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REVIEW

Roles of Exosomal miRNAs in Asthma: Mechanisms and Applications

Xiaoxue Liu[1], Jiawei Gao[2], Liuxin Yang[2], Xingxing Yuan[2,3]

[1]Department of Paediatrics, Harbin Hospital of Traditional Chinese Medicine, Harbin, 150010, People's Republic of China; [2]Heilongjiang University of Chinese Medicine, Harbin, 150040, People's Republic of China; [3]Department of Gastroenterology, Heilongjiang Academy of Traditional Chinese Medicine, Harbin, 150006, People's Republic of China

Correspondence: Xingxing Yuan, Heilongjiang University of Chinese Medicine, Harbin, Heilongjiang, 150040, People's Republic of China, Email yuanxingxing80@163.com

Abstract: Asthma is a chronic inflammatory disorder of the airways, characterized by a complex interplay of genetic, environmental, and immunological factors that contribute to its onset and progression. Recent advances in researches have illuminated the critical role of exosomal microRNAs (miRNAs) in the pathogenesis and development of asthma. Exosomes are nano-sized extracellular vesicles that facilitate intercellular communication by transporting a variety of bioactive molecules, including miRNAs, and play a crucial role in regulating gene expression and immune responses, which are central to the inflammatory processes underlying asthma. Exosomal miRNAs are emerging as key players in asthma due to their involvement in various aspects of the disease, including the regulation of inflammation, airway hyperresponsiveness, and remodeling. Their ability to influence the behavior of target cells and tissues makes them valuable both as diagnostic biomarkers and as potential therapeutic targets. This review aims to provide a comprehensive overview of the biogenesis of exosomes, the functional roles of exosomal miRNAs in asthma, and their clinical potential. It will explore the mechanisms by which these miRNAs contribute to asthma pathophysiology, discuss their utility in diagnosing and monitoring the disease, and highlight ongoing research efforts to harness their therapeutic potential.

Keywords: asthma, exosome, miRNA, biomarker, therapy

Introduction

Asthma is a prevalent chronic respiratory disease that affects over 300 million individuals worldwide. It is characterized by episodic airflow obstruction, bronchial hyperresponsiveness, and underlying inflammation of the airways.[1,2] Symptoms include wheezing, shortness of breath, chest tightness, and coughing, which can vary in intensity and frequency.[3] Despite advances in understanding the pathophysiology of asthma and the development of new therapeutic strategies, there remain significant gaps in effective disease management, especially for patients with severe asthma.[4] Asthma is a heterogeneous disease with various phenotypes, driven by complex interactions between genetic predisposition and environmental factors.[5,6] This complexity necessitates the need for personalized approaches to diagnosis and treatment.

Recent studies have increasingly focused on the role of extracellular vesicles (EVs) in asthma, particularly exosomes, which are small, nano-sized vesicles (30–150 nm in diameter) that originate from the endosomal compartment of cells.[7,8] They are released into the extracellular environments when multivesicular bodies fuse with the plasma membrane, and carry a cargo of proteins, lipids, and nucleic acids, including microRNAs (miRNAs), which are short non-coding RNA molecules that regulate gene expression at the post-transcriptional level.[9,10] MiRNAs are involved in various biological processes, including development, differentiation, proliferation, and apoptosis.[11] Dysregulation of miRNAs has been implicated in a range of diseases, including cancer, cardiovascular diseases, and inflammatory conditions such as asthma.[12] In asthma, exosomal miRNAs have emerged as key regulators of immune responses and airway remodeling. They facilitate communication between different cell types within the airway microenvironment, including epithelial cells, immune cells, and fibroblasts, which are crucial for the initiation and propagation of inflammatory responses and

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for maintaining tissue homeostasis.[13–15] For instance, exosomal miRNAs have been shown to influence the differentiation and activation of various immune cell subsets, such as T lymphocytes, B cells, and macrophages, thereby shaping the immune landscape of this disease.[16–18] Given their stability in biological fluids and their ability to reflect the physiological state of parent cells, exosomal miRNAs hold great promise as non-invasive biomarkers for asthma.[19] Thus, profiling exosomal miRNAs could improve early diagnosis, monitor disease activity, and predict treatment responses, thereby enabling more precise and personalized management of asthma. Compared to other relevant review papers,[7,15,18] this review emphasizes the paradoxical role of exosomal miRNAs in asthma through its detailed description of molecular pathways, and it focuses on the potential of mesenchymal stem cells-derived exosomal miRNAs for developing new therapeutic strategies.

This review concisely discusses the pathological mechanisms of asthma and the biogenesis of exosomal miRNAs, as well as emphasizes the roles of exosomal miRNAs in asthma, identifying gaps that need to be addressed to translate these insights into clinical practice. Through a detailed examination of exosomal miRNAs, we hope to shed light on their potential to transform asthma diagnosis and therapy, ultimately improving outcomes for patients with this disease.

The Pathogenesis of Asthma

The pathogenesis of asthma involves a complex interplay of factors, including airway hyperresponsiveness, reversible bronchial obstruction, inflammation, and structural changes in the airways.[20] Inflammatory cells, such as lymphocytes, macrophages, eosinophils, and mast cells, play crucial roles in inducing airway remodeling and damage.[21] Additionally, the involvement of various immune cells, including group 2 innate lymphoid cells (ILC2) and type 2 T-helper (Th2) lymphocytes, in releasing cytokines like interleukin (IL)-4, IL-5, and IL-13, further contributes to the inflammatory response and bronchial hyperreactivity.[22] Airway inflammation in asthma is a complex process involving various proinflammatory cytokines and cascades, which are associated with elevated levels of eosinophils, immunoglobulin E, and fractional exhaled nitric oxide, serving as biomarkers for airway inflammation.[23] The pathophysiology of airway inflammation is driven by both the innate and adaptive immune systems, which further lead to airway remodeling, mucus production, and tissue damage.[24]

Chronic inflammation observed in asthma results in structural alterations within the airways, commonly referred to as airway remodeling.[25] This phenomenon encompasses epithelial injury, enlargement of mucous glands, deposition of collagen beneath the epithelium, and enhanced proliferation of airway smooth muscle cells (ASMCs).[26–28] These modifications are implicated in the sustained restriction of airflow and increased sensitivity of the airways.[29] The process of airway remodeling is influenced by a variety of elements, among which transforming growth factor-beta (TGF-β) plays a significant role.[30] TGF-β is predominantly secreted by bronchial epithelial cells and eosinophils, triggering the differentiation of fibroblasts, $CD4^+$ T cells, and Th2 cells, while concurrently suppressing the activation of regulatory T cells (Tregs).[31–33] Consequently, this exacerbates both airway hyperresponsiveness and inflammation.

Numerous signaling pathways play a role in the development of asthma. The nuclear factor-kappaB (NF-κB) pathway, a key regulator of airway inflammation, is activated by various stimuli such as pro-inflammatory factors, viruses, drugs, and cigarette smoke.[34,35] Activation of NF-κB results in its translocation to the nucleus where it enhances the expression of inflammatory genes.[36] Another crucial signaling pathway in asthma is the Toll-like receptor 4 (TLR4)/myeloid differentiation primary response 88 (MyD88) pathway, which is responsible for initiating the inflammatory response.[37] Lipopolysaccharide (LPS) acts as a potent pro-inflammatory agent in the context of asthma, contributing to both the initiation and exacerbation of the disease through the activation of immune pathways, promotion of Th2 responses, and enhancement of airway remodeling and hyperresponsiveness.[38] The binding of LPS to TLR4 triggers the activation of MyD88, leading to the nuclear translocation of NF-κB and exacerbating inflammation.[39] Additionally, the phosphatidylinositol 3-kinase (PI3K)/Akt and Wnt/β-catenin pathways are associated with airway remodeling and hyperresponsiveness.[40,41] These pathways play a role in ASMCs proliferation, migration, and epithelial-mesenchymal transition (EMT), ultimately contributing to airway remodeling.[42,43]

Biogenesis of Exosomal miRNAs

Exosomes are a subset of EVs that are generated through a highly regulated biogenesis pathway originating from the endosomal system.[44] The formation and secretion of exosomes involve several key steps, including endocytosis,

multivesicular body formation, and exosome release, which govern the generation of exosomes and the selective incorporation of miRNAs into vesicles.[45]

The biogenesis of exosomes begins with the inward budding of the plasma membrane, forming early endosomes.[46] This process, known as endocytosis, is initiated when the cell membrane invaginates to engulf extracellular material, resulting in the formation of endocytic vesicles. These vesicles then mature into early endosomes, which are dynamic structures involved in sorting and trafficking of internalized molecules.[47] Early endosomes undergo further maturation into late endosomes, also known as multivesicular bodies, which are characterized by the presence of intraluminal vesicles that are formed by the inward budding of the endosomal membrane.[48] This process is orchestrated by the endosomal sorting complexes that are required for transport machinery, playing crucial roles in recognizing and sequestering ubiquitinated cargo, deforming the endosomal membrane, and facilitating vesicle scission.[49] MiRNAs are selectively incorporated into intraluminal vesicles and consequently into exosomes. Specific RNA-binding proteins such as argonaute 2 and ALG-2 interacting protein X, are involved in recognizing and sorting miRNAs into intraluminal vesicles.[50] Additionally, specific sequence motifs within miRNAs can dictate their inclusion into exosomes. This selectivity ensures that exosomes carry specific miRNAs that reflect the physiological or pathological state of the parent cell.[51,52] Once multivesicular bodies are formed, they either fuse with lysosomes for degradation of their content, or they fuse with the plasma membrane to release intraluminal vesicles as exosomes into the extracellular space.[53,54] The fusion of multivesicular bodies with the plasma membrane is facilitated by Rab GTPases, such as Rab27a and Rab27b, which are critical regulators of vesicle docking and fusion.[55] Upon fusion, the intraluminal vesicles are released as exosomes, carrying their cargo of proteins, lipids, and nucleic acids, including miRNAs, to the extracellular environment.[11]

Exosomes can travel through bodily fluids and be taken up by recipient cells, where their cargo can exert functional effects. The uptake of exosomes by recipient cells can occur through various mechanisms, including endocytosis, phagocytosis, and direct membrane fusion.[56] Upon entry into recipient cells, exosomal miRNAs can modulate gene expression by binding to complementary sequences in the 3' untranslated regions of target mRNAs, leading to mRNA degradation or translational repression.[57] Exosomal miRNAs are implicated in a wide range of biological processes, including immune modulation, inflammation, and tissue remodeling.[58]

Understanding the biogenesis of exosomal miRNAs is critical for developing therapeutic strategies that harness these vesicles. In the context of asthma, exosomal miRNAs play pivotal roles in orchestrating the inflammatory response and regulating airway remodeling. Future research should focus on uncovering the molecular determinants of miRNA sorting into exosomes, optimizing techniques for exosome purification, and developing exosome-based delivery systems for therapeutic miRNAs. Additionally, investigating the role of exosomal miRNAs in various stages of asthma, from early onset to chronic disease, will provide deeper insights into their potential as diagnostic biomarkers and therapeutic targets.

Effects of Exosomal miRNAs on Asthma

Asthma is a chronic inflammatory disorder characterized by airway inflammation, bronchial hyperresponsiveness, mucus overproduction, and structural remodeling of the airway walls.[59] The pathogenesis of asthma involves complex interactions between genetic and environmental factors, leading to dysregulated immune responses and chronic inflammation.[60] Exosomal miRNAs have emerged as critical regulators in these processes, influencing immune cell function, epithelial-mesenchymal transition, and tissue remodeling.[61] Compared with healthy controls, differentially expressed exosomal miRNAs in mild asthmatic patients are associated with various immunologic characteristics, such as Th1 and Th2 differentiation, and IL-10 and IL-13 release, which affect asthmatic phenotypes and pulmonary functions.[62] Further analyses of exosomal miRNA profiles from bronchial epithelial cells of asthmatic subjects reveal that they act on mechanistic target of rapamycin (mTOR) and mitogen-activated protein kinase (MAPK) signaling pathways, as well as regulate immune functions through T and B cell receptor signaling.[63] Of interest, breast milk-derived extracellular vesicle miRNAs may have effects on child health outcomes associated with maternal asthma and atopy via modulating TGF-β signaling and extracellular matrix-receptor interaction.[64] Indeed, exosomal miRNAs exert the paradoxical roles in the pathogenesis of asthma, highlighting key findings from recent studies and their implications for disease progression (Table 1).

Table 1 The Role of Exosomal miRNAs in Asthma

Origin	Exosomal miRNAs	Downstream targets	Outcomes	Disease progression	Experimental design	Ref.
AECs	miR-381-3p	TGF-β3	Inhibit the proliferation of ASMCs and decrease the expression of α-SMA and collagen I in ASMCs	Inhibit	PCI-34051-treated AECs	[13]
M2 macrophage	miR-30b-5p	NLRP3, caspase-1, IL-1β, and IRF7	Inhibit mitochondrial swelling and cell pyroptosis in airway epithelial cells	Inhibit	OVA-sensitized mice	[14]
DCs	miR-493-5p	FOXO1	Inhibit Th9 cell differentiation and asthma development	Inhibit	OVA-sensitized mice	[16]
M2 macrophage	miR-370	FGF1/MAPK/STAT1	Inhibit ASMCs proliferation and invasion, as well as alleviate pulmonary inflammation and fibrosis	Inhibit	PDGF-treated ASMCs, OVA-sensitized mice	[65]
Mast cells	miR-146a	IL-33/ST2	Reduce the IL-6 expression and asthmatic inflammation	Inhibit	IL-33-treated mice	[66]
Neutrophils	miR-21	Unknown	Attenuate the proliferation of ASMCs and the thickening of the bronchial wall	Inhibit	Asthmatic horses, LPS-treated ASMCs	[67]
AECs	miR-92b, miR-210, miR-34a	Unknown	Regulate Th2 polarization and dendritic cell maturation	Promote	IL-13-stimulated AECs	[68]
BALF	54 miRNAs	IL-13, IL-5Ra	Participate in allergic airway inflammation	Promote	HDM-sensitized mice	[69]
Mast cells	miR-21	DDAH1/Wnt/β-catenin	Decrease the expression of antioxidant enzymes and increase the infiltration of inflammatory cells	Promote	LPS-stimulated AECs, OVA-induced mice	[70]
Neutrophils	miR-155	Extracellular traps	Promote the extracellular release of dsDNA and exacerbates allergic lung inflammation,	Promote	Triple-allergen-induced mice	[71]
Peripheral blood	miRNA-126	DNMT1	Participate in the pathogenesis of bronchial asthma	Promote	Asthmatic patients, OVA-induced mice	[72]
Macrophages	miR-21-5p	TGFβ-1/Smad	Promote EMT in tracheal epithelial cells and airway remodeling	Promote	OVA-induced rats, LPS-stimulated macrophages	[73]

Abbreviations: AECs, airway epithelial cells; ASMCs, airway smooth muscle cells; α-SMA, α-smooth muscle actin; BALF, bronchoalveolar lavage fluid; DCs, dendritic cells; DDAH1, dimethylarginine dimethylaminohydrolase 1; DNMT1, DNA methyltransferase 1;dsDNA, double-stranded DNA; EMT, epithelial-mesenchymal transition; FGF1, fibroblast growth factor 1; FOXO1, forkhead box O1; HDM, house-dust mite; IL, interleukin; IRF, interferon regulatory factor family; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; miRNAs, microRNAs; NLRP3, NOD-like receptor pyrin domain-containing 3; OVA, ovalbumin; PDGF, platelet derived growth factor; STAT1, signal transducer and activator of transcription 1; TGF-β, transforming growth factor-beta; Th, T-helper.

Promoting Asthma Progression

Exosomal miRNAs are involved in dysregulated immune responses in asthma. They can influence the differentiation and function of various immune cells, including T cells, B cells, macrophages, and dendritic cells.[65,74–76] In asthma, the dysfunction of these miRNAs can skew the immune response towards a more pro-inflammatory state, exacerbating disease severity.[77,78] For instance, secretion of miRNAs from the airway epithelium, like miR-34a, miR-92b, and miR-210, have been shown to regulate Th2 polarization and dendritic cell maturation in the airways, thus participating in the early development of asthma.[68] Also, miRNAs derived from infiltrating immune cells, including miR-223 and miR-142a, are able to alter the local extracellular environment in inflamed tissues and contribute to allergic airway inflammation.[79] These findings suggest that exosomal miRNAs can modulate the differentiation, activation, and function of immune cells, thereby shaping the inflammatory response in asthma. In house-dust mite sensitized mice, the amount of exosomal miRNAs is increased in bronchoalveolar lavage fluid (BALF), which regulate the expression of IL-13 and IL-5Ra and further mediate the inflammatory lung damage and aggravate allergic airway inflammation.[69] Likewise, in LPS-treated airway epithelial cells and asthmatic mice, elevated miR-21 in mast cells downregulates the expression of antioxidant enzymes and facilitates inflammatory cell infiltration through suppressing DDAH1 and further stimulating the Wnt/β-

catenin signaling, thereby accentuating oxidative stress and inflammation.[70] Besides, extracellular traps released from neutrophils consist of double-stranded DNA, histones, and granule contents, which contribute to the pathophysiology of asthma.[71] Further investigation observed that exosomal miR-155 is responsible for the extracellular release of double-stranded DNA (dsDNA), which exacerbates allergic lung inflammation and neutrophilic asthma phenotype, implying that targeting dsDNA release represents a promising therapeutic target for mitigating severe asthma.[71] In addition, exosomal miRNAs affect remodeling processes by regulating the expression of genes involved in smooth muscle hypertrophy, extracellular matrix production, and tissue repair. For example, exosomal miRNAs can be transferred between airway epithelial cells and causes mucin hypersecretion, playing an important role in airway biology and epithelial remodeling in asthma.[80] It is reported that miR-126 in peripheral blood exosomes from patients with allergic asthma is increased, which is related to narrowed bronchial lumen, thickened wall, and overt inflammatory cell infiltration in bronchial and peripheral vessels, indicating a pathogenic role of miR-126 in airway remodeling.[72] Similarly, in macrophages of rats with ovalbumin (OVA)-induced asthma, the level of exosome-derived miR-21-5p is elevated and subsequently promotes EMT in tracheal epithelial cells through the TGF-β1/Smad signaling pathway by downregulating Smad7,[73] which could lead to increased collagen deposition and fibrosis in the asthmatic airway.

In conclusion, exosomal miRNAs play a crucial role in promoting asthma progression by modulating immune responses, inflammation, and airway remodeling (Figure 1). Their stability and ability to mediate intercellular communication make them attractive candidates for therapeutic intervention. Targeting exosomal miRNAs offers a novel approach to managing asthma, with the potential to reduce inflammation and reverse airway remodeling. Future research should focus on understanding the precise mechanisms by which exosomal miRNAs contribute to asthma pathogenesis and developing targeted therapies that can effectively modulate their levels in asthmatic patients. In this context, strategies aimed at suppressing exosomal miRNA levels like the use of miRNA inhibitors, which can be delivered to

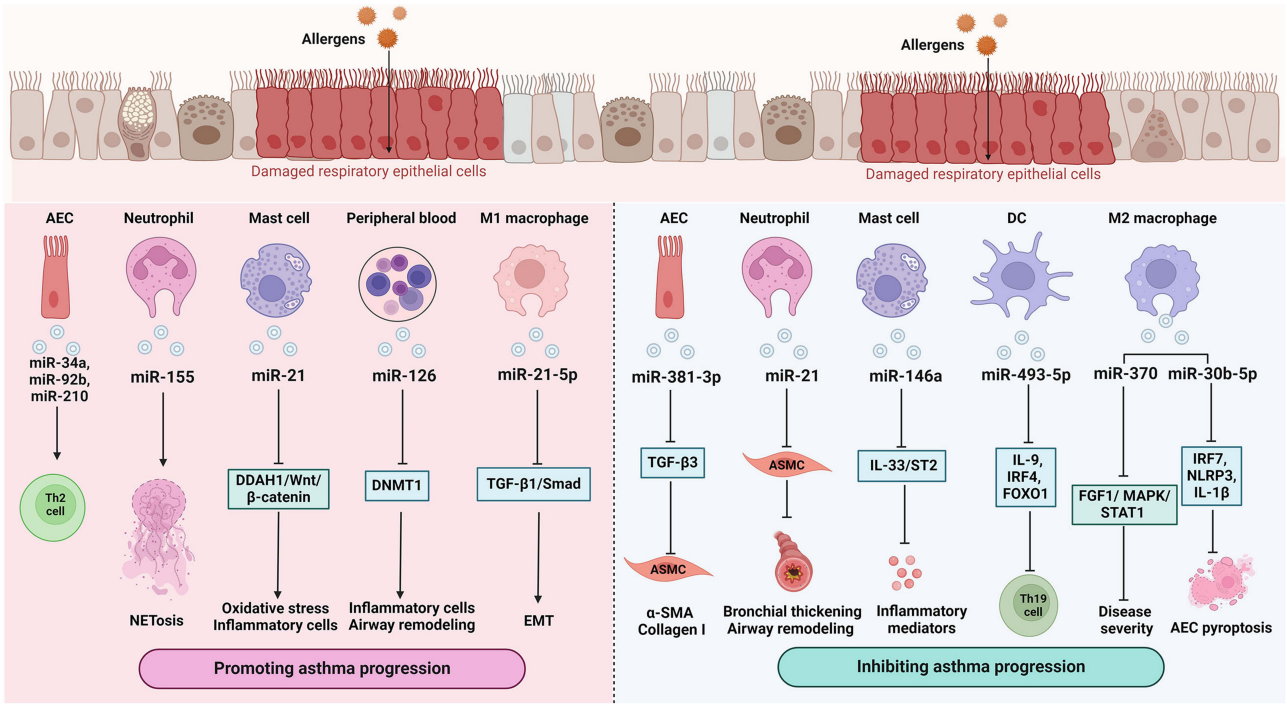

Figure 1 The role of exosomal miRNAs in asthma. Some exosomal miRNAs, such as miR-34a, miR-155, miR-21, miR-126, and miR-21-5p, play a crucial role in promoting asthma progression by enhancing Th2 cell proliferation, NETosis, oxidative stress, inflammation infiltration, and EMT; whereas, other exosomal miRNAs, like miR-381-3p, miR-21, miR-146a, miR-493-5p, miR-370, and miR-30b-5p, suppress asthma progression through inhibiting ASMC proliferation, Th19 cell activation, inflammatory cytokine production, and AEC pyroptosis. AECs, airway epithelial cells; ASMC, airway smooth muscle cell; α-SMA, α-smooth muscle actin; DCs: dendritic cells; DDAH1, dimethylarginine dimethylaminohydrolase 1; DNMT1, DNA methyltransferase 1; EMT, epithelial-mesenchymal transition; FGF1, fibroblast growth factor 1; FOXO1, forkhead box O1; IL, interleukin; IRF, interferon regulatory factor family; MAPK, mitogen-activated protein kinase; miRNAs, microRNAs; NETosis, neutrophil extracellular trap formation; NLRP3, NOD-like receptor pyrin domain-containing 3; STAT1, signal transducer and activator of transcription 1; TGF-β, transforming growth factor-beta; Th, T-helper. → indicates a promoting effect and ⊥ indicates an inhibitory effect.

specific cell types via engineered exosomes might serve as innovative treatments that can improve outcomes for individuals suffering from asthma.

Inhibiting Asthma Progression

In asthma, miRNAs have been identified as key regulators of immune responses and airway remodeling.[81,82] These miRNAs can be packaged into exosomes and transported to recipient cells, where they modulate cellular functions, which include controlling the differentiation and activation of immune cells, modulating the expression of inflammatory factors, and influencing the extracellular matrix composition.[78,83,84] The immunomodulatory effects of exosomal miRNAs are pivotal in asthma management. Exosomal miR-493-5p that derived from dendritic cells, for example, has been implicated in repressing the differentiation and function of Th9 by decreasing the expression of the IL-9, interferon regulatory factor family (IRF) 4 and FOXO1, playing a critical role in maintaining immune hemostasis during the development of asthma.[16] In addition, exosomal miRNAs have been shown to exert anti-inflammatory effects, which are crucial in mitigating asthma progression. For instance, miR-30b-5p carried by M2 macrophage-derived exosomes targets and downregulates the level of pyroptosis-related proteins, including IRF7, NOD-like receptor pyrin domain-containing (NLRP) 3, caspase-1, and IL-1β, thereby inhibiting mitochondrial swelling and pyroptosis in airway epithelial cells, thereby mitigating severe asthma.[14] MiR-370, another M2 macrophage-derived exosomal miRNA, is verified to block the expression of fibroblast growth factor 1 and further inactivate the MAPK/STAT1 signaling pathway, alleviating asthma progression in OVA-induced asthmatic mice.[65] Similarly, exosomal miR-146a from bone marrow-derived mast cells can inhibit the IL-33/ST2 signaling, a key regulator of inflammatory responses in asthma, leading to decreased production of inflammatory cytokines and chemokines.[66] Furthermore, exosomal miRNAs can inhibit airway remodeling by targeting key signaling pathways during asthma progression. For example, exosomal miR-381-3p derived from airway epithelial cells has been demonstrated to repress the TGF-β3 pathway, which is involved in fibroblast activation and extracellular matrix production. By reducing the level of α-smooth muscle actin (α-SMA) and collagen I in ASMCs, exosomal miR-381-3p can reduce fibrosis and airway wall thickening.[13] Likewise, neutrophil-derived exosomal miR-21 is decreased in severe equine asthma, which is associated with the proliferation of ASMCs, thereby reducing the thickening of the bronchial wall and airway remodeling in asthma.[67]

In sum, exosomal miRNAs represent a novel and promising approach to modulating asthma progression. Their ability to exert anti-inflammatory effects, modulate immune responses, and inhibit airway remodeling highlights their therapeutic potential (Figure 1). As research in this field advances, exosomal miRNA-based therapies may emerge as effective and targeted treatments for asthma, offering new hope for patients with this chronic and debilitating condition. For instance, exosomes loaded with anti-inflammatory miRNAs could be administered to patients to reduce airway inflammation and improve lung function. Additionally, combining exosomal miRNA therapy with existing asthma treatments, such as corticosteroids and bronchodilators, could enhance therapeutic efficacy and reduce treatment-related side effects. Therefore, exploring and harnessing the inhibitory effects of exosomal miRNAs can pave the way for innovative and personalized therapeutic strategies that address the underlying mechanisms of asthma and improve patient outcomes.

Diagnostic and Therapeutic Potential of Exosomal miRNAs in Asthma

Diagnostic Markers

Exosomal miRNAs hold significant promise as diagnostic biomarkers for various diseases due to their stability in bodily fluids, ability to reflect disease states, and non-invasive nature.[85–87] Exosomal miRNAs act as potential biomarkers for the diagnosis of asthma. These miRNAs exhibit distinct expression patterns in asthmatic patients compared to healthy individuals, and their levels correlate with disease severity, phenotype.[88,89] For instance, exosomal miRNAs from BALF of asthmatic patients are remarkably different from healthy control subjects, providing classification of patients with mild non-symptomatic asthma from healthy populations.[90] As for the obesity-associated low type-2 asthma, plasma exosomal miRNA signatures are identified to participate in impairment of lung function, which serve as basis for stratified treatment response.[91] Besides, asthma is a heterogeneous disease with multiple phenotypes, including allergic asthma, non-allergic asthma, and severe asthma.[92] Exosomal miRNA profiles can help differentiate various phenotypes, allowing

for more tailored treatment approaches. For example, elevated exosomal miR-21-5p and miR-126-3p levels are indicative of $T2^{high}$ atopic asthma, while decreased miR-21-5p, miR-126-3p and miR-146a-5p levels may signal neutrophilic asthma.[93] Coincidentally, it has been reported that exosomal miR-122-5p is increased in plasma and sputum supernatant derived from patients with severe asthma, which might sub-differentiate different phenotypes of asthma, such as neutrophilic from eosinophilic asthma.[94] Moreover, estimating the severity of asthma is essential for optimizing therapeutic strategies. Changes in exosomal miRNA levels can reflect the severity of disease and help adjust therapy accordingly.[85] For instance, it is observed that the expression levels of miR-125b in serum exosomes of patients with intermittent, mildly persistent, moderately persistent, and severely persistent asthma are significantly higher than those in the healthy controls, suggesting serum exosomal miR-125b has a high diagnostic efficacy and could serve as a noninvasive diagnostic marker for asthma severity.[95] In moderate asthmatic patients, plasma exosomal miR-223 and miR-21 are elevated compared to healthy controls, indicating their potential for biomarkers.[88] Also, in severe asthma patients, levels of exosomal miR-124, miR-133b, and miR-130a are reduced but miR-125b is increased, which is linked to inflammatory reactions, implying this miRNA profile is useful for diagnosis and discrimination of clinical phenotypes of asthma.[96]

It can be concluded that exosomal miRNAs can serve as potential biomarkers for early diagnosis, disease phenotyping, and monitoring treatment responses in asthma. Hence, ongoing research should be focused on validating the diagnostic utility of exosomal miRNAs in larger and more diverse patient cohorts. Additionally, efforts are being made to standardize methods for exosome isolation and miRNA analysis to ensure reproducibility and accuracy in clinical settings. Technological advancements, such as high-throughput sequencing and digital PCR, are being leveraged to enhance the sensitivity and specificity of exosomal miRNA detection. Besides, integrating exosomal miRNA profiling with other omics technologies, such as proteomics and metabolomics, could provide a more comprehensive understanding of asthma pathogenesis and identify novel biomarkers. Additionally, developing point-of-care diagnostic devices for rapid exosomal miRNA detection could revolutionize asthma management by enabling real-time monitoring and personalized treatment adjustments.

Therapeutic Potential of Mesenchymal stem cells (MSCs) Derived Exosomal miRNAs

MSCs are now known to be present in virtually all post-natal organs and tissues, including bone marrow, adipose tissue, umbilical cord, and placenta.[97,98] Under appropriate conditions, MSCs can differentiate into osteoblasts, adipocytes, and chondroblasts, which make them promising candidates for therapeutic applications owing to their plastic properties.[99,100] MSC-derived exosomes are critical in mediating the therapeutic effects of MSCs. Exosomes from MSCs promote tissue repair and regeneration by transferring growth factors and miRNAs that enhance cell proliferation and differentiation.[101,102] In asthma, MSC-derived exosomal miRNAs exert immunomodulatory effects to impede disease progression. For example, exosomal miR-146a-5p is verified to inhibit Th2 cell differentiation by downregulating the expression of plasminogen activator inhibitor-2, repressing the overactivation of immune system.[103] Also, miR-1470 within MSC-derived exosomes is confirmed to facilitate the differentiation of $CD4^+CD25^+FOXP3^+$ Tregs in asthmatic patients by upregulating $p27^{kip1}$, a cyclin-dependent kinase regulator that controls cell differentiation program.[104,105] In addition, it is reported that MSC-derived exosomal miR-146a-5p hinders the function of ILC2s, as well as reduces inflammatory cell infiltration, pulmonary mucus production, and Th2 cytokine secretion, thus alleviating airway hyperresponsiveness in a mouse ILC2-dominant asthma model.[106] By inhibiting the JARID2/Wnt/β-catenin axis, miR-188 from MSC-derived exosomes is verified to lessen inflammatory cell infiltration, mucus production, and collagen deposition in lung tissues of asthmatic mice.[107] Likewise, exosomal miR-301a-3p from adipose-derived MSCs decreases the secretion of inflammatory factors, including TNF-α, IL-1β and IL-6, in ASMCs treated with platelet-derived growth factor, along with suppressed proliferation and migration of ASMCs, thus alleviating airway inflammation and remodeling in OVA-induced asthma mouse model.[108] These studies highlight the significant potential of MSC-derived exosomes in modulating airway inflammation in asthma. Furthermore, it has been demonstrated that exosomal miR-221-3p derived from human bone marrow MSCs can restrict ASMC proliferation, migration, and extracellular matrix deposition by targeting fibroblast growth factor 2 and thus inhibiting the ERK1/2 signaling pathway, which lessens airway hyperresponsiveness and histopathological damage in an OVA-induced asthmatic mouse model.[109] Similarly, exosomal miR-

146a-5p derived from human umbilical cord MSCs cultured under hypoxic conditions is capable of decreasing the expression of profibrogenic markers such as α-SMA and collagen-1, which is associated with the suppression of TGF-β1/Smad2/3 signaling pathway, thus ameliorating airway remodeling in chronic asthma mice.[110] Li et al unveiled that miR-223-3p, highly expressed in bone marrow MSC-derived exosomes, mitigates airway inflammation and remodeling by targeting the NLRP3-induced ASC/Caspase-1/GSDMD signaling pathway,[111] which accelerates the restoration of the epithelial barrier function and reduces mucus hypersecretion. Therefore, these findings imply the therapeutic potential of MSC-derived exosomes in addressing airway remodeling in asthma.

Thus, MSC-derived exosomal miRNAs exert inhibitory effects in asthma, offering a novel therapeutic approach for this disease (Figure 2). Strategies to modulate exosomal miRNA activity include the use of miRNA mimics to restore the function of downregulated miRNAs and miRNA inhibitors to block the activity of upregulated miRNAs. Additionally, engineering exosomes to deliver therapeutic miRNAs to specific cell types represents a promising avenue for targeted therapy. A recent study has revealed that RNA nanoparticles with mannose decorated exosomal miR-511-3p can penetrate the airway mucus barrier and deliver functional miR-511-3p to lung macrophages, which alleviates airway inflammation and confers protection against asthma.[17] Hence, effective delivery of therapeutic miRNAs is critical for their clinical success. Several delivery methods are being explored to ensure that miRNAs reach their target cells in

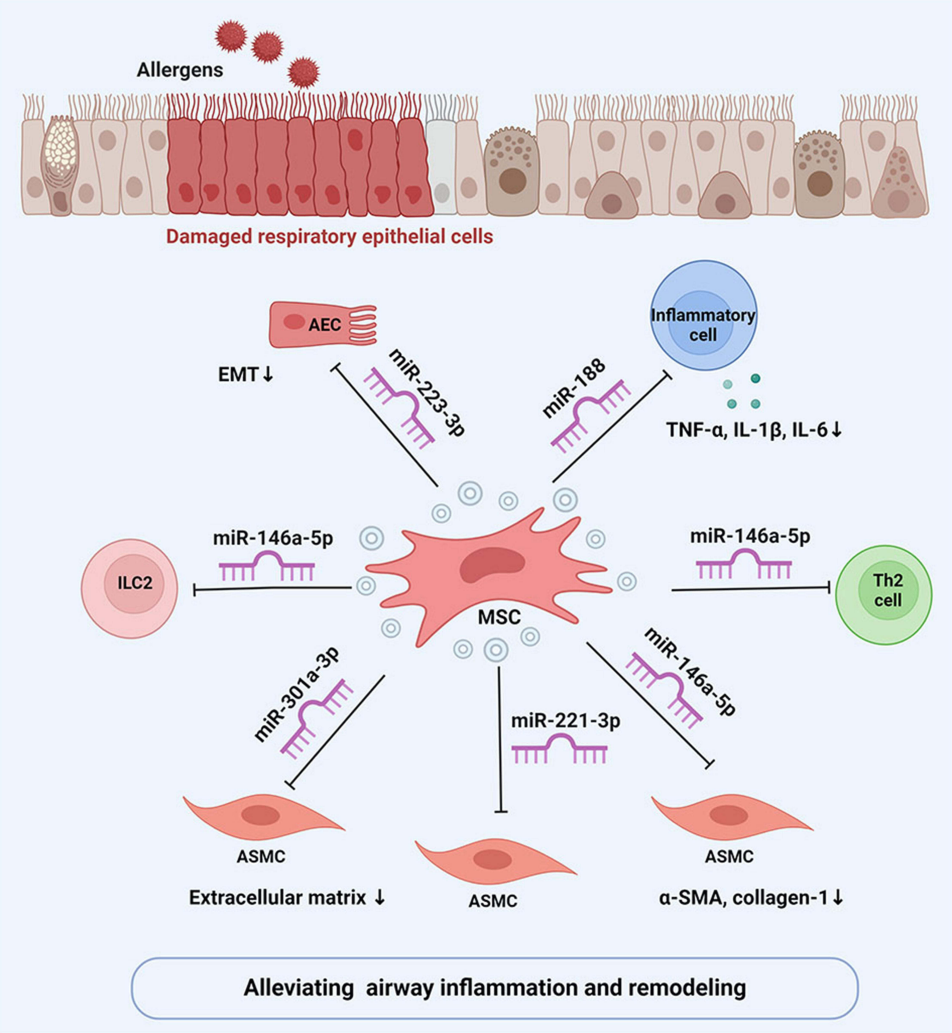

Figure 2 The therapeutic potential of MSC-derived exosomal miRNAs in asthma. MSC-derived exosomal miRNAs, including miR-146a-5p, miR-223-3p, miR-188, miR-221-3p, and miR-301a-3p, mitigate airway inflammation and remodeling via inhibiting the secretion of inflammatory cytokines, the proliferation of ILC2, Th2 cells and ASMC, as well as the production of extracellular matrix, α-SMA, and collagen-1. AECs, airway epithelial cells; ASMC, airway smooth muscle cell; α-SMA, α-smooth muscle actin; EMT, epithelial-mesenchymal transition; IL, interleukin; miRNAs, microRNAs; Th, T-helper. ⊥ indicates an inhibitory effect and ↓ indicates downregulation.

sufficient quantities while maintaining their stability and functionality. One of the main challenges in developing exosomal miRNA therapies is ensuring efficient delivery to target cells. The biological barriers in the respiratory system, such as mucus and cellular uptake mechanisms, can limit the effectiveness of exosomal delivery. Future research should focus on optimizing delivery systems, such as using nanoparticles or liposomes to enhance the stability and bioavailability of exosomal miRNAs.

Conclusions

Exosomal miRNAs are central to the regulation of inflammatory and remodeling processes in asthma, offering valuable insights into disease mechanisms and presenting new opportunities for diagnosis and treatment. Their stability, accessibility in body fluids, and disease-specific expression profiles make them ideal candidates for non-invasive biomarkers. Moreover, the ability to modulate exosomal miRNA activity holds promise for developing targeted therapies that could improve disease management and patient outcomes. Continued research in this field will enhance our understanding of exosomal miRNAs and pave the way for innovative clinical applications in asthma.

While the potential of exosomal miRNAs as diagnostic and therapeutic tools is promising, several challenges remain. These include the need for standardized methods for exosome isolation and characterization, understanding the mechanisms of miRNA sorting and delivery, and addressing the potential off-target effects of miRNA-based therapies. Future research should focus on elucidating the precise molecular mechanisms by which exosomal miRNAs influence asthma pathogenesis, optimizing exosome-based delivery systems, and conducting clinical trials to evaluate the safety and efficacy of exosomal miRNA-based therapies. For example, the uptake of exosomes by recipient cells and the subsequent release and function of miRNAs within these cells are critical aspects that require further investigation. Understanding these processes can help in designing more effective exosome-based therapies. Exploring combination therapies that integrate exosomal miRNAs with existing asthma treatments can enhance therapeutic efficacy and provide synergistic benefits. For instance, combining exosomal miRNA therapies with corticosteroids or biologics could provide a more comprehensive approach to managing asthma. Exosomal miRNAs could modulate underlying molecular pathways, enhancing the anti-inflammatory effects of corticosteroids and the targeted action of biologics. Investigating the potential of combining exosomal miRNAs with emerging therapeutic agents, such as small molecule inhibitors or gene editing technologies (CRISPR/Cas9), could open new avenues for asthma treatment.

Abbreviations

ASMCs,airway smooth muscle cells; α-SMA, α-smooth muscle actin; BALF, bronchoalveolar lavage fluid; dsDNA, double-stranded DNA; EMT, epithelial-mesenchymal transition; EVs, extracellular vesicles; IL, interleukin; ILC2, group 2 innate lymphoid cells; IRF, interferon regulatory factor family; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; miRNAs, microRNAs; mTOR, mechanistic target of rapamycin; MSCs, mesenchymal stem cells; MyD88, myeloid differentiation primary response 88; NF-κB, nuclear factor-kappaB; NLRP3, NOD-like receptor pyrin domain-containing 3; OVA, ovalbumin; PI3K, phosphatidylinositol 3-kinase; TGF-β, transforming growth factor-beta; Th2, type 2 T-helper; TLR4, Toll-like receptor 4; Tregs, regulatory T cells.

Data Sharing Statement

The data presented in this study are available in the article.

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Appreciate all participants for their contributions.

Author Contributions

Xiaoxue Liu and Xingxing Yuan wrote the manuscript. Jiawei Gao and Liuxin Yang searched PubMed and Web of Science for citations and prepared figures. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took

part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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