Exosomal miRNAs in Inflammatory Diseases

Sufan Guo[1], Xiaoli Lou[1], Liyuan Yang[1], Li Zhou[1], Yanqiang Hou[1*] and Song Guo Zheng[2,3*]

Author Affiliations:

1.Department of Clinical Laboratory, Songjiang Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai 201600, China.

2.Department of Immunology, School of Cell and Gene Therapy, Songjiang Research Institute, Songjiang Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, 201600, China.

3.Songjiang Lab, State Key lab of Innovative Immunotherapy at Shanghai Jiao Tong University, 201600, China

*Corresponding authors：Song Guo Zheng, Song.Zheng@shsmu.edu.cn; Yanqiang Hou, houyq960@shsmu.edu.cn.

Abstract

Exosomal miRNAs are a type of non-coding RNA molecules present in exosomes. MiRNAs are involved in the regulation of a variety of physiological and pathological processes by transmitting information between cells through the exosome, a carrier of intercellular communication. During inflammatory responses, exosomal miRNAs can be involved in regulating the activation of inflammatory cells and the release of inflammatory mediators, thus affecting the development of inflammatory diseases. Therefore, exosomal miRNAs may be promising biomarkers for monitoring disease progression based on their functions and changes. In addition, since exosome prevents miRNAs from being degraded by RNase, drug development targeting the release of exosomal miRNA contents lays the foundation for innovative targeted therapies in the future. This review focuses on exosomal miRNAs with the aim of combing and mastering its latest developments in the current research of inflammatory diseases.

Keywords

miRNAs; inflammatory diseases; exosomal; biomarkers

Introduction

MicroRNAs (miRNAs) are a class of single-stranded non-coding RNAs approximately 21-23 nucleotides in length that regulate gene expression by binding to the 3′-untranslated region (3′-UTR) of specific mRNAs[1]. MiRNAs account for 1-5% of all genes in the human genom[2] and regulate approximately one-third of the human genome through their multiple targets[3]. MiRNAs, as pivotal regulators of gene expression, intricately govern various biological cascades including differentiation, growth, development and metabolism. The complexity arising from their diminutive size, expression levels, numerous repetitive sequences within the genome and distinct modes of action poses singular hurdles in unraveling the intricate functional landscape of miRNAs[4].

Extracellular vesicles (EVs) have been shown to carry many biomolecules RNA, DNA, lipids, proteins, and metabolites[5], which also include miRNAs[6]. In recent years, numerous investigations have underscored the pivotal role of miRNAs in employing exosomes as effective vehicles for facilitating intercellular signaling and communication. Inflammatory diseases are a group of disorders in which tissue damage and inflammatory processes occur as a result of an abnormal response of the body's immune system due to a variety of causes[7-9]. Over the past three decades, epidemiological investigations have revealed a notable increase in the occurrence of inflammatory disorders[10]. It is noted that they are often associated with a high risk for cancer[11,12].

The pivotal function of exosomal miRNAs in modulating gene expression, along with their unregulated expression patterns have been observed to be altered significantly across various types of human cancers, has garnered considerable research interest and attention, but studies on exosomal miRNAs in inflammatory diseases are less clear. The purpose of this review is to further summarize the potential influence of exosomal miRNAs on inflammatory conditions, aiming to provide deep insights.

Exosomal miRNAs biogenesis and function

In 1993, Ambros and his team made a groundbreaking discovery, unveiling the role of a gene named lin-4 in the developmental processes of the nematode Caenorhabditis elegans, and was in fact a small non-protein-coding RNA molecule. This revelation marked the inception of the miRNA field[13]. In the 2000, another miRNA, let-7, was discovered, which regulates the timing of development in Hidradenitis elegans[14]. The discovery of this miRNA is a major step forward in the development of the nematode.

The production of miRNA begins in the nucleus and ends in the cytoplasm[15]. Initially, miRNA synthesis is mainly transcribed through the action of RNA polymerase II[16]. It then undergoes the process of capping, splicing, and addition of polyadenylate tails, which results in the formation of primitive miRNAs (pri-miRNAs) containing at least one hairpin structure[17,18]. Within the nucleus, the primary miRNAs (pri-miRNAs) undergo cleavage by the enzyme Drosha, aided by its cofactor DGCR8, resulting in the formation of precursor miRNAs (pre-miRNAs) that range in length from 70 to 100 nucleotides[19]. The pre-miRNAs traverse the nuclear pore and enter the cytoplasm with the assistance of Exportin-5[20]. Within the cytoplasm, the enzyme Dicer processes the pre-miRNAs, resulting in the formation of a double-stranded RNA duplex that includes the mature miRNA and its matching antisense strand[21]. Following cleavage, the deconjugating enzyme separates the double-stranded RNA, yielding a mature miRNA single strand, which subsequently associates with the RNA-induced silencing complex (RISC) that includes the Argonaute protein (Ago2)[22]. Upon binding, the RISC complex engages with the 3' untranslated region (3'UTR) of the target mRNA, triggering its degradation and suppressing its translation, thus regulating gene expression[23,24] (**Figure 1**).

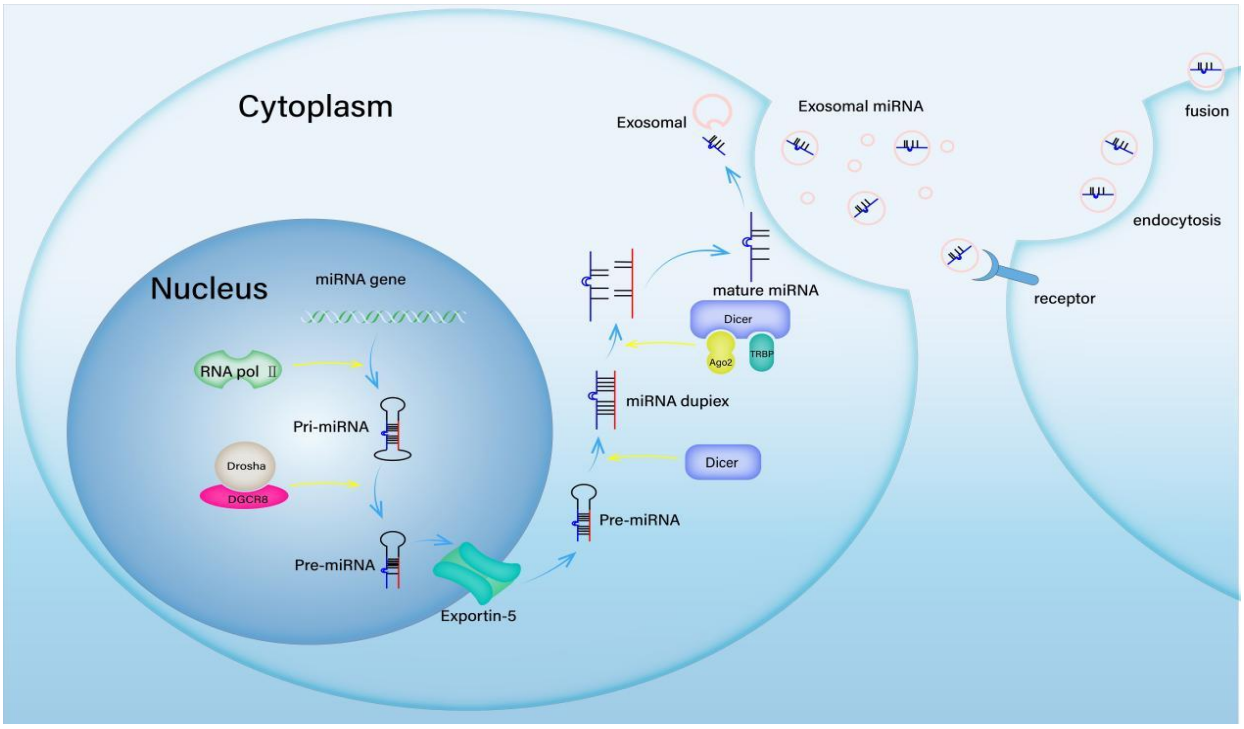

Figure 1. The synopsis of miRNA synthesis and exosomal miRNA uptake

Over a decade ago, Valadi H and colleag ues introduced the notion that miRNAs a nd mRNAs can be exchanged between c ells via vesicular transport and protein-mediated mechanisms. Their groundbre aking research unveiled the presence of these molecules within extracellular vesi cles (EVs) released by various cell lines. T his study confirmed that these EVs can b e efficiently taken up by recipient cells, f acilitating the delivery of their molecular contents into target cells[25].

Exosomes typically featuring diameters within the range of 40 to 160 nanometer s, which classify them as smaller than 20 0 nm in diameter, distinguishing them a s a distinct type of small EVs (sEVs)[26-28]. Exosomes exhibit a ubiquitous presence across various bodily fluids in humans, e ncompassing saliva, urine, breast milk, s emen, cerebrospinal fluid, as well as asci tes fluid[29,30]. Numerous investigations c onducted recently have shown that miR NAs communicate with one another bet ween cells by using exosomes as a carrier[31,32]. In particular, exosomal miRNAs are relea sed by donor cells through mechanisms of paracrine or distal secretion, and then taken up by recipient cell in a variety of f orms such as fusion, endocytosis and rec eptor[33]. Among the intricate mechanis ms governing miRNA incorporation into exosomes, the nerve sphingomyelinase 2 (nsMase2)-related pathway was the th e first protein reported to be intimately li nked with the secretion of miRNAs into e xosomes. Its down-regulation reduces th e amounts of exosomal miRNAs, wherea s its overexpression increases exosomal miRNA levels[34]. The level of Ago2 and it s phosphorylation participate in the relea se of certain exosomal miRNA[35]. Furthe rmore, the heterogeneous nuclear ribon ucleoprotein (hnRNP) family of proteins participates in the exosomal miRNA pac kaging. Specifically, hnRNPA2B1 and hn RNPA1 exhibit a remarkable ability to re cognize recognize specific miRNA

tetranucleotide sequences, facilitating their selective loading into exosomes[36]. RNA sequencing of human B cells and their associated exosomes by Koppers-Lalic D *et al* yielded that miRNAs featuring adenylated 3' termini were predominantly retained within the cells, whereas those with uridylylated 3' ends were preferentially sorted into exosomes[37].Due to their role in immunity and gut barrier function, exosomal miRNAs can be used as biomarkers. The non-invasive nature and ease of collection of urinary diagnostics and salivary are attracting increasing attention today. For example, miR-2909 has emerged as a specific and noninvasive biomarker in urinary exosomes of prostate cancer patients[38]. A group of exosomal miRNAs, including let-7a, miR-21, miR-23a, miR-150, miR-223, miR-1229 and miR-1246, can be used as diagnostic biomarkers for patients with colorectal cancer[39].

In addition to its key role in tumor growth and development, exosomal miRNAs has also been proved to play a crucial function in the regulation of gene expression. The breast cancer cell lines MCF-10A and MDA-MB-231 can reduce ZO-1 gene expression in endothelial cells by releasing of miR-105 via exosomes, thereby facilitating metastasis to the lung and brain, emphasizing its role in cancer progression[40].Exosomal miRNAs have also been found to have immune response modulation. Fabbri M et al. discovered that exosomal miRNAs function as ligands, capable of binding to toll-like receptors (TLRs) and triggering immune cells activation, highlighting their immunomodulatory potential[41]. Exosomal miRNAs are capable of reprogramme immunoreactive factors and the function of immune target cells such as T lymphocytes, dendritic cells (DCs) and natural killer (NK) cells[42]. We recently reported that exosomes secreted from regulatory T cells and gingival-derived mensenchymal stem cells treated inflammatory arthritis and the miRNAs play a key role in controlling inflammatory cells and disease onset and development[43, 44]. Epstein-Barr Virus (EBV) is the first virus known to encode miRNAs (EBV-miRNAs)[45]. Pegtel DM *et al* demonstrated that mature microRNAs encoded by EBV, when produced by infected B cells, are released through exosomes and subsequently function in uninfected recipient cells[46] (**Table 1**).

Table 1. Exosomal miRNAs in Inflammatory Diseases.

recipient-cell uptake	**fusion**	**endocytosis**	**receptor-ligand**	**macropinocytosis**
mechanism	nerve sphingomyelinase 2 (nsMase2)-related pathway	Argonaute protein (Ago2)	heterogeneous nuclear ribonucleoprotein (hnRNP) family proteins	3’-end miRNA
function	intercellular communication	biomarkers	gene expression regulation	immune response modulation

Inflammatory diseases and exosomal miRNAs

Inflammation is an immune response that can be triggered by non-infectious or infectious stimuli, for example, toxins, physical injury and cellular damage[47,48]. Exosomes inhibit or stimulate the activation of inflammasome, and there is considerable evidence that inflammatory diseases of many etiologies result in exosomal miRNAs that differ in content from basal production of exosomes[49,50]. Exosomal miRNAs can be involved in the regulation of inflammatory cell activation and release of inflammatory mediators[51]. For example, exosomes derived from human umbilical cord mesenchymal stem cells (huc-MSCs) attenuate mechanical anomalous pain and thermal hyperalgesia in inflammatory pain via miR-146a-5p/TRAF6[52]. Exosomes derived from huc-MSCs mediate miR-181c to attenuate burn-induced excessive inflammation[53] Other miRNAs may promote the activation of inflammatory cells and exacerbate the inflammatory response. Exosomes of osteoarthritic chondrocytes can enhance mature IL-1β production and aggravate osteoarthritic synovitis via osteoarthritis by miR-449a-5p[54].

This dual role makes exosomal miRNAs playing an important role in the development and progression of inflammatory diseases. Numerous studies have demonstrated that changes in the levels of specific exosomal miRNAs are associated with a variety of inflammatory diseases including autoimmune diseases, diabetes, cardiovascular diseases, and neuroinflammatory diseases. Next, we will describe in each system separately **(Table 2)..**

Disease		Exosomal miRNA	Correlation with the disease (positive/negative)	Origin of exosome	effective object	Target gene	Significance	References
autoimmune disease	synovitis in osteoarthritis	miR-449a-5p	positive	Osteoarthritic chondrocytes	macrophages	IL-1β	aggravated synovitis in osteoarthritis	[54]
	Systemic lupus erythematous (SLE)	miR-129, miR-142, miR-148b	positive		Circulating macrophages		illustrate the curative promise of directing interventions at miRNAs in individuals with SLE	[55,56]
	Lupus nephritis (LN)	Let-7a, miR-21	negative	urine				[57]

	Lupus nephritis (LN)	Let-7a, miR-21	negative	urine				[57]
	Rheumatoid arthritis (RA)	miR-6089	negative	serum			MiR-6089 regulates the production of inflammatory cytokines, including IL-6, IL-29, and TNF-α, through modulation of TLR4 signaling pathways	[58]
		miR-150-5p	negative	mesenchymal stem cells		MMP14 and VEGF	inhibiting synoviocyte hyperplasia and angiogenesis	[59]
		miR-885-5p, miR-6894-3p, miR-1268a					Biomarkers, diagnosis and prediction	[60]
	Multiple sclerosis (MS)	miR-26a, miR-122-5p					potential targets, biomarkers and therapeutic tools	[61,62]
	experimental autoimmune encephalomyelitis	miR-23b-3p	negative	bone mesenchymal stem cells	microglial		via suppression of microglial pyroptosis	[63]
	myasthenia gravis (MG)	miR-106a-5p					correlates with MG severity and expected to be an early-onset myasthenia gravis biomarker in adults	[64,65]

cardiovascular system	atherogenesis	miR-27b-3p	positive	obesity-induced visceral adipocytes		PPARα	promotes endothelial inflammation and facilitates atherogenesis	[66]
	acute myocardial infarction，AMI	miR-152-3p, let-7i-5p	negative	hypoxia-induced		Atg12 and Faslg	produce anti-apoptotic effects	[67]
		miR-93-5p		adipose-derived stromal cells	inflammatory cytokine	Atg7 and Toll-like receptor 4 (TLR4)	attenuates myocardial damage	[68]
		miR-125		Bone marrow mesenchymal stem cells	cardiomyocyte		facilitates ischemic cardiac repair	[69]
metabolic inflammation	obesity	miR-690	negative	M2 polarized bone marrow-derived macrophages	obese mice		improve glucose tolerance and insulin sensitivity, may be a novel therapeutic insulin sensitizer	[70]
		miR-1249-3p	negative	natural killer cell-derived exosome miR-1249-3p from lean mice	mice with type 2 diabetes induced by obesity		attenuates obese insulin resistance and inflammation, enhance insulin sensitivity and relieve inflammation in adipocytes and hepatocytes	[71]
		miR-155	positive	adipose tissue macrophages in obese mice	lean mice	PPARγ	insulin resistance and glucose intolerance	[72]

		miR-155	positive	adipose tissue macrophages in obese mice	lean mice	PPARγ	insulin resistance and glucose intolerance	[72]
	Type 2 diabetes	miR-320a, miR-27a					metabolic Imbalance in Type 2 Diabetic Individuals	[73]
	nonalcoholic fatty liver disease	miR-122	positive	adipocyte-derived		Sirt1	promotes the progression of NAFLD	[74]
neurodegenerative diseases	Alzheimer's disease	miR-135a, miR-384 and miR-193b		Serum			clinical biomarkers, therapeutic targets	[75]
		miR-16-5p, miR-125b-5p, miR-451a and miR-605-5p		colony stimulating factor			detected in patients with early-onset AD,	[76]
	Parkinson's disease	miR-125, miR-210, miR-450b and miR-669b	positive				exacerbate mitochondrial impairment, immune imbalance, and inflammationand then promote contribute to the overexpression and accumulation of manganese-dependent α-synuclein,	[77,78]

		miR-1, Let-7g-3p, miR-19b, miR-19b-3p, miR-10a-5p, miR-153, miR-24, miR-331-5p, miR-409-3p, miR-505 and miR195					potential to become biomarkers	[79-81]
	Amyotrophic lateral sclerosis	miR-155, miR-146		Microglia			influence the neuroinflammatory	[82]
		miR-27a-3p		serum			potential for clinical diagnosis	[83]
Other Inflammatory Diseases	Inflammatory bowel disease	miR-155	positive	intestinal epithelial cells	intestinal immune cells and inflammatory cytokines		exacerbating intestinal inflammation	[84]
	colitis	miR-378a-5p	negative	Human umbilical cord mesenchymal stem cell	macrophage	NLRP3	attenuate colitis	[85]
	acute lung injury	miR-155	positive	serum	macrophage	SHIP1 and SOCS1	promotes macrophage proliferation and inflammation	[86]
	retinal inflammation	miR-126	negative	mesenchymal stem cell		HMGB1	ameliorate Hyperglycemia-Induced Retinal Inflammation	[87]

periodontitis	miR-143-3p		Inflammatory Periodontal Ligament Stem Cells	macrophage	PI3K/AKT/NF-κB Signaling	Drive M1 Macrophage Polarization, potential new target for periodontitis treatment	[88]

Exosomal miRNAs in the autoimmune diseases

There is no doubt that microRNAs play a pivotal regulatory role in the immune system[89]. Their transfer mechanism through exosome-mediated transfer may constitute a highly efficient pathway for fine-tuning gene expression during the immune response, enhancing the coordination of the immune response, and also significantly increasing the complexity of inter-cellular communication[90]. Exosomal miRNAs secreted by immune cells such as B, T cells, MSCs, macrophages, DCs and other immune cells play an important role in physiological immune responses, as well as in the development of autoimmune diseases[91].

It has been shown that T cell-derived miRNAs regulate specific targets in the APC and that exosomes loaded with microRNAs are unidirectionally transferred from T cells to antigen-presenting cells[92].

Systemic lupus erythematosus (SLE) is a chronic diffuse connective tissue disease caused by abnormal activation of the immune system and attack its own tissues, poses challenges in both its early therapeutic intervention and precise diagnostic process[93]. Exosomal miRNAs can regulate the pathogenesis of SLE mechanism, and several researches reported that in patients with SLE, the expression of miR-142, miR-148b, and miR-129 is upregulated within circulating macrophages [55,56]. There is still a major morbidity and mortality associated with lupus nephritis (LN) in SLE[94]. Let-7a and miR-21 are reduced in urinary exosomes during LN flares[57]. In addition, Chen F *et al*found that patients diagnosed with SLE and LN display notably higher levels of exosomal miR-7974 and miR-4796-5p compared to SLE patients without LN. These elevated miRNA expressions could potentially serve as valuable biomarkers to differentiate whether SLE patients with LN and distinguish autoimmune nephritis cases more broadly[95].

Rheumatoid arthritis (RA) is a systemic autoimmune condition marked by persistent inflammation of synovial tissue, ultimately leading to irreparable damage to the joints[96,97]. Exosomes derived miR-6089 regulates LPS/TLR4, which mediates the inflammatory response in patients with RA[58].

Exosomes derived from MSCs containing miR-150-5p exhibit a therapeutic potential to mitigate joint destruction in rheumatoid arthritis by suppressing angiogenesis and synovial cell proliferation[59]. Exosomes derived from Serum, especially miR-1268a, miR-6894-3p and miR-885-5p have potential as biomarkers for prediction and early diagnosis of RA[60]. Systemic sclerosis (SSc) is an uncommon autoimmune disorder affecting the central nervous system, distinguished by persistent inflammation, demyelination, fibrotic tissue formation and a diverse array of clinical manifestations[98]. Research indicates that miRNA profiles associated with exosomes may act as an prognostic indicator for monitoring treatment responsiveness in individuals diagnosed with multiple sclerosis(MS)[99]. MiR-26a and miR-122-5p may play a role in the pathogenesis of MS[61,62]. Exosomal miR-23b-3p, released by bone marrow mesenchymal stem cells (BMSCs), exhibits a pivotal role in mitigating the severity of experimental autoimmune encephalomyelitis (EAE). This therapeutic effect is mediated through the suppression of microglial pyroptosis[63]. The expression of exosomal miR-106a-5p varies significantly across distinct subtypes of myasthenia gravis (MG), displaying a correlation with the severity of the disease[64]. Serum exosomal miRNAs are expected to be an early-onset myasthenia gravis biomarker in adults[65].

Exosomal miRNAs in the cardiovascular system

The most important role of exosomal miRNAs is intercellular communication. Atherosclerosis is an inflammatory vascular disease[100,101]. Exosomal miRNAs are key mediators of intercellular communication during the development of atherosclerosis, inducing or inhibiting the atherosclerosis by driving proatherogenic inducers or vasoprotective mediators [102–104]. Tang Y *et al* discovered that exosomal miR-27b-3p, originating from obesity-triggered visceral adipocytes, exerts a pro-inflammatory effect on endothelial cells and accelerates the development of atherosclerosis through the inhibition of PPARα[66]. Conversely, studies have shown that exosomes derived from M2-like macrophages, which are induced by IL-4, possess the capability to regulate inflammatory conditions in mice, including atherosclerosis[105]. Myocardial infarction is usually caused by excessive or prolonged inflammatory response[106]. In acute myocardial infarction (AMI), the elevated levels of exosomal microRNAs that induced by low oxygen environments, counteract the apoptosis induced by hypoxia, in which let-7i-5p and miR-152-3p targeting Faslg and Atg12 respectively, to produce anti-apoptotic effects[67]. The exosomal miR-93-5p from adipose-derived stromal cells has a protective effect against AMI-induced myocardial injury[68]. Bone marrow-derived mesenchymal stem cells

exhibit a cardioprotective role against myocardial infarction by releasing exosomal miR-125b, thereby mitigating cardiomyocyte apoptosis and fostering cardiac rejuvenation[69].

miR-146a is a well-known anti-inflammatory miRNA[27]. Exosomal miR-146a-5p from cardiomyocytes stimulated M1 macrophage polarization induced the onset of an inflammatory response. On the contrary, it targets TRAF 6 to exert anti-inflammatory effects[107].

Exosomal miRNAs in the metabolic inflammation

Metabolic inflammation is a chronic low-grade inflammation caused by excess nutrients and energy[108]. Inflammation is the link between metabolic syndrome, type 2 diabetes and obesity[109]. An important pathophysiological defect in type 2 diabetes and obesity is insulin resistance[110,111] and exosomal miRNAs play a key role in pathogenesis. Research has demonstrated that exosomes miR-690, released by M2-polarized bone marrow-derived macrophages in obese mice, exhibit the potential to insulin sensitivity tolerance and enhance glucose in obese mice upon administration, hence, miR-690 could represent a new treatment approach as an insulin sensitizer in the context of metabolic disorders[70]. Exosomes originating from NK cells of lean mice, carrying miR-1249-3p, were discovered to mitigate inflammation and insulin resistance in obese mice with type 2 diabetes. Additionally, these exosomes from lean NK cells augment insulin sensitivity and alleviate inflammation in adipocytesand hepatocytes[71]. Conversely, exosomes emanating from obese adipose tissue macrophages (ATMs) and containing miR-155 have been caused glucose intolerance and insulin resistance[72]. In type 2 diabetics, exosomes miR-320 and miR-27a are dysregulated[73].

Nonalcoholic steatohepatitis (NASH) and its associated liver cirrhosis are two intermediate and posterior stages in the progression of nonalcoholic fatty liver disease (NAFLD), in which inflammation plays a key role[112]. Chen K *et al*found that the adipocyte-derived exosome miR-122 promotes the progression of NAFLD by targeting Sirt1[74]. In addition, myeloid-specific IL-6 signaling promotes the production of exosomes enriched in miR-223 to attenuate NAFLD-associated fibrosis[113].

Exosomal miRNAs in neurodegenerative diseases

Neurodegenerative diseases (NDs) are a class of neurological system disorders arises due to irregularities within the neurogenic inflammatory, which usually involve in the dysfunctions of the nervous system leading to aberrant activation of inflammatory responses[114,115]. Exosomal miRNAs play a dual function in the regulation of neuroinflammation. Firstly, they facilitate intercellular communication among neurons, enabling the coordinated response to inflammatory stimuli within the

central nervous system (CNS). Secondly, exosomal miRNAs exhibit the remarkable capability to traverse the blood brain barrier (BBB), effectively bridging the gap between the peripheral immune system and the CNS. By crossing the BBB, these miRNAs can transmit inflammatory signals originating from the periphery, allowing the CNS to respond appropriately to systemic challenges[116].

Alzheimer's disease (AD) is one of the most prevalent form of chronic neurodegenerative disorder globally that leads to impaired cognition and memory[117]. The etiology of AD is intricately linked with inflammatory processes, potentially exacerbating cellular injury and contributing to neuronal cell death[118]. Exosomal miRNAs provide new insights in the screening and prevention of AD. In patients with AD, serum-derived exosomes exhibit distinct patterns of miRNA expression, particularly for miR-193b, miR-384, and miR-135a, which are differentially abundant compared to healthy individuals[75]. Furthermore, exosomes derived from colony stimulating factor (CSF) in individuals diagnosed with early-stage AD reveal notable variations in the levels of miR-16-5p, miR-125b-5p, miR-605-5p, and miR-451a, suggesting these miRNAs mayserve as potential biomarkers for the early detection of AD[76].

Parkinson's disease (PD) is the second most common ND after AD. Exosome miR-450b, miR-125, miR-669b and miR-210 exacerbate mitochondrial dysfunction, immune dysregulation, and inflammatory processes *via* diverse signaling cascades. This, in turn, fosters the overexpression and accumulation of manganese-dependent α-synuclein, a pivotal factor in the progression of PD[77,78]. Multiple studies showed that exosomal miR-1, Let-7g-3p, miR-10a-5p, miR-19b, miR-19b-3p, miR-24, miR-153, miR195, miR-331-5p, miR-409-3p and miR-505 are all aberrantly expressed in PD and have the potential to become PD biomarkers[79-81].

Amyotrophic lateral sclerosis (ALS) is a catastrophic chronic progressive ND[119], microglia release exosomes rich in miR-155 and miR-146 that influence the neuroinflammatory processes of ALS[82]. An investigation contrasting of miR-27a-3p expression within serum exosomes between ALS patients and healthy individuals uncovered a potential link between decreased miR-27a-3p levels and ALS progression. This discovery emphasizes the promising role of this exosomal miRNA as a diagnostic biomarker for ALS, offering a potential tool for early detection and monitoring of the disease[83].

Exosomal miRNAs in other inflammatory diseases

Inflammatory bowel disease (IBD) is a recurrent and chronic inflammatory disease[120], and exosomes released from intestinal epithelial cells containing miR-155 are able to modulate the activation of intestinal immune cells and the production of inflammatory cytokines, thereby exacerbating intestinal inflammation[84]. Conversely, miR-146a with anti-inflammatory, effectively hinder the synthesis of inflammatory mediators, thereby to reduce the occurrence of inflammation[121]. NLRP3 inflammasome are large intracellular multimeric protein complexes formed in the cytosol, which play a central act as in the occurrence of inflammation[122,123]. It has been shown that intracellular inflammatory responses and cellular pyroptosis following NLRP3 activation promote the production and release of exosomes[124]. These exosomes, abundant in distinct miRNA molecules, modulate the inflammatory responses of recipient cells via diverse mechanisms[87,125]. For example, exosomes derived from hucMSCs mitigate colitis by modulating macrophage pyroptosis *via* the miR-378a-5p/NLRP3 pathway[85].

Jiang K *et al* observed a significant enrichment of serum exosomes in the peripheral blood of mice exhibiting adverse lung inflammation acute lung injury (ALI). These exosomes are selectively loaded with miRNAs and miR-155 being the most abundant. *In vivo*, these exosomes exhibited the capacity to interact with lung macrophages, contributing to lung injury. In vitro, analysis revealed that miR-155, originating from the serum exosomes, promoted inflammation and macrophage proliferation by regulating key genes such as SOCS1 and SHIP1, respectively[86].

Exosomes derived from MSCs regulate miR-126 by targeting HMGB1 to ameliorate retinal inflammation induced by hyperglycemia[87]. Periodontal ligament stem cells (PDLSCs) during inflammatory conditions have been shown to enhance M1 macrophage polarization *via* a mechanism involving exosomal miR-143-3p. This exosomal miRNA modulates the PI3K/AKT/NF-κB signaling pathway, thereby facilitating the polarization process[88].

Exosomal miRNAs detection and treatment capacity

MiRNAs are ubiquitous in all body fluid types tested. The use of specific miRNA concentrations in body fluids has the potential to be used as a biomarker to detect and monitor a variety of physiopathological conditions[126]. Currently, diverse techniques facilitate the detection of exosomal miRNA, including quantitative reverse transcriptase-polymerase chain reaction (qRT-PCR), ratiometric fluorescent bioprobes, and some quantitative tests based on surface-enhanced Raman scattering (SERS), ratiometric electrochemistry and localized surface plasmon resonance (LSPR), respectively[127].

Exosomes, as cellular vehicles, exhibit immense promise as therapeutic tools for diverse pathologies, owing to their efficient capacity to transport small molecules between cells, facilitating targeted delivery and communication[128]. They act as cell-to-cell "couriers", delivering critical molecular information with pinpoint accuracy. A notable benefit of utilizing exosomal miRNAs as intercellular signaling molecules lies in their protective shield against degradation by RNase enzymes, subsequently enhancing the the efficiency of miRNA delivery to target cells[129] and they can be securely preserved in *vitro* under 4° C conditions for a duration of 48 hours, maintaining their stability[126]. Meanwhile, due to the crucial role of exosomal miRNAs in the onset and progression of numerous diseases, attention has shifted towards to be placed on the targeted release of exosomal miRNA contents for drug development. Existing data demonstrate that manipulation of exosomal miRNAs *in vitro* may be as an efficacious means for delivering miRNAs to target organs, thereby enhancing their therapeutic efficacy[130]. Exosomes have proven effective in transporting siRNAs to targeted cell types within mice, showcasing their versatility in targeted delivery systems[131]. Furthermore, exosomes possess the ability to traverse the BBB, and various investigations have been undertaken exploring their potential as a therapeutic miRNA delivery vehicle for ND[116].

Discussion

In summary, although significant progress has been made in recent years in the study of the relationship between exosomal miRNAs and diseases, there are still many uncharted areas and challenges that need to be further explored. Firstly, in-depth studies on the specific mechanisms of action and regulatory networks of exosomal miRNAs in different types of diseases are needed to reveal their key roles in the disease process. Second, novel therapeutic strategies and drugs targeting exosomal miRNAs need to be developed to provide new ideas and approaches for disease prevention and treatment. The study of exosomes and their miRNA contents not only determines the mechanism of their intercellular communication, but also opens up a brand-new pathway for the treatment of diseases. Exosomes miRNAs can be used as therapeutic targets or miRNAs can be delivered to the target cells through the exosomes in order to achieve the precise treatment of diseases, which demonstrates a great potential for application and a broad prospect for development.

Reference

1. Zhao, L.; Wu, Q.; Long, Y.; Qu, Q.; Qi, F.; Liu, L.; Zhang, L.; Ai, K. microRNAs: Critical Targets for Treating Rheumatoid Arthritis Angiogenesis. *J Drug Target* **2024**, *32*, 1-20, doi:10.1080/1061186X.2023.2284097.

2. Friedman, R.C.; Farh, K.K.-H.; Burge, C.B.; Bartel, D.P. Most Mammalian mRNAs Are Conserved Targets of microRNAs. *Genome Res* **2009**, *19*, 92-105, doi:10.1101/gr.082701.108.

3. Syed, N.H.; Mussa, A.; Elmi, A.H.; Jamal Al-Khreisat, M.; Ahmad Mohd Zain, M.R.; Nurul, A.A. Role of MicroRNAs in Inflammatory Joint Diseases: A Review. *Immunol Invest* **2024**, *53*, 185-209, doi:10.1080/08820139.2023.2293095.

4. Krützfeldt, J.; Poy, M.N.; Stoffel, M. Strategies to Determine the Biological Function of microRNAs. *Nat Genet* **2006**, *38 Suppl*, S14-19, doi:10.1038/ng1799.

5. Wu, Y.; Wang, Y.; Wei, M.; Han, X.; Xu, T.; Cui, M. Advances in the Study of Exosomal lncRNAs in Tumors and the Selection of Research Methods. *Biomed Pharmacother* **2020**, *123*, 109716, doi:10.1016/j.biopha.2019.109716.

6. Xu, R.; Rai, A.; Chen, M.; Suwakulsiri, W.; Greening, D.W.; Simpson, R.J. Extracellular Vesicles in Cancer - Implications for Future Improvements in Cancer Care. *Nat Rev Clin Oncol* **2018**, *15*, 617-638, doi:10.1038/s41571-018-0036-9.

7. Regmi, S.; Pathak, S.; Kim, J.O.; Yong, C.S.; Jeong, J.-H. Mesenchymal Stem Cell Therapy for the Treatment of Inflammatory Diseases: Challenges, Opportunities, and Future Perspectives. *Eur J Cell Biol* **2019**, *98*, 151041, doi:10.1016/j.ejcb.2019.04.002.

8. Liu, Y.; Luo, X.; Chen, Y.; Dang, J.; Zeng, D.; Guo, X.; Weng, W.; Zhao, J.; Shi, X.; Chen, J.; et al. Heterogeneous

Ferroptosis Susceptibility of Macrophages Caused by Focal Iron Overload Exacerbates Rheumatoid Arthritis. *Redox Biol* **2024**, *69*, 103008, doi:10.1016/j.redox.2023.103008.

9. Chen, Y.; Liang, R.; Shi, X.; Shen, R.; Liu, L.; Liu, Y.; Xue, Y.; Guo, X.; Dang, J.; Zeng, D.; et al. Targeting Kinase ITK Treats Autoimmune Arthritis via Orchestrating T Cell Differentiation and Function. *Biomed Pharmacother* **2023**, *169*, 115886, doi:10.1016/j.biopha.2023.115886.

10. Harrell, C.R.; Jovicic, N.; Djonov, V.; Arsenijevic, N.; Volarevic, V. Mesenchymal Stem Cell-Derived Exosomes and Other Extracellular Vesicles as New Remedies in the Therapy of Inflammatory Diseases. *Cells* **2019**, *8*, 1605, doi:10.3390/cells8121605.

11. Shah, S.C.; Itzkowitz, S.H. Colorectal Cancer in Inflammatory Bowel Disease: Mechanisms and Management. *Gastroenterology* **2022**, *162*, 715-730.e3, doi:10.1053/j.gastro.2021.10.035.

12. de Mattos, Â.Z.; Debes, J.D.; Boonstra, A.; Yang, J.-D.; Balderramo, D.C.; Sartori, G.D.P.; de Mattos, A.A. Current Impact of Viral Hepatitis on Liver Cancer Development: The Challenge Remains. *World J Gastroenterol* **2021**, *27*, 3556–3567, doi:10.3748/wjg.v27.i24.3556.

13. Lee, R.C.; Feinbaum, R.L.; Ambros, V. The C. Elegans Heterochronic Gene Lin-4 Encodes Small RNAs with Antisense Complementarity to Lin-14. *Cell* **1993**, *75*, 843–854, doi:10.1016/0092-8674(93)90529-y.

14. Reinhart, B.J.; Slack, F.J.; Basson, M.; Pasquinelli, A.E.; Bettinger, J.C.; Rougvie, A.E.; Horvitz, H.R.; Ruvkun, G. The 21-Nucleotide Let-7 RNA Regulates Developmental Timing in Caenorhabditis Elegans. *Nature* **2000**, *403*, 901–906, doi:10.1038/35002607.

15. Komatsu, S.; Kitai, H.; Suzuki, H.I. Network Regulation of microRNA Biogenesis and Target Interaction. *Cells* **2023**, *12*, 306, doi:10.3390/cells12020306.

16. Sempere, L.F.; Azmi, A.S.; Moore, A. microRNA-based Diagnostic and Therapeutic Applications in Cancer Medicine. *Wiley Interdiscip Rev RNA* **2021**, *12*, e1662, doi:10.1002/wrna.1662.

17. Yu, W.; Wang, S.; Wang, Y.; Chen, H.; Nie, H.; Liu, L.; Zou, X.; Gong, Q.; Zheng, B. MicroRNA: Role in Macrophage Polarization and the Pathogenesis of the Liver Fibrosis. *Front Immunol* **2023**, *14*, 1147710, doi:10.3389/fimmu.2023.1147710.

18. Cadoni, E.; Manicardi, A.; Madder, A. PNA-Based MicroRNA Detection Methodologies. *Molecules* **2020**, *25*, 1296, doi:10.3390/molecules25061296.

19. Ho, P.T.B.; Clark, I.M.; Le, L.T.T. MicroRNA-Based Diagnosis and Therapy. *Int J Mol Sci* **2022**, *23*, 7167, doi:10.3390/ijms23137167.

20. Ali Syeda, Z.; Langden, S.S.S.; Munkhzul, C.; Lee, M.; Song, S.J. Regulatory Mechanism of MicroRNA Expression in Cancer. Int J Mol Sci 2020, 21, 1723, doi:10.3390/ijms21051723.

21. Hussen, B.M.; Hidayat, H.J.; Salihi, A.; Sabir, D.K.; Taheri, M.; Ghafouri-Fard, S. MicroRNA: A Signature for Cancer Progression. Biomedicine & Pharmacotherapy 2021, 138, 111528, doi:10.1016/j.biopha.2021.111528.

22. Syed, N.H.; Zunaina, E.; Shima, S.W.-N.; Sharma, M.; Shatriah, I. MicroRNA and Their Potential Role in Conjunctival Disorders. Korean J Ophthalmol 2022, 36, 452–462, doi:10.3341/kjo.2022.0010.

23. Zhang, H.-C.; Du, Y.; Chen, L.; Yuan, Z.-Q.; Cheng, Y. MicroRNA Schizophrenia: Etiology, Biomarkers and Therapeutic Targets. Neuroscience & Biobehavioral Reviews 2023, 146, 105064, doi:10.1016/j.neubiorev.2023.105064.

24. Tealdi, S.; Ferro, E.; Campa, C.C.; Bosia, C. microRNA-Mediated Encoding and Decoding of Time-Dependent Signals in Tumorigenesis. Biomolecules 2022, 12, 213, doi:10.3390/biom12020213.

25. Valadi, H.; Ekström, K.; Bossios, A.; Sjöstrand, M.; Lee, J.J.; Lötvall, J.O. Exosome-Mediated Transfer of mRNAs and microRNAs Is a Novel Mechanism of Genetic Exchange between Cells. Nat Cell Biol 2007, 9, 654–659, doi:10.1038/ncb1596.

26. Kowal, J.; Tkach, M.; Théry, C. Biogenesis and Secretion of Exosomes. Curr Opin Cell Biol 2014, 29, 116–125, doi:10.1016/j.ceb.2014.05.004.

27. Fang, S.-B.; Zhang, H.-Y.; Wang, C.; He, B.-X.; Liu, X.-Q.; Meng, X.-C.; Peng, Y.-Q.; Xu, Z.-B.; Fan, X.-L.; Wu, Z.-J.; et al. Small Extracellular Vesicles Derived from Human Mesenchymal Stromal Cells Prevent Group 2 Innate Lymphoid Cell-Dominant Allergic Airway Inflammation through Delivery of miR-146a-5p. J Extracell Vesicles 2020, 9, 1723260, doi:10.1080/20013078.2020.1723260.

28. Fang, S.-B.; Zhang, H.-Y.; Meng, X.-C.; Wang, C.; He, B.-X.; Peng, Y.-Q.; Xu, Z.-B.; Fan, X.-L.; Wu, Z.-J.; Wu, Z.-C.; et al. Small Extracellular Vesicles Derived from Human MSCs Prevent Allergic Airway Inflammation via Immunomodulation on Pulmonary Macrophages. Cell Death Dis 2020, 11, 409, doi:10.1038/s41419-020-2606-x.

29. Kalluri, R.; LeBleu, V.S. The Biology, Function, and Biomedical Applications of Exosomes. Science 2020, 367, eaau6977, doi:10.1126/science.aau6977.

30. György, B.; Szabó, T.G.; Pásztói, M.; Pál, Z.; Misják, P.; Aradi, B.; László, V.; Pállinger, E.; Pap, E.; Kittel, A.; et al. Membrane Vesicles, Current State-of-the-Art: Emerging Role of Extracellular Vesicles. Cell Mol Life Sci 2011, 68, 2667–2688, doi:10.1007/s00018-011-0689-3.

31. Wei, W.; Ao, Q.; Wang, X.; Cao, Y.; Liu, Y.; Zheng, S.G.; Tian, X. Mesenchymal Stem Cell-Derived Exosomes: A Promising Biological Tool in Nanomedicine. Front Pharmacol 2020, 11, 590470, doi:10.3389/fphar.2020.590470.

32. Yu, Z.; Wen, Y.; Jiang, N.; Li, Z.; Guan, J.; Zhang, Y.; Deng, C.; Zhao, L.; Zheng, S.G.; Zhu, Y.; et al. TNF-α Stimulation Enhances the Neuroprotective Effects of Gingival MSCs Derived Exosomes in Retinal Ischemia-Reperfusion Injury via the MEG3/miR-21a-5p Axis. Biomaterials 2022, 284, 121484, doi:10.1016/j.biomaterials.2022.121484.

33. K, A.; Z, S.; F, A.; J, A.; M, M.-T.; F, G.; R, A.; Mr, H.; H, M. Exosomal microRNAs Derived from Mesenchymal Stem Cells: Cell-to-Cell Messages. Cell communication and signaling : CCS 2020, 18, doi:10.1186/s12964-020-00650-6.

34. Zhu, J.; Lu, K.; Zhang, N.; Zhao, Y.; Ma, Q.; Shen, J.; Lin, Y.; Xiang, P.; Tang, Y.; Hu, X.; et al. Myocardial Reparative Functions of Exosomes from Mesenchymal Stem Cells Are Enhanced by Hypoxia Treatment of the Cells via Transferring microRNA-210 in an nSMase2-Dependent Way. *Artif Cells Nanomed Biotechnol* **2018**, *46*, 1659–1670, doi:10.1080/21691401.2017.1388249.

35. McKenzie, A.J.; Hoshino, D.; Hong, N.H.; Cha, D.J.; Franklin, J.L.; Coffey, R.J.; Patton, J.G.; Weaver, A.M. KRAS-MEK Signaling Controls Ago2 Sorting into Exosomes. *Cell Rep* **2016**, *15*, 978–987, doi:10.1016/j.celrep.2016.03.085.

36. Villarroya-Beltri, C.; Gutiérrez-Vázquez, C.; Sánchez-Cabo, F.; Pérez-Hernández, D.; Vázquez, J.; Martin-Cofreces, N.; Martinez-Herrera, D.J.; Pascual-Montano, A.; Mittelbrunn, M.; Sánchez-Madrid, F. Sumoylated hnRNPA2B1 Controls the Sorting of miRNAs into Exosomes through Binding to Specific Motifs. *Nat Commun* **2013**, *4*, 2980, doi:10.1038/ncomms3980.

37. Koppers-Lalic, D.; Hackenberg, M.; Bijnsdorp, I.V.; van Eijndhoven, M.A.J.; Sadek, P.; Sie, D.; Zini, N.; Middeldorp, J.M.; Ylstra, B.; de Menezes, R.X.; et al. Nontemplated Nucleotide Additions Distinguish the Small RNA Composition in Cells from Exosomes. *Cell Rep* **2014**, *8*, 1649–1658, doi:10.1016/j.celrep.2014.08.027.

38. Wani, S.; Kaul, D.; Mavuduru, R.S.; Kakkar, N.; Bhatia, A. Urinary-Exosomal miR-2909: A Novel Pathognomonic Trait of Prostate Cancer Severity. *J Biotechnol* **2017**, *259*, 135–139, doi:10.1016/j.jbiotec.2017.07.029.

39. Ogata-Kawata, H.; Izumiya, M.; Kurioka, D.; Honma, Y.; Yamada, Y.; Furuta, K.; Gunji, T.; Ohta, H.; Okamoto, H.; Sonoda, H.; et al. Circulating Exosomal microRNAs as Biomarkers of Colon Cancer. *PLoS One* **2014**, *9*, e92921, doi:10.1371/journal.pone.0092921.

40. Zhou, W.; Fong, M.Y.; Min, Y.; Somlo, G.; Liu, L.; Palomares, M.R.; Yu, Y.; Chow, A.; O'Connor, S.T.F.; Chin, A.R.; et al. Cancer-Secreted miR-105 Destroys Vascular Endothelial Barriers to Promote Metastasis. *Cancer Cell* **2014**, *25*, 501–515, doi:10.1016/j.ccr.2014.03.007.

41. Fabbri, M.; Paone, A.; Calore, F.; Galli, R.; Gaudio, E.; Santhanam, R.; Lovat, F.; Fadda, P.; Mao, C.; Nuovo, G.J.; et al. MicroRNAs Bind to Toll-like Receptors to Induce Prometastatic Inflammatory Response. *Proc Natl Acad Sci U S A* **2012**, *109*, E2110–E2116, doi:10.1073/pnas.1209414109.

42. Que, R.; Lin, C.; Ding, G.; Wu, Z.; Cao, L. Increasing the Immune Activity of Exosomes: The Effect of miRNA-Depleted Exosome Proteins on Activating Dendritic Cell/Cytokine-Induced Killer Cells against Pancreatic Cancer. *J Zhejiang Univ Sci B* **2016**, *17*, 352–360, doi:10.1631/jzus.B1500305.

43. Chen, J.; Huang, F.; Hou, Y.; Lin, X.; Liang, R.; Hu, X.; Zhao, J.; Wang, J.; Olsen, N.; Zheng, S.G. TGF-β-Induced CD4+ FoxP3+ Regulatory T Cell-Derived Extracellular Vesicles Modulate Notch1 Signaling through miR-449a and Prevent Collagen-Induced Arthritis in a Murine Model. Cell Mol Immunol 2021, 18, 2516–2529, doi:10.1038/s41423-021-00764-y.

44. Chen, J.; Shi, X.; Deng, Y.; Dang, J.; Liu, Y.; Zhao, J.; Liang, R.; Zeng, D.; Wu, W.; Xiong, Y.; et al. miRNA-148a-Containing GMSC-Derived EVs Modulate Treg/Th17 Balance via IKKB/NF-κB Pathway and Treat a Rheumatoid Arthritis Model. JCI Insight 2024, 9, e177841, doi:10.1172/jci.insight.177841.

45. Pfeffer, S.; Zavolan, M.; Grässer, F.A.; Chien, M.; Russo, J.J.; Ju, J.; John, B.; Enright, A.J.; Marks, D.; Sander, C.; et al. Identification of Virus-Encoded microRNAs. Science 2004, 304, 734–736, doi:10.1126/science.1096781.

46. Pegtel, D.M.; Cosmopoulos, K.; Thorley-Lawson, D.A.; van Eijndhoven, M.A.J.; Hopmans, E.S.; Lindenberg, J.L.; de Gruijl, T.D.; Würdinger, T.; Middeldorp, J.M. Functional Delivery of Viral miRNAs via Exosomes. Proc Natl Acad Sci U S A 2010, 107, 6328–6333, doi:10.1073/pnas.0914843107.

47. Noonin, C.; Thongboonkerd, V. Exosome-Inflammasome Crosstalk and Their Roles in Inflammatory Responses. Theranostics 2021, 11, 4436–4451, doi:10.7150/thno.54004.

48. Luo, Y.; Zheng, S.G. Hall of Fame among Pro-Inflammatory Cytokines: Interleukin-6 Gene and Its Transcriptional Regulation Mechanisms. Front Immunol 2016, 7, 604, doi:10.3389/fimmu.2016.00604.

49. Thomou, T.; Mori, M.A.; Dreyfuss, J.M.; Konishi, M.; Sakaguchi, M.; Wolfrum, C.; Rao, T.N.; Winnay, J.N.; Garcia-Martin, R.; Grinspoon, S.K.; et al. Adipose-Derived Circulating miRNAs Regulate Gene Expression in Other Tissues. Nature 2017, 542, 450–455, doi:10.1038/nature21365.

50. Bala, S.; Marcos, M.; Kodys, K.; Csak, T.; Catalano, D.; Mandrekar, P.; Szabo, G. Up-Regulation of microRNA-155 in Macrophages Contributes to Increased Tumor Necrosis Factor {alpha} (TNF{alpha}) Production via Increased mRNA Half-Life in Alcoholic Liver Disease. J Biol Chem 2011, 286, 1436–1444, doi:10.1074/jbc.M110.145870.

51. Wozniak, A.L.; Adams, A.; King, K.E.; Dunn, W.; Christenson, L.K.; Hung, W.-T.; Weinman, S.A. The RNA Binding Protein FMR1 Controls Selective Exosomal miRNA Cargo Loading during Inflammation. J Cell Biol 2020, 219, e201912074, doi:10.1083/jcb.201912074.

52. Hua, T.; Yang, M.; Song, H.; Kong, E.; Deng, M.; Li, Y.; Li, J.; Liu, Z.; Fu, H.; Wang, Y.; et al. Huc-MSCs-Derived Exosomes Attenuate Inflammatory Pain by Regulating Microglia Pyroptosis and Autophagy via the miR-146a-5p/TRAF6 Axis. J Nanobiotechnology 2022, 20, 324, doi:10.1186/s12951-022-01522-6.

53. Li, X.; Liu, L.; Yang, J.; Yu, Y.; Chai, J.; Wang, L.; Ma, L.; Yin, H. Exosome Derived From Human Umbilical Cord Mesenchymal Stem Cell Mediates MiR-181c Attenuating Burn-Induced Excessive Inflammation. EBioMedicine 2016, 8, 72–82, doi:10.1016/j.ebiom.2016.04.030.

54. Ni, Z.; Kuang, L.; Chen, H.; Xie, Y.; Zhang, B.; Ouyang, J.; Wu, J.; Zhou, S.; Chen, L.; Su, N.; et al. The Exosome-like Vesicles from Osteoarthritic Chondrocyte Enhanced Mature IL-1β Production of Macrophages and Aggravated Synovitis in Osteoarthritis. Cell Death Dis 2019, 10, 522, doi:10.1038/s41419-019-1739-2.

55. Song, W.; Li, C.; Qiu, J.; Dong, J.; Liu, D.; Dai, Y. Differential Expression of Exosomal miRNAs and Proteins in the Plasma of Systemic Lupus Erythematous Patients. Heliyon 2023, 9, e13345, doi:10.1016/j.heliyon.2023.e13345.

56. Xiao, P.; Dong, C.; Yue, Y.; Xiong, S. Dynamic Expression of microRNAs in M2b Polarized Macrophages Associated with Systemic Lupus Erythematosus. Gene 2014, 547, 300–309, doi:10.1016/j.gene.2014.06.065.

57. Tangtanatakul, P.; Klinchanhom, S.; Sodsai, P.; Sutichet, T.; Promjeen, C.; Avihingsanon, Y.; Hirankarn, N. Down-Regulation of Let-7a and miR-21 in Urine Exosomes from Lupus Nephritis Patients during Disease Flare. Asian Pac J Allergy Immunol 2019, 37, 189–197, doi:10.12932/AP-130318-0280.

58. Xu, D.; Song, M.; Chai, C.; Wang, J.; Jin, C.; Wang, X.; Cheng, M.; Yan, S. Exosome-Encapsulated miR-6089 Regulates Inflammatory Response via Targeting TLR4. J Cell Physiol 2019, 234, 1502–1511, doi:10.1002/jcp.27014.

59. Chen, Z.; Wang, H.; Xia, Y.; Yan, F.; Lu, Y. Therapeutic Potential of Mesenchymal Cell-Derived miRNA-150-5p-Expressing Exosomes in Rheumatoid Arthritis Mediated by the Modulation of MMP14 and VEGF. J Immunol 2018, 201, 2472–2482, doi:10.4049/jimmunol.1800304.

60. Gong, J.; Zhang, X.; Khan, A.; Liang, J.; Xiong, T.; Yang, P.; Li, Z. Identification of Serum Exosomal miRNA Biomarkers for Diagnosis of Rheumatoid Arthritis. Int Immunopharmacol 2024, 129, 111604, doi:10.1016/j.intimp.2024.111604.

61. Potenza, N.; Mosca, N.; Mondola, P.; Damiano, S.; Russo, A.; De Felice, B. Human miR-26a-5p Regulates the Glutamate Transporter SLC1A1 (EAAT3) Expression. Relevance in Multiple Sclerosis. Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease 2018, 1864, 317–323, doi:10.1016/j.bbadis.2017.09.024.

62. Selmaj, I.; Cichalewska, M.; Namiecinska, M.; Galazka, G.; Horzelski, W.; Selmaj, K.W.; Mycko, M.P. Global Exosome Transcriptome Profiling Reveals Biomarkers for Multiple Sclerosis. Ann Neurol 2017, 81, 703–717, doi:10.1002/ana.24931.

63. Wang, J.; Sun, H.; Guo, R.; Guo, J.; Tian, X.; Wang, J.; Sun, S.; Han, Y.; Wang, Y. Exosomal miR-23b-3p from Bone Mesenchymal Stem Cells Alleviates Experimental Autoimmune Encephalomyelitis by Inhibiting Microglial Pyroptosis. Exp Neurol 2023, 363, 114374, doi:10.1016/j.expneurol.2023.114374.

64. Xu, H.; Bao, Z.; Liang, D.; Li, M.; Wei, M.; Ge, X.; Liu, J.; Li, J. Plasma Exosomal miR-106a-5p Expression in Myasthenia Gravis., doi:10.1002/mus.26785.

65. Mu, Y.; Huang, X.; Yang, Y.; Huang, Z.; Chen, J.; Li, S.; Dong, Y.; Chen, F.; Zhang, R.; Chen, J.; et al. Study of Serum Exosome miRNA as a Biomarker for Early Onset Adult Ouclar Myastthenia Gravis. Gene 2024, 896, 148034, doi:10.1016/j.gene.2023.148034.

66. Tang, Y.; Yang, L.-J.; Liu, H.; Song, Y.-J.; Yang, Q.-Q.; Liu, Y.; Qian, S.-W.; Tang, Q.-Q. Exosomal miR-27b-3p Secreted by Visceral Adipocytes Contributes to Endothelial Inflammation and Atherogenesis. Cell Reports 2023, 42, doi:10.1016/j.celrep.2022.111948.

67. Zhang, J.; Ma, J.; Long, K.; Qiu, W.; Wang, Y.; Hu, Z.; Liu, C.; Luo, Y.; Jiang, A.; Jin, L.; et al. Overexpression of Exosomal Cardioprotective miRNAs Mitigates Hypoxia-Induced H9c2 Cells Apoptosis. *International Journal of Molecular Sciences* **2017**, *18*, doi:10.3390/ijms18040711.

68. Liu, J.; Jiang, M.; Deng, S.; Lu, J.; Huang, H.; Zhang, Y.; Gong, P.; Shen, X.; Ruan, H.; Jin, M.; et al. miR-93-5p-Containing Exosomes Treatment Attenuates Acute Myocardial Infarction-Induced Myocardial Damage. *Mol Ther Nucleic Acids* **2018**, *11*, 103-115, doi:10.1016/j.omtn.2018.01.010.

69. Zhu, L.-P.; Tian, T.; Wang, J.-Y.; He, J.-N.; Chen, T.; Pan, M.; Xu, L.; Zhang, H.-X.; Qiu, X.-T.; Li, C.-C.; et al. Hypoxia-Elicited Mesenchymal Stem Cell-Derived Exosomes Facilitates Cardiac Repair through miR-125b-Mediated Prevention of Cell Death in Myocardial Infarction. *Theranostics* **2018**, *8*, 6163-6177, doi:10.7150/thno.28021.

70. Ying, W.; Gao, H.; Dos Reis, F.C.G.; Bandyopadhyay, G.; Ofrecio, J.M.; Luo, Z.; Ji, Y.; Jin, Z.; Ly, C.; Olefsky, J.M. MiR-690, an Exosomal-Derived miRNA from M2-Polarized Macrophages, Improves Insulin Sensitivity in Obese Mice. *Cell Metab* **2021**, *33*, 781-790.e5, doi:10.1016/j.cmet.2020.12.019.

71. Wang, Y.; Li, M.; Chen, L.; Bian, H.; Chen, X.; Zheng, H.; Yang, P.; Chen, Q.; Xu, H. Natural Killer Cell-Derived Exosomal miR-1249-3p Attenuates Insulin Resistance and Inflammation in Mouse Models of Type 2 Diabetes. *Signal Transduct Target Ther* **2021**, *6*, 409, doi:10.1038/s41392-021-00805-y.

72. Ying, W.; Riopel, M.; Bandyopadhyay, G.; Dong, Y.; Birmingham, A.; Seo, J.B.; Ofrecio, J.M.; Wollam, J.; Hernandez-Carretero, A.; Fu, W.; et al. Adipose Tissue Macrophage-Derived Exosomal miRNAs Can Modulate In Vivo and In Vitro Insulin Sensitivity. *Cell* **2017**, *171*, 372-384.e12, doi:10.1016/j.cell.2017.08.035.

73. Karolina, D.S.; Tavintharan, S.; Armugam, A.; Sepramaniam, S.; Pek, S.L.T.; Wong, M.T.K.; Lim, S.C.; Sum, C.F.; Jeyaseelan, K. Circulating miRNA Profiles in Patients with Metabolic Syndrome. *J Clin Endocrinol Metab* **2012**, *97*, E2271-2276, doi:10.1210/jc.2012-1996.

74. Chen, K.; Lin, T.; Yao, W.; Chen, X.; Xiong, X.; Huang, Z. Adipocytes-Derived Exosomal miR-122 Promotes Non-Alcoholic Fat Liver Disease Progression via Targeting Sirt1. Gastroenterol Hepatol 2023, 46, 531-541, doi:10.1016/j.gastrohep.2022.12.003.

75. Yang, T.T.; Liu, C.G.; Gao, S.C.; Zhang, Y.; Wang, P.C. The Serum Exosome Derived MicroRNA-135a, -193b, and -384 Were Potential Alzheimer's Disease Biomarkers. Biomed Environ Sci 2018, 31, 87-96, doi:10.3967/bes2018.011.

76. McKeever, P.M.; Schneider, R.; Taghdiri, F.; Weichert, A.; Multani, N.; Brown, R.A.; Boxer, A.L.; Karydas, A.; Miller, B.; Robertson, J.; et al. MicroRNA Expression Levels Are Altered in the Cerebrospinal Fluid of Patients with Young-Onset Alzheimer's Disease. Mol Neurobiol 2018, 55, 8826-8841, doi:10.1007/s12035-018-1032-x.

77. Harischandra, D.S.; Ghaisas, S.; Rokad, D.; Zamanian, M.; Jin, H.; Anantharam, V.; Kimber, M.; Kanthasamy, A.; Kanthasamy, A.G. Environmental Neurotoxicant Manganese Regulates Exosome-Mediated Extracellular miRNAs in Cell Culture Model of Parkinson's Disease: Relevance to α-Synuclein Misfolding in Metal Neurotoxicity. Neurotoxicology 2018, 64, 267-277, doi:10.1016/j.neuro.2017.04.007.

78. Danzer, K.M.; Kranich, L.R.; Ruf, W.P.; Cagsal-Getkin, O.; Winslow, A.R.; Zhu, L.; Vanderburg, C.R.; McLean, P.J. Exosomal Cell-to-Cell Transmission of Alpha Synuclein Oligomers. Mol Neurodegener 2012, 7, 42, doi:10.1186/1750-1326-7-42.

79. Gui, Y.; Liu, H.; Zhang, L.; Lv, W.; Hu, X. Altered microRNA Profiles in Cerebrospinal Fluid Exosome in Parkinson Disease and Alzheimer Disease. Oncotarget 2015, 6, 37043-37053.

80. Cao, X.-Y.; Lu, J.-M.; Zhao, Z.-Q.; Li, M.-C.; Lu, T.; An, X.-S.; Xue, L.-J. MicroRNA Biomarkers of Parkinson's Disease in Serum Exosome-like Microvesicles. Neurosci Lett 2017, 644, 94–99, doi:10.1016/j.neulet.2017.02.045.

81. Yao, Y.-F.; Qu, M.-W.; Li, G.-C.; Zhang, F.-B.; Rui, H.-C. Circulating Exosomal miRNAs as Diagnostic Biomarkers in Parkinson's Disease. Eur Rev Med Pharmacol Sci 2018, 22, 5278–5283, doi:10.26355/eurrev_201808_15727.

82. Vaz, A.R.; Pinto, S.; Ezequiel, C.; Cunha, C.; Carvalho, L.A.; Moreira, R.; Brites, D. Phenotypic Effects of Wild-Type and Mutant SOD1 Expression in N9 Murine Microglia at Steady State, Inflammatory and Immunomodulatory Conditions. Front Cell Neurosci 2019, 13, 109, doi:10.3389/fncel.2019.00109.

83. Xu, Q.; Zhao, Y.; Zhou, X.; Luan, J.; Cui, Y.; Han, J. Comparison of the Extraction and Determination of Serum Exosome and miRNA in Serum and the Detection of miR-27a-3p in Serum Exosome of ALS Patients. Intractable Rare Dis Res 2018, 7, 13–18, doi:10.5582/irdr.2017.01091.

84. Liu, Y.; Zhu, F.; Li, H.; Fan, H.; Wu, H.; Dong, Y.; Chu, S.; Tan, C.; Wang, Q.; He, H.; et al. MiR-155 Contributes to Intestinal Barrier Dysfunction in DSS-Induced Mice Colitis via Targeting HIF-1α/TFF-3 Axis. Aging (Albany NY) 2020, 12, 14966–14977, doi:10.18632/aging.103555.

85. Cai, X.; Zhang, Z.-Y.; Yuan, J.-T.; Ocansey, D.K.W.; Tu, Q.; Zhang, X.; Qian, H.; Xu, W.-R.; Qiu, W.; Mao, F. hucMSC-Derived Exosomes Attenuate Colitis by Regulating Macrophage Pyroptosis via the miR-378a-5p/NLRP3 Axis. Stem Cell Res Ther 2021, 12, 416, doi:10.1186/s13287-021-02492-6.

86. Jiang, K.; Yang, J.; Guo, S.; Zhao, G.; Wu, H.; Deng, G. Peripheral Circulating Exosome-Mediated Delivery of miR-155 as a Novel Mechanism for Acute Lung Inflammation. Mol Ther 2019, 27, 1758–1771, doi:10.1016/j.ymthe.2019.07.003.

87. Zhang, W.; Wang, Y.; Kong, Y. Exosomes Derived From Mesenchymal Stem Cells Modulate miR-126 to Ameliorate Hyperglycemia-Induced Retinal Inflammation Via Targeting HMGB1. Invest Ophthalmol Vis Sci 2019, 60, 294–303, doi:10.1167/iovs.18-25617.

88. Wang, Y.; Zhang, X.; Wang, J.; Zhang, Y.; Ye, Q.; Wang, Y.; Fei, D.; Wang, Q. Inflammatory Periodontal Ligament Stem Cells Drive M1 Macrophage Polarization via Exosomal miR-143-3p-Mediated Regulation of PI3K/AKT/NF-κB Signaling. Stem Cells 2023, 41, 184–199, doi:10.1093/stmcls/sxac087.

89. Sonkoly, E.; Ståhle, M.; Pivarcsi, A. MicroRNAs and Immunity: Novel Players in the Regulation of Normal Immune Function and Inflammation. Seminars in Cancer Biology 2008, 18, 131–140, doi:10.1016/j.semcancer.2008.01.005.

90. Bauer, K.M.; Round, J.L.; O'Connell, R.M. No Small Matter: Emerging Roles for Exosomal miRNAs in the Immune System. FEBS J 2022, 289, 4021–4037, doi:10.1111/febs.16052.

91. Wang, W.; Yue, C.; Gao, S.; Li, S.; Zhou, J.; Chen, J.; Fu, J.; Sun, W.; Hua, C. Promising Roles of Exosomal microRNAs in Systemic Lupus Erythematosus. Front Immunol 2021, 12, 757096, doi:10.3389/fimmu.2021.757096.

92. Mittelbrunn, M.; Gutiérrez-Vázquez, C.; Villarroya-Beltri, C.; González, S.; Sánchez-Cabo, F.; González, M.Á.; Bernad, A.; Sánchez-Madrid, F. Unidirectional Transfer of microRNA-Loaded Exosomes from T Cells to Antigen-Presenting Cells. Nat Commun 2011, 2, 282, doi:10.1038/ncomms1285.

93. Xiao, Z.X.; Miller, J.S.; Zheng, S.G. An Updated Advance of Autoantibodies in Autoimmune Diseases. Autoimmun Rev 2021, 20, 102743, doi:10.1016/j.autrev.2020.102743.

94. Dang, J.; Xu, Z.; Xu, A.; Liu, Y.; Fu, Q.; Wang, J.; Huang, F.; Zheng, Y.; Qi, G.; Sun, B.; et al. Human Gingiva-Derived Mesenchymal Stem Cells Are Therapeutic in Lupus Nephritis through Targeting of CD39-CD73 Signaling Pathway. J Autoimmun 2020, 113, 102491, doi:10.1016/j.jaut.2020.102491.

95. Chen, F.; Shi, B.; Liu, W.; Gong, J.; Gao, J.; Sun, Y.; Yang, P. Circulating Exosomal microRNAs as Biomarkers of Lupus Nephritis. Front Immunol 2023, 14, 1326836, doi:10.3389/fimmu.2023.1326836.

96. Smolen, J.S.; Aletaha, D.; Koeller, M.; Weisman, M.H.; Emery, P. New Therapies for Treatment of Rheumatoid Arthritis. Lancet 2007, 370, 1861–1874, doi:10.1016/S0140-6736(07)60784-3.

97. Wang, C.; Xiao, Y.; Lao, M.; Wang, J.; Xu, S.; Li, R.; Xu, X.; Kuang, Y.; Shi, M.; Zou, Y.; et al. Increased SUMO-Activating Enzyme SAE1/UBA2 Promotes Glycolysis and Pathogenic Behavior of Rheumatoid Fibroblast-like Synoviocytes. JCI Insight 2020, 5, e135935, 135935, doi:10.1172/jci.insight.135935.

98. Volkmann, E.R.; Andréasson, K.; Smith, V. Systemic Sclerosis. Lancet 2023, 401, 304–318, doi:10.1016/S0140-6736(22)01692-0.

99. Manna, I.; Iaccino, E.; Dattilo, V.; Barone, S.; Vecchio, E.; Mimmi, S.; Filippelli, E.; Demonte, G.; Polidoro, S.; Granata, A.; et al. Exosome-associated miRNA Profile as a Prognostic Tool for Therapy Response Monitoring in Multiple Sclerosis Patients., doi:10.1096/fj.201701533R.

100. Kobiyama, K.; Ley, K. Atherosclerosis. Circ Res 2018, 123, 1118–1120, doi:10.1161/CIRCRESAHA.118.313816.

101. Zhang, X.; Huang, F.; Li, W.; Dang, J.-L.; Yuan, J.; Wang, J.; Zeng, D.-L.; Sun, C.-X.; Liu, Y.-Y.; Ao, Q.; et al. Human Gingiva-Derived Mesenchymal Stem Cells Modulate Monocytes/Macrophages and Alleviate Atherosclerosis. Front Immunol 2018, 9, 878, doi:10.3389/fimmu.2018.00878.

102. Baruah, J.; Wary, K.K. Exosomes in the Regulation of Vascular Endothelial Cell Regeneration. Front Cell Dev Biol 2020, 7, 353, doi:10.3389/fcell.2019.00353.

103. Huber, H.J.; Holvoet, P. Exosomes: Emerging Roles in Communication between Blood Cells and Vascular Tissues during Atherosclerosis. Curr Opin Lipidol 2015, 26, 412–419, doi:10.1097/MOL.0000000000000214.

104. Heo, J.; Kang, H. Exosome-Based Treatment for Atherosclerosis. *Int J Mol Sci* **2022**, *23*, 1002, doi:10.3390/ijms23021002.

105. Bouchareychas, L.; Duong, P.; Covarrubias, S.; Alsop, E.; Phu, T.A.; Chung, A.; Gomes, M.; Wong, D.; Meechoovet, B.; Capili, A.; et al. Macrophage Exosomes Resolve Atherosclerosis by Regulating Hematopoiesis and Inflammation via MicroRNA Cargo. *Cell Rep* **2020**, *32*, 107881, doi:10.1016/j.celrep.2020.107881.

106. Reed, G.W.; Rossi, J.E.; Cannon, C.P. Acute Myocardial Infarction. *Lancet* **2017**, *389*, 197–210, doi:10.1016/S0140-6736(16)30677-8.

107. Chen, C.; Cai, S.; Wu, M.; Wang, R.; Liu, M.; Cao, G.; Dong, M.; Yiu, K.-H. Role of Cardiomyocyte-Derived Exosomal MicroRNA-146a-5p in Macrophage Polarization and Activation. *Dis Markers* **2022**, *2022*, 2948578, doi:10.1155/2022/2948578.

108. Russo, S.; Kwiatkowski, M.; Govorukhina, N.; Bischoff, R.; Melgert, B.N. Meta-Inflammation and Metabolic Reprogramming of Macrophages in Diabetes and Obesity: The Importance of Metabolites. *Front Immunol* **2021**, *12*, 746151, doi:10.3389/fimmu.2021.746151.

109. Esser, N.; Legrand-Poels, S.; Piette, J.; Scheen, A.J.; Paquot, N. Inflammation as a Link between Obesity, Metabolic Syndrome and Type 2 Diabetes. *Diabetes Res Clin Pract* **2014**, *105*, 141–150, doi:10.1016/j.diabres.2014.04.006.

110. Johnson, A.M.F.; Olefsky, J.M. The Origins and Drivers of Insulin Resistance. *Cell* **2013**, *152*, 673–684, doi:10.1016/j.cell.2013.01.041.

111. Kahn, S.E.; Hull, R.L.; Utzschneider, K.M. Mechanisms Linking Obesity to Insulin Resistance and Type 2 Diabetes. *Nature* **2006**, *444*, 840–846, doi:10.1038/nature05482.

112. Machado, M.V.; Diehl, A.M. Pathogenesis of Nonalcoholic Steatohepatitis. *Gastroenterology* **2016**, *150*, 1769–1777, doi:10.1053/j.gastro.2016.02.066.

113. Hou, X.; Yin, S.; Ren, R.; Liu, S.; Yong, L.; Liu, Y.; Li, Y.; Zheng, M.-H.; Kunos, G.; Gao, B.; et al. Myeloid Cell-Specific IL-6 Signaling Promotes miR-223-Enriched Exosome Production to Attenuate NAFLD-Associated Fibrosis. *Hepatology* **2021**, *74*, 116–132, doi:10.1002/hep.31658.

114. Xanthos, D.N.; Sandkühler, J. Neurogenic Neuroinflammation: Inflammatory CNS Reactions in Response to Neuronal Activity. *Nat Rev Neurosci* **2014**, *15*, 43–53, doi:10.1038/nrn3617.

115. Amanollahi, M.; Jameie, M.; Heidari, A.; Rezaei, N. The Dialogue Between Neuroinflammation and Adult Neurogenesis: Mechanisms Involved and Alterations in Neurological Diseases. *Mol Neurobiol* **2023**, *60*, 923–959, doi:10.1007/s12035-022-03102-z.

116. Wang, X.; Zhou, Y.; Gao, Q.; Ping, D.; Wang, Y.; Wu, W.; Lin, X.; Fang, Y.; Zhang, J.; Shao, A. The Role of Exosomal microRNAs and Oxidative Stress in Neurodegenerative Diseases. *Oxid Med Cell Longev* **2020**, *2020*, 3232869, doi:10.1155/2020/3232869.

117. Ballard, C.; Gauthier, S.; Corbett, A.; Brayne, C.; Aarsland, D.; Jones, E. Alzheimer's Disease. Lancet 2011, 377, 1019–1031, doi:10.1016/S0140-6736(10)61349-9.

118. Wang, L.; Zhang, L. Circulating Exosomal miRNA as Diagnostic Biomarkers of Neurodegenerative Diseases. Front Mol Neurosci 2020, 13, 53, doi:10.3389/fnmol.2020.00053.

119. Chen, Q.Y.; Wen, T.; Wu, P.; Jia, R.; Zhang, R.; Dang, J. Exosomal Proteins and miRNAs as Mediators of Amyotrophic Lateral Sclerosis. Front Cell Dev Biol 2021, 9, 718803, doi:10.3389/fcell.2021.718803.

120. Wu, Q.; Cao, F.; Tao, J.; Li, X.; Zheng, S.G.; Pan, H.-F. Pentraxin 3: A Promising Therapeutic Target for Autoimmune Diseases. Autoimmun Rev 2020, 19, 102584, doi:10.1016/j.autrev.2020.102584.

121. Zhu, F.; Yang, T.; Ning, M.; Liu, Y.; Xia, W.; Fu, Y.; Wen, T.; Zheng, M.; Xia, R.; Qian, R.; et al. MiR-146a Alleviates Inflammatory Bowel Disease in Mice through Systematic Regulation of Multiple Genetic Networks. Front Immunol 2024, 15, 1366319, doi:10.3389/fimmu.2024.1366319.

122. Li, Z.; Chen, X.; Tao, J.; Shi, A.; Zhang, J.; Yu, P. Exosomes Regulate NLRP3 Inflammasome in Diseases. Front Cell Dev Biol 2022, 9, 802509, doi:10.3389/fcell.2021.802509.

123. Madouri, F.; Guillou, N.; Fauconnier, L.; Marchiol, T.; Rouxel, N.; Chenuet, P.; Ledru, A.; Apetoh, L.; Ghiringhelli, F.; Chamaillard, M.; et al. Caspase-1 Activation by NLRP3 Inflammasome Dampens IL-33-Dependent House Dust Mite-Induced Allergic Lung Inflammation. J Mol Cell Biol 2015, 7, 351–365, doi:10.1093/jmcb/mjv012.

124. Besnard, A.-G.; Togbe, D.; Couillin, I.; Tan, Z.; Zheng, S.G.; Erard, F.; Le Bert, M.; Quesniaux, V.; Ryffel, B. Inflammasome-IL-1-Th17 Response in Allergic Lung Inflammation. J Mol Cell Biol 2012, 4, 3–10, doi:10.1093/jmcb/mjr042.

125. Dai, Y.; Wang, S.; Chang, S.; Ren, D.; Shali, S.; Li, C.; Yang, H.; Huang, Z.; Ge, J. M2 Macrophage-Derived Exosomes Carry microRNA-148a to Alleviate Myocardial Ischemia/Reperfusion Injury via Inhibiting TXNIP and the TLR4/NF-κB/NLRP3 Inflammasome Signaling Pathway. J Mol Cell Cardiol 2020, 142, 65–79, doi:10.1016/j.yjmcc.2020.02.007.

126. Weber, J.A.; Baxter, D.H.; Zhang, S.; Huang, D.Y.; Huang, K.H.; Lee, M.J.; Galas, D.J.; Wang, K. The MicroRNA Spectrum in 12 Body Fluids. Clin Chem 2010, 56, 1733–1741, doi:10.1373/clinchem.2010.147405.

127. Sun, Z.; Shi, K.; Yang, S.; Liu, J.; Zhou, Q.; Wang, G.; Song, J.; Li, Z.; Zhang, Z.; Yuan, W. Effect of Exosomal miRNA on Cancer Biology and Clinical Applications. Molecular Cancer 2018, 17, doi:10.1186/s12943-018-0897-7.

128. Hu, G.; Drescher, K.M.; Chen, X.-M. Exosomal miRNAs: Biological Properties and Therapeutic Potential. Front Genet 2012, 3, 56, doi:10.3389/fgene.2012.00056.

129. Brossa, A.; Tapparo, M.; Fonsato, V.; Papadimitriou, E.; Delena, M.; Camussi, G.; Bussolati, B. Coincubation as miR-Loading Strategy to Improve the Anti-Tumor Effect of Stem Cell-Derived EVs. Pharmaceutics 2021, 13, 76, doi:10.3390/pharmaceutics13010076.

130. Akao, Y.; Iio, A.; Itoh, T.; Noguchi, S.; Itoh, Y.; Ohtsuki, Y.; Naoe, T. Microvesicle-Mediated RNA Molecule Delivery System Using Monocytes/Macrophages. Mol Ther 2011, 19, 395-399, doi:10.1038/mt.2010.254.

131. Alvarez-Erviti, L.; Seow, Y.; Yin, H.; Betts, C.; Lakhal, S.; Wood, M.J.A. Delivery of siRNA to the Mouse Brain by Systemic Injection of Targeted Exosomes. Nat Biotechnol 2011, 29, 341-345, doi:10.1038/nbt.1807.

Funding

This work was supported by Shanghai Natural Science Foundation (23ZR1457300), Key Discipline Project of Shanghai Songjiang District Municipal Health Commission (24SJYXZDA06) and Shanghai Municipal Key Discipline of health system (2024ZDXK0065)

Conflicts of interest

All authors declare no competing interests.

Author Contributions

YH designed and conceived the study. SG drafted and completed the manuscript. SZ revised the manuscript. XL, LY and LZ provided advice and technical assistance. All authors have contributed to and approved the final manuscript.

Ethics Approval and Consent to Participate

Not applicable.

Consent for publication

All authors have Consented for publication

Acknowledgment

This work was supported by National Natural Science Foundation (82371817and81871224), Foundation of State Key Laboratory of Pathogenesis, Prevention and Treatment of High Incidence Diseases in Central Asia (SKL_x0002_HIDCA-2024-GD3), Innovation Cluster Project of Shanghai Health Commission (2024CXJQ01), Shanghai Natural Science Foundation (23ZR1457300), Research Project of Shanghai Municipal Health Commission (202240095), Shanghai Municipal Key Discipline of health system (2024ZDXK0065), and Shanghai Songjiang District Research Project (2024SJKJGG071)