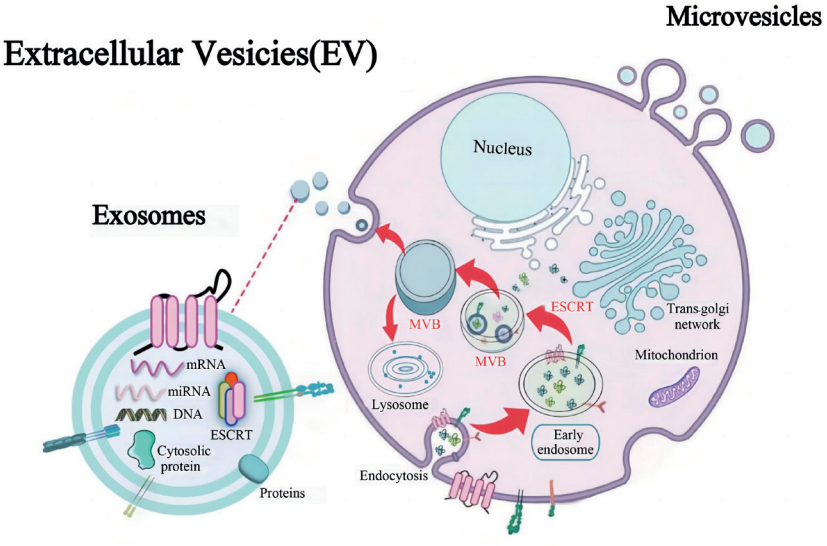

Figure 1. Mechanism of production and secretion of intracellular and extracellular EXO. EXOs, are early endosome formed by cell invagination. Under the action of transport complex ESCRT and related proteins, early cell membrane invagination sprouts inward to form vesicles, and then transforms into MVB. MVB is fused with cell membrane under the action of RAB enzyme and secreted to the extracellular by budding.

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In recent years, the diverse biological effects of various sources of EXOs have been extensively explored in AIDs, highlighting their unique advantages in scientific research and clinical applications. Consequently, this article comprehensively summarizes the current research on the diagnostic, pathogenic, and therapeutic applications of EXOs in AIDs. It also highlights the limitations and future directions in this field of AIDs research.

EXOs AND SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

SLE is a chronic diffuse connective tissue disease that can affect various systems within the entire body, resulting in damage to the multiple organs and tissues. It is also called diffuse collagen disease due to its degenerative effects on collagen fibers and matrix, along with the presence of fibrin-like substances in different organs. The lupus nephritis, a severe complication of SLE, is the primary culprit behind the accelerated renal failure and premature demise of SLE patients (15). However, the pathogenesis of SLE is still not fully understood.

In SLE, autoantigens primarily originate from the defective clearance of apoptotic bodies and the accumulation of their metabolites. Extracellular vesicles (EVs) have emerged as potential regulators of AIDs and serve as key players in modulating inflammation (16). According to the findings of Lee et al. (17) levels of serum EXOs in SLE patients (n=13) were significantly higher in comparison to the healthy population (n=8). These SLE-specific EXOs can promote the secretion of variety of cytokines such as INF-α, IL-1 β, and IL-6. Interestingly, in the absence of EXOs there was no significant cytokine production in SLE serum, thus indicating a potential correlation between EXOs levels and disease progression. It has been found that (18,19) EXOs derived from bone marrow mesenchymal stem cells miR-10a-5p can significantly down-regulates the expression of UV radiation resistance associated gene (UVRAG), thereby inhibiting the proliferation and promoting apoptosis of PBMCs in SLE. In addition, miR-125b also from PBMCs can affect the regulation of UVRAG and inhibit the autophagy process in SLE patients. Despite this, there are still few reports related to miR-125b, especially its role in AIDs. Understanding the mechanism of miR-125b in SLE may provide exciting opportunities for developing new treatments. *In vitro* experiments and bioinformatics analysis of PBMCs treated with EXOs from human umbilical cord mesenchymal stem cells (UC-BSCs) revealed that upregulation of miR-19b can decrease the expression of its target gene *KLF13* (20). Interestingly, an imbalance in miR-19b and *KLF13* gene expression has been reported in SLE patients. UC-BSCs-EXOs can modulate the Th17/Treg cell balance through miR-19b/*KLF13* and attenuate the expression of various inflammatory factors expression, thus exerting pronounced immunosuppressive and anti-inflammatory effects. In addition, prior studies have indicated that (21) the specific urinary EXOs miR-3135b and miR-654-5p show good sensitivity and specificity in diagnosing type IV lupus nephritis with cytosolic crescent and could potentially serve as a non-invasive diagnostic tool for this condition. According to Huang et al. (22) patients with SLE have significantly elevated levels of plasma EXOs as well as immune complex circulating-free DNA, combined with autoantibodies and thus exhibit enhanced stimulatory activity against macrophages and dendritic cells (DCs), suggesting that suggesting that reducing the level of circulating-free DNA may contribute to the improvement of SLE. Additionally, Xu et al. (23) detected the serum EXOs of 10 SLE patients and 10 normal controls, and found that snoU13, SNORA31, and SCARNA20 could be used as specific markers for early renal injury in SLE. Although the precise mechanism is not yet understood, substances related to EXOs that are expressed differently have important implications for diagnosing and treating SLE. For example, a prior study indicated that (24),

increased expression levels of miRNA-146a-5p, miRNA-23a-3p, and miRNA-21-5p in the plasma secretion were significantly associated with the disease activity of SLE patients, and the combined model of the three could be potentially employed for SLE diagnosis. Given the unique biological structure of EXOs, they can cross different biological barriers and play a significant role. As our knowledge about EXOs expands, research indicates that exosomal miRNAs could potentially revolutionize disease diagnosis.

To sum up, there is a significant correlation between SLE and differences in the composition of EXOs. It has been found that various sources of exosomal miRNAs can participate in autoimmune regulation by targeting UVRAG and *KLF13* expression to regulate cell proliferation and apoptosis. The development of new diagnostic methods for SLE is greatly aided by the high specificity and sensitivity of urinary EXOs, offering a non-invasive and convenient approach. However, research in this field is relatively sparse and requires further exploration.

EXOs AND RHEUMATOID ARTHRITIS (RA)

RA is a chronic inflammatory AID that involves inflammation of the joints, leading to pain, swelling, and limited mobility. An elevated level of chronic inflammation in the body can lead to higher mortality rates. The exact cause behind development of RA is not yet fully understood, there is no specific drug available to cure it (25).

Numerous studies have indicated that (26) EXOs released from synovial fluid or synovial fibroblasts actively contribute to the development of joint ailments. Conversely, blood-derived EXOs have proven effective in detecting joint diseases, while EXOs extracted from stem cells have been found to play a role in joint repair. The reason for the differences in the functions of EXOs may be due to the different components of EXOs from different cell sources, such as synovial fluid or synovial fibroblasts, which release EXOs containing pro-inflammatory cytokines, while stem cell-derived EXOs may contain molecules beneficial for joint repair. Wang et al. (27) found that the decreased prevalence of circulating regulatory T cells could be a sign of inflammatory RA (28). They also observed that plasma-derived exosomal miR-17 can suppress Treg induction by inhibiting the expression of transforming growth factor expressed by T cells. The decrease of Treg may promote the onset of RA, but MSC-derived EXOs promote the proliferation of Treg cells and exert a protective effect against inflammation. By isolating MSC-EXOs from overexpressed miR-146a/miR-155, the production of proinflammatory cytokines can be reduced. This process can also play a pivotal role in the regulating Th1/Th2, Th17/Treg balance and regulation of immune response, which provides a novel approach for the treatment of RA with miRNA. Thus, EXOs contained in specific types of cells can provide insights into the cell's role, such as the proliferation and differentiation potential of stem cell-derived EXOs. Interestingly, it was found that (29,30) TNF-α was present in a membrane-bound form in fibroblast EXOs derived from RA patients, whereas osteoarthritic fibroblast EXOs were devoid of TNF-α. Furthermore, TNF-α-stimulated exosomal lncRNA (TRAF1)-4:1 derived from RA-FLS can effectively degrade Chondrocyte extracellular matrix, by up-regulating the target gene *CXCL1* of miR-27a-3p, which has a pronounced effect on inhibiting the proliferation and migration of chondrocytes. These observations suggested that EXOs from RA patients fibroblasts might influence the biological functions of this condition and possibly contribute to its pathogenesis. Chen et al. (31) discovered that the use of miR-486-5p in EXOs derived from RA-FLSs-exo can alleviate the damage to bones caused by RA. This is achieved by reducing the expression of its target

gene *Tob1* and enhancing the differentiation of osteoblasts. This differentiation was facilitated by activating the BMP/Smad signaling pathway and inhibiting *Tob1*, which was found to be beneficial for RA alleviation. In addition, other studies found that (32) RA-FLS-exo contained an inhibitor of DNA binding 1, which could be activated by the JNK signaling pathway and promote angiogenesis at the site of inflammation, causing FLS proliferation. It is reported (33) that ultrasmall Prussian blue nanoparticles(uPB-Exos) can selectively neutralize the various pro-inflammatory factors and attenuate oxidative stress in activated fibroblastoid synoviocytes. This not only improves joint injury and reduces inflammation in CIA rats but also regulates the Th17/Treg cell balance. These discoveries emphasize the potential of engineered EXOs in treating RA, opening up new opportunities for cell-free therapy and regulation of T cell balance. Moreover, In the CIA mouse model (34), it has been observed that exosomal miR-150-5p, originating from MSC-EXOs, can effectively block the proliferation and invasion of RA chondrocytes. This is achieved by targeting *MMP14* and *VEGF*, which in turn can inhibit angiogenesis and synovial hyperplasia to significantly mitigate joint destruction, thus highlighting the superiority of EXOs as a therapeutic carrier. Interestingly, hUCMSC-Exos loaded with miR-451a can inhibit the proliferation, migration, and invasion of synovial fibroblasts in CIA rat models by targeting ATF2, thereby improving joint inflammation (35). This finding not only improves our understanding of joint inflammation but also suggests a potential therapeutic application of EXOs as drug delivery vehicles. Other study further supports this notion by demonstrating the anti-inflammatory properties of EXOs carrying the super-repressor IκB in animal models and in co-cultures with immune cells from RA patients (36). These findings provide strong evidence that EXOs can be used as therapeutic drug delivery vehicles. Furthermore, Yao et al. (5) discovered that the down-regulation of lncRNA HOTTIP of RASF-derived EXOs can substantially attenuate the deterioration of RA through the miR-1908-5p/STAT 3 (signal transducer and activator of transcription 3) axis, thus suggesting HOTTIP could serve as an effective therapeutic tool for RA patients which has been shown to correlate with Th17/Treg cell ratio balance in in-vitro experiments. The imbalance between the activities of pro-inflammatory M1 and anti-inflammatory M2 macrophages in RA can lead to synovitis and autoimmunity. Interestingly, macrophage biomimetic load M2 EXOs can target and exhibit notable anti-inflammatory properties (37).

To sum up, the pathogenesis of RA can be modulated by EXOs secreted by various cells, particularly through differences in the population of T cells. Notably, the differential expression of endogenous miRNA within these EXOs can either promote or suppress inflammation, further influencing the development of RA.

EXOs AND AUTOIMMUNE THYROID DISEASES (AITDs)

AITDs is a group of thyroid diseases caused by autoimmune disorders, characterized by the detection of autoantibodies against thyroid Ags in the blood of patients, lymphocyte infiltration in the thyroid tissue, and destruction of follicular structures. Common AITDs include Graves' disease (GD) and Hashimoto's thyroiditis (HT). It has been reported that genetic susceptibility and environmental factors are involved in the pathogenesis of AITDs. However, the pathogenesis of autoimmune thyroiditis is not fully understood, and its treatment regimen is not well established (38).

Several factors contribute to the pathogenesis of AITDs. A study found (39) that miR-326 in PBMCs and thyroid tissue can target regulate Th17 cells in HT patients, thereby participating

in autoimmune thyroiditis. However, after targeted inhibition of miR-326 in AITDs rat model, abnormal expression of Ets-1 and ADAM17 proteins and the degree of inflammation was significantly reduced. This suggests that miR-326 can target and regulate Ets-1 and ADAM17 to affect Th17 cell differentiation and participate in the pathogenesis of AITDs. Moreover, another report indicated that (40) HT patient serum derived exosomes (HT-EXOs) can activate NF-κB signaling pathway in DCs, thereby causing an up-regulation in the expression of costimulatory molecules and an increase in IL-6 release. In addition, HT-EXOs can bind with DCs TLR 2/3increasing their expression and can effectively regulate the differentiation and cytokine secretion of Th1, Th17 and Treg cells. This provides the first evidence that the effect of HT-EXOs on $CD4^+$ T lymphocytes differentiation may be mediated by DCs, providing new insights into the pathogenesis of HT. Moreover, Cui et al. (41) found that HT-EXOs can present Ag to DCs and bind to TLR2/3. NF-κB signaling pathway can also cause DCs activation, leading to an imbalance in $CD4^+$T lymphocyte differentiation, thus potentially promoting HT. Another study found (42) that the serum EXOs of GD patients can stimulate the expression of TLR2 and TLR3 in DCs. In addition, HSP60 in EXOs can bind to TLR2 in DCs, thus stimulating PBMCs to secrete different inflammatory factors such as IL-6 and IL-1β, which are involved in the pro-inflammatory response. A study conducted by Hiratsuka et al. (43) found that the serum secretion levels of miR-23b-5p and miR-92a-39 in remitting GD patients increased significantly in comparison to with refractory and remitting GD patients, whereas the levels of Let-7g-3p and miR-339-5p were decreased significantly. In addition, it was also observed in this study that the miRNAs present in the serum EXOs of refractory GD patients showed elevated expression of IL-1β and TNF-α mRNA compared to the healthy controls. These findings could have significant implications for both understanding the pathogenesis of GD and developing effective treatments. According to one report (44), analysis of plasma EXOs from GD patients can display a specific increase in the expression of hsa_circRNA_000102, which may mediate multiple immune activation pathways in GD, particularly related to viral infection and IFN-β signal transduction.

Overall, EXOs are essential contributors to disease development as they specifically impact the expression of regulatory proteins. Moreover, due to their Ag presentation specificity, they can activate NF-κB, IFN-β signaling and viral infection pathways. The identification of differentially expressed miRNAs provide a basis for accurate diagnosis of GD. Currently, there is a limited amount of research on the mechanism of EXOs in AITDs, indicating the need for further exploration.

EXOs AND SJOGREN'S SYNDROME (SS)

SS is a chronic AID that primarily affects the lacrimal glands, salivary glands, and other exocrine glands. This disease is also known as autoimmune exocrine gland disease and its key symptoms include dry cornea, conjunctivitis, as well as xerostomia. SS is a chronic AID that mainly affects exocrine glands such as the lacrimal and salivary glands. Typical symptoms include dry mouth and eyes, fatigue, and joint pain, and may also include blood system damage such as leukopenia, anemia, and thrombocytopenia. Due to the diverse clinical manifestations, SS is easily overlooked or misdiagnosed. Currently, there is no specific treatment for the disease. Although some therapeutic drugs show some effect, they also increase the risk of infection and malignancy in patients. The cause and pathogenesis are not fully understood (45,46).

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It has been reported that (47) EXOs are closely related to the progression of SS. For example, in SS patients, the immune system can identify the Ags present in the EXOs secreted by salivary gland epithelial cells. These EXOs contain various cytoskeletal protein, anti-Ro/SSA, anti-La/SSB and Sm ribonucleoprotein, and their antigenicity can be recognized by the immune system. Cortes-Troncoso et al. (48) found that the T cell-derived EXOs miR-142-3p was substantially overexpressed in the salivary glands of SS patients. miR-142-3p was found to target expression of various proteins (such as SERCA2B, RyR2, AC9), which has been implicated in calcium signaling and protein secretion of salivary gland endothelial cells, thereby affecting intracellular Ca^{2+} signaling, epithelial cell function as well as reducing cAMP and amylase production. These findings suggest that miR-142-3p could potentially play a role in the pathogenesis of SS. Furthermore, Gallo et al. (49) discovered that the transfer of Epstein-Barr virus (EBV) infected B-cell-specific miRNA (ebv-miR-BART13-3p) from B-cells to salivary gland epithelial cells occurred through EXOs. This transfer had an impact on the calcium signaling function, which may be related to the occurrence and development of SS due to EBV. It is worth investigating whether other microorganisms, aside from viruses, can have a similar impact on cells, considering that virus-infected EXOs can also affect various diseases. Additionally, other reports have indicated that (50), the EXOs derived from the lip gland mesenchymal stem cells (LGMSCs) can inhibit the differentiation of Th17 and promote the expression of Treg cells in SS peripheral lymphocytes *in vitro*, whereas expression of IL-17, IFN-γ and IL-6 decreased, but that of TGF-β and IL-10 was increased. This discovery opens a novel avenue for the therapeutic use of LGMSCs in SS treatment. Furthermore, EXOs (51) obtained from the supernatant of stem cells derived from human exfoliated deciduous tooth can significantly augment ZO-1 expression and paracellular permeability in glandular epithelial cells. This was achieved by inhibiting Akt/GSK-3/Slug pathway, thus improving the salivary secretion deficiency caused by SS and providing a promising direction for treating SS induced sialadenitis. An important observation is that (52,53), T cells have also been found to play an essential role in primary Sjogren's syndrome (pSS) as well. In patients with pSS, lymphatic tissues can secrete different cytokines that stimulate the expression of Th1, Th2, and Th17 cells. Additionally, there is a noticeable increase in the expression levels of follicular helper T cells markers CXCR5 and IL-21. The occurrence of disease is promoted due to an imbalance between the number of Treg cells and the number of Th17 cells when compared to the healthy control. Other studies have also found that (54) human umbilical cord mesenchymal stem cell-derived exosomes can inhibit abnormal proliferation of $CD4^+$T cells and their apoptosis. They can also regulate the balance of Th17 and Treg cell numbers, suppress the secretion of pro-inflammatory factors like IFN-γ, TNF-α, IL-6, IL-17A, as well as IL-17F from $CD4^+$ T cells and induce the secretion of anti-inflammatory factors like IL-10 and TGF-β. These results are crucial in understanding $CD4^+$T cell immune regulation and cytokine balance, potentially opening doors for new therapeutic targets in pSS treatment.

In summary, EXOs play a multifunctional role in immune presentation. They exhibit differential expression in their miRNA, protein, and self-content, which are beneficial to the diagnosis and treatment of SS by affecting the Ca^{2+} and Akt/GSK-3/Slu signaling pathways. Furthermore, EXOs can regulate the inflammatory response in SS by influencing the expression of peripheral lymphocytes.

EXOs AND MYASTHENIA GRAVIS (MG)

MG is an AID that can be classified into two major types: ophthalmic myasthenia gravis (OMG) and generalized myasthenia gravis (GMG). The development of this disease occurs due to the reduction of acetylcholine receptors at the nerve junctions and is primarily mediated by T cell-dependent anti-acetylcholine receptor antibodies. The main characteristics include fatigue and weakness of local or systemic striated muscle activity. Due to the complex causes of MG, there is currently no quick and effective method to cure MG.

Interestingly, a study encompassing 18 individuals with OMG, 26 patients with GMG, and 44 healthy controls has revealed significant variations in the expression levels of miR-1224-5p isolated from plasma EXOs across the three groups (55). In comparison to the healthy controls, both studies found that (56,57) hsa-miR-1273f was significantly downregulated in GMG but upregulated in OMG. The expression of miR-23a-5p was increased in GMG whereas that of hsa-miR-516-5p was significantly decreased. Both miR-6843-3p and miR-3128 levels were upregulated in GMG, while miR-106a-5p levels were significantly reduced in OMG and GMG. These abnormal levels of miRNA may play a role in the development of MG by regulating gene expression, potentially serving as a diagnostic biomarker for MG. Furthermore, exosomal miRNA was found to be differentially expressed in MG patients, with a significant reduction in miR-106a-5p levels. These reduced levels correlated with the severity of MG, as indicated by quantitative MG scores, thus suggesting the importance of miR-106a-5p expression in different types of MG (58,59). However, overexpression of exosomal miRNA-146a derived from DCs has an inhibitory effect on experimental autoimmune MG and can effectively decrease the levels of both CD80 and CD86. These findings provide a novel basis for Ag-specific treatment of MG (60). Moreover, Lu et al. (61) conducted a study involving the sequencing of exosomal lncRNAs and found that expression of lncRNAs was significantly abnormal in MG patients, with 378 up-regulated and 348 down-regulated. The various differentially expressed lncRNAs genes may be involved in the regulation of MG biology and immune-related pathways. Furthermore, another study (62) reported that reduction in serum exosomal miR-150-5p and alleviation of MG symptoms in 12 acetylcholine receptor Ab-positive with refractory MG patients were affected by low-dose rituximab. This drug is known for its therapeutic impact on acetylcholine receptor Ab-positive MG and can reduce autoantibodies by targeting the B lymphocyte membrane protein CD20. This association could be potentially related to the communication between miR-150-5p and $CD19^+$, $CD27^+$ cells. In addition, EXOs can regulate muscle development and repair damage in several muscle diseases. For example, EXOs derived from skeletal muscle have been shown to promote the proliferation of skeletal muscle stem cells while inhibiting their differentiation, thereby regulating the function of skeletal muscle stem cells (63,64). The relevant regulatory mechanisms involved in the release of multiple signaling molecules from EXOs still need to be investigated further. In MG, abnormal expression of EXOs-associated miRNA can potentially regulate the inflammatory response, thus offering a fresh perspective for both disease treatment and diagnosis. A research project aimed at identifying miRNA present in human serum EXOs as potential diagnostic markers for severe ophthalmoplegia is currently in progress (NCT05888558).

Currently, there are few studies that investigate the function of EXOs in MG. Scientific research has revealed that the differential expression of exosomal miRNA is linked to the regulation of genes and the immune system. In relation to MG, it is possible that miR-1273f and miR-106a-5p could function as innovative diagnostic markers and offer fresh approaches to treatment.

EXOs AND TYPE 1 DIABETES (T1DM)

T1DM is an AID, which occurs when the cells responsible for producing insulin in the pancreas are targeted and destroyed by the body's immune system, leading to inadequate insulin production. In clinical settings, physicians encounter significant obstacles when it comes to managing steady blood sugar levels, preventing as well as treating multiple complications, and enhancing the quality of life for patients. Moreover, scientists are actively pursuing more effective treatment options, such as pancreatic islet cell transplantation or gene therapy, all the while addressing the ethical and regulatory obstacles that come along with them.

For instance, a study revealed that miR-25, derived from MSC-EXOs, could down-regulate the expression of *CXCR3* on T cells. This implies that it has the potential to suppress the immune-modulating role of activated T cells, mitigate T cell infiltration into the pancreas and produce a positive impact in alleviating the symptoms of T1DM. Additionally, it was observed that EXOs derived from MSCs demonstrate greater therapeutic and regenerative effects in T1DM compared to MSCs alone (65,66). Zhang et al. (67) utilized mass spectrometry to meticulously examine the protein composition of plasma EXOs derived from six individuals with type 1 diabetes and six healthy individuals. They discovered a remarkable 159 proteins that exhibited distinct expression patterns between the two groups, with 37 proteins being up-regulated and 122 proteins down-regulated. The KEGG pathway enrichment analysis of these proteins pinpointed intriguing connections to the coagulation and complement cascade as well as cholesterol metabolism. This groundbreaking research offers fresh perspectives for the diagnosis of T1DM (65). Moreover, another study indicated that (68), TNF-α-treated human umbilical cord mesenchymal stem cell-derived EXOs (TNF-α-EXOs) can also show promising potential in effectively treating T1DM.These EXOs have been observed to reduce the proportion of $CD4^+$T, Th1 and Th17 cells, while increasing the proportion of Tregs cells. This unique mechanism allows TNF-α-EXOs to actively contribute to immune suppression through the PD-L1/PD-1 signaling pathway, playing a vital role in maintaining immune tolerance and inflammation regulation. Furthermore, exosomal lncRNAs have been reported (69), to be significantly associated with T1DM and involved in regulating organ communication, cell viability, insulin signaling. In another elegant study, Pang et al. (70) found plasma-derived exosomal lncRNAs were differentially expressed. When compared with the healthy controls, 77 out of 162 differentially expressed exosomal lncRNAs were up-regulated and 85 were down-regulated. By analyzing the expression profile of plasma exosomal lncRNAs through whole-genome RNA sequencing of circulating leukocytes in T1DM patients identified 9 significantly differentially expressed lncRNAs (71). Another study conducted an analysis and proposed that a set of 26-lncRNA features could be utilized to identify T1DM and healthy individuals. Furthermore, these lncRNAs were found to have a specific role in in signal pathway conduction and regulation of immune response (72).

The above studies have demonstrated a significant association between the levels of proteins, lncRNAs, miRNAs, and other substances derived from EXOs, and AIDs. These substances actively participate in the regulation of various signaling pathways, immune tolerance, and inflammation. Thus, these substances may serve as a novel diagnostic and therapeutic strategy for T1DM, and have enormous potential in the pathogenesis of T1DM.

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EXOs AND MULTIPLE SCLEROSIS (MS)

MS is an AID primarily characterized by an inflammatory demyelinating lesion in the central nervous system white matter. The main manifestations are numbness of hands and feet, weakness of limbs, dizziness and foot pain, unstable walking, as well as decreased vision (73). Although it is currently believed that MS is mainly caused by genetic susceptibility and exposure to environmental factors, the exact pathogenesis of MS remains unclear.

MS can be broadly divided into relapsing-remitting MS (RRMS) and secondary progressive MS (SPMS). A study conducted by Galazka et al. (74), observed that EXOs derived from the serum, cerebrospinal fluid, and PBMCs of patients with RRMS and SPMS primarily contained three myelin proteins-myelin basic protein, proteolipid protein, and myelin oligodendrocyte glycoprotein (MOG). Interestingly, the amount of MOG EXOs was significantly elevated in comparison to the control group. Serum-derived EXOs were found to induce the proliferation of MOG-T cells and enhanced or prolonged the anti-myelin immune response in MS, thus suggesting that MOG EXOs are significantly associated with the disease and could serve as a novel marker. Zhang et al. (75) and Li et al. (76) jointly found that BMSCs-EXOs have the ability to balance the M1/M2 phenotype of microglia in EAE mouse model. This was achieved by promoting the transition from the M1 pro-inflammatory phenotype to the M2 anti-inflammatory phenotype, thereby alleviating inflammation and demyelination in the central nervous system. Furthermore, these EXOs could also inhibit the expression of TNF-α and IL-12 but enhance the expression of IL-10 and TGF-β. And may have tremendous potential in the treatment of various neuroinflammatory diseases, In the cuprizone diet model (75), MSCS-EXOs derived from rhesus monkey were found to possess the ability to not only cross the blood-brain barrier to target nerve cells, but also to increase the level of myelin basic protein, which has a significant effect on enhancing remyelination. In addition, BMSCs-EXOs that contained miR-23b-3p (77), were able to effectively reduced microglial inflammation and pyroptosis *in vivo* by specifically binding to and inhibiting *NEK7* expression. BMSCs-EXOs-miR-367-3p (78) also inhibited microglial ferroptosis by targeting *EZH2* and mediating SLC7A11 expression to alleviate the different symptoms associated with EAE. Another potential avenue for treating and preventing MS arises with the specific targeting of miR-23b-3p and miR-367-3p. Intriguingly, small RNA sequencing of the blood serum-derived EXOs revealed that their miRNAs were differentially expressed in RRMS (miR-15b-5p, miR-451a, miR-30b-5p, miR-342-3p) and SPMS (miR-127-3p, miR-370-3p, miR-409-3p, miR-432-5p), thus presenting fresh implications for MS classification, diagnosis, and potential use as new biomarkers (79). Furthermore, it was found that (80) the EXOs derived from neural stem cells with overexpression of platelet-derived growth factor-A exhibited targeted delivery ability and the combination of traditional Chinese medicine with stem cell-derived EVs displayed great potential in stimulating the nerve and myelin regeneration in MS (81).

Various studies have indicated that EXOs, originating from different sources are playing an increasingly vital role in the classification and diagnosis of MS. They not only aid in in reducing inflammatory responses and boosting the myelin regeneration but also possess the capability to cross the biological barrier and target the expression of nerve cells. It is worthwhile to explore the potential therapeutic application of MSC-derived EXOs in regulating immunity in the experimental autoimmune encephalomyelitis (EAE) mouse models. This could lead to the development of more efficient approaches in developing novel treatments and preventive measures for MS.

APPLICATION PROSPECT OF EXOs TREATMENT

At present, EXOs have demonstrated immense potential in the therapeutic field. With continuous in-depth research, there is an anticipation that EXOs could evolve into a novel form of therapeutic drug. EXOs can exhibit therapeutic potential across multiple areas, including joint repair, pro-inflammation, anti-inflammation, angiogenesis, tissue repair, and organ transplantation. The transfer of EXO-miRNA represents a novel mode of communication between immune cells and insulin-producing cells. EXO (miR-142-3p, miR-142-5p, miR-155) from the rodent and human T cells can be effectively transferred to β cells in an active form to promote apoptosis. This process has been found to play a crucial role in insulin regulation, reduction of inflammatory response and protection against the development of diabetes in non-obese diabetic mice (82). Exosomal miR-204-5p, derived from the plasma can mediate the communication between immune and synovial fibroblasts cells, inhibit cell proliferation and alleviate the symptoms of CIA mice, which can be employed as a potential biomarker for RA (83). EXOs derived from IFN-γ -stimulated MSCs (IFNγ-EXOs) can significantly elevate $CD4^+CD25^+FOXP3^+$ levels in the spinal cord of EAE mice. This increase can lead to a higher count of Tregs cells, thereby generating immune tolerance and playing an essential anti-inflammatory and neuroprotective role in autoimmune and central nervous system diseases (84). In addition, IL-6 secreted by olfactory ecto-mesenchymal stem cell-derived EXOs can activate Jak2-signal transducer and activator of Stat3 signaling pathway in myeloid-derived suppressor cells and subsequently enhance the immunosuppressive function of myeloid-derived suppressor cells to alleviate the development of mice with experimental Sjögren's syndrome. Interestingly, BAF2 can inactivate Jak2/stat3 pathway, whereas BMSCS-EXOs can inhibit miR-5189-3p to promote apoptosis of FLS through BAF2/Jak2/stat3 pathway. This observation could form the foundation for using BMSCs in the treatment of ankylosing spondylitis (AS) (85,86). Despite these findings, there are limited reports on AS, posing a significant challenge in identifying other potential therapeutic targets. Another study discovered elevated expression levels of miR-155 in PBMC derived EXOs obtained from Chilean patients with T1DM, in comparison with the control group. Conversely, the expression of miR-146a and miR-326 was found to be decreased, thereby suggesting a strong correlation with novel markers of autoimmunity or inflammation (87). Currently, it is understood that EXOs derived from various sources can substantially impact the progress of AIDs and possess promising potential to serve as therapeutic drugs and new biomarkers. Further research is needed to unravel whether additional signaling pathways, mediated by EXOs, can effectively contribute to the development of AIDs. Such exploration would set the foundation for the widespread application of EXOs as novel drug modulators, therapeutic vectors, and cell-free therapies.

SUMMARY AND PROSPECT

EXOs have proven to be highly versatile in their effects on AIDs. They have the ability to impact various aspects of the immune system, including the inflammatory response, immune regulation, immune presentation, immune tolerance, cell expression, gene regulation, cytokine regulation, tissue loss as well as repair, cell proliferation, apoptosis, and the modulation of effector functions through associated signaling pathways. The differential expression of EXO-related substances, including miRNA and proteins is involved in targeting and versatility can play a significant role in management of different AIDs (**Table 1**). These EXOs specific functions, targeting capabilities, and driving mechanisms have been shown to

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Table 1. The role of non-coding RNAs in the pathogenesis of AIDs

Types of autoimmune diseases	Source	RNAs/Expression	Function	References
SLE	BMMSCs-Exos	miR-10a-5p↑	Promoted cell proliferation and inhibited apoptosis	(18)
SLE	Plasma-Exos	miRNA-146a-5p ↑ miRNA-23a-3p↑ miRNA-21-5p↑	Auxiliary diagnosis	(24)
RA	BMSC-Exos	miR-146a/miR-55	Regulation of immunity	(28)
RA	RA-FLS-Exos	lncRNA (TRAF1)-4:1↑ miR-486-5p	Regulation of chondrocyte expression Activation of BMP/Smad signaling pathways	(30,31)
RA	MSC-Exos	miR-150-5p↑	Targeted expression inhibits synovial hyperplasia and angiogenesis	(34)
RA	MSC-Exos hUcMSC-Exos	miR-205-5p↑ miR-140-3p↓	Inhibition of inflammatory response and related signaling pathways, up-regulation of SGK1 can reduce joint damage	(88,89)
SS	T-EXOs	miR-142-3p↑	Signaling pathway transduction Targeted Protein Expression	(48)
MG	Plasma -EXO	miR-23a-5p↑ hsa-miR-516-5p↓ hsa-miR-1273f↓ miR-3182↑ miR-6843-3p↑ miR-106a-5p↓	Differential expression provides AIDvantages for MG subtype diagnosis	(56-59)
MG	DC-EXOs	miRNA-146a↑	CD80/CD60 reduce	(60)
T1DM	PBMC-EXOs	miR-155↑ miR-146a↓ miR-326↓	Autoinmmunity (ZnT8) and inflammatory status (vCAM).	(87)
T1DM	MSCs-EXOs	miR-25↑	Targeting CXCR3 expression T-cell differentiation was reduced	(65)
MS	BMSCs-EXOs	miR-23b-3p↑ miR-367-3p↑	Targeted regulation of cellular expression Reduce inflammation	(77,78)

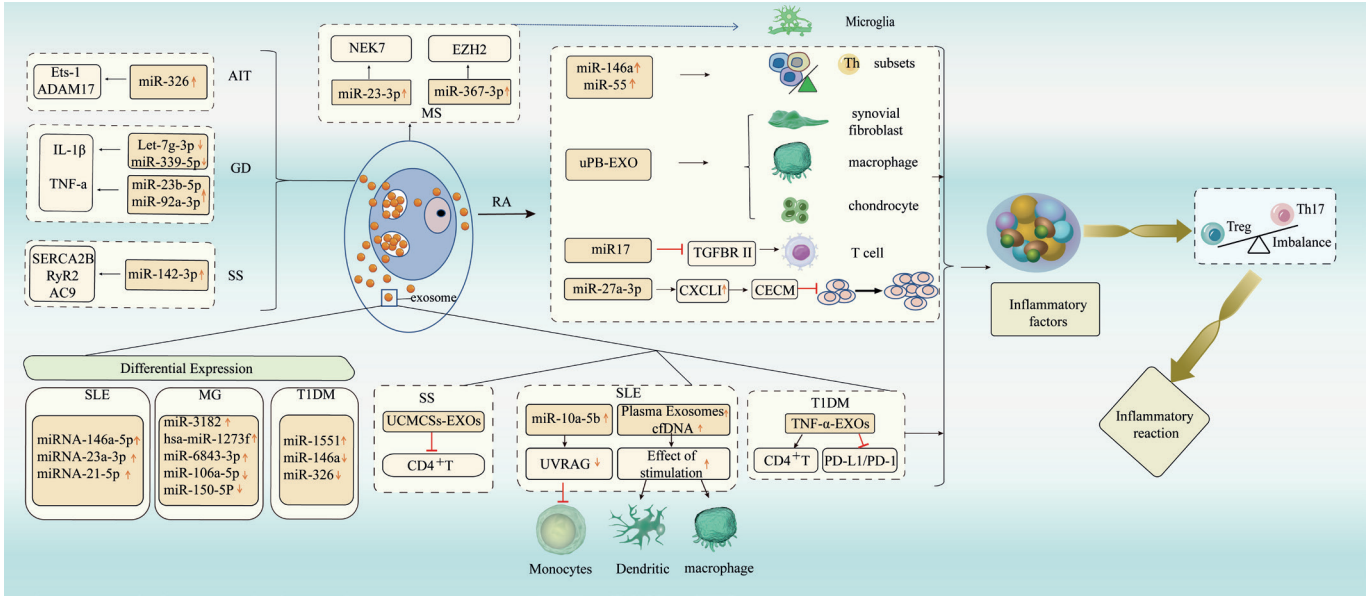

Figure 2. Abnormal levels of EXO are involved in the occurrence and development of AIDs. Exosome-related proteins and miRNAs are abnormally expressed in autoimmune diseases, playing an important role in suppressing inflammation or promoting inflammatory responses.

be vital in facilitating cell communication (**Fig. 2**). Furthermore, the differential expression of related substances have reference value for disease diagnosis and treatment, potentially serving as new biomarkers.

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Although EXOs exhibit numerous biological functions, ensuring the production of highly pure and high-quality EXOs preparations on a consistent basis remains a significant challenge. Furthermore, the accuracy and specificity of EXOs in the diagnosis of AIDS is still limited, as most studies have been conducted on a small scale. Larger-scale studies are needed to validate these findings. Additionally, the diversity of EXOs sources and the selection of suitable carriers for EXOs packaging pose significant challenges. Despite all of this knowledge, the precise intrinsic mechanism, intrinsic activity diagnostic mechanism, and exact therapeutic target of EXOs in AIDs have yet to be fully understood. Therefore, future research should focus on uncovering the exact intrinsic mechanism and exploring the potential clinical therapeutic applications of EXOs. This could pave the way for novel drugs and additional options for diagnosing and treating AIDs as well as other related conditions.

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