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REVIEW

Advancements in understanding the role of microRnas in regulating macrophage polarization during acute lung injury

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ABSTRACT

Acute lung injury (ALI)/acute respiratory distress syndrome (ARDS) is a critical and life-threatening illness that causes severe dyspnea, and respiratory distress and is often caused by a variety of direct or indirect factors that damage the alveolar epithelium and capillary endothelial cells, leading to inflammation factors and macrophage infiltration. Macrophages play a crucial role in the progression of ALI/ARDS, exhibiting different polarized forms at different stages of the disease that control the disease outcome. MicroRNAs (miRNA) are conserved, endogenous, short non-coding RNAs composed of 18–25 nucleotides that serve as potential markers for many diseases and are involved in various biological processes, including cell proliferation, apoptosis, and differentiation. In this review, we provide a brief overview of miRNA expression in ALI/ARDS and summarize recent research on the mechanism and pathways by which miRNAs respond to macrophage polarization, inflammation, and apoptosis. The characteristics of each pathway are also summarized to provide a comprehensive understanding of the role of miRNAs in regulating macrophage polarization during ALI/ARDS.

Acute lung injury (ALI) is a clinical syndrome characterized by alveolar epithelial and lung capillary endothelial cell damage, increased alveolar-capillary permeability, and gas exchange dysfunction. It can be caused by various direct or indirect factors, such as severe infection, septicemia, trauma, shock, burn, and poisoning (Table 1). Neutrophil infiltration, inflammation, and oxidative stress are hallmarks of ALI [1–3], and uncontrolled inflammation can result in acute respiratory distress syndrome (ARDS), and eventually multi-organ dysfunction [2].

Microribonucleic acid (miRNA) is a conserved, endogenous, short non-coding ribonucleic acid composed of 18–25 nucleotides. It is abundant in the body and post-transcriptionally regulates gene expression by incomplete complementary base-pairing with target sites in the 3´-terminal untranslated region of the mRNA, reducing its stability, mediating mRNA cleavage, or inhibiting the process of translation. miRNA is a key regulator involved in various biological processes, including cell proliferation, differentiation, metabolism, apoptosis, inflammation, tumorigenesis, and vascularization [4–9]. Numerous studies have shown that miRNAs play a role in ALI through different mechanisms. Therefore, miRNA is closely linked to the occurrence and development of ALI.

This review summarizes some specific miRNAs associated with ALI, including their role in macrophage polarization, inflammation, and apoptosis, as well as specific regulatory mechanisms. It also describes the relationship between miRNAs and related therapeutic modalities, as well as in vivo miRNAs delivery pathways.

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Table 1. Related factors causing ALI/ARDS.

Causes/ Classification	Direct factors	Indirect factors
	Severe lung infection	Sepsis
	Reflux aspiration	Severe non-chest injury
	Poisonous gases	Severe pancreatitis
	Drowning	Extensive burns
	Oxygen poisoning	A large number of blood transfusion
	Pulmonary embolism	Disseminated intravascular coagulation

Abbreviations: ALI, acute lung injury;ARDS, acute respiratory distress syndrome.

1 Macrophage polarization and acute lung injury

The pathogenesis of ALI is well-known to exhibit both early and late stages of lung injury. In the early stage, occurring from the first few hours to several days, histopathological changes in the lungs include alveolar epithelial and capillary endothelial cell damage, increased microvascular permeability, exudation of inflammatory cells and cytokines, and tiny alveolar consolidation and edema. The late stage, occurring several days later, is characterized by lung tissue fibrosis [10–12]. Despite the numerous scientific and technological advancements, ALI still poses a significant threat to human life and health, given its rapid clinical development, high pathogenic rate, lack of effective treatment, poor prognosis, and high mortality rate. Therefore, research focusing on potential clinical solutions to improve and even eradicate ALI is essential.

Recently, there has been an increasing amount of evidence indicating that macrophages play a key role in the pathogenesis of ALI [13,14]. Macrophages are relatively long-lived cells with many important functions. They are responsible for the destruction of invading microorganisms through phagocytosis, which is an important first line of defense in innate immunity. Additionally, they modulate adaptive immune responses to different pathogens via antigen processing and presentation [15]. Macrophages not only participate in the early stages of lung injury but also play a vital role in the repair and fibrosis stages of lung injury [16]. Macrophages can be classified into two types: M1 (classical activation) and M2 (alternative activation). M1, also referred to as pro-inflammatory phenotype, primarily produces pro-inflammatory cytokines such as tumor necrosis factor, IL-6, IL-1 β, and IL-8, etc., and mainly functions in the early stages of inflammation. M2 type, or the anti-inflammatory phenotype, mainly releases a variety of cytokines such as IL-10, TGF-β, and VEGF, exerting anti-inflammatory effects in the late inflammatory response and promoting wound repair and fibrosis. M2 macrophages can be further divided into subtypes such as M2a, M2b, M2c, and M2d [17]. Therefore, different macrophage types play different roles in the occurrence and development of lung damage at different stages. When subjected to severe infection or inflammation, macrophages first exhibit the M1 phenotype to release TNF-α, IL-1β, IL-12, and IL-23 to fight stimuli. However, if the M1 phase continues, it can lead to tissue damage. Thus, M2 macrophages secrete large amounts of IL-10 and TGF-β to inhibit inflammation, contribute to tissue repair, remodeling, angiogenesis, and preserve homeostasis [18,19]. Therefore, exploring the mechanism of macrophage polarization transformation, and regulating the initiation, development, and end of the inflammatory response by targeting signaling pathways and molecular changes in the local microenvironment to transform macrophages into appropriate phenotypes will have excellent therapeutic prospects.

Macrophages play a crucial role in acute lung injury. Firstly, nonendogenous pathogen-associated molecular patterns (PAMPs), such as lipopolysaccharides and lipoteichoic acid, bind to pattern recognition receptors (PRRs), initiating an intra-inflammatory signaling cascade that results in the release of pro-inflammatory cytokines, such as tumor necrosis factor α (TNF-α), interleukin (IL)-1β, and IL-8 [20]. Secondly, mitochondrial damage-associated molecular patterns (DAMPs) released from damaged cells, such as cardiolipin, formyl peptides, and mitochondrial DNA [21,22], further stimulate the production of the pro-inflammatory cytokine IL-8, which in turn activates neutrophils, which migrate to the alveolus [23]. Activated neutrophils secrete matrix metalloproteinases (MMPs), reactive oxygen species (ROS), and neutrophil extracellular traps (NETs) [24,25], which exert bactericidal effects. MMPs are the primary proteolytic enzymes in extracellular matrix (ECM) and are involved in

cell migration and invasion [26]. Numerous studies have shown that MMPs are closely linked to tumor progression. Under the influence of cytokines such as IL-1 β, and TNF-α, MMPs act on microvascular endothelial cells, transforming them into interstitial fibroblasts. This process is known as endothelial mesenchymal transformation (EndMT) [27,28]. In the late stage of acute lung injury, MMPs may play a vital role in the formation of pulmonary fibrosis, which is also associated with the participation of transforming growth factor β (TGF-β) [29,30].

Macrophages are not only directly involved in the progression of ALI, but also indirectly induce other inflammatory cells to participate in the occurrence and development of ALI. Therefore, exploring macrophage function will further reveal the mechanism of acute lung injury. The schematic diagram presented in Figure 1 shows cellular changes at different stages during the development of acute lung injury, including the type of macrophage polarization, neutrophils, and monocyte infiltration, which secrete large amounts of inflammatory cytokines, and thus directly or indirectly
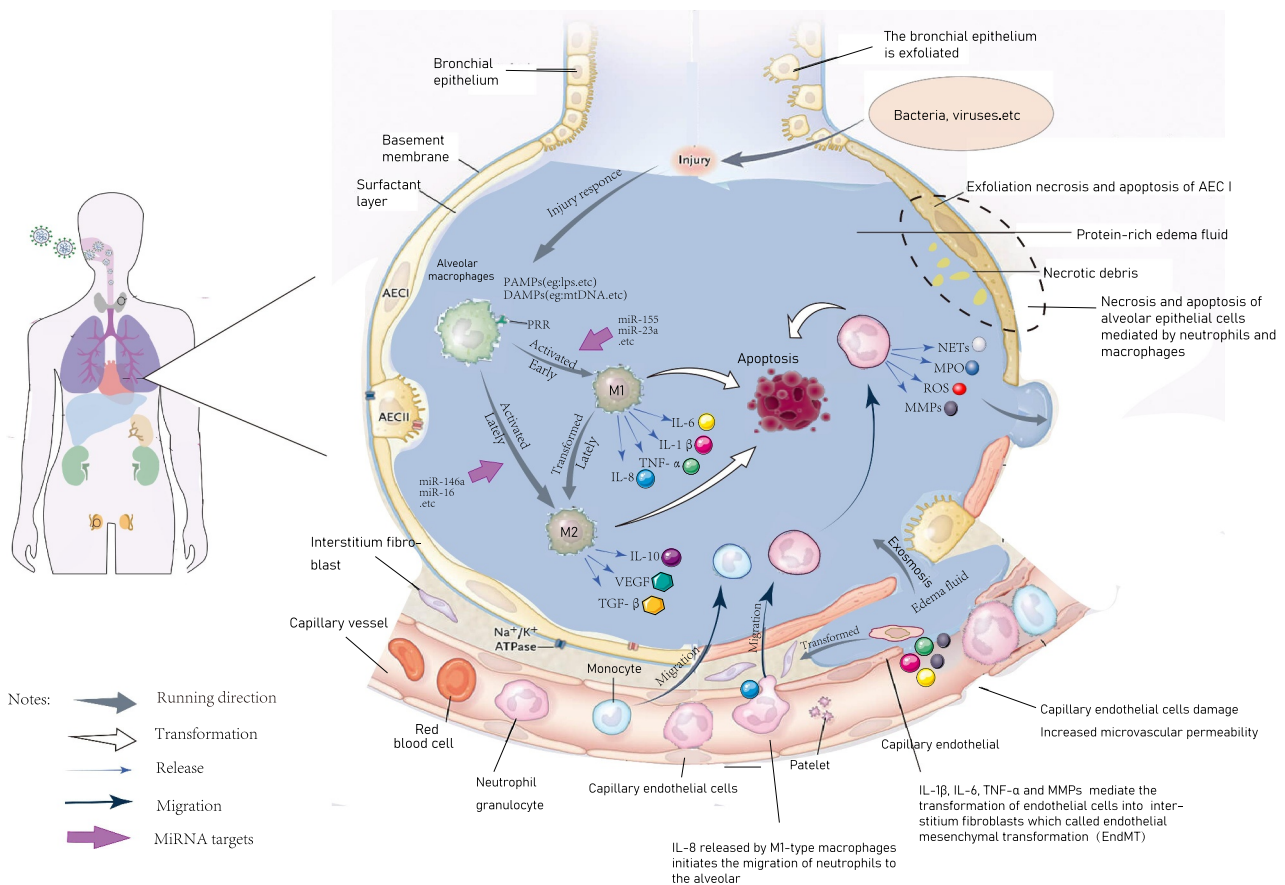

Figure 1. Cell response plots of acute lung injury. When infected bacteria or viruses, macrophages act as the first line of defense, the alveolar macrophages identify PAMPs (such as bacterial lipopolysaccharides, phosphate acid, etc.), and polarize to M1 type, release proinflammatory cytokines, including IL-6, IL-8, TNF-α in response to damage, then cell endogenous damage product DAMPs (such as mitochondrial DNA, etc.), combined with macrophage surface receptor, further stimulate the production of pro-inflammatory cytokines. The release of a large number of inflammatory factors then leads to tissue damage. Therefore, in the late stage of injury, macrophages are polarized to M2 type to cope with the pro-inflammatory changes of M1 type, release anti-inflammatory cytokines such as IL-10, and maintain the counterbalance of inflammation in the body. When uncontrolled inflammation breaks the balance between pro-inflammatory and anti-inflammatory conditions, it then leads to epithelial and endothelial cell damage, which eventually develops into acute lung injury. On the other hand, the proinflammatory cytokine IL-8 promotes neutrophil activation and migration to the alveoli, and releases MMPs, MPO, as well as NETs, to exert antibacterial effects. In the later stage of the disease, under the combination of proinflammatory cytokines such as IL-1 β and TNF-α, MMPs released by neutrophils act on microvascular endothelial cells to transform endothelial cells into stromal fibroblasts, further disrupt microvascular structure, affect gas exchange, and eventually develop into ARDS. PAMPs, nonendogenous pathogen-associated molecular patterns; DAMPs, damage associated molecular patterns; MMPs, matrix metalloproteinases; MPO, myeloperoxidase; NETs, neutrophil extracellular traps; ARDS, acute respiratory distress syndrome.

participate in the occurrence and development of acute lung injury.

2 miRNA and acute lung injury

2.1 miRNA basics

MiRNAs function is similar to that of endogenous or synthetic short interfering RNA (siRNAs); however, miRNAs play more complex and subtle roles than suggested by the "switch" model [1,4,31]. miRNA expression is highly tissue-dependent. For instance, miR-451 is expressed the most in the kidney, miR-181a, miR-181b, and miR-214 in the liver, and miR-214, miR-24, miR-9, and miR-124 in the brain [32], whereas other miRNAs are expressed in the heart tissue [33]. Therefore, differential expression of miRNAs can be useful as potential biomarkers for monitoring various diseases [34–36].

MicroRNA undergoes a lengthy and intricate process from generation to function, involving dynamic changes from initial transcription to binding with target mRNA. miRNAs play a predominant role in the complex network of balanced relationships between pro-inflammatory and anti-inflammatory factors, adapting and coordinating with different clinical manifestations of high or low expression of inflammatory factors. The dynamic changes in RNA can monitor the state of health and disease in real-time, allowing
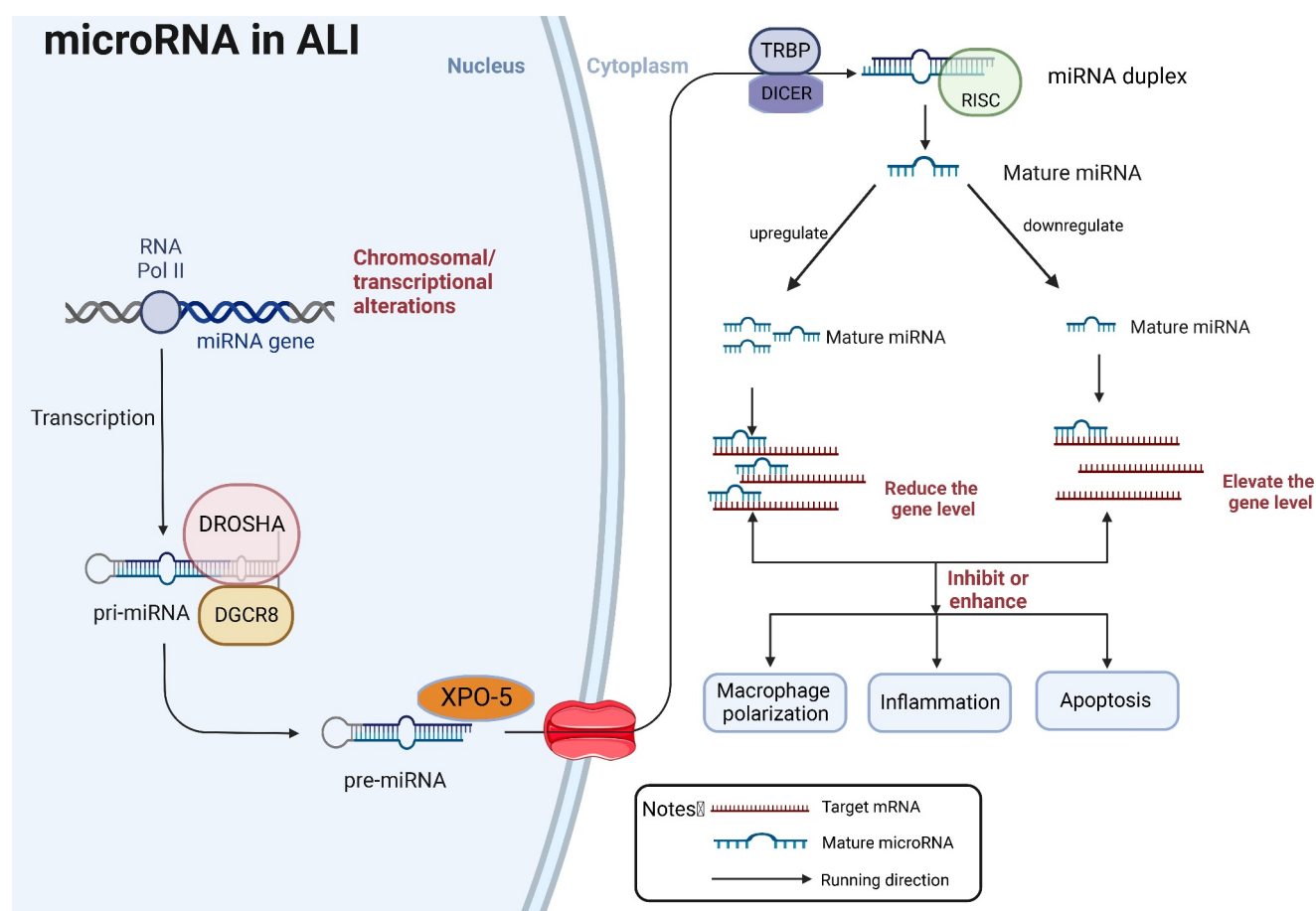

Figure 2. A schematic illustration of miRNA biogenesis and functions in ALI. RNA polymerase II (RNA Pol II) ordinate the synthesis of pre-miRNA. Then pre-miRNA was exported to the cytoplasm where pre-miRNA generates a mature miRNA. Mature miRNAs mediate the transcription and translation inhibition of target mRNAs and the degradation of their own mRNAs. In the development of ALI, miRNA itself is up-regulated or down-regulated, leading to the reduction or improvement of the level of target genes, which then leads to the enhancement or inhibition of downstream inflammatory and apoptotic pathways, and mediates macrophage polarization, thereby aggravating or alleviating the progress of ALI. Pri-miRNA, primitive miRNA; miRNA, microRNA; pre-miRNA, recursor-miRNA; DROSHA, RNase III endonuclease; DGCR8, DiGeorge syndrome critical region 8; XPO-5, exportin 5; TRBP, transactivation-responsive RNA-binding protein; DICER, RNase III; RISC, RNA-induced silencing complex. Created with BioRender.com.

for early identification of risks, intervention, and improved pathological and clinical performance at the initial stages of the disease. MiRNAs also play an indispensable role in the prognosis, diagnosis, and treatment of the disease [37]. However, the conclusions of many studies involving various miRNAs are not uniform, as the expression of miRNAs can be either upregulated or downregulated. Additionally, the response mechanisms and pathways to inflammation and apoptosis can also differ. In this review, we summarize the entire process of miRNA from generation to function, emphasizing that up or down-regulation of

miRNA in acute lung injury can subsequently inhibit or strengthen downstream inflammatory or apoptotic pathways by interfering with the target mRNA (as depicted in Figure 2).

2.2 Regulation of the miRNA expression in acute lung injury

The expression level of miRNA expression directly influences the developmental outcome of ALI. How is the miRNA expression regulated? In response to bacterial or viral stimulation, alveolar macrophages first exhibit the M1 type and produce numerous pro-

Table 2. miRNAs in ALI.

MiRNA	Target	Expression level	Fuction (the result is the uprgulation or downregulation of miRNAs)
miR-223	Nlrp3	Upregulated	Inhibit macrophage activation and lung inflammation [41,42]
miR-146a	Notch1/PPARg	Upregulated	Regulate the M2-type polarization of macrophages and inhibit the release of inflammatory factors [43]
	IRAK1,IRF5	Upregulated	Control the immune response and promote M2 phenotype [44,45]
miR-181a	SIRT1	Upregulated	Regulate cell apoptosis and cell proliferation [46]
	Fax	Downregulated	Improve LPS-induced apoptosis and inflammation [38]
miR-155	SOCS1, SHIP1	Upregulated	Promote macrophage M1 polarization and stimulate the activation of NF-κB signaling pathway [47,48]
	C/EBPβ	Upregulated	Down-regulate IL-10 secretion and M2-like phenotype of macrophages [49]
miR-135a	BCL-2,PI3K	Upregulated	Reduce the proinflammatory factor, proapoptotic protein factor level [5]
miR-23a	PTEN/PI3K/AKT	Upregulated	Inhibit cell apoptosis and affect cell cycle [50]
	PLK1	Upregulated	Regulate macrophage M1 polarization [51]
miR-21	TLR-4	Upregulated	Inhibit the activation of NF-κB signaling pathway and reduce inflammatory response [1]
	PTEN/AKT	Upregulated	Improve the inflammatory response and oxidative stress in sepsis mice [12,34]
	STAT-3	Upregulated	Inhibit PGE2 induced M2-type polarization of macrophages [52,53]
miR-15a	TLR-4/IRAK-1	Upregulated	Biomarkers for diagnosis and prognosis of neonatal sepsis and downregulated the LPS-induced inflammatory pathway [54]
miR-16	TLR-4	Upregulated	Promote M2 polarization and inhibit macrophage inflammation [55]
miR-138-5p	EZH2	Downregulated	Promote M2 macrophages polarization [56]
miR-27a	TLR4/MyD88	Upregulated	Inhibit the activation of NF-κB signaling pathway, reduce inflammation and apoptosis [57]
	NFKB1	Upregulated	Promote M2 macrophages polarization and inhibit lung inflammation [58]
miR-9-5p	/	Upregulated	Promote M1 macrophages polarization [59]
miR-30d-5p	SOCS-1, SIRT1	/	Enhanced M1 macrophage polarization and induced macrophage pyroptosis to promote lung inflammation [60]
	AMPKα	Downregulated	Its overexpression attenuated lung inflammation, oxidative damage, and dysfunction in ALI mice [61]
miR-33	MEF2	Upregulated	Promote M1 macrophages polarization [62]
miR-34a	Klf4	Upregulated	Favour pro-inflammatory M1 phenotype, inhibition of M2 polarization, and intensify LPS-induced lung injury [63]
miR-451	MIF/PI3K/AKT	Upregulated	Modulate macrophage M2 polarization and alleviate acute lung injury [64]
miR-429	DUSP-1	Upregulated	Promote M1 phenotype and activate of inflammatory response [65]
miR-127	BCL-6/DUSP-1	Upregulated	Enhance M1 type polarization in macrophages and promote the release of pro-inflammatory cytokines [66]

Abbreviations: ALI,acute lung injury;miRNA,microRNA;Nlrp3,NOD-like receptor thermal protein domain associated protein 3;ACE2, angiotensin-converting enzyme 2;NF-κB,nuclear factor kappa-B;Notch1, one of the core factors of the NOTCH signaling pathway; PPARg, peroxisome proliferator – activated receptor g; IRAK1, interleukin receptor activated kinase 1;IRF5,interferon regulatory factor 5;SIRT1, sirtuin-1;SOCS1, suppressor of cytokine signaling −1;SHIP1,src homology inositol phosphatase 1; C/EBPβ, CCAAT/enhancer-binding protein β;BCL-2,B-cell lymphoma-2;PI3K,phosphoinositide 3-kinase;PTEN, phosphate and tension homology deleted on chromosome ten;AKT,protein kinase B;TLR-4, toll-like receptor 4;MyD88,myeloid differentiation primary-response protein 88;EZH2,enhancer of zeste homolog 2;NFKB1,nuclear factor kappa B subunit 1; AMPKα, adenosine monophosphate activated protein kinase α; MEF2,transcription factor myocyte enhancer factor 2;Klf4, kruppel like factor 4;MIF, macrophage migration inhibitory factor;DUSP-1, dual-specificity phosphatase 1;BCL-6, B cell lymphoma-6.

inflammatory cytokines, such as IL-6, IL-1 β, IL-8 and TNF- α, which subsequently stimulates the expression of pro-inflammatory microRNAs, such as miRNA-155, miRNA-23a, and miRNA-34a. These miRNAs further aggravate inflammatory and apoptotic signals, promoting the progression of lung injury. However, at the same time, the expression of some anti-inflammatory miRNAs, such as miRNA-223, miRNA-146a, miRNA-135a, and miRNA-21, is also up-regulated. This may be due to the passive up-regulation response of the body to achieve a balance between pro-inflammatory and anti-inflammatory signals, which exerts a protective effect. In addition, some non-coding RNAs, such as lncRNA and cicRNA [38–40], can adsorb specific miRNAs to increase the levels of downstream target genes, which also indirectly affects miRNA expression.

This paper briefly describes the expression of miRNAs in ALI, along with the response mechanisms and pathways of miRNAs to macrophage polarization, inflammation, and apoptosis. However, there are conflicting conclusions (as summarized in Table 2).

3 miRNA associated with macrophage polarization in lung injury

3.1 miRNA 223 and miRNA 142

miR-223, originally identified through bioinformatics and characterized in the hematopoietic system, is highly expressed in neutrophil lines and is considered a specific miRNA for neutrophils [67,68]. It plays a key role in controlling excessive inflammatory responses and neutrophil activation [69,70]. Recent studies have demonstrated that EV-derived miR-223 inhibits liver inflammation and fibrosis gene expression, facilitates neutrophil-hepatocyte communication, and slows the progression of the nonalcoholic steatohepatitis (NASH) [71]. Another RNA that is crucial for neutrophil differentiation and maturation is miRNA-142, which has been shown to result in abnormal reduction and over-maturation of neutrophils during eventual myelogenesis, as well as impaired inflammatory migration of neutrophils during fetal production [72]. Investigating the function of neutrophils, including activation, maturation, and migration, using a combination of miR-223

and miR-142 may lead to significant breakthroughs.

In ALI/ARDS, there is still no agreement on the upregulation or downregulation of miR-223/142 expression. Some studies have shown that miR-223/142 is down-regulated, and its over-expression inhibits macrophage activation and lung inflammation, and apoptosis [41,73]. With regards to neutrophil function, Ly6G+ neutrophils can enhance the expression of miR-223, and the elevated miR-223 can negatively regulate bone marrow-derived Ly6G+ neutrophil differentiation and inhibits peripheral cytokine release. MiR-223 also targets the inhibition of NLRP3 expression and IL-1β release, ultimately alleviating MTD-induced ALI [42]. Although most studies suggest that overexpression of miR-233 is beneficial for improving acute lung injury, whether it is upregulated or downregulated remains unclear. However, most research has focused on the role of miR-233 and miR-142 in neutrophil differentiation and maturation. Future studies can concentrate on the pivotal role of neutrophil migration to the alveoli, which may reveal new therapeutic targets for the treatment of acute lung injury.

3.2 MiRNA-146a

Inflammatory conditions have been associated with elevated expression of miRNA-146a in white adipose tissue. Transfection of miR-146a into white adipocytes has been demonstrated to down-regulate the expression of inflammatory cytokine [74]. This miRNA has been found to inhibit the release of inflammatory factors such as tumor necrosis factor-αand interleukin-6, and has been shown to play a crucial role in reducing inflammation [75–77], alleviate excessive inflammation and multi-organ function impairment, reduce mortality, and regulate immune response responses in splenic macrophages [78]. Recent studies have demonstrated that miRNA-146a regulates the M2-type polarization of macrophages by targeting Notch1, thereby enhancing the anti-inflammatory effect [43]. In addition, miR-146a controls the immune response and promotes the M2 phenotype by inhibiting the expression of proteins such as IRAK1 and IRF5 [44,45]. Interestingly, miRNA-146a is highly expressed in patients with acute

lung injury due to sepsis, and has the potential to serve as an early diagnostic marker [79].

It is evident that miRNA-146a not only directly participates in the occurrence of lung injury inflammation, but also indirectly regulates macrophages to M2-type polarization and exerts anti-inflammatory effects. Upregulation of miRNA-146a can be beneficial in improving acute lung injury. Several studies have demonstrated that miRNA-146a can distinguish between sepsis and systemic inflammatory response syndrome, making it a highly specific and sensitive biomarker [80,81]. Moreover, the levels of miRNA-146a correlate with the severity of inflammation and the levels of inflammatory factors [82]. However, the limited sample size of some studies has lowered the credibility of the findings. Therefore, research on miRNAs cannot be used as an independent individual study, and the study of target sites of miRNAs cannot be confined to a single regulatory level.

3.3 MiRNA-181a

miRNA-181a belongs to the miRNA-181 family, which is characterized by highly conserved gene sequences [83]. Studies have shown conflicting results regarding miRNA-181a expression in the LPS-induced acute lung injury (ALI) model [84]. While some studies suggest that overexpression of miRNA-181a promotes the expression of caspase-3, inhibits BCL-2, and aggravates the progression of lung injury, others report that the downregulation of miRNA-181a expression improves LPS-induced apoptosis and inflammation. By targeting to SIRT1, it can be protected against sepsis-induced acute lung injury in mice by inhibiting miR-181a expression [46]. Recently, Liu et al [38] have reported that the downregulation of miR-181a-5p was detected in ALI/ARDS patients, and in vitro experiments suggest that overexpression of miR-181a-5p can target Fax and improve LPS-induced apoptosis and inflammation. In addition, miR-181a can inhibit the expression of TLR-4, reduce LPS-induced inflammation in vivo and in vitro, and improve acute lung injury [85]. In a rat model of pulmonary hypertension, upregulation of miRNA-181a-5p expression significantly

reduced right ventricular remodeling and lung injury [86].

Further research is needed to clarify the exact relationship and specific mechanism between miRNA-181a and lung injury. However, it is clear that miRNA-181a is only a member of the miRNA-181 family, and the relationship between independent individuals and the whole, as well as the mutual causal relationship between miRNAs and acute lung injury, cannot be ignored. Therefore, it is essential to continue studying miRNA-181a as an independent entity while considering the broader context of the miRNA-181 family. Nevertheless, the aforementioned relationship between different miRNAs and their causal relationship with acute lung injury cannot be ignored.

3.4 MiRNA-155

MiRNA-155 was first identified in the LPS-induced ALI model by Jesper Worm [47], and later studies showed that pre-treatment with anti-sense oligonucleotides could inhibit its expression [49]. Several studies have reported that miRNA-155 is upregulated in the LPS-induced ALI model and that inhibiting its expression can produce anti-inflammatory effects by suppressing the release of pro-inflammatory factors [87–89], including interleukin-6, interleukin-8, and tumor necrosis factor- α [48,90]. This can also affect the expression of heat shock proteins, such as heat shock protein-10, in endothelial cells and exert anti-inflammatory effects, playing an important role in sepsis-induced lung injury [91]. Additionally, Kangfeng Jiang. et al [92]found that miR-155 is found to promote M1 macrophage activation, exacerbating lung inflammation and tissue damage in macrophages. Specifically, miR-155 targets and down-regulates C/EBPβ, which leads to increased activation of M1 response [49,93]. Inhibition of miRNA-155 expression has been shown to reduce inflammation and intestinal barrier dysfunction by inactivating NF-κB signaling during sepsis [94].

Moreover, miRNA-155 can inhibit the activation of the JAK/STAT signaling pathway [95], reduce the levels of transaminase and urea nitrogen, and delay the damage to the liver, kidney, and

other organs [96]. By increasing the proportion of T-lymphocytes, miRNA-155 also plays a critical role in the immune system and immune response, accelerating the recovery process of ALI [49,97]. Additionally, it has been suggested that miRNA-155 can serve as a predictor of the prognosis of lung injury [98]. Thus, inhibiting miRNA-155 expression can play a positive role in the treatment of ALI.

3.5 MiRNA-135a

During ALI, miRNA-135a expression is significantly upregulated. Inhibition of miRNA-135a expression enhances the expression of the anti-inflammatory factor BCL-2 and ameliorated LPS-induced lung injury [5]. miRNA-135a is involved in inflammation, oxidative stress, and apoptosis by reducing the levels of pro-inflammatory factors, reactive oxygen species, and pro-apoptotic protein factors, thus maintaining the integrity of the endothelial barrier function and protecting vascular endothelial cells from ventilator-induced lung injury [50].

Despite the promising results, the current number of studies on miRNA-135a is limited, and further research is necessary to demonstrate its practical role. Increasing the variety of miRNA types and tissues studied, and combining in vivo and in vitro research, while considering the possible synergistic or antagonistic effects of various miRNAs, may overcome some of the limitations of existing research. In-depth studies of the relevant mechanisms and therapeutic targets using both in vivo and in vitro models are needed to achieve unified and positive results, and to fully realize the clinical potential of miRNA-135a.

3.6 MiRNA-23a and miRNA-23b

The expression of miRNA-23a in ALI models remains controversial. While database results and quantitative fluorescence PCR detection have revealed that miRNA-23a is down-regulated in ALI models with high confidence, other studies have reported that miRNA-23a is upregulated during ALI and can improve ALI symptoms by promoting a reduction in apoptosis, affecting the cell

cycle [99], and elevating macrophage polarization to M1 via regulation of polo-like kinase 1(PLK1) in vivo and in vitro models [100].

In contrast, miRNA-23b expression was found to be downregulated in A549 and vascular endothelial cells, which promoted *S. pneumoniae*-induced apoptosis and inflammatory responses [51,101]. Inhibition of miRNA-23b expression in cardiomyocytes has been shown to alleviate the progression of myocardial fibrosis in late sepsis, alleviate the progression of myocardial fibrosis in late sepsis, alleviate myocardial dysfunction, and improve survival rates [102].

Although miRNA-23a and miRNA-23b belong to different clusters and have distinct sites, miRNA-23a and miRNA23b are often studied as joint-related factors, such as in non-small cell lung cancer and osteoarthritis. Therefore, results of miRNA-23a and miRNA-23b expression are considered more reliable when studied together.

3.7 MiRNA-21

miRNA-21 was first identified as an oncogenic RNA highly expressed in cancerous tissues. However, recent studies have revealed that miR-21 is also involved in the development of multiple inflammatory conditions. Inhibition of miRNA-21 expression has been shown to promote the recovery of motor function and inhibit the inflammatory response by blocking the IL-6 R/JAK/STAT pathway, facilitating the recovery and reconstruction of spinal cord nerves after spinal cord injury [52]. Inhibition of the JAK/STAT signaling pathway, thereby alleviating the release of tumor necrosis factor- α in acute pancreatitis and controlling the inflammatory response [103,104]. miRNA-21 has also been reported to improve sepsis survival by specific inhibitory effects at appropriate concentrations without causing obvious organ dysfunction and liver injury [105].

In ALI, most studies have found that miRNA-21 is upregulated, by inhibiting the TLR-4/NF-κB signaling pathway can help alleviate inflammation, reinforcing the first-line defense role of alveolar macrophages in lung tissue [1]. Moreover, miRNA-21 may reduce lung tissue damage by inhibiting the target gene PTEN,

improving the inflammatory response and oxidative stress in septic mice [106]. However, simultaneous inhibition of PGE2 and miRNA-21 induces macrophage M2-type polarization via inhibiting STAT-3 expression [53]. It has also been shown that miRNA-21 and its downstream signaling pathway can inhibit sodium ion channels in alveolar epithelial cells and aggravate pulmonary edema caused by sepsis-induced ALI [107]. In addition, miRNA-21 plays an important protective role in chronic lung injuries such as radiation lung injury, as reported by Pengtao Bao et al [108]. Animal experiments have also further confirmed the protective effect of miRNA-21 overexpression. However, unlike in ALI, miRNA-21 inhibits M1 polarization of alveolar macrophages in the chronic phase.

It is evident that miRNA-21 can have different roles in lung injury depending on the stage of the injury, and the regulation of macrophage polarization can also vary. Moreover, the protective effect of miRNA-21 on lung injury depends upon the balance between anti-inflammatory and pro-inflammatory pathways. Understanding the mechanisms influencing this balance will be a major research focus in the future, and further research is required to clarify the role of miRNA-21 in lung injury.

3.8 MiRNA-15a and miRNA-16

MiRNA-15a and miRNA-16 have emerged as biomarkers for sepsis and systemic inflammatory response syndromes, and appear to be superior to inflammatory factors such as procalcitonin, C reactive protein, and interleukin-6, of which the discriminatory advantage of miRNA-15a is more pronounced [109].

In neonatal sepsis, upregulated expression of miRNA-15a/miRNA-16 can inhibit the inflammatory response [39,54], as demonstrated in a mouse model [110]. MiRNA-15a/miRNA-16 could bear potential as a marker for the diagnostic and prognostic outcome of neonatal sepsis, but whether it can be a biomarker for adult sepsis as well as its role in inducing acute lung injury remains to be verified. Moreover, miRNA-16 can promote the polarization of M2 macrophages and reduce lung damage in mice with sepsis via

suppressing TLR4 [55]. Additionally, the mechanism by which the host allows the harmful upregulation of miRNA levels deserves further study, as shown by the conflicting results reported in Moon et al [111].

3.9 MiRNA-138-5p

miRNA-138-5p is a well-studied tumor suppressor that inhibits the proliferation of various cancer cells [112,113] and plays an important role in inflammation. Recent studies have demonstrated that miRNA-138-5p improved LPS-induced hippocampal neuronal inflammation in rats by inhibiting NLRP3/Caspase1 activation [114].

Recent studies have found that miRNA-138-5p is significantly downregulated in patients with sepsis-induced ARDS and that its overexpression can promote the production of M2 macrophages while inhibiting M1 macrophage polarization, thereby improving acute lung injury [56]. However, these findings are based on the regulation of circular RNAs(circRNAs), which along with lncRNAs, are a part of a growing research area focused on circular networks based on circRNA/miRNA/mRNA. Further research is needed to identify the upstream target of miRNA-138-5p and explore its full biological potential. The limited number of studies on miRNA-138-5p and macrophage function in ALI reduces its current credibility, but it lays a foundation for further research in this area.

3.10 MiRNA-27a

miRNA-27a expression is elevated in patients with sepsis and serves as a potential biomarker for diagnosis and prognosis in patients with sepsis [115]. In addition, miRNA-27a alleviates lung tissue damage by inhibiting TLR4/MyD88/NF-κB signaling pathway, which subsequently inhibits lung tissue inflammation and apoptosis [57]. In vitro and in vitro experiments as well as studies on macrophage function have shown that miRNA-27a-3p expression is elevated in LPS-induced acute lung injury, and promotes M2 polarization of macrophages to further relieve lung tissue damage [58].

Based on these studies, miRNA-27a is upregulated in ALI and can reduce ALI-associated inflammation and lung tissue damage by affecting macrophage M2 polarization and downstream inflammatory pathways. However, further studies are required to understand the specific role of miRNA-27a in macrophage polarization.

3.11 MiRNA-9-5p and miRNA-30d-5p

Studies of miR-9-5p in lung tissues have mainly focused on its role in promoting the progression of lung adenocarcinoma [116]. However, recent research has highlighted its involvement in acute lung injury, where its expression was found to be significantly increased in both ALI model mice and patients. Moreover, miR-9-5p deficiency was shown to alleviate LPS-induced inflammatory infiltration in lung tissue by promoting the polarization of alveolar macrophages to the M2 phenotype [59]. Despite the limited number of studies on miR-9-5p in acute lung injury, these findings offer valuable insights into the specific mechanisms underlying macrophage polarization.

Another important microRNA that affects macrophage polarization is miR-30d-5p. Accumulating evidence has revealed its role in the development and progression of different cancer types. For example, miR-30d-5p targeting suppresses the cellular activity of non-small cell lung cancer cancer [117]and is involved in the progression of esophageal squamous cell carcinoma [118]. Moreover, miR-30d-5p is considered a potential critical tumor biomarker. Recently, it was found that exosome-delivered miR-30d-5p promotes lung inflammation by targeting SOCS-1 and SIRT 1 to enhance M1 macrophage polarization and induces macrophage pyroptosis [60]. In contrast, Li W.et al [61] found that the expression of miR-30d-5p was decreased in lung tissues of mice with ALI, and its overexpression could improve lung inflammation, oxidative stress, and LPS-induced dysfunction via activation of AMPK α. The results of these two studies are contradictory. However, the number of studies on miR-30d-5p in lung injury is limited, and further research is required to establish the credibility of these findings.

3.12 MiRNA-33 and miRNA-34a

Recent studies have revealed that miRNA-33 and miRNA-34a are upregulated in ALI, contributing to the development of lung inflammation and pathological damage. MiRNA-33 has been shown to play important roles in inflammation [119], metabolism [120], and mitochondrial function. Inflammatory macrophage polarization mediated by NLRP3 has been identified as a key function of miRNA-33 [121]. Previous research has shown that Er miao San (EMS) downregulates miRNA-33 expression in rheumatoid arthritis and promotes M1-type macrophage polarization via NLRP3 [122,123]. Similar results were observed in ALI, where miR-33 was found to be highly expressed in M1 type macrophages, and in vivo experiments demonstrated that miR-33 promotes M1 type polarization by inhibiting MEF 2 in alveolar macrophages [62]. Similarly, miR-34a expression was found to be elevated in mice with acute LPS-induced lung injury. Inhibition of miR-34a resulted in significant amelioration of lung histopathological changes and promoted M2 type macrophage polarization [63].

Despite the promising findings, few studies have been conducted on miRNA-33 and miRNA-34a, and the limited sample size also reduces the confidence of the study. Nonetheless, these findings have updated our understanding of miRNA-33 and miRNA-34a in the context of ALI and provided insight into the disease regulatory mechanisms that drive its progression.

3.13 MiRNA-451

The expression of miRNA-451 is increased in burn-induced ALI, but it is known to increase endothelial cell permeability and suppresses angiogenesis [124]. Interestingly, a study has found that miRNA-451 is upregulated in exosomes of human umbilical cord MSCs [125] and can alleviate burn-induced acute lung injury by regulating macrophage M2 polarization via the MIF-PI3K-AKT signaling pathway [64]. These findings appear to contradict each other, as the former focuses on the effects of miRNA-451 on nonimmune cells while the latter explores the specific mechanism of immune cell response to acute lung injury.

Similarly, several other miRNAs are involved in macrophage polarization in acute lung injury. For example, miR-429 promotes the M1 phenotype by inhibiting the DUSP-1 protein, which is a negative regulator of p38 MAPK signaling, leading to the activation of inflammatory response and M1 polarization [65]. MiR-127 also enhances M1 type polarization and promotes the release of pro-inflammatory cytokines by inhibiting BCL-6/Dusp-1 [66]. Overall, microRNAs are either upregulated or downregulated in lung injury, regulated through different mechanisms in macrophage polarization and inflammation, which can either aggravate or alleviate ALI. Thus, up-regulated or downregulated microRNAs can become therapeutic targets for ALI. Furthermore, various interactions among microRNAs constitute a complex closed loop, which jointly regulates the occurrence and development of ALI.

4 MicroRnas-The treatment targets for acute lung injury

As previously mentioned, microRNAs play an essential role in the development of ALI, regulating the disease prognosis through their upregulation or downregulation. Numerous studies have shown that microRNAs modulate ALI progression by regulating apoptosis, inflammatory response, and oxidative stress. Differential expression of miRNAs also highlights their potential as therapeutic targets for ALI. Additionally, overexpression or knockdown of miRNAs have been demonstrated to ameliorate acute lung injury through various mechanisms. In this review, we summarize the current approaches for microRNA substitution, including inhibitory therapy, and in vitro and vivo delivery of microRNA, to either enhance or suppress downstream target gene expression and alleviate ALI (Figure 3).
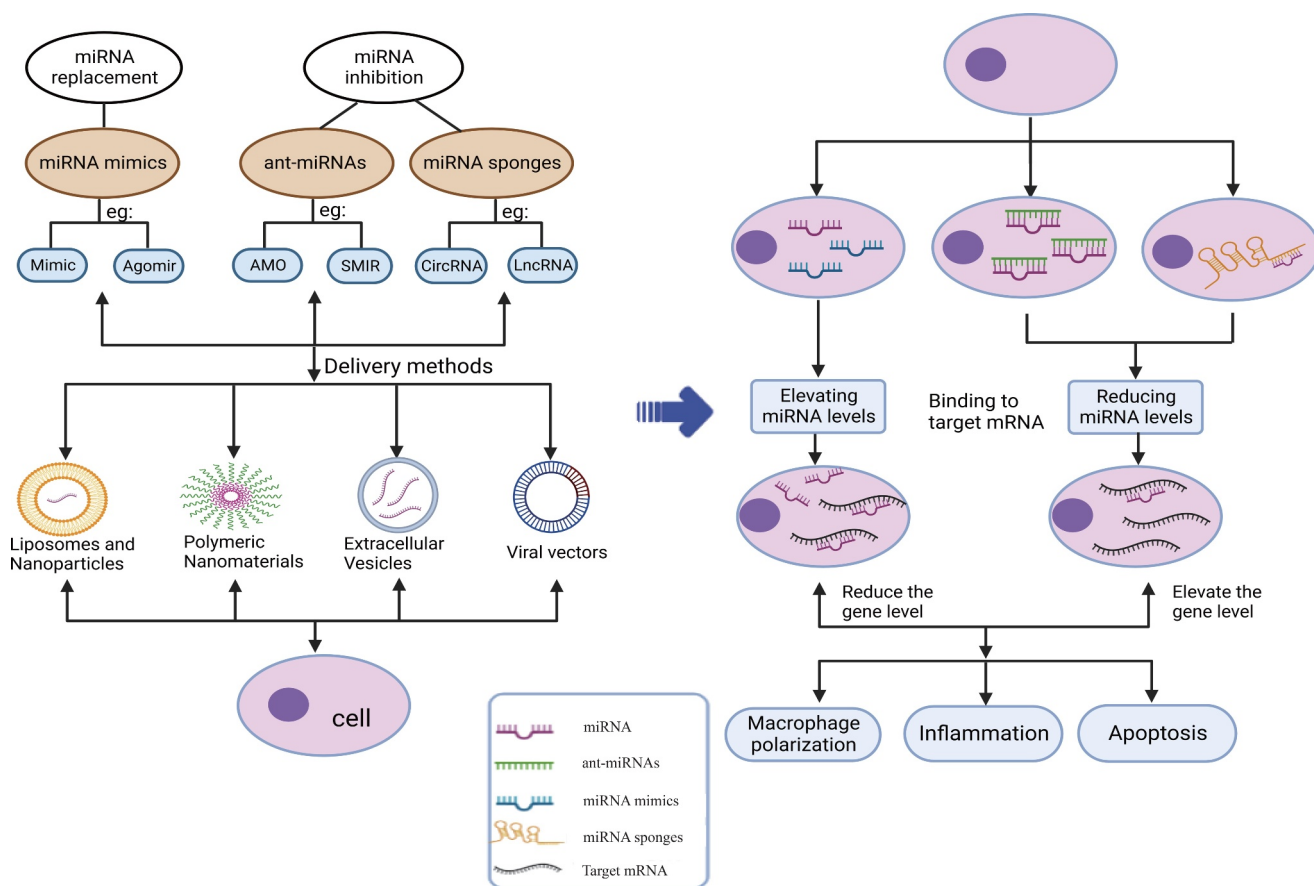
Figure 3. Schematic diagram of miRNAs regulation and therapeutic targets in ALI. With respect to miRNA delivery, there are four commonly used delivery methods to transfer miRNA modifications into cells. The level of miRNA can be restored by modification of miRNA. miRNA binds to target mRNA and then regulates its level, thus participating in pathological processes such as macrophage polarization, inflammation and apoptosis. In conclusion, miRNA plays an integral role in acute lung injury. Created with BioRender.com.

At present, the application of miRNAs in regulating disease progression mainly includes miRNA mimics, miRNA inhibitors, and miRNA sponges. miRNA mimics are double-stranded RNA molecules that mimic endogenous miRNA duplexes and are processed into single-stranded RNA upon entering the cells. They can restore the downregulated RNA levels and the biological function of specific RNA, thereby treating diseases. However, the transfection of RNA mimics may not always achieve the desired therapeutic effects due to the failure of the guide strand of the transfected miRNA mimic to integrate into the RNA-induced silencing complex [9]. Moreover, miRNA mimics are unstable in cells and may be prone to degradation by endogenous nucleases. Therefore, chemically modified miRNA agomirs have been developed through numerous experimental reforms, and are more widely used in clinical practice. MiRNA inhibitors are more stable than mimics since they do not require cell treatment to exert their effects, and they also have relatively few transfection problems. The miRNA inhibitors mainly include anti-miRNA oligonucleotides (AMOs) and small molecular inhibitors of specific miRNAs (SMIRs). AMOs are perfectly complementary to the target miRNA, bind to the guide strand, and inactivate the miRNA by inhibiting its binding to the target mRNA or promoting its degradation by recruitment of RNase H [126].

MiRNA sponges are an important tool for studying miRNA function in vivo and in vitro. They consist of repetitive miRNA antisense sequences acting as competitive inhibitors and separating the endogenous miRNA from its target to affect the biological function of the endogenous miRNA [127]. Natural endogenous miRNA sponges, such as long non-coding RNAs (lncRNAs), circular RNAs (circRNAs), and mRNAs, bind to miRNAs and competitively isolate them from target cells. These are called competitive endogenous RNAs (ceRNAs) [40].

Currently, there are various therapeutic vectors for delivering miRNAs, such as viruses, exosomes [39], nanometer particles [128], and other synthetic materials [129–131]. Synthetic materials can be cation and condensed through electrostatic interaction with negative electric poly (nucleic acid). Compared with virus-based vectors, synthetic delivery systems have considerable advantages, such as the ability to control their molecular composition, simplified manufacturing, modification, and analysis, cargo size tolerance, and relatively low immunogenicity. However, their efficiency may be lower than that of virus-based vectors [129]. In the future, more exploration of clinically efficient delivery methods of microRNAs may be needed to target tissues more efficiently.

5 Preclinical stage of microRnas therapy in ALI/ARDS

ALI is a challenging condition to treat, and currently, there are no effective radical measures available. Conservative treatment measures such as lung-protective ventilation, restricted fluid management, combined use of glucocorticoids, and extracorporeal membrane oxygenation [132,133] have been adopted, but long-term mechanical ventilation can lead to complications such as ventilator-associated pneumonia and pulmonary fibrosis.

To address this challenge, mesenchymal stromal cells (MSCs) have emerged as a research hotspot for the treatment of various diseases. These cells are found in various tissues, such as bone marrow, muscle, adipose tissue, dental tissue, synovial fluid, skin, and placenta [134], and can be detected in all vascular tissues of the body, including the upper and lower respiratory tract of lung tissue [135]. Additionally, they can induce macrophages to polarize to the M2 type, which indirectly exerts anti-inflammatory effects and further promotes lung tissue repair [136–139]. Mechanistically, MSCs can reduce the expression of miR-193b-5p and improve sepsis-induced acute lung injury [140]. Therefore, MSCs have good therapeutic prospects for acute lung injury, and MSCs can be used as target delivery cells to make miRNAs. This approach is free from the degradation of human nucleases, making it more efficient in targeting lung tissue. However, further clinical trials are required to validate this potential therapy.

6 Development and outlook

miRNA expression can be either up-regulated or down-regulated in the same model, and the effect

of these changes on the host is still unknown. Furthermore, there may be antagonism or synergistic effects between miRNAs, and the difference between the leading and auxiliary effects of miRNAs cannot be ignored. More studies are needed to further summarize the complex interactions between miRNAs in different disease states and processes.

The interaction between miRNAs and macrophage polarization is particularly relevant in regulating the balance between anti-inflammatory and pro-inflammatory responses, and miRNAs are being increasingly recognized as having an important role in many diseases, including ALI. Because miRNA expression is tissue-specific, different disease states and different disease processes may have different effects, and macrophages of different tissue origins may exhibit different polarization responses to the same miRNA. Because diseases change dynamically over time and in different environments, macrophages may also exhibit different phenotypes, making the identification of the dominant polarized phenotypes their controlling miRNAs a complex challenge. Therefore, the dynamic monitoring of miRNA levels poses a great challenge to the research work.

ALI/ARDS is an acute and critical life-threatening illness in clinical work, often accompanied by secondary damage to distant organ tissues in addition to local tissue damage. As mentioned above, exploring miRNA regulatory pathways and finding suitable targets may help in effectively alleviating disease progression and improving patient survival. Macrophages as the first line of defense in immunity, its polarized form also determines the development process of the disease, so finding microRNAs to control macrophage activation will also achieve the purpose of treating the disease from the source. This is also the main aim of most microRNA studies. However, there are still many unanswered questions that must be addressed. For example, most studies focus on a single miRNA pathway and do not consider the interaction and leading role of each miRNA in disease occurrence. Additionally, the number of studies on miRNAs affecting macrophage polarization is relatively small, reducing the confidence of the study. Finally,

differentially expressed miRNAs in animal models must be validated in patients with established ALI/ARDS for extrapolation in humans, making the development of miRNA therapy a significant challenge.

To address these limitations, future research should focus on identifying the key factors that affect macrophage polarization and identifying miRNAs that favor the polarization and dominant role of M2-type macrophages. Interventions to strengthen the effects of these miRNAs may help promote disease recovery. Additionally, research should explore whether miRNAs can be used to control the occurrence of complications in the treatment of local clinical symptoms. Further in-depth research is required to explore the clinical value of miRNAs in the future.

Disclosure statement

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