SPANDIDOS PUBLICATIONS

BIOMEDICAL REPORTS 4: 523-527, 2016

MicroRNAs: Novel regulatory molecules in acute lung injury/acute respiratory distress syndrome (Review)

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Received October 19, 2015; Accepted January 19, 2016

DOI: 10.3892/br.2016.620

Abstract. Acute lung injury (ALI) and the more severe acute respiratory distress syndrome (ARDS) are common and complex inflammatory lung diseases. MicroRNAs (miRNAs), a type of non-coding RNA molecule that regulate gene expression at the post-transcriptional level, have emerged as a novel class of gene regulators, which have critical roles in a wide range of human disorders and diseases, including ALI. Certain types of miRNAs are abnormally expressed in response to lung injury. miRNAs can regulate inflammation pathways by targeting specific molecules and modulate immune response in the process of lung injury and repair. The regulation of miRNA can relieve injury response and promote the recovery of ALI/ARDS. Therefore, miRNAs may serve as novel therapeutic targets in ALI/ARDS.

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Key words: miRNAs, acute lung injury, inflammation, targets, immune response

1. Introduction

Acute lung injury (ALI) is a devastating disease caused by direct or indirect injury factors, such as pneumonia, pulmonary contusion, severe sepsis, gastroesophageal reflux, shock, transfusion, drug toxicity and acute pancreatitis, and is characterized by the increased permeability of alveolar epithelial cells and capillary endothelial cells, diffused pulmonary interstitial and alveolar edema, impaired gas exchange and progressive and refractory hypoxemia, leading to arterial hypoxemia and respiratory failure (1-5). The pathological process of ALI is the destruction of the epithelium-capillary interface, the rupture of alveolar septa, the collapse of alveolar, the extravasation of protein-rich fluid, the release of inflammatory cytokines and chemokines, and the infiltration of neutrophils, monocytes and other inflammatory cells (6,7). Reduced lung volume, decreased lung compliance, imbalanced ventilation/perfusion and hypoxemia are the pathophysiological characteristics of ALI. The more severe form of ALI is known as acute respiratory distress syndrome (ARDS), which can lead to persistent respiratory failure and increased susceptibility to multiorgan dysfunction or mortality (4,8).

According to previous surveys, ALI/ARDS has a high incidence (200,000 per year in the US) and the overall mortality rate is as high as 40% (9). ALI is one of the significant threats to life in critically ill patients. During ALI/ARDS, the injured cells trigger a cascade of events including acute inflammatory response, recruitment of immune cells such as T/B cells and monocytes/macrophages, release of cytokines [interleukin-1 (IL-1), IL-6, IL-8, IL-10 and tumor necrosis factor-α (TNF-α)], chemokines, growth factors and prostaglandins (3). The inflammation and immune response cooperate to promote the recovery of injury and maintain the homeostasis of the body.

Although there is a good understanding of the pathogenesis of ALI, little is known regarding the regulation mechanism at the level of gene. In recent years, it has been reported that microRNAs (miRNAs) have an important role in a number of basic physiological and pathological processes, such as cell proliferation, differentiation, migration, apoptosis, metabolism, inflammation, immune response, organogenesis and oncogenesis, and therefore, miRNAs may potentially affect the development of ALI/ARDS (1,4,10-12).

2. miRNAs: Biogenesis and function

miRNAs are highly conserved, and are composed of ~22-nucleotide, single-stranded, small non-coding RNAs that can extensively regulate the expression of target genes at the post-transcriptional level (13-16). Mature miRNA is formed via cleavage of the primary transcript (pri-miRNA) by the RNase III type endonucleases Drosha (also known as RN3) and Dicer, followed by incorporation into the RNA-induced silencing complex, which interacts with mRNA and regulates the expression of target gene (17-21). To date, >2,000 miRNA genes have been identified in the human genome (15).

miRNAs regulate target genes either through translational inhibition or mRNA degradation, via binding to the complementary sequences in the 3'-untranslated region (3'-UTR) of target mRNAs and thus negatively influencing the synthesis of the corresponding protein and ultimately regulating cellular processes (22,23). miRNAs also regulate transcription factors by methylation or deacetylation, and therefore, changes in gene expression indirectly (24,25). Notably, a single miRNA can regulate the expression of multiple genes and multiple miRNAs can cooperate to modulate the same target (26,27). Furthermore, the expression of miRNAs possesses the characteristic of tissue- and cell-specificity, and spatial and temporal specificity, and therefore, they can represent useful clinical biomarkers (10).

3. Expression profiles of miRNAs in acute lung injury

In recent years, certain studies have investigated the potential involvement of miRNAs in ALI or ARDS. Studies have shown that certain types of miRNAs were significantly upregulated and others were downregulated in ALI (Table I). Cai *et al* (4) established a model of lung-injury in mice using intratracheal administration of lipopolysaccharide (LPS) into mouse lungs and reported that miR-26a, miR-30, miR-181a, miR-181b, miR-199a and miR-214 preferentially expressed in the mouse lung tissue. The study also found that the expression of miR-21, miR-26b and miR-30 were not altered, while the expression levels of miR-214 and miR-451 were significantly upregulated and miR-16, miR-23a, miR-24, miR-181a, miR-181b and miR-199a were significantly downregulated in LPS-induced injury lungs. Zeng *et al* (1) also suggested that LPS causes upregulation of miR-146a *in vivo* and *in vitro*. Xie *et al* (3) analyzed miRNA expression following immunoglobulin G (IgG) immune complex (IgG IC) and bleomycin-induced lung injury and identified that miR-127 was downregulated in an animal model of ALI. Vaporidi *et al* (28) investigated pulmonary microRNA profiling in a mouse model of high tidal volume ventilation (HVTV)-induced lung injury and results show that of the 335 miRNAs examined, the expression of 50 miRNAs increased >2-fold, expression of 15 miRNAs decreased by more than half and the miRNAs with the greatest increase in expression after 4 h of HVT were miR-7b, miR-189 and miR-223, whereas the miRNAs with the greatest decrease in expression were miR-503 and miR-211. In addition, Tili *et al* (29) reported that LPS stimulation of mouse Raw 264.7 macrophages resulted in the upregulation of miR-155 and downregulation of miR-125b levels.

Of note, the expression levels of the majority of miRNAs changed rapidly and transiently, and fluctuated at different time-points in mouse lung tissue following LPS injection, which is consistent with the development of lung injury. Guo *et al* (18) demonstrated that 76 miRNAs were significantly upregulated and 35 miRNAs were downregulated at different time-points following LPS injection using miRNA microarray analysis. Moschos *et al* (15) also reported a rapid and transient increase in the mean (4.3-fold) and individual levels of miRNA expression (46 miRNAs), which peaked at 3 h. This increase was associated with a reduction in the expression of TNF-α, keratinocyte-derived chemokine and macrophage inflammatory protein-2, which indicates a potential role for miRNAs in the regulation of inflammatory cytokine production. Individual miRNA expression profiles showed time-dependent increases in miR-21, -25, -27b, -100, -140, -142-3p, -181c, -187, -194, -214, -223 and -224 following exposure to LPS in mouse lungs (15).

Alterations in the expression of certain miRNAs participate in the regulation of the inflammatory process and tissue repair in ALI/ARDS, as these changes are concomitant to the increased levels of the inflammatory mediators, including the pro-inflammatory cytokines such as IL-1β, TNF-α, IL-6 and

Table I. MicroRNAs implicated in ALI/ARDS.

Expression	MicroRNA
Upregulation	miR-7b
	miR-21
	miR-25
	miR-27b
	miR-100
	miR-140
	miR-142-3p
	miR-146
	miR-155
	miR-181c
	miR-187
	miR-189
	miR-194
	miR-214
	miR-223
	miR-224
	miR-451
	miR-224
Downregulation	miR-16
	miR-23a
	miR-24
	miR-127
	miR-181a
	miR-181b
	miR-199a
	miR-211
	miR-125b
	miR-503

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

Table II. Targets and function of microRNA in ALI/ARDS.

MicroRNA	Target	Function
miR-146	IRAK1 IRF5 TRAF6	Anti-inflammatory and inhibiting innate immune response
miR-127	FcγRI/CD64	Anti-inflammatory
miR-155	C/EBPb	Participate in innate immune response
miR-21	SMAD, TGFβR2 and BMPR2, TGF-β, and TGF-β ligands receptors	Inhibiting TGF-β signaling pathway
miR-106		
miR-146		
miR-181a	Importin-α3	Anti-inflammatory
miR-181b		
miR-199a		

ALI, acute lung injury; ARDS, acute respiratory distress syndrome; IRAK1, IL-1 receptor activated kinase 1; IRF5, interferon regulatory factor 5; TRAF6, tumor receptor factor-associated factor 6; FcγRI, Fcγ receptor I; C/EBPb, CCAAT/enhancer-binding protein β; SMAD, *Drosophila* mothers against decapentaplegic; TGF-β, transforming growth factor-β.

IL-8 and the anti-inflammatory factors including IL-1, IL-10 and IL-13, as well as the recruitment of T/B cells and other immune cells in the lung (16,30,31). Therefore, miRNAs have a considerable regulatory function in inflammation process and immune response in ALI.

4. Effect of miRNAs on the inflammatory responses

The primary cause of ALI is excessive pulmonary inflammatory response. The imbalance between inflammation and anti-inflammation responses leads to the development of disease. Recently, studies have provided evidence that miRNAs act as potent regulators of the inflammation pathways by targeting specific molecules. Toll-like receptor (TLR4) signaling was shown to have an important role in the activation of inflammation cell and the release of inflammatory cytokines in animal models of ALI. TLR4 signaling is regulated by the anti-inflammatory miRNA, miR-146a, which targets and suppresses several downstream signaling molecules, such as IL-1 receptor activated kinase 1 (IRAK1), interferon regulatory factor 5 (IRF5) and tumor receptor factor-associated factor 6 (TRAF6), all of which promote the inflammation response (1,7,28,32-34). miR-146a overexpression significantly suppressed LPS-induced inducible nitric oxide synthase, TNF-α, IL-6 and IL-1β by repressing IRAK1, IRF5 and TRAF6 expression, whereas miR-146a inhibition increased the release of cytokine (1,35). Therefore, miR-146a negatively regulates the inflammatory response induced by LPS. miR-127 was shown to attenuate lung inflammation in an IgG IC-induced lung injury model. Overexpression of miR-127 significantly decreased exaggerated inflammatory responses by targeting IgG Fcγ receptor I [FcγRI/cluster of differentiation 64 (CD64)], resulting in the downregulation of CD64 (3). Guo *et al* (8) employed miR-155 antisense oligonucleotides (ASO) to assess the effect of miR-155 on the development of ALI and results have shown that the concentration of pro-inflammatory factors, for example, TNF-α and IL-12, as well as monocyte chemotactic peptide-1 and regulated upon activation normal T-cell expressed and secreted decreased significantly in miR-155 ASO-treated groups compared with those in the control group, while the concentration of anti-inflammatory factors, such as IL-10, notably increased Furthermore, the study also reported that miR-155 could significantly repress the secretion of IL-10 from macrophage by downregulating CCAAT/enhancer-binding protein β (8). Sun *et al* (36) indicated that miR-181b may inhibit nuclear factor-κ-gene binding (NF-κB)-mediated endothelial cell activation and vascular inflammation in response to pro-inflammatory stimuli. The inhibitory role of miR-181b on NF-κB signaling pathway is primarily by directly targeting the expression of importin-α3, a protein critical for NF-κB nuclear translocation. Overexpression of miR-181b inhibited the activity of a luciferase reporter construct containing importin-α3 3'-UTR in a dose-dependent manner, while inhibition of miR-181b potentiated LPS-induced NF-κB-regulated gene expression and NF-κB activity (36). Vaporidi *et al* (28) also observed that a number of the miRNAs induced by HVTV (and their target mRNAs) participated in a transforming growth factor-β (TGF-β)-signaling pathways, which are involved in lung barrier function and inflammation. miRNAs could contribute to inhibition of TGF-β signaling pathway by targeting specific molecules. *Drosophila* mothers against decapentaplegic proteins, downstream molecules of TGF-β signaling pathway, as well as TGFβR2 and BMPR2, TGF-β and TGF-β ligands receptors, have all been identified as direct targets of miRNAs including miR-146, miR-106 and miR-21. Therefore, miRNAs have an important role in the regulation of the TGF-β signaling miRNA-gene network (28).

Of note, numerous studies observed that miRNAs and inflammatory signaling pathways form a negative-feedback regulation network. For example, miR-146a controls TLRs and cytokines through downregulation of IRAK1 and TRAF6 mRNAs in TLRs signaling transduction pathways. By contrast, TLR stimulation activates downstream NF-κB signaling, leading to subsequent induction of immune-response genes, including the gene for miR-146, miR-147, miR-9, miR-148 and miR-152, to prevent excessive inflammatory responses (37,38). Thus, a negative-feedback loop exists between miRNAs and inflammatory signaling pathways that contribute to development of lung injury and repair (37,39).

5. Role of miRNAs in immune response

The innate immune response and/or adaptive immune responses are initiated following experiences of the body with injury stimulus. Studies have shown that miRNAs have unique expression profiles in immune cells indicating their potential role in immune response. There are >100 different miRNAs expressed by cells of the immune system, and they have the potential to broadly influence the molecular pathways that control the development and function of innate and adaptive immune responses (32). Subsequent studies also revealed that not only can miRNAs modulate development of immune system, but they can also cause activation, proliferation and differentiation of immune cells as well as production of immune molecules during inflammation (1,12,37,38).

Innate immunity is a phylogenetically ancient biological system that multicellular organisms have evolved to defend themselves from invading pathogens (38). The innate immune response mediated by epithelial cells and immune cells, such as macrophages, neutrophils, dendritic cells and natural killer (NK) cells, provide an important first-line of defense against infection, inflammatory and injury (20,32,40). An LPS-induced innate immune response was associated with widespread, rapid and transient increases in miRNA expression in the mouse lung (37). Vaporidi *et al* (28) indicated that innate immune responses have been associated with increases in levels of miR-146, miR-155, miR-125 and miR-9, as well as a decrease in let-7 levels. Additionally, miR-181b could inhibit NF-κB, a pivotal transcriptional factor that regulates all aspects of the innate immunity response from synthesis of pro-inflammatory cytokines, such as IL-1β and TNF-α, to regulation of immune cell migration and remodeling of tissues following the successful termination of the inflammatory response and thus have a significant influence on innate immunity response (38).

miRNAs also regulate adaptive immune responses. For example, impaired Th2 responses in the lung occurs following silencing of miR-126 by antagomir. Through targeting Bcl-2 and CD69 and mediating positive selection, miR-181a appears to act as a negative regulator of T-cell receptor signaling. Additionally, miR-155 has a role in regulating T-helper cell differentiation and the germinal center reaction to produce an optimal T cell-dependent antibody response (3).

6. Functional roles of microRNA in ALI/ARDS

The expression levels of miRNAs changed significantly in ALI and miRNA have a significant influence on inflammatory and immune responses; therefore, miRNA has pivotal functional roles of microRNA in ALI/ARDS. miR-146a contributes to the suppression of inflammatory responses in LPS-induced ALI (1) and miR-127 also promotes the reduction of lung inflammation (3). Treatment with miR-16 reduces the expression of the proinflammatory cytokines IL-6 and TNF-α in macrophages after the exposure to LPS (31). Studies showed that miR-146 not only relieve acid-induced lung injury (25), but also inhibited innate immune responses NF-κB-dependent signaling molecules (34). Anti-miR-21 ameliorated indices of HVTV (28), while miR-181b decreased lung injury and mortality in endotoxemic mice (36). Furthermore, miR-155 ASO treatment could enhance the recovery of ALI (8).

7. Challenge and further perspective

Although the annual mortality rate is slowly declining, given that ALI is a common disease and the mortality rate is high, the regulation of miRNAs in the pathogenesis of ALI remains to be further investigation. In addition, the accumulated evidence revealed that miRNA could regulate inflammation pathways and immune response by targeting specific molecule in ALI/ARDS (Table II), therefore miRNAs and their target genes as novel therapeutic targets look promising. The miRNAs that repress inflammation pathways during ALI could possibly be upregulated using miRNA mimics and thereby restrain the development of disease. By contrast, the production of miRNAs promoting an inflammation response could be blocked by antisense oligonucleotides or miRNA antagonists and achieve the purpose of treating disease.

At present, the study regarding the mechanism of miRNAs in ALI/ARDS remains at its nascent stage. Out of the miRNAs that have been identified, only a small number of miRNAs were studied in ALi. Whether other miRNAs also have pivotal roles and how they are regulated as well as how they regulate inflammation and immune response in ALI remain to be elucidated, therefore, more basic studies on miRNAs and the gene targets regulated by these small RNA molecules are necessary.

Although there has been certain promising evidence, the current studies on the associations between miRNAs and ALI/ARDS are mainly conducted in animal models. Therefore, these results can aid in the future studies on patient samples and future relevant research. However, caution is required for the interpretation of these results as not all results from animal models are relevant to humans. Therefore, expansion of the present studies to human cell lines, tissues and human subjects would provide direct evidence to the role of miRNAs in the development of inflammatory lung disease.

It is now evident that aberrant expression of miRNAs influences the development of ALI, so therefore, proper regulation of miRNA expression appears to be crucial for disease prevention and treatment.

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