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Exosomal non-coding RNAs: gatekeepers of inflammation in autoimmune disease

Mohamed J. Saadh[1*], Omer Qutaiba B. Allela[2], Ali Fawzi Al-Hussainy[3], Lalji Baldaniya[4], M. M. Rekha[5], Deepak Nathiya[6], Parjinder Kaur[7], Zafar Aminov[8], Hayder Naji Sameer[9], Huda Ghassan Hameed[10], Zainab H. Athab[11] and Mohaned Adil[12]

Abstract

Autoimmune diseases (AIDs) are marked by systemic inflammation and immune dysregulation, yet current therapies often fail to target their underlying causes. Emerging evidence positions exosomal non-coding RNAs (ncRNAs)—including miRNAs, lncRNAs, and circRNAs—as key regulators of inflammatory pathways, providing critical insights into AID pathogenesis. This review synthesizes recent advances in how these ncRNAs orchestrate immune cell communication, modulate inflammatory mediators, and drive microglial activation in neuroinflammatory AIDs. It evaluates their dual role as disease amplifiers (e.g., miR-155 in lupus, miR-326 in rheumatoid arthritis) and therapeutic targets, emphasizing their potential to reprogram immune responses or deliver anti-inflammatory agents. In this review, we first provide a glimpse into the pathogenesis of autoimmune diseases and delve into the structure and function of exosomes, emphasizing their role in cell-cell communication. We then discuss the regulatory roles of exosomal ncRNAs in immune modulation, detailing their types, functions, and mechanisms of action. Finally, we examine the implications of exosomes and exosomal ncRNAs in the context of autoimmune diseases, with a particular focus on microglial activation and its contribution to neuroinflammation.

Keywords Autoimmune diseases (AIDs), Inflammation, Exosomes, Intercellular communication, Non-coding RNAs

*Correspondence:
Mohamed J. Saadh
msaadhmeu.edu.jo@proton.me
[1]Faculty of Pharmacy, Middle East University, Amman 11831, Jordan
[2]College of Pharmacy, Alnoor University, Nineveh, Iraq
[3]College of Pharmacy, Ahl Al Bayt University, Kerbala, Iraq
[4]Department of Pharmacy, Faculty of Health Sciences, Marwadi University Research Center, Marwadi University, Rajkot, Gujarat 360003, India
[5]Department of Chemistry and Biochemistry, School of Sciences, JAIN (Deemed to be University), Bangalore, Karnataka, India
[6]Department of Pharmacy Practice, Institute of Pharmacy, NIMS University Rajasthan, Jaipur, India
[7]Chandigarh Pharmacy College, Chandigarh Group of Colleges-Jhanjeri, Mohali, Punjab 140307, India
[8]Department of Public Health and Healthcare management, Samarkand State Medical University, 18 Amir Temur Street, Samarkand, Uzbekistan
[9]Collage of Pharmacy, National University of Science and Technology, Dhi Qar 64001, Iraq
[10]Gilgamesh Ahliya University, Baghdad, Iraq
[11]Department of Pharmacy, Al-Zahrawi University College, Karbala, Iraq
[12]Pharmacy College, Al-Farahidi University, Baghdad, Iraq

Introduction

Autoimmune diseases (AIDs) represent a spectrum of disorders characterized by the immune system's failure to distinguish self from non-self, leading to chronic inflammation and tissue damage [1, 2]. Central to AID pathogenesis is the dysregulation of immune tolerance, where autoreactive T and B lymphocytes are erroneously activated, perpetuating cycles of inflammation [1, 2]. Pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β play pivotal roles in amplifying these responses, often through inflammasome-mediated pathways like NLRP3, which promote caspase-1 activation and subsequent release of IL-1β and IL-18 [3]. This cascade drives immune cell infiltration and autoantibody production, contributing to disease manifestations such as synovial inflammation in rheumatoid arthritis, immune complex

deposition in systemic lupus erythematosus, and mucosal barrier disruption in inflammatory bowel disease [4–7].

Emerging evidence highlights the importance of exosomes—nanoscale extracellular vesicles secreted by various cell types—in regulating immune responses and mediating intercellular communication [8, 9]. Exosomes carry diverse molecular cargoes, including proteins, lipids, non-coding RNAs (ncRNAs) such as microRNAs (miRNA), long-non coding RNAs, and circularRNAs as well as cytokines, enabling them to modulate recipient cell behavior [8–10]. For instance, exosomes derived from mesenchymal stem cells or regulatory T cells exhibit immunomodulatory effects, suppressing pro-inflammatory cytokine secretion and enhancing regulatory T-cell activity [11]. Conversely, exosomes released by activated macrophages may propagate inflammation, underscoring their dual role in AID pathogenesis [12]. Therefore, understanding the intricate relationships between inflammation, immune dysregulation, and exosomal communication provides novel insights into AID pathobiology and opens avenues for innovative treatments to restore immune homeostasis [13, 14]. This review examines the critical role of exosomal ncRNAs in AIDs, focusing on their impact on immune dysregulation, inflammation, and neuroinflammation. It evaluates their dual role as both drivers of disease pathogenesis and potential therapeutic targets, while highlighting the promise of exosome-based strategies to restore immune balance and advance precision medicine through biomarker discovery, engineered therapeutics, and targeted drug delivery. By linking exosome biology with ncRNA mechanisms, the review provides insights into innovative interventions targeting the exosomal ncRNA-inflammation axis to improve patient outcomes.

The review was compiled by searching PubMed, and Google Scholar using keywords such as 'exosomes,' 'non-coding RNAs,' 'autoimmune diseases,' and 'inflammation.' Studies were selected based on their relevance to exosomal ncRNAs in AID pathogenesis, immune regulation, and therapeutic potential, prioritizing recent publications (2005–2025) and seminal works.

Pathogenesis of autoimmune diseases

Mechanisms of autoimmunity: self vs. non-self recognition

AIDs are characterized by the immune system's erroneous identification and attack on the body's own tissues, perceived as foreign. Fundamental mechanisms underlying autoimmunity involve complex interactions among genetic, environmental, and immunological factors that lead to dysregulated immune responses [15, 16].

At the core of autoimmune pathology is the failure of central and peripheral tolerance mechanisms, which normally differentiate self from non-self [17]. Central tolerance occurs in the thymus during T cell development, where thymocytes expressing high-affinity receptors for self-antigens are eliminated through negative selection. However, this process is not infallible, and autoreactive T cells can escape into peripheral tissues, where they may contribute to autoimmunity [18, 19]. Peripheral tolerance mechanisms, including anergy, clonal deletion, and the activity of regulatory T cells (Tregs), are essential for suppressing autoreactive lymphocytes that evade central tolerance. A breakdown of these mechanisms can activate and expand autoreactive T cell populations [20]. For instance, recent studies have shown that defective Treg function in systemic lupus erythematosus (SLE) leads to increased effector T cell activation, perpetuating autoimmunity [21].

Additionally, the concept of molecular mimicry, wherein foreign antigens share structural similarities with self-antigens, can precipitate autoimmunity [22]. A notable example is rheumatic fever, where cross-reactivity occurs between streptococcal M protein and cardiac myosin, leading to autoimmune damage in the heart after bacterial infection (Fig. 1) [23].

Chronic inflammation and immune dysregulation

Chronic inflammation drives AID by disrupting immune balance, impairing self-recognition, and causing tissue damage. This persistent inflammation intensifies autoimmune reactions, accelerates disease progression, and perpetuates a destructive cycle that worsens tissue destruction and sustains autoimmunity. Initially, an inflammatory response may be beneficial, aiding in pathogen clearance; however, in AIDs, this response becomes pathological. Chronic inflammation is marked by persistent immune cell recruitment, including T cells, B cells, macrophages, and dendritic cells, which release pro-inflammatory cytokines and chemokines, further amplifying the immune response [22, 24, 25].

Key cytokines, such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1 beta (IL-1β), are pivotal in driving inflammation across various AIDs [26, 27]. In rheumatoid arthritis, TNF-α has been implicated in joint tissue destruction by promoting synovial inflammation and osteoclast activation [28]. In SLE, elevated levels of IL-6 contribute to B cell activation and autoantibody production, exacerbating tissue damage [29]. A recent clinical study found that blocking IL-6 receptor (IL-6R) improved disease activity in patients with chronic inflammatory diseases, affirming its role as a therapeutic target [30, 31].

This persistent inflammatory milieu mediates tissue injury and poses a therapeutic target, as evidenced by the efficacy of anti-TNF therapies in both RA and SLE.

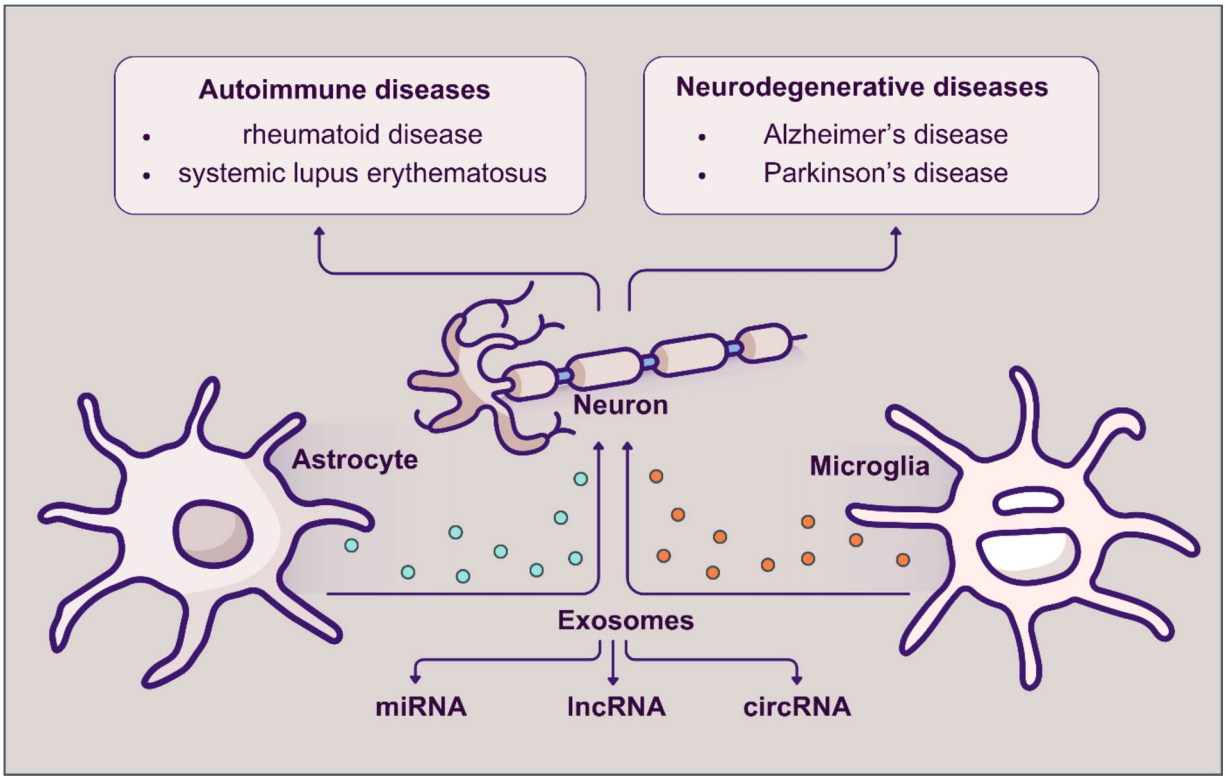

Fig. 1 The roles of exosomal non-coding RNAs (ncRNAs) in human autoimmune diseases. This figure illustrates the pivotal roles of exosomal ncRNAs in various human autoimmune diseases, including rheumatoid arthritis, systemic lupus erythematosus, Alzheimer's disease, and parkinson. Exosomal ncRNAs, such as microRNAs and long non-coding RNAs, are involved in regulating inflammatory responses and immune cell activation, contributing to the pathogenesis and progression of these diseases. Notably, altered profiles of exosomal ncRNAs in patients highlight their potential as non-invasive biomarkers for disease diagnosis, monitoring progression, and assessing treatment responses

Environmental and genetic triggers of autoimmunity

The complexities of AID pathogenesis are underscored by the involvement of various inflammatory mediators and signaling pathways. The nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway plays a central role in activating immune cells and regulating pro-inflammatory cytokines [32, 33]. Aberrant NF-κB signaling has been associated with several AIDs, including multiple sclerosis (MS) and RA, highlighting its potential as a therapeutic target. Recent studies have indicated that inhibiting NF-κB can reduce the production of inflammatory cytokines, paving the path for novel therapeutic interventions [34].

Inflammasomes, multi-protein complexes activating inflammatory caspases (e.g., caspase-1), are crucial for the maturation and secretion of pro-inflammatory cytokines such as IL-1β. Dysregulated inflammasome activity has been implicated in the pathogenesis of diseases, including systemic sclerosis and type 1 diabetes [35, 36]. The NLRP3 inflammasome has been shown to play a significant role in type 1 diabetes by contributing to pancreatic β-cell apoptosis through IL-1β secretion, underscoring inflammasome activation as a pivotal event in autoimmunity [1, 37, 38].

Furthermore, the interplay between inflammatory mediators and environmental factors, such as infections, exposure to toxins, and dietary influences, can significantly affect the onset and progression of AIDs [39]. For instance, alterations in gut microbiota have been shown to influence immune responses, correlating with the development of autoimmune pathology [40]. Recent findings suggest that certain bacterial strains (e.g., *Lactobacillus* spp, *Bifidobacterium* spp, *Faecalibacterium prausnitzii*, etc.) can enhance Treg function, proffering a potential preventive strategy against AIDs [41–43].

Exosomes: biogenesis, structure, and function

Overview of exosome biogenesis and secretion

Exosomes are nanoscale extracellular vesicles that play a pivotal role in intercellular communication and biomolecular transport within the extracellular environment [44, 45]. They are defined as small, membrane-bound vesicles ranging from 30 to 150 nanometers in diameter and are released by various cell types into the extracellular space [46]. Exosomes constitute a subtype of extracellular vesicles, distinguishable from larger microvesicles (ranging from 150 to 1,000 nanometers) and apoptotic bodies (larger vesicles formed during programmed cell

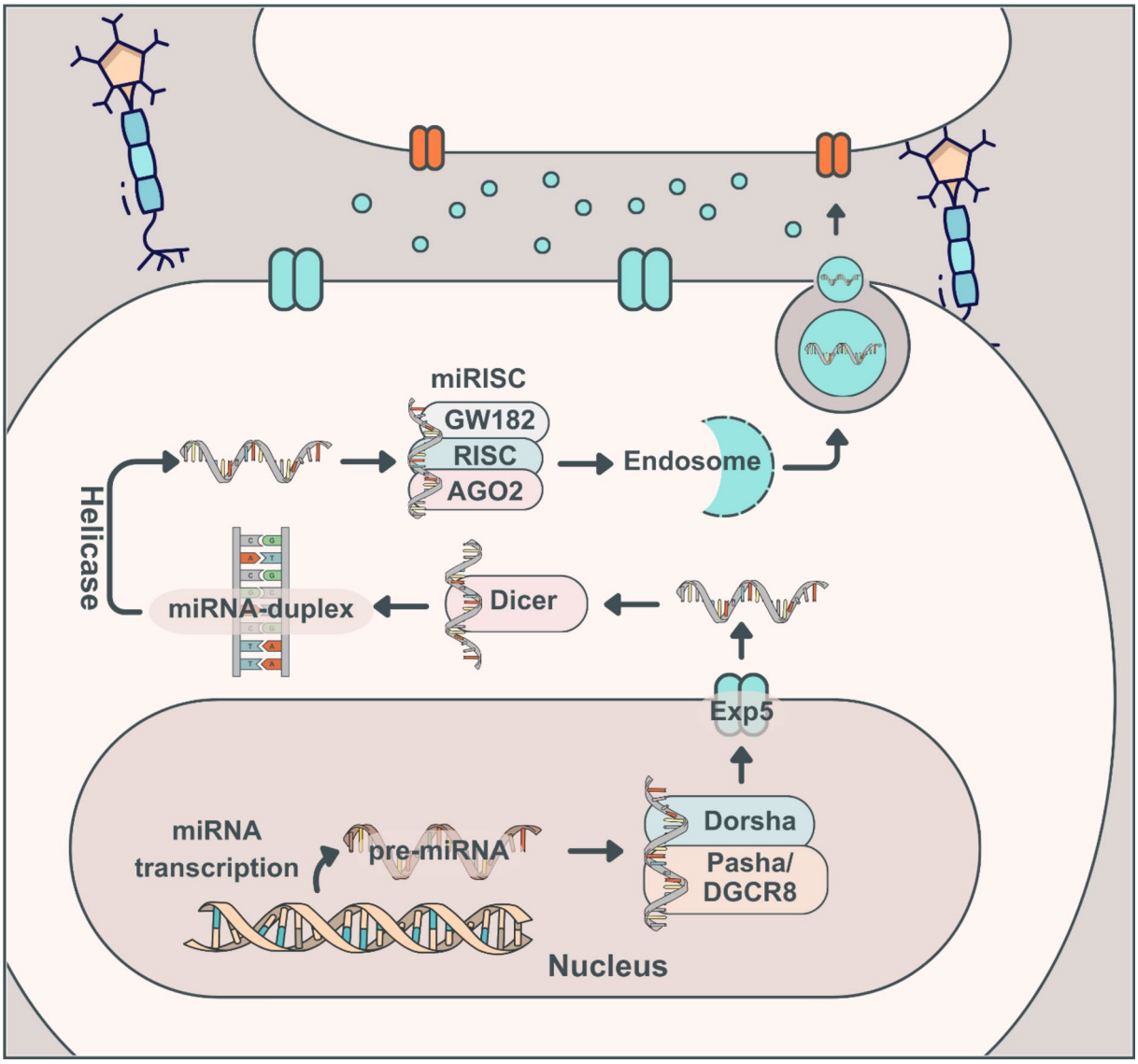

Fig. 2 This figure illustrates the biogenesis of exosomal microRNAs (miRNAs) and their trafficking pathways. The process begins with the transcription of primary miRNA (pri-miRNA) in the nucleus, where it is processed by different enzymes (including Drosha and Dicer) to form mature miRNAs. Once formed, these miRNAs are incorporated into the cytoplasmic RNA-induced silencing complex (RISC). Exosomes are generated from multivesicular bodies (MVBs) within the endosomal pathway, where miRNAs can be selectively packaged. The exosomes then bud off and are released into the extracellular space, facilitating intercellular communication. These exosomal miRNAs can influence recipient cells by regulating gene expression, thus playing critical roles in various biological processes and disease mechanisms

death). Their biogenic distinction primarily arises from their mode of formation and release [47].

Exosomes are composed of a lipid bilayer membrane encapsulating a diverse array of biomolecules, including proteins, lipids, RNA species, and metabolites [48]. The lipid composition of exosomes often features a predominance of sphingolipids and cholesterol, contributing to their stability and functionality. Proteomic analyses reveal that exosomes carry a unique cargo of proteins such as tetraspanins (e.g., CD63, CD81), heat shock proteins, major histocompatibility complex (MHC) molecules, and various enzymes that denote their cellular origin and function in interactions with recipient cells [49, 50]. As previously discussed, the molecular cargoes of exosomes play a critical role in facilitating intercellular communication (see "Introduction"). These cargoes enable the transfer of genetic information and modulate gene expression profiles in recipient cells, as illustrated in Fig. 2.

Exosome biogenesis begins with inward budding of the endosomal membrane, generating multivesicular bodies (MVBs) [51]. Within these MVBs, intraluminal vesicles are formed and subsequently released into the extracellular space upon fusion of MVBs with the plasma

membrane [52]. This process involves numerous cellular mechanisms regulated by proteins like the endosomal sorting complex required for transport (ESCRT) machinery, sphingolipid metabolism, and tetraspanin proteins [53].

The ESCRT machinery, including ESCRT-0, ESCRT-I, ESCRT-II, and ESCRT-III complexes, coordinates sorting of ubiquitinated proteins and lipid-rich regions into intraluminal vesicles, with proteins such as Alix and Tsg101 critical for the membrane remodeling necessary for the budding process. Specific lipids, including ceramide and phosphatidylserine, are implicated in membrane dynamics supporting exosome formation [54].

Exosomes can also be released in response to various stimuli, including cellular stress and cytokine signaling. This modulation can result in alterations in exosomal molecular composition, emphasizing the dynamic nature of exosomal secretion [55].

Exosomes as key regulators of intercellular communication

Exosomes facilitate intercellular communication through bioactive molecule transfer, enabling a myriad of biological effects in recipient cells. They can influence physiological processes such as immune modulation, tissue repair, and neuronal communication [56–58].

A key role of exosomes in immune modulation lies in their capacity to present antigens and facilitate immune responses [59]. Dendritic cells, for example, release exosomes containing MHC molecules and co-stimulatory signals, activating T cells and eliciting adaptive immune responses [60]. Furthermore, evidence suggests that tumor-derived exosomes can reprogram recipient immune cells to foster an immunosuppressive environment conducive to tumor growth and metastasis. For example, exosomal PD-L1 (programmed death-ligand 1) can inhibit T-cell activation and promote tumor progression [61, 62].

Exosomes also contribute to tissue repair processes. In myocardial infarction, cardiac stem cell-derived exosomes enhance reparative mechanisms by transferring mRNAs and miRNAs that promote angiogenesis and cardiomyocyte survival [52]. For instance, stem cell-derived exosomal miRNAs, such as miR-19a, miR-21, and others, show cardioprotective effects by improving cardiomyocyte survival and reducing fibrosis [63].

In the nervous system, exosomes facilitate communication through the transfer of neurotrophic factors and RNA species involved in synaptic transmission and plasticity. For instance, pathogenic proteins like amyloid-beta and tau may spread through exosomes in neurodegenerative diseases, suggesting a mechanism for propagating neurodegeneration within neuron networks [64, 65].

In summary, exosomes are integral mediators of intercellular communication characterized by distinct biogenic pathways and cargo composition [66]. Their abilities to facilitate favorable biological effects position them as significant players in various physiological and pathological processes, offering insights into potential therapeutic targets and biomarkers across disease landscapes [67].

Regulatory roles of exosomal non-coding RNAs in immune modulation

Types and functions of non-coding RNAs in exosomes

The intricate landscape of immunological regulation has expanded with the recognition that non-coding RNAs (ncRNAs), particularly those encapsulated within exosomes, play critical roles in modulating immune responses and influencing various pathological processes [68, 69]. Exosomes comprise diverse ncRNA types, broadly classified into microRNAs (miRNAs) and long non-coding RNAs (lncRNAs) [70].

MiRNAs, consisting of approximately 21–23 nucleotides, act as post-transcriptional regulators of gene expression. Numerous studies have demonstrated that exosomal miRNAs, such as miR-155 [71, 72], involved in T cell differentiation and macrophage function regulation, modulate immune responses by binding target messenger RNAs (mRNAs), resulting in mRNA degradation or translation inhibition [64].

LncRNAs, exceeding 200 nucleotides in length, emerge as critical regulators of gene expression through mechanisms such as chromatin remodeling and transcriptional interference. Exosomal lncRNAs, like lnc-IL7R, influence T helper cell differentiation and cytokine production during immune responses. Recent findings suggest that exosomal lncRNAs can also modulate gut microbiota interactions, thus influencing systemic inflammation and autoimmunity [73, 74].

CircRNAs are characterized by their covalently closed-loop structure generated from pre-mRNA back-splicing, making them resistant to exonuclease degradation. Exosomal circRNAs can act as competitive endogenous RNAs (ceRNAs), modulating miRNA availability for target mRNAs. For example, circRNA CDR1as effectively absorbs miR-7, consequently influencing immune-related gene expression in recipient cells [75, 76].

Exosomal NcRNAs in immune cell crosstalk

Exosomal ncRNAs influence immune responses through direct interactions with immune cell types, modulation of signaling pathways, and regulation of gene expression in recipient cells. For instance, exosomes derived from activated T cells are internalized via endocytosis by dendritic cells, releasing miR-146a to target IRAK1 and TRAF6, impairing antigen presentation and reducing T cell activation, thereby fostering an anti-inflammatory environment [77, 78]. MiR-146a is taken up by dendritic

cells via endocytosis and targets IRAK1/TRAF6, which reduces NF-κB signaling, mitigating neuroinflammation in conditions such as Alzheimer's disease [79].

Exosomal ncRNAs also regulate cytokine synthesis and release. For instance, exosomal miR-29a directly targets specific mRNAs involved in cytokine synthesis, modulating TNF-α and IL-6 production in macrophages, delineating a pathway for exosomes to impose regulatory effects on immune responses [80–82]. By degrading target mRNAs or inhibiting translation, exosomal ncRNAs finely tune protein production essential for maintaining immune homeostasis. For example, exosomes containing miR-181a specifically target Egr2 mRNA in T cells, which disrupts Egr2-mediated signaling pathways critical for T cell development and function [83].

Exosomal ncRNAs significantly influence inflammatory pathways, acting as amplifiers or suppressors depending on the delivery context and recipient cell state [84]. In rheumatoid arthritis, miR-326, derived from immune cells, enhances pro-inflammatory cytokine production by targeting Id1, promoting Th17 cell differentiation [85]. Conversely, exosomal miR-223 has demonstrated protective effects in acute inflammation by suppressing macrophage activation [86]. For example, a recent study showed that manipulating exosomal miR-223 could effectively reduce inflammation in animal models of osteoarthritis [87]. MiR-223 achieves this by targeting Stat3, which reduces pro-inflammatory cytokines, thereby enhancing its protective mechanism [86].

In neurodegenerative conditions, exosomal ncRNAs regulate neuroinflammatory processes. For instance, exosomal miR-146a is implicated in modulating inflammatory pathways in microglia, influencing neuroinflammation associated with Alzheimer's disease [88]. As mentioned above, miR-146a suppresses IRAK1 and TRAF6 signaling, dampening NF-κB activation in microglial cells, which switches microglial phenotypes to resist pathological processes and cognitive degradation [79].

Exosomal ncRNAs represent a critical axis in regulating immune responses and inflammatory pathways. Their diverse roles underscore the complexity of immune modulation, highlighting their potential for therapeutic exploitation in various diseases characterized by immune dysregulation. Recent findings emphasize the potential of exosomal ncRNAs as biomarkers and therapeutic agents, with specific examples like miR-223 and miR-146a showing promise in preclinical studies [89, 90].

Exosome-mediated immune dysregulation in autoimmune pathogenesis

The burgeoning field of exosome research reveals substantial insights into their involvement in AIDs, particularly through mediating intercellular communication and modulating immune processes [91, 92]. Exosomes, small extracellular vesicles, serve as carriers for proteins, lipids, and both coding and ncRNAs, significantly influencing AID pathogenesis. This section elucidates the involvement of exosomes in signaling pathways linked to inflammatory mediators, effects on innate immune cells, and impacts on adaptive immune responses [93].

Exosomal cargo as drivers of pro-inflammatory signaling

Exosomes actively participate in signaling pathways associated with inflammatory mediators, shaping the immune environment characteristic of AIDs [94]. They transport pro-inflammatory cytokines, chemokines, and signaling molecules, propagating inflammatory signals among various cell types [95]. In rheumatoid arthritis, exosomes from synovial fibroblasts have been shown to carry elevated levels of pro-inflammatory cytokines, such as IL-1β, TNF-α, and IL-6, which enhance the inflammatory response when engulfed by other immune cells, thereby perpetuating disease-associated chronic inflammation [96, 97].

Dual roles of exosomal NcRNAs in autoimmune amplification

The role of exosomal microRNAs is significant in modulating inflammatory signaling pathways. For example, exosomal miR-155 is frequently upregulated in systemic lupus erythematosus and multiple sclerosis; it targets Suppressor of Cytokine Signaling 1 (SOCS1), enhancing signaling through the Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway [98, 99]. This pathway is crucial in SLE pathogenesis [100]. Moreover, a recent study reported that miR-21 could modulate macrophage polarization in type 1 diabetes, promoting a pro-inflammatory state [101]. Moreover, miR-223 modulates innate immune responses, influencing cytokine production and immune cell differentiation [102]. On the other hand, it has been demonstrated that miR-125b contributes to the regulation of inflammatory processes by affecting pro-inflammatory cytokine production [103]. Additionally, miR-124 has been shown to suppress immune cell activity and reduce pro-inflammatory mediators, demonstrating anti-inflammatory effects [104]. MiR-31 is linked to the regulation of inflammation in response to stimuli, whereas miR-34a affects inflammatory signaling pathways by targeting specific mediators [105, 106]. Collectively, these exosomal miRNAs offer insights into the complex regulation of inflammation and hold therapeutic potential for inflammatory diseases [107].

Recently, it has been showed that exosomes derived from T cells of patients with relapsing-remitting MS exhibited elevated levels of miR-326, a miRNA previously implicated in promoting Th17 differentiation [108].

This suggests that miR-326 can actively contribute to the inflammatory response characteristic of MS by enhancing pathways that lead to immune activation and tissue damage. The altered expression of this miRNA in exosomes not only highlights its potential role in MS pathogenesis but also positions it as a prospective biomarker for disease activity and prognosis.

In examining the fluctuating expression of miRNAs across disease phases, recent studies have illuminated their associations with inflammation and cognitive function in MS [109]. The differential expression of miRNA, notably miR-155 and miR-301a, correlates with clinical parameters indicative of disease activity and neuropsychiatric states such as depression. Lower levels of these miRNAs during remission phases suggest a potential relationship between their expression and regulatory mechanisms governing immune tolerance and psychological health in MS patients. The presence of such correlations indicates that exosomal miRNAs might serve as valuable biomarkers for not only tracking disease progression but also for tailoring interventions aimed at mitigating cognitive deficits associated with MS. The utility of exosomal miRNAs in diagnostic and therapeutic applications is further supported by findings from cerebrospinal fluid (CSF) studies, where increased levels of specific miRNAs such as miR-21 and miR-146a/b were correlated with active inflammatory lesions [110]. These miRNAs may act as candidates for monitoring disease activity and response to treatment due to their ability to reflect ongoing inflammatory processes in the CNS. The identification of these miRNA profiles reinforces the notion that they could serve crucial roles in both the diagnosis and progression monitoring of MS, providing a non-invasive approach to evaluating disease status.

The role of exosomal miRNAs in regulating inflammation in rheumatoid arthritis (RA) is highlighted across various studies, each contributing insights into different mechanisms and potential therapeutic applications. For example, exosomal miR-150-5p, demonstrates its ability to modulate inflammation by targeting matrix metalloproteinase 14 (MMP14) and VEGF in fibroblast-like synoviocytes (FLSs). MSC-derived exosomes containing miR-150-5p can effectively decrease FLS migration and invasion, thereby mitigating joint damage associated with RA [111]. The therapeutic potential of this exosomal miRNA underscores the possibility of engineering exosomes as a delivery vehicle for anti-inflammatory agents in RA treatment. In this context, miR-204-5p is another important exosomal miRNA significantly downregulated in RA patients and collagen-induced arthritis (CIA) models [112]. The decrease in miR-204-5p levels correlates with heightened inflammatory responses in FLSs, highlighting the intricate communication between immune cells and synovial fibroblasts in RA's pathogenesis [112]. The therapeutic implications of restoring miR-204-5p levels suggest a strategy complementary to that of targeting MMP14 and VEGF via miR-150-5p.

In one study, the lncRNA NEAT1 was shown to be upregulated in exosomes derived from peripheral blood mononuclear cells (PBMCs) of RA patients [113]. The research revealed that NEAT1 can inhibit the expression of miR-23a, leading to the upregulation of MDM2, which, in turn, negatively affects Sirtuin 6 (SIRT6) levels. This cascade results in enhanced inflammatory responses and FLS proliferation. Importantly, the downregulation of NEAT1 or the overexpression of miR-23a impeded the deterioration of RA in murine models, suggesting that NEAT1 and the miR-23a/MDM2/SIRT6 axis offer potential therapeutic targets in RA treatment. This study reinforces the concept that lncRNAs can modulate miRNA activity, affecting cellular responses in inflammatory conditions such as RA. Further elucidating the role of lncRNAs, another study investigated the lncRNA HOTTIP in RA, revealing its upregulation in RA synovial fibroblasts and its negative regulation of miR-1908-5p, leading to the activation of STAT3, a known facilitator of pro-inflammatory responses [114]. In vivo experiments demonstrated that overexpression of HOTTIP exacerbated inflammation in RA mice, further indicating that HOTTIP contributes to the inflammatory milieu of RA through its regulation of key signaling pathways. This study emphasizes how exosomal lncRNAs can influence inflammatory pathways and cellular interactions, reinforcing the potential for targeting these molecules in RA therapy. The evidence presented in a recent study demonstrated the presence of HAND2-AS1 in exosomes from mesenchymal stem cells and its role in inhibiting RA-FLS activation via the miR-143-3p/TNFAIP3/NF-κB axis [115]. The study illuminated how HAND2-AS1 can act as a sponge for miR-143-3p, thereby enhancing TNFAIP3 expression, which negatively regulates NF-κB signaling. This regulatory network indicates the potential for using MSC-derived exosomal lncRNAs as therapeutic agents to modulate immune responses and mitigate inflammation in RA.

Expanding on the therapeutic potential of mesenchymal stem cells, Huang et al. [116] emphasize the significance of miR-223 in exosomes derived from bone marrow mesenchymal stem cells (BMSCs). They reported that miR-223 suppresses the NLRP3 inflammasome pathway in macrophages, exhibiting another layer of anti-inflammatory regulation within the context of RA [116]. This finding connects to the earlier studies by reinforcing the notion that MSCs can generate exosomes containing various miRNAs (including miR-150-5p and miR-223) that collectively exert immunomodulatory effects, thus presenting a multipronged therapeutic approach to RA. Furthermore, MiR-320a delivered through MSC-derived

exosomes was shown to suppress CXCL9, another important mediator in RA's inflammatory milieu [117]. The study suggests that enhancing miR-320a levels may be an effective strategy to combat FLS activation and migration, consistent with the other studies' findings that emphasize the role of miRNAs in modulating inflammatory responses through direct targeting of inflammatory mediators [117]. Overall, these studies collectively reinforce the understanding that exosomal miRNAs from various cellular origins significantly influence inflammation in RA. The interconnected roles of miR-150-5p, miR-204-5p, miR-223, miR-320a, and miR-17 illustrate a complex regulatory network while providing a compelling rationale for developing exosome-based therapies that can deliver these miRNAs to affected tissues in RA, thereby enhancing therapeutic efficacy and potential patient outcomes.

Exosome-dependent crosstalk between innate and adaptive immunity

Exosomes profoundly affect innate immune cells, which are crucial in initiating and maintaining autoimmune responses. In lupus, exosomes from activated B cells can transfer their contents to dendritic cells, enhancing antigen-presenting capabilities and subsequently leading to robust T cell activation skewed toward autoimmunity [118, 119]. Studies indicate that exosomal miRNAs from lupus patients can promote monocyte differentiation into macrophages, adopting an M1-like pro-inflammatory phenotype [120]. Moreover, exosomes derived from mesenchymal stem cells (MSCs) have emerged as promising therapeutic agents in the management of autoimmune diseases, particularly MS [121]. By influencing the polarization of microglia—resident immune cells in the CNS—MSC-derived exosomes can tilt the balance from a pro-inflammatory M1 phenotype towards a protective M2 phenotype. This modulation is crucial for reducing inflammation and facilitating remyelination, as demonstrated in experimental models of EAE, which closely mirror MS pathology. Another study indicated that the expression of exosomal miR-122-5p was significantly correlated with disease activity indices, such as the systemic lupus erythematosus disease activity index (SLEDAI) and levels of double-stranded DNA (dsDNA) antibodies [122]. Inhibition of miR-122-5p led to a considerable reduction in M1 macrophage polarization, suggesting that exosomal miR-122-5p is instrumental in the inflammatory processes associated with SLE. The targeted downregulation of FOXO3 by miR-122-5p enhances the NF-κB pathway's activation, which is critical for the pro-inflammatory response in macrophages, thereby exacerbating the clinical manifestations of lupus nephritis [122]. Such findings emphasize the importance of exosomal miRNAs as mediators of cross-talk between various immune cells and underscore their potential as novel biomarkers and therapeutic targets for managing autoimmune inflammation in SLE.

Li et al. [123] recently found that small extracellular vesicles (sEVs) derived from human umbilical cord mesenchymal stem cells (hUC-MSC-sEVs) can reduce autoimmune dacryoadenitis by promoting M2 macrophage polarization and enhancing regulatory T cell (Treg) differentiation through the delivery of miR-100-5p. This mechanism leads to reduced inflammation and improved tissue repair in a rabbit model of Sjögren's syndrome dry eye. Their results demonstrated that hUC-MSC-sEVs significantly shifted macrophages from a pro-inflammatory M1 phenotype to an anti-inflammatory M2 phenotype. miR-100-5p was identified as crucial for this polarization effect, as its inhibition reduced both M2 macrophage polarization and Treg generation. In autoimmune conditions like Sjögren's syndrome, an excess of M1 macrophage activation contributes to chronic inflammation and tissue damage, highlighting the importance of promoting M2 macrophage activity [123]. Overall, the findings support the idea that exosomal miRNAs, especially miR-100-5p, play a significant role in mediating immune modulation via hUC-MSC-sEVs. This research points to the potential for developing new therapeutic strategies that leverage exosomal miRNAs for managing autoimmune diseases effectively. Further investigations may uncover additional pathways through which exosomal miRNAs can be applied clinically.

Furthermore, exosomal miRNAs released from macrophages have been shown to exacerbate intestinal barrier dysfunction in inflammatory bowel disease (IBD) by regulating TMIGD1 through miR-223 [124]. Elevated levels of miR-223 in macrophage-derived exosomes were linked to increased intestinal inflammation, highlighting how exosomes can influence both innate and adaptive immune responses in the context of autoimmune diseases [124].

Exosomal miRNAs derived from bone marrow-derived mesenchymal stem cells (BMMSCs) play a pivotal role in modulating macrophage polarization and inflammation in systemic lupus erythematosus (SLE), as demonstrated by recent findings [125]. In a pristane-induced murine lupus nephritis model, BMMSC-derived exosomes significantly alleviated renal pathology by promoting the anti-inflammatory polarization of macrophages, characterized by upregulated CD206, B7H4, CD138, and arginase-1 (Arg-1), alongside downregulated pro-inflammatory markers such as CD86 and inducible nitric oxide synthase (iNOS) [125]. Mechanistically, these exosomes delivered miR-16 and miR-21, which targeted PDCD4 and PTEN in macrophages, respectively, to suppress pro-inflammatory signaling pathways and enhance efferocytosis activity [125]. This polarization shift correlated

with increased secretion of anti-inflammatory cytokines (IL-10, TGF-β) and chemokine CCL20, facilitating the recruitment of IL-17 + regulatory T (Treg) cells, which contributed to immune tolerance [125]. Critically, depletion of miR-16 and miR-21 in exosomes abolished their therapeutic effects, underscoring the miRNAs' essential role in mitigating SLE progression [125]. These findings highlight exosomal miRNAs as key mediators of macrophage reprogramming and propose a novel therapeutic strategy for autoimmune diseases by harnessing exosome-mediated miRNA transfer to restore immune homeostasis.

In multiple sclerosis, exosomal miR-230 has been linked to myeloid-derived suppressor cell (MDSC) modulation, expanding the population of IL-10-producing cells that can further influence T cell responses [126]. Exosomes from peripheral blood mononuclear cells in RA can modify macrophage behavior, heightening pro-inflammatory cytokine production and leading to increased joint tissue damage [127].

Exosomes also significantly influence adaptive immune responses, notably by amplifying autoreactive T cell activation [128]. They can carry autoantigens and facilitate their presentation to naïve T cells [129]. For example, exosomes from monosodium urate crystals stimulate dendritic cells to present inflammatory signals, promoting T cell differentiation into Th17 cells, which are profoundly linked to arthritis pathogenesis [130, 131].

In AIDs like psoriasis, exosomal miR-146a has been associated with exacerbated inflammation by promoting NF-κB signaling pathway activation in keratinocytes and T cells, further perpetuating the cycle of inflammation [132]. Moreover, exosomes from patients with psoriatic arthritis have been shown to contain fragments of the IL-17 A gene, indicating possible roles in the heightened inflammatory state observed in these patients [133, 134].

The manipulation of T cell activation through exosomes also manifests in conditions such as SLE [135]. Exosomal transport of antigenic material can facilitate autoantigen presentation to T cells, promoting their activation and differentiation into autoreactive effector cells. Exosomes from SLE patients carry high levels of anti-nuclear antibodies (ANA), a hallmark of the disease, indicating their contribution to autoantigen recognition and T cell activation [136, 137]. Furthermore, the exosomal miRNA let-7i presents a distinct mechanism of action, specifically inhibiting the differentiation of regulatory T cells (Tregs) that are essential for maintaining immune homeostasis [138]. The overexpression of let-7i in exosomes from MS patients appears to downregulate receptors critical for Treg function, such as IGF1R and TGFBR1, thereby impairing the Tregs' ability to modulate inflammation effectively. This dysregulation can significantly impact the pathogenesis of MS by fostering an imbalance between regulatory and inflammatory T cells. Recognizing the intricate interplay between exosomal miRNAs and Treg functionality paves the way for novel therapeutic strategies aimed at restoring immune balance in MS patients. Following this line of inquiry, another study focused on the role of exosomal RNA fragments derived from MSCs, specifically tsRNA-21,109, which was found to suppress M1 macrophage polarization, a key contributor to systemic lupus erythematosus (SLE) pathology [139]. The findings demonstrated that MSC-derived exosomes containing tsRNA-21109 significantly reduced pro-inflammatory cytokine production associated with M1 macrophages while promoting an M2 phenotype. This highlights the capacity of exosomal RNA fragments to regulate immune responses and suggests their utility in therapeutic applications for autoimmune diseases, such as RA and SLE.

In type 1 diabetes mellitus (T1DM), miR-25 derived from MSCs has been shown to inhibit T cell migration into the pancreatic islets, thereby alleviating inflammation and protecting β-cell function [140]. This effect is mediated by a significant reduction in the expression of the chemokine receptor CXCR3 on T cells, which is crucial for the recruitment of these cells to inflamed tissues [140]. The ability of exosomal miR-25 to downregulate CXCR3 highlights the potential of utilizing MSC-derived exosomes as a therapeutic strategy to counteract the pathological behaviors of immune cells in autoimmune conditions.

In SLE, marked by dysregulated immune responses, exosomes derived from umbilical cord blood mesenchymal stem cells (UC-BSCs) have been found to modulate the balance of T helper 17 (Th17) and regulatory T (Treg) cells [141]. Notably, exosomal miR-19b plays a pivotal role in this process by targeting KLF13, a transcription factor implicated in T cell differentiation. The UC-BSC-derived exosomes increase miR-19b levels in PBMCs from SLE patients, thereby restoring the Treg/Th17 balance and reducing inflammation [141]. This regulatory action emphasizes the potential for exosomal miRNAs to influence immune cell behavior, offering new avenues for therapeutic intervention in autoimmune diseases like SLE. Moreover, exosomal miRNAs are implicated in the pathogenesis of Sjögren's syndrome (SS), a condition characterized by systemic manifestations and sicca symptoms. Research has shown that secretory miR-29a-3p from SHED-derived exosomes can suppress Th1 cell responses by targeting T-bet, a transcription factor essential for Th1 differentiation [142]. By lowering Th1 response and reducing inflammatory cytokines, SHED-derived exosomes may ameliorate SS symptoms, demonstrating how exosomal miRNAs can act as key regulators in autoimmune processes.

Expanding on the role of exosomes in inflammation, recent findings regarding Behçet's uveitis (BU) suggest that plasma-derived exosomal miR-19b-3p facilitates a Treg/Th17 cell imbalance by downregulating CD46, a crucial protein involved in Treg induction and IL-10 production [143]. The dysregulated expression of miR-19b-3p in exosomes from patients with active BU not only leads to increased Th17 cell differentiation but also hinders the development of Tregs, thus contributing to disease progression [143]. This illustrates the intricate relationship between exosomal miRNAs and immune dysregulation in autoimmune diseases.

Exosomes serve as integral mediators in AIDs, influencing inflammatory signaling, modulating innate immune cell functions, and shaping adaptive immune responses [144]. Their capacity to facilitate communication among immune cells and disseminate inflammatory mediators underscores their critical role in AID pathogenesis [94]. Insights into exosomal biology may pave the way for novel therapeutic strategies targeting exosomal components to restore immune balance and mitigate the detrimental effects of autoimmunity [145].

Microglial activation and exosome dynamics in neuroinflammation

Microglia, the resident immune cells of the central nervous system (CNS), play a crucial role in maintaining homeostasis within the brain and spinal cord [146]. Strategically positioned to respond to various stimuli through activation, microglial response can become dysregulated in neuroinflammatory conditions [147]. Recent research advancements indicate that exosomes, small extracellular vesicles secreted by various cell types, significantly mediate communication between microglia and other CNS cells [148]. This section explores the relationship between exosomes and microglial activation, examining the role of exosomal components in glial cell behavior modulation and their implications for neuroinflammatory disorders [149].

The interplay between exosomes and microglial activation

Exosomes released from both microglia and other cell types facilitate intercellular communication, particularly during neuroinflammation [150, 151]. Studies demonstrate that microglial activation stimulates exosome release containing pro-inflammatory mediators, including cytokines, chemokines, and bioactive lipids. Activated microglia release exosomes loaded with TNF-α and IL-1β, critical drivers of neuroinflammation. The presence of these pro-inflammatory factors in exosomes allows for the amplification of inflammatory signals and can influence neighboring neurons and glial cells [152, 153].

Moreover, microglial exosomes contribute to clearing cellular debris and misfolded proteins that accumulate in pathological states [154, 155]. In Alzheimer's disease, for instance, microglial-derived exosomes carrying amyloid-beta (Aβ) peptides may promote neurotoxic aggregate spread, contributing to synaptic dysfunction and neuroinflammation. The balance between protective and damaging exosomal cargo becomes crucial for overall neural health [156–158].

MiRNAs have emerged as potential modulators of microglial activation, suggesting therapeutic avenues for preventing neurodegeneration [159]. Ni et al. [160] have demonstrated that intracerebroventricular injection of let-7c-5p mimics diminished infarction volume and neurological deficits by inhibiting microglial activation through caspase-3 regulation [160]. Additionally, miR-203 directly targets MyD88 in microglia, repressing NF-κB signaling and preventing neuronal injury [161]. Similarly, miR-145-5p binds to Nurr1 mRNA to alleviate neuronal injury in ischemia models [162]. MiR-199b inhibits the IKKβ-NF-κB pathway in spinal cord injury, while miR-424 treatment reduces brain edema and infarction size after ischemia by repressing microglial activation [163].

Other notable examples include miR-7, which ameliorates microglial activation in PD models, and miR-27a, which regulates inflammatory cytokine production through TLR4/IRAK4 inhibition [164, 165]. Furthermore, miR-181c also targets TLR4 to mitigate neuroinflammation in hypoxic conditions. In amyotrophic lateral sclerosis (ALS), miR-125b enhances NF-κB activation and microglial function, while anti-miR-143 promotes microglial survival in methamphetamine-induced neurotoxicity [159]. Several microRNAs (miRNAs), including miR-146b, miR-29b, let-7a/b, miR-27b, miR-21, miR-210, and miR-155, exhibit upregulated expression in ALS. Additionally, elevated levels of miR-9 have been observed specifically in the ventral horn of the spinal cord, the site of neurodegeneration associated with this disease. Notably, among the aforementioned miRNAs, miR-155, miR-146b, and miR-125b are recognized as integral constituents of the innate immune system [166–168]. Lastly, miR-146a has shown potential in restoring cognitive function by targeting specific inflammation-related proteins [159, 169].

Microglial activation state also influences the composition of secreted exosomes. Quiescent microglia primarily release exosomes loaded with neuroprotective factors and anti-inflammatory cytokines, whereas activated microglia predominantly secrete exosomes with cytotoxic components that heighten inflammation and induce neuronal cell death [170, 171]. Recent findings have shown that exosomes from alternatively activated

microglia can promote repair and regeneration, thereby highlighting their dual role [172, 173].

Impact of microglial-derived exosomes on other glial cells

The contents of microglial exosomes profoundly affect neighboring glial cells, including astrocytes and oligodendrocytes [174]. Exosomal miRNAs regulate astrocyte functions by influencing their transition between pro-inflammatory and neuroprotective states. For example, exosomal miR-223 released from activated microglia has been shown to increase the expression of inflammatory factors within astrocytes, illustrating how microglial exosomes can perpetuate neuroinflammatory processes [175, 176]. Lauforcade et al. suggested that exosomes containing miRNAs from astrocytes, such as miR-26a, are compromised in various CNS disorders, potentially affecting neuronal structure and synaptic communication [177]. Additionally, Xin et al. indicated that exosomes derived from multipotent mesenchymal stromal cells (MSCs) overexpressing miR-33b can enhance neural plasticity and facilitate functional recovery following a stroke in rats. This effect appears linked to the stimulated secondary release of exosomes from astrocytes, which promote neurite growth [178].

Exosomal contents can also influence oligodendrocyte functions, particularly relevant in demyelinating disorders like MS. Research indicates that exosomes derived from activated microglia may contain proteins that disrupt oligodendrocyte maturation and myelination, leading to impaired neuronal function and increased neurodegeneration. Conversely, exosomes from quiescent microglia may carry neuroprotective factors that promote oligodendrocyte survival and remyelination, underscoring the importance of exosomal content in modulating glial behavior [153, 179, 180].

During microglial activation, exosomes may carry various receptors, signaling molecules, and proteins that can directly interact with neighboring cells. Microglial-derived exosomes can transfer Fas ligand (FasL) to induce apoptosis in neurons, highlighting their role in promoting neuroinflammation and cell death, which further contributes to neurological dysfunction [149, 181]. Furthermore, Song et al. showed that exosomes derived from M2 microglia can reduce ischemic brain damage and enhance neuronal survival through exosomal miR-124 and its downstream target USP14, indicating the therapeutic potential of exosomes from M2 microglia in ischemic stroke [182].

Implications for neuroinflammatory disorders

The interplay between exosomal signaling and microglial activation has significant implications for neuroinflammatory disorders, such as Alzheimer's disease, Parkinson's disease (PD), and MS. In Alzheimer's disease, the accumulation of amyloid-beta plaques induces chronic microglial activation, leading to increased exosome secretion that propagates inflammatory signals, exacerbating neuronal damage. Additionally, microglial-derived exosomes have been implicated in tau protein dissemination, contributing to the spread of tau pathology in the brain [181, 183]. Elevated levels of the miRNA let-7 have been observed in patients with Alzheimer's disease (AD). It has been postulated that let-7 activates the RNA-sensing Toll-like receptor 7 (TLR7), thereby contributing to neurodegenerative processes in these individuals. Experimental studies utilizing TLR7 knockout (KO) mice have demonstrated that these mice exhibit resistance to neurodegenerative factors. However, the precise mechanism by which let-7 miRNA accesses the endosomal TLR7 receptor within the central nervous system (CNS) remains uncertain. Notably, investigations concerning metastatic gastric cancer have revealed that let-7 miRNA is released into the extracellular environment through exosomal transport mechanisms [184, 185].

In PD, the expression levels of let-7, alongside miR-205 and miR-184, have been correlated with the expression of alpha-synuclein (α-syn) and leucine-rich repeat kinase 2 (LRRK2), two genes significantly associated with PD [186]. A recent study has demonstrated that let-7 represses α-syn expression and is downregulated in models of PD. Furthermore, an increasing body of evidence suggests a significant relationship between PD and TLRs. It has recently been shown that extracellular α-synuclein enhances the expression of TLR1, TLR2, TLR3, and TLR7 [185, 187, 188]. In the context of PD, microglial exosomes are implicated in the disease's pathogenesis; exosomes secreted from activated microglia carry pro-inflammatory cytokines that can induce dopaminergic neuron death, thus participating in the neurodegenerative processes characteristic of PD [189, 190]. Moreover, studies suggest that exosomal cargo may serve as potential biomarkers for assessing disease progression. Elevated levels of certain exosomal miRNAs, including miR-29a, miR-125b-5p, and miR-153-3p, in the cerebrospinal fluid of PD patients have been associated with disease severity and neuronal loss, marking a potential avenue for therapeutic intervention and diagnostic purposes [191–194].

MS exemplifies the dual role of microglial exosomes. In this context, exosomes can contribute to the demyelination process by transferring inflammatory mediators that disrupt the function and survival of oligodendrocytes. Conversely, there is significant potential for utilizing exosomes as therapeutic vehicles. Exosomes engineered to contain anti-inflammatory agents or neuroprotective factors may offer innovative strategies for mitigating neuroinflammation while promoting recovery in demyelinating diseases [195]. Manna et al. [196]. examined exosome-associated miRNAs in MS patients

both prior to and following interferon-beta (IFN-β) therapy. They discovered that 14 miRNAs (miR-26a-5p, miR-142-3p, miR-486-5p, miR-451a, miR-146a-5p, miR-let-7b-5p, miR-19b-3p, miR-15b-3p, miR-320b, miR-122-5p, miR-215-5p, miR-23a-3p, miR-320d, and miR-223-3p) were significantly downregulated, whereas two miRNAs (miR-22-3p and miR-660-5p) were notably upregulated in relapsing-remitting MS patients treated with IFN-β who responded to therapy, compared to those who did not respond. Furthermore, a serum miRNA panel was identified that could be useful for monitoring responses to IFN-β treatment. Overall, these findings suggest that profiling circulating exosome-associated miRNAs may serve as a readily detectable biomarker for both the disease and treatment efficacy [196].

Overall, the relationship between microglial activation and exosomes is pivotal in neuroinflammatory disorders. Exosomes serve as key mediators of neuroinflammation, carrying bioactive molecules that influence glial cell behavior and neuronal homeostasis. Understanding the dynamics of microglial-derived exosomes and their impact on CNS health may pave the way for innovative therapeutic strategies aimed at ameliorating neuroinflammation and protecting neuronal integrity in various neurodegenerative diseases [197, 198]. As research progresses, the exploration of exosomal biology promises to unveil potential targets for intervention, offering new hope for patients suffering from neuroinflammatory disorders.

Conclusion and future perspective

Exosomes have emerged as pivotal players in the pathogenesis of AIDs, driving immune dysregulation and chronic inflammation through their role as intercellular messengers. This review has underscored how exosomal ncRNAs—such as miR-155 in systemic lupus erythematosus, miR-326 in rheumatoid arthritis, and miR-146a across multiple AIDs—orchestrate immune cell communication and modulate inflammatory pathways signaling. These ncRNAs exhibit a dual nature, amplifying disease states (e.g., miR-155 targeting SOCS1 to enhance JAK-STAT signaling) while also offering therapeutic promise (e.g., miR-146a suppressing inflammation and enhancing Treg function). Additionally, in neuroinflammatory AIDs, exosomal ncRNAs like miR-223 and miR-124 regulate microglial activation, influencing neurodegenerative processes.

The therapeutic potential of exosomes lies in their ability to deliver bioactive molecules and serve as biomarkers. Engineering exosomes to carry anti-inflammatory agents or silence pathogenic ncRNAs (e.g., miR-326) could reprogram immune responses, offering targeted treatments for AIDs. Moreover, exosomal cargo profiles—such as elevated miR-155 in SLE or miR-29a in Parkinson's disease—enable early diagnosis and personalized therapy, aligning with precision medicine goals. However, challenges persist, including incomplete understanding of exosome biogenesis, cargo sorting, and uptake mechanisms, as well as the lack of standardized isolation techniques, which hinder clinical translation.

Future research should prioritize elucidating the molecular pathways governing ncRNA packaging into exosomes and developing technologies for real-time in vivo tracking of exosomal dynamics. Interdisciplinary efforts combining molecular biology, nanotechnology, and bioinformatics could yield synthetic exosomes with enhanced stability and specificity or decode complex ncRNA-immune interactions. In neuroinflammation, exploring exosomal delivery of neuroprotective factors (e.g., miR-124 to quiescent microglia) could mitigate neuronal damage in diseases like multiple sclerosis or Alzheimer's.

Autophagy is a cellular process where cells degrade and recycle damaged components to maintain homeostasis, crucial in neurons for clearing misfolded proteins and maintaining function. Exosomes by carrying molecules like ncRNAs, which can regulate inflammatory pathways [199]. Besides, the intersection of these pathways is supported by general research, indicating that autophagy can influence exosome biogenesis and cargo, particularly through shared endosomal pathways and molecular components like ALIX and ESCRT complexes. It has been reported that autophagy and exosomal pathways are known to intersect in maintaining neuronal cellular homeostasis crosstalk between exosomes and autophagy [200–202]. Recent studies have highlighted the role of autophagy in AIDs affecting the nervous system, such as Myasthenia Gravis, multiple sclerosis, and the involvement of brain-derived neurotrophic factor (BDNF) signaling in MS [200–202]. Some reviews have prioritized the role of exosomal non-coding RNAs (ncRNAs) in AIDs. Therefore, future research should investigate how autophagy influences the cargo of exosomes, particularly ncRNAs, in these diseases to uncover novel mechanisms and potential therapeutic targets.

By addressing these gaps, exosome-based strategies stand poised to transform AID management. From disrupting chronic inflammation to restoring immune balance, these approaches promise innovative therapies and improved patient outcomes, redefining treatment paradigms for autoimmune and neuroinflammatory disorders.

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Authors' contributions

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References

1. Shadab A, et al. The interplay between mitochondrial dysfunction and NLRP3 inflammasome in multiple sclerosis: therapeutic implications and animal model studies. Biomed Pharmacother. 2024;175:116673.
2. Wang L, Wang FS, Gershwin ME. Human autoimmune diseases: a comprehensive update. J Intern Med. 2015;278(4):369–95.
3. Duan L, Rao X, Sigdel KR. Regulation of inflammation in autoimmune disease. J Immunol Res. 2019;2.
4. Xiang Y, et al. The role of inflammation in autoimmune disease: a therapeutic target. Front Immunol. 2023;14:1267091.
5. Duan L, et al. Exosomes in autoimmune diseases: a review of mechanisms and diagnostic applications. Clin Rev Allergy Immunol. 2025;68(1):5.
6. Suh JH, et al. Therapeutic application of exosomes in inflammatory diseases. Int J Mol Sci. 2021;22(3):1144.
7. Zou J, Peng H, Liu Y. The roles of exosomes in immunoregulation and autoimmune thyroid diseases. Front Immunol. 2021;12:757674.
8. Dai R, Ahmed SA. MicroRNA, a new paradigm for understanding immunoregulation, inflammation, and autoimmune diseases. Transl Res. 2011;157(4):163–79.
9. Eslami N, et al. SARS-CoV-2: receptor and co-receptor tropism probability. Curr Microbiol. 2022;79(5):133.
10. Rahimian N, et al. Exosomal MicroRNA profiling. In: Rani S, editor. MicroRNA profiling: methods and protocols. New York: Springer US; 2023. pp. 13–47.
11. Bennett JM, et al. Inflammation–nature's way to efficiently respond to all types of challenges: implications for understanding and managing the epidemic of chronic diseases. Front Med. 2018;5:316.
12. McComb S, et al. Introduction to the immune system. Immunoproteomics. 2019;2024:1–24.
13. Li XB, et al. Role of exosomes in immune regulation. J Cell Mol Med. 2006;10(2):364–75.
14. Barros FM, et al. Exosomes and immune response in cancer: friends or foes? Front Immunol. 2018;9:730.
15. Rosenblum MD, Remedios KA, Abbas AK. Mechanisms of human autoimmunity. J Clin Investig. 2015;125(6):2228–33.
16. Atassi MZ, et al. Molecular mechanisms of autoimmunity. Autoimmunity. 2008;41(2):123–32.
17. Mueller DL. Mechanisms maintaining peripheral tolerance. Nat Immunol. 2010;11(1):21–7.
18. Pisetsky DS. Pathogenesis of autoimmune disease. Nat Rev Nephrol. 2023;19(8):509–24.
19. Theofilopoulos AN, Kono DH, Baccala R. The multiple pathways to autoimmunity. Nat Immunol. 2017;18(7):716–24.
20. Zeng H, et al. Type 1 regulatory T cells: a new mechanism of peripheral immune tolerance. Cell Mol Immunol. 2015;12(5):566–71.
21. Pacheco Y, et al. Bystander activation and autoimmunity. J Autoimmun. 2019;103:102301.
22. Johnson D, Jiang W. Infectious diseases, autoantibodies, and autoimmunity. J Autoimmun. 2023;137:102962.
23. Karthikeyan G, Guilherme L. Acute rheumatic fever. Lancet. 2018;392(10142):161–74.
24. Iversen R, Sollid LM. Autoimmunity provoked by foreign antigens. Science. 2020;368(6487):132–3.
25. Yin Y, Li Y, Mariuzza RA. Structural basis for self-recognition by autoimmune T-cell receptors. Immunol Rev. 2012;250(1):32–48.
26. Dalgleish AG, O'Byrne KJ. Chronic immune activation and inflammation in the pathogenesis of AIDS and cancer. 2002.
27. Zheng C, Zhou X-W, Wang J-Z. The dual roles of cytokines in Alzheimer's disease: update on interleukins, TNF-α, TGF-β and IFN-γ. Transl Neurodegener. 2016;5:1–15.
28. Pasquereau S, Kumar A, Herbein G. Targeting TNF and TNF receptor pathway in HIV-1 infection: from immune activation to viral reservoirs. Viruses. 2017;9(4):64.
29. Gulati K, et al. Cytokines and their role in health and disease: a brief overview. Moj Immunol. 2016;4(2):00121.
30. Ataie-Kachoie P, Pourgholami MH, Morris DL. Inhibition of the IL-6 signaling pathway: a strategy to combat chronic inflammatory diseases and cancer. Cytokine Growth Factor Rev. 2013;24(2):163–73.
31. Aletaha D, et al. Consensus statement on blocking interleukin-6 receptor and interleukin-6 in inflammatory conditions: an update. Ann Rheum Dis. 2023;82(6):773–87.
32. Zhang T, et al. NF-κB signaling in inflammation and cancer. MedComm. 2021;2(4):618–53.
33. Pflug KM, Sitcheran R. Targeting NF-κB-Inducing kinase (NIK) in immunity, inflammation, and cancer. Int J Mol Sci. 2020;21(22):8470.
34. Zhou Y, et al. Nuclear factor KB (NF-κB)–mediated inflammation in multiple sclerosis. Front Immunol. 2020;11:1–13.
35. Barrera M-J, et al. Dysfunctional mitochondria as critical players in the inflammation of autoimmune diseases: potential role in Sjögren's syndrome. Autoimmun Rev. 2021;20(8):102867.
36. De Luca G, et al. Interleukin-1 and systemic sclerosis: getting to the heart of cardiac involvement. Front Immunol. 2021;12:1–13.
37. Yu Z-W, et al. A new research hot spot: the role of NLRP3 inflammasome activation, a key step in pyroptosis, in diabetes and diabetic complications. Life Sci. 2020;240:117138.
38. Khanaliha K, et al. Analyzing the expression pattern of the noncoding RNAs (HOTAIR, PVT-1, XIST, H19, and miRNA-34a) in PBMC samples of patients with COVID-19, according to the disease severity in Iran during 2022–2023: a cross-sectional study. Health Sci Rep. 2024;7(2):e1861.
39. Ramos-Lopez O, et al. Epigenetic signatures underlying inflammation: an interplay of nutrition, physical activity, metabolic diseases, and environmental factors for personalized nutrition. Inflamm Res. 2021;70(1):29–49.
40. Bayat M, et al. Bile effects on the *pseudomonas aeruginosa* pathogenesis in cystic fibrosis patients with gastroesophageal reflux. Heliyon. 2023;9(11).
41. Ashraf R, et al. Lactic acid bacteria and probiotic organisms induce different cytokine profile and regulatory T cells mechanisms. J Funct Foods. 2014;6:395–409.
42. Zhou L, et al. Faecalibacterium prausnitzii produces butyrate to maintain Th17/Treg balance and to ameliorate colorectal colitis by inhibiting histone deacetylase 1. Inflamm Bowel Dis. 2018;24(9):1926–40.
43. Jia L, et al. Porphyromonas gingivalis and Lactobacillus rhamnosus GG regulate the Th17/Treg balance in colitis via TLR4 and TLR2. Clin Transl Immunol. 2020;9(11):e1213.
44. Bayat M, Sadri Nahand J. Exosomal MiRNAs: the tumor's trojan horse in selective metastasis. Mol Cancer. 2024;23(1):167.
45. Mohamadi S, et al. The tumor microenvironment's Gambit: exosomal pawns on the board of head and neck cancer. Biochim et Biophys Acta Rev Cancer. 2024;1879(6):189189.
46. Hessvik NP, Llorente A. Current knowledge on exosome biogenesis and release. Cell Mol Life Sci. 2018;75:193–208.
47. Butler JS. The Yin and Yang of the exosome. Trends Cell Biol. 2002;12(2):90–6.
48. Jeppesen DK, et al. Reassessment of exosome composition. Cell. 2019;177(2):428–45. e18.
49. Bobrie A, et al. Exosome secretion: molecular mechanisms and roles in immune responses. Traffic. 2011;12(12):1659–68.
50. Chen J, et al. Review on strategies and technologies for exosome isolation and purification. Front Bioeng Biotechnol. 2022;9:811971.
51. Sadri Nahand J, et al. Virus, exosome, and MicroRNA: new insights into autophagy. In: Turksen K, editor. Cell biology and translational medicine, volume 17: stem cells in tissue differentiation, regulation and disease. Cham: Springer Nature Switzerland; 2022. pp. 97–162.

52. Mousavi SM, et al. Microfluidics for detection of exosomes and MicroRNAs in cancer: state of the art. Mol Ther Nucleic Acids. 2022;28:758–91.
53. Mollazadeh S, Sadri Nahand J. Virus, exosome, and MicroRNA: new insights into autophagy. Adv Exp Med biol. 2022;1351:1–22.
54. Olmos Y. The ESCRT machinery: remodeling, repairing, and sealing membranes. Membranes. 2022;12(6):633.
55. Krylova SV, Feng D. The machinery of exosomes: biogenesis, release, and uptake. Int J Mol Sci. 2023;24(2):1337.
56. Mirzaei H, et al. Exosomes. In: Mirzaei H et al., editors. Exosomes and MicroRNAs in biomedical science. Cham: Springer International Publishing; 2022. pp. 79–92.
57. Ghorbani S, et al. Expression levels of miR-22, miR-30c, miR-145, and miR-519d and their possible associations with inflammatory markers among patients with coronary artery disease. ARYA Atheroscler. 2022;18(3):1–10.
58. Mirzaei H, et al. Exosomes and cancer. In: Mirzaei H et al., editors. Exosomes and MicroRNAs in biomedical science. Cham: Springer International Publishing; 2022. pp. 93–113.
59. Amersfoort J, Eelen G, Carmeliet P. Immunomodulation by endothelial cells — partnering up with the immune system? Nat Rev Immunol. 2022;22(9):576–88.
60. Tavasolian F, et al. The impact of immune cell-derived exosomes on immune response initiation and immune system function. Curr Pharm Des. 2021;27(2):197–205.
61. Zhang L, et al. The role of the programmed cell death protein-1/programmed death-ligand 1 pathway, regulatory T cells and T helper 17 cells in tumor immunity: a narrative review. Ann Transl Med. 2020;8(22):1526.
62. Kornepati AVR, Vadlamudi RK, Curiel TJ. Programmed death ligand 1 signals in cancer cells. Nat Rev Cancer. 2022;22(3):174–89.
63. Moghaddam AS, et al. Cardioprotective MicroRNAs: lessons from stem cell-derived exosomal MicroRNAs to treat cardiovascular disease. Atherosclerosis. 2019;285:1–9.
64. Mirzaei H, et al. MicroRNAs in non-malignant diseases. In: Mirzaei H et al., editors. Exosomes and MicroRNAs in biomedical science. Cham: Springer International Publishing; 2022. pp. 41–68.
65. Nouri Z, et al. Exosomes as therapeutic and drug delivery vehicle for neurodegenerative diseases. J Nanobiotechnol. 2024;22(1):463.
66. Bayat M, et al. War or peace: viruses and metastasis. Biochim et Biophys Acta Rev Cancer. 2024;1879(6):189179.
67. Wang X, et al. The role of exosomal MicroRNAs and oxidative stress in neurodegenerative diseases. Oxidative Med Cell Longev. 2020;2020(1):3232869.
68. Eslami M, et al. MiRNA-related metastasis in oral cancer: moving and shaking. Cancer Cell Int. 2023;23(1):182.
69. Kesheh MM, et al. MicroRNAs and human viral diseases: a focus on the role of microRNA-29. Biochim et Biophys Acta Mol Basis Dis. 2025;1871(1):167500.
70. Bannazadeh Baghi H, et al. Regulatory role of MicroRNAs in virus-mediated inflammation. J Inflamm. 2024;21(1):43.
71. Abbasi-Kolli M, et al. The expression patterns of MALAT-1, NEAT-1, THRIL, and miR-155-5p in the acute to the post-acute phase of COVID-19 disease. Braz J Infect Dis. 2022;26(3):102354.
72. Mirzaei H, et al. MicroRNA: a novel target of curcumin in cancer therapy. J Cell Physiol. 2018;233(4):3004–15.
73. Li K, Wang Z. LncRNA NEAT1: key player in neurodegenerative diseases. Ageing Res Rev. 2023;86:101878.
74. Yang S, et al. Long non-coding RNAs in neurodegenerative diseases. Neurochem Int. 2021;148:105096.
75. Li J, et al. Role of circrnas in neurodevelopment and neurodegenerative diseases. J Mol Neurosci. 2021;71(9):1743–51.
76. Wu D-P, et al. Circular RNAs: emerging players in brain aging and neurodegenerative diseases. J Pathol. 2023;259(1):1–9.
77. Mirzaei H, et al. Role of exosomes in the treatment of diseases. In: Mirzaei H et al., editors. Exosomes and MicroRNAs in biomedical science. Cham: Springer International Publishing; 2022. pp. 137–159.
78. Mirzaei H, et al. Exosomes and non-cancer diseases. In: Mirzaei H et al., editors. Exosomes and MicroRNAs in biomedical science. Cham: Springer International Publishing; 2022. pp. 115–136.
79. Liang C, et al. MicroRNA-146a switches microglial phenotypes to resist the pathological processes and cognitive degradation of Alzheimer's disease. Theranostics. 2021;11(9):4103–21.
80. Li C, et al. Roles and mechanisms of exosomal non-coding RNAs in human health and diseases. Signal Transduct Target Therapy. 2021;6(1):383.
81. Liu T, et al. Adipose tissue macrophage-derived exosomal miR-29a regulates obesity-associated insulin resistance. Biochem Biophys Res Commun. 2019;515(2):352–8.
82. Sun Y, et al. Expression of *miRNA-29* in pancreatic β cells promotes inflammation and diabetes via TRAF3. Cell Rep. 2021;34(1).
83. Chatterjee B, et al. MicroRNAs: as critical regulators of tumor- associated macrophages. Int J Mol Sci. 2020;21(19):7117.
84. Dolati S, et al. The role of exosomal non-coding RNAs in aging-related diseases. BioFactors. 2021;47(3):292–310.
85. Zhang J, et al. Therapeutic potential of exosomal circrna derived from synovial mesenchymal cells via targeting circEDIL3/miR-485-3p/PIAS3/STAT3/VEGF functional module in rheumatoid arthritis. Int J Nanomed. 2021;16:7977–94.
86. Wang X, et al. Exosomal miR-223 contributes to mesenchymal stem cell-elicited cardioprotection in polymicrobial sepsis. Sci Rep. 2015;5(1):13721.
87. Poon K-S, et al. Plasma exosomal miR-223 expression regulates inflammatory responses during cardiac surgery with cardiopulmonary bypass. Sci Rep. 2017;7(1):10807.
88. Yang J, et al. Lipopolysaccharide-induced exosomal miR-146a is involved in altered expression of Alzheimer's risk genes via suppression of TLR4 signaling. J Mol Neurosci. 2021;71:1245–55.
89. Vergadi E, Vaporidi K, Tsatsanis C. Regulation of endotoxin tolerance and compensatory anti-inflammatory response syndrome by non-coding RNAs. Front Immunol. 2018;9:2705.
90. Shen J, et al. Exosomal NcRNAs: the pivotal players in diabetic wound healing. Front Immunol. 2022;13:1005307.
91. Pant S, Hilton H, Burczynski ME. The multifaceted exosome: biogenesis, role in normal and aberrant cellular function, and frontiers for pharmacological and biomarker opportunities. Biochem Pharmacol. 2012;83(11):1484–94.
92. Ebrahim T, Ebrahim AS, Kandouz M. Diversity of intercellular communication modes: a cancer biology perspective. Cells. 2024;13(6):495.
93. Shenoda BB, Ajit SK. Modulation of immune responses by exosomes derived from antigen-presenting cells. Clin Med Insights Pathol. 2016;9:CPath. S39925.
94. Gong T, Liu Y-T, Fan J. Exosomal mediators in sepsis and inflammatory organ injury: unraveling the role of exosomes in intercellular crosstalk and organ dysfunction. Mil Med Res. 2024;11(1):24.
95. Wang C, et al. Spotlight on pro-inflammatory chemokines: regulators of cellular communication in cognitive impairment. Front Immunol. 2024;15:1421076.
96. Alturaiki W, et al. Assessment of IL-1β, IL-6, TNF-α, IL-8, and CCL 5 levels in newly diagnosed Saudi patients with rheumatoid arthritis. Int J Rheum Dis. 2022;25(9):1013–9.
97. Koper-Lenkiewicz OM, et al. Proinflammatory cytokines (IL-1,-6,-8,-15,-17,-18,-23, TNF-α) single nucleotide polymorphisms in rheumatoid arthritis—a literature review. Int J Mol Sci. 2022;23(4):2106.
98. Yu H, et al. Exosomes derived from hypertrophic cardiomyocytes induce inflammation in macrophages via miR-155 mediated MAPK pathway. Front Immunol. 2021;11:606045.
99. Ge X, et al. Exosomal miR-155 from M1-polarized macrophages promotes EndoMT and impairs mitochondrial function via activating NF-κB signaling pathway in vascular endothelial cells after traumatic spinal cord injury. Redox Biol. 2021;41:101932.
100. He J, et al. Advances in systemic lupus erythematosus pathogenesis via mTOR signaling pathway. In: Seminars in arthritis and rheumatism. Amsterdam: Elsevier; 2020.
101. Madhyastha R, et al. MicroRNA 21 elicits a pro-inflammatory response in macrophages, with exosomes functioning as delivery vehicles. Inflammation. 2021;44:1274–87.
102. Wang H, et al. Pro-inflammatory miR-223 mediates the cross-talk between the IL23 pathway and the intestinal barrier in inflammatory bowel disease. Genome Biol. 2016;17(1):58.
103. Zhao D, et al. Plasma miR-125a and miR-125b in sepsis: correlation with disease risk, inflammation, severity, and prognosis. J Clin Lab Anal. 2020;34(2):e23036.
104. Sun Y, et al. MicroRNA-124 mediates the cholinergic anti-inflammatory action through inhibiting the production of pro-inflammatory cytokines. Cell Res. 2013;23(11):1270–83.
105. Shi J, et al. MiR-31 mediates inflammatory signaling to promote re-epithelialization during skin wound healing. J Invest Dermatol. 2018;138(10):2253–63.
106. Jiang P, et al. MiR-34a inhibits lipopolysaccharide-induced inflammatory response through targeting Notch1 in murine macrophages. Exp Cell Res. 2012;318(10):1175–84.

107. Cheng D-L, et al. MicroRNA-34a promotes iNOS secretion from pulmonary macrophages in septic suckling rats through activating STAT3 pathway. Biomed Pharmacother. 2018;105:1276–82.
108. Azimi M, et al. Altered expression of miR-326 in T cell-derived exosomes of patients with relapsing-remitting multiple sclerosis. Iran J Allergy Asthma Immunol. 2019;18.
109. Niwald M, et al. Evaluation of selected MicroRNAs expression in remission phase of multiple sclerosis and their potential link to cognition, depression, and disability. J Mol Neurosci. 2017;63:275–82.
110. Muñoz-San Martín M, et al. Analysis of MiRNA signatures in CSF identifies upregulation of miR-21 and miR-146a/b in patients with multiple sclerosis and active lesions. J Neuroinflamm. 2019;16:1–10.
111. Chen Z, et al. 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):2472–82.
112. Wu LF, et al. Identification of novel rheumatoid arthritis-associated MiRNA-204-5p from plasma exosomes. Exp Mol Med. 2022;54(3):334–45.
113. Rao Y, et al. Delivery of long non-coding RNA NEAT1 by peripheral blood monouclear cells-derived exosomes promotes the occurrence of rheumatoid arthritis via the MicroRNA-23a/MDM2/SIRT6 axis. Front Cell Dev Biology. 2020;8:p551681.
114. Yao X, et al. LncRNA HOTTIP from synovial fibroblast-derived exosomes: a novel molecular target for rheumatoid arthritis through the miR-1908–5p/STAT3 axis. Exp Cell Res. 2021;409(2):112943.
115. Su Y, et al. Mesenchymal stem cell-originated exosomal LncRNA HAND2-AS1 impairs rheumatoid arthritis fibroblast-like synoviocyte activation through miR-143-3p/TNFAIP3/NF-κB pathway. J Orthop Surg Res. 2021;16:1–14.
116. Huang Y, et al. miR-223 in exosomes from bone marrow mesenchymal stem cells ameliorates rheumatoid arthritis via downregulation of NLRP3 expression in macrophages. Mol Immunol. 2022;143:68–76.
117. Meng Q, Qiu B. Exosomal MicroRNA-320a derived from mesenchymal stem cells regulates rheumatoid arthritis Fibroblast-Like synoviocyte activation by suppressing CXCL9 expression. Front Physiol. 2020;11:68–76.
118. Schell SL, Rahman ZS. miRNA-mediated control of B cell responses in immunity and SLE. Front Immunol. 2021;12:683710.
119. Park JS, Perl A. Endosome traffic modulates pro-inflammatory signal transduction in CD4 + T Cells—implications for the pathogenesis of systemic lupus erythematosus. Int J Mol Sci. 2023;24(13):10749.
120. Wang W, et al. Promising roles of exosomal MicroRNAs in systemic lupus erythematosus. Front Immunol. 2021;12:757096.
121. Li Z, et al. Exosomes derived from mesenchymal stem cells attenuate inflammation and demyelination of the central nervous system in EAE rats by regulating the polarization of microglia. Int Immunopharmacol. 2019;67:268–80.
122. Ji J, et al. Circulating plasma derived exosomes from systemic lupus erythematosus aggravate lupus nephritis through miR-122-5p/FOXO3-mediated macrophage activation. J Nanobiotechnol. 2024;22(1):779.
123. Li N, et al. MSC-derived small extracellular vesicles attenuate autoimmune dacryoadenitis by promoting M2 macrophage polarization and inducing tregs via miR-100-5p. Front Immunol. 2022;13.
124. Chang X, et al. Macrophage-derived exosomes promote intestinal mucosal barrier dysfunction in inflammatory bowel disease by regulating TMIGD1 via mircroRNA-223. Int Immunopharmacol. 2023;121:110447.
125. Zhang M, 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):484.
126. Glass MC, et al. Human IL-10-producing B cells have diverse states that are induced from multiple B cell subsets. Cell Rep. 2022;39(3):484.
127. Sun H, et al. IL-10-producing ILCs: molecular mechanisms and disease relevance. Front Immunol. 2021;12:650200.
128. Ehteshamfar SM, et al. Anti-inflammatory and immune-modulatory impacts of Berberine on activation of autoreactive T cells in autoimmune inflammation. J Cell Mol Med. 2020;24(23):13573–88.
129. Horst AK, et al. Antigen presentation, autoantibody production, and therapeutic targets in autoimmune liver disease. Cell Mol Immunol. 2021;18(1):92–111.
130. Hong HS, et al. OXPHOS promotes apoptotic resistance and cellular persistence in TH17 cells in the periphery and tumor microenvironment. Sci Immunol. 2022;7(77):eabm8182.
131. Perez LG, et al. TGF-β signaling in Th17 cells promotes IL-22 production and colitis-associated colon cancer. Nat Commun. 2020;11(1):2608.
132. Stafa K, et al. miR-146a is a critical target associated with multiple biological pathways of skin aging. Front Physiol. 2024;15:1291344.
133. Hot A, Miossec P. Effects of Interleukin (IL)-17A and IL-17F in human rheumatoid arthritis synoviocytes. Ann Rheum Dis. 2011;70(5):727–32.
134. Yang H-Y, et al. Role of IL-17 gene polymorphisms in osteoarthritis: a meta-analysis based on observational studies. World J Clin Cases. 2020;8(11):2280.
135. Jin K, et al. Regulatory T cells in autoimmune vasculitis. Front Immunol. 2022;13:844300.
136. Cortes-Troncoso J, et al. T cell exosome–derived miR-142-3p impairs glandular cell function in Sjögren's syndrome. JCI Insight. 2020;5(9).
137. Fenton KA, Pedersen HL. Advanced methods and novel biomarkers in autoimmune diseases–a review of the recent years progress in systemic lupus erythematosus. Front Med. 2023;10:1183535.
138. Kimura K, et al. Circulating exosomes suppress the induction of regulatory T cells via let-7i in multiple sclerosis. Nat Commun. 2018;9(1):17.
139. Dou R, et al. Mesenchymal stem cell Exosomal tsRNA-21109 alleviate systemic lupus erythematosus by inhibiting macrophage M1 polarization. Mol Immunol. 2021;139:106–14.
140. Zhou B, et al. Exosomal miR-25 from mesenchymal stem cells inhibits T cells migration and alleviates type 1 diabetes mellitus by targeting CXCR3 models. Gene. 2025;936:149098.
141. Tu J, et al. UC-BSCs exosomes regulate Th17/Treg balance in patients with systemic lupus erythematosus via miR-19b/KLF13. Cells. 2022;11(24):4123.
142. Du Z-H, et al. SHED-derived exosomes ameliorate Sjögren's syndrome-induced hyposalivation by suppressing Th1 cell response via the miR-29a-3p/T-bet Axis. ACS Appl Mater Interfaces. 2025.
143. Jiang Q, et al. Effects of plasma-derived Exosomal miRNA-19b-3p on Treg/T helper 17 cell imbalance in Behçet's uveitis. Investig Ophthalmol Vis Sci. 2023;64(4):28–28.
144. Alshahrani MY, et al. A comprehensive insight into the immunomodulatory role of MSCs-derived exosomes (MSC-Exos) through modulating pattern-recognition receptors (PRRs). Cell Biochem Funct. 2024;42(4):e4029.
145. Samarpita S, Li X. Leveraging exosomes as the next-generation bio-shuttles: the next biggest approach against Th17 cell catastrophe. Int J Mol Sci. 2023;24(8):7647.
146. Prinz M, et al. Microglia and central nervous system–associated macrophages—from origin to disease modulation. Annu Rev Immunol. 2021;39(1):251–77.
147. Di Benedetto G, et al. Role of microglia and astrocytes in Alzheimer's disease: from neuroinflammation to Ca2 + homeostasis dysregulation. Cells. 2022;11(17):2728.
148. Pistono C, et al. Glia-derived extracellular vesicles: role in central nervous system communication in health and disease. Front Cell Dev Biol. 2021;8:623771.
149. Raffaele S, et al. TNF production and release from microglia via extracellular vesicles: impact on brain functions. Cells. 2020;9(10):2145.
150. Rezaei M, et al. The association between HPV gene expression, inflammatory agents and cellular genes involved in EMT in lung cancer tissue. BMC Cancer. 2020;20(1):916.
151. Nahand JS, et al. Possible role of HPV/EBV coinfection in Anoikis resistance and development in prostate cancer. BMC Cancer. 2021;21(1):926.
152. Brás JP, et al. TNF-alpha-induced microglia activation requires miR-342: impact on NF-kB signaling and neurotoxicity. Cell Death Dis. 2020;11(6):415.
153. Pascual M, Ibáñez F, Guerri C. Exosomes as mediators of neuron-glia communication in neuroinflammation. Neural Regen Res. 2020;15(5):796–801.
154. Guo M, et al. Microglial exosomes in neurodegenerative disease. Front Mol Neurosci. 2021;14:630808.
155. Gao C, et al. Microglia in neurodegenerative diseases: mechanism and potential therapeutic targets. Signal Transduct Target Therapy. 2023;8(1):359.
156. Ge X, et al. Increased microglial exosomal miR-124-3p alleviates neurodegeneration and improves cognitive outcome after RmTBI. Mol Ther. 2020;28(2):503–22.
157. Enache TA, Oliveira-Brett AM. Alzheimer's disease amyloid beta peptides in vitro electrochemical oxidation. Bioelectrochemistry. 2017;114:13–23.
158. Cheignon C, et al. Oxidative stress and the amyloid beta peptide in Alzheimer's disease. Redox Biol. 2018;14:450–64.
159. Guo Y, et al. MicroRNAs in microglia: how do MicroRNAs affect activation, inflammation, polarization of microglia and mediate the interaction between microglia and glioma? Front Mol Neurosci. 2019;12.
160. Ni J, et al. MicroRNA let-7c-5p protects against cerebral ischemia injury via mechanisms involving the inhibition of microglia activation. Brain Behav Immun. 2015;49:75–85.
161. Yang Z, et al. miR-203 protects microglia mediated brain injury by regulating inflammatory responses via feedback to MyD88 in ischemia. Mol Immunol. 2015;65(2):293–301.

162. Xie X, et al. miR-145-5p/Nurr1/TNF-α Signaling-induced microglia activation regulates neuron injury of acute cerebral ischemic/reperfusion in rats. Front Mol Neurosci. 2017;10.
163. Zhou H-J, et al. Downregulation of miR-199b promotes the acute spinal cord injury through IKKβ-NF-κB signaling pathway activating microglial cells. Exp Cell Res. 2016;349(1):60–7.
164. Zhao H, et al. MiRNA-424 protects against permanent focal cerebral ischemia injury in mice involving suppressing microglia activation. Stroke. 2013;44(6):1706–13.
165. Lv Y-N, Ou-yang A-J, Fu L-S. MicroRNA-27a negatively modulates the inflammatory response in Lipopolysaccharide-Stimulated microglia by targeting TLR4 and IRAK4. Cell Mol Neurobiol. 2017;37(2):195–210.
166. Koval ED, et al. Method for widespread microRNA-155 Inhibition prolongs survival in ALS-model mice. Hum Mol Genet. 2013;22(20):4127–35.
167. Parisi C, et al. Dysregulated MicroRNAs in amyotrophic lateral sclerosis microglia modulate genes linked to neuroinflammation. Cell Death Dis. 2013;4(12):e959.
168. Zhou F, et al. miRNA-9 expression is upregulated in the spinal cord of G93A-SOD1 transgenic mice. Int J Clin Exp Pathol. 2013;6(9):1826–38.
169. Chen L, et al. MicroRNA-146a protects against cognitive decline induced by surgical trauma by suppressing hippocampal neuroinflammation in mice. Brain Behav Immun. 2019;78:188–201.
170. Sobhi Amjad Z, et al. Oncoviruses: induction of cancer development and metastasis by increasing Anoikis resistance. Heliyon. 2023;9(12).
171. Brites D, Fernandes A. Neuroinflammation and depression: microglia activation, extracellular microvesicles and MicroRNA dysregulation. Front Cell Neurosci. 2015;9.
172. Gouwens LK, et al. Aβ42 protofibrils interact with and are trafficked through microglial-derived microvesicles. ACS Chem Neurosci. 2018;9(6):1416–25.
173. Peng H, et al. Neuron-derived extracellular vesicles modulate microglia activation and function. Biology. 2021;10(10):948.
174. Nutma E, et al. Astrocyte and oligodendrocyte cross-talk in the central nervous system. Cells. 2020;9(3):600.
175. Mancuso R, et al. Circulatory miR-223-3p discriminates between Parkinson's and Alzheimer's patients. Sci Rep. 2019;9(1):9393.
176. Galloway DA, et al. miR-223 promotes regenerative myeloid cell phenotype and function in the demyelinated central nervous system. Glia. 2019;67(5):857–69.
177. Lafourcade C, et al. MIRNAS in astrocyte-derived exosomes as possible mediators of neuronal plasticity:supplementary issue: brain plasticity and repair. J Experimental Neurosci. 2016;10s1:JENS39916.
178. Xin H, et al. Secondary release of exosomes from astrocytes contributes to the increase in neural plasticity and improvement of functional recovery after stroke in rats treated with exosomes harvested from MicroRNA 133b-overexpressing multipotent mesenchymal stromal cells. Cell Transplant. 2017;26(2):243–57.
179. Selmaj I, et al. The role of exosomes in CNS inflammation and their involvement in multiple sclerosis. J Neuroimmunol. 2017;306:1–10.
180. Ebrahimkhani S, et al. Exosomal MicroRNA signatures in multiple sclerosis reflect disease status. Sci Rep. 2017;7(1):14293.
181. Gao G, et al. Glutaminase C regulates microglial activation and pro-inflammatory exosome release: relevance to the pathogenesis of Alzheimer's disease. Front Cell Neurosci. 2019;13:264.
182. Song Y, et al. M2 microglia-derived exosomes protect the mouse brain from ischemia-reperfusion injury via exosomal miR-124. Theranostics. 2019;9(10):2910–23.
183. Zhao Y, et al. The potential roles of exosomes carrying APP and Tau cleavage products in Alzheimer's disease. J Clin Med. 2023;12(5):1883.
184. Lehmann SM, et al. An unconventional role for MiRNA: let-7 activates Toll-like receptor 7 and causes neurodegeneration. Nat Neurosci. 2012;15(6):827–35.
185. Ohshima K, et al. Let-7 MicroRNA family is selectively secreted into the extracellular environment via exosomes in a metastatic gastric cancer cell line. PLoS ONE. 2010;5(10):e13247.
186. Maciotta S, Meregalli M, Torrente Y. The involvement of MicroRNAs in neurodegenerative diseases. Front Cell Neurosci. 2013;7:265.
187. Junn E, et al. Repression of alpha-synuclein expression and toxicity by microRNA-7. Proc Natl Acad Sci U S A. 2009;106(31):13052–7.
188. Béraud D, et al. α-Synuclein alters toll-like receptor expression. Front Neurosci. 2011;5:80.
189. Li K-L, et al. Role of exosomes in the pathogenesis of inflammation in Parkinson's disease. Neural Regen Res. 2022;17(9):1898–906.
190. Guo M, et al. Microglial exosomes facilitate α-synuclein transmission in Parkinson's disease. Brain. 2020;143(5):1476–97.
191. He S, et al. Several MiRNAs derived from serum extracellular vesicles are potential biomarkers for early diagnosis and progression of Parkinson's disease. Transl Neurodegen. 2021;10(1):25.
192. Manna I, et al. Exosomal MiRNA as peripheral biomarkers in Parkinson's disease and progressive supranuclear palsy: a pilot study. Parkinsonism Relat Disord. 2021;93:77–84.
193. Wang L, Zhang L. Circulating exosomal MiRNA as diagnostic biomarkers of neurodegenerative diseases. Front Mol Neurosci. 2020;13.
194. Gui Y, et al. Altered MicroRNA profiles in cerebrospinal fluid exosome in Parkinson disease and Alzheimer disease. Oncotarget. 2015;6(35):37043–53.
195. Fan Y, Chen Z, Zhang M. Role of exosomes in the pathogenesis, diagnosis, and treatment of central nervous system diseases. J Transl Med. 2022;20(1):291.
196. Manna I, et al. Exosome-associated MiRNA profile as a prognostic tool for therapy response monitoring in multiple sclerosis patients. FASEB J. 2018;32(8):4241–6.
197. Mohamadzadeh O, et al. Non-coding RNAs and exosomal non-coding RNAs in traumatic brain injury: the small player with big actions. Mol Neurobiol. 2023;60(7):4064–83.
198. Beylerli O, et al. Role of exosomal NcRNAs in traumatic brain injury. Noncoding RNA Res. 2023;8(4):686–92.
199. Sadri Nahand J, et al. Virus, exosome, and MicroRNA: new insights into autophagy. In: Cell biology and translational medicine, volume 17: stem cells in tissue differentiation, regulation and disease. Berlin, Heidelberg: Springer; 2022. p. 97–162.
200. Al-Kuraishy HM, et al. Defective autophagy and autophagy activators in myasthenia Gravis: a rare entity and unusual scenario. Autophagy. 2024;20(7):1473–82.
201. Al-Kuraishy HM, et al. The beneficial role of autophagy in multiple sclerosis: yes or no? Autophagy. 2024;20(2):259–74.
202. Al-Kuraishy HM, et al. The compelling role of brain-derived neurotrophic factor signaling in multiple sclerosis: role of BDNF activators. CNS Neurosci Ther. 2024;30(12):e70167.

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