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Review article

Long non-coding RNA review and implications in acute lung inflammation

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ABSTRACT

Acute lung inflammatory diseases severely affect the patients’ recovery and outcomes worldwide. Unregulated acute inflammatory response is fundamentally central to acute lung inflammation including acute lung injury (ALI) and acute respiratory distress syndrome (ARDS). To limit the potentially deleterious effects of acute lung inflammation, complex transcriptional and posttranscriptional regulatory networks have been explored, which often involves long noncoding RNAs (lncRNA). LncRNAs are RNAs that longer than 200 nucleotides, functioning as scaffolds or decoys in the cytoplasm or nucleus. By now, lncRNAs have been found to join in all major cellular processes including cell proliferation, metabolism, stress response or death. Extensive advance over the last decade furthermore indicated a fundamental role of lncRNAs in acute lung inflammation. This article reviews and summarizes the current knowledge on lncRNA in acute lung inflammatory response.

1. Introduction

Being one of main target organs of pro-inflammatory mediators released and secreted globally during trauma, sepsis, and major surgery, the lung was at high risk of acute lung inflammatory diseases. The unregulated acute inflammatory response would cause acute lung injury (ALI) and its severe form, known as acute respiratory distress syndrome (ARDS), which lead to high morbidity and mortality [1]. Acute lung inflammation was characterized fundamentally by dysfunction of the barrier properties of the pulmonary epithelium and endothelium due to direct pulmonary insults as well as indirect systemic inflammatory responses. Although a variety of anti-inflammation pharmacotherapy have been applied, the morbidity and outcome of ALI/ARDS patients were still poor. It is of particular importance to explore the new mechanism of acute lung inflammation for early diagnosis and treatment.

To limit the potentially deleterious effects of acute lung inflammation, complex transcriptional and posttranscriptional regulatory networks have been explored, which often involves long noncoding RNAs (lncRNA). LncRNAs, regarded as transcripts exceed 200 nucleotides, found to involve in diverse biological processes, such as cell differentiation, proliferation, apoptosis, pyroptosis, and participate in various stress responses [2]. It was reported that lncRNAs might regulate gene expression by several different ways, including binding to microRNAs, mRNAs or proteins via the regulation of epigenetic modifications, transcriptional and posttranscriptional processing [3].

At present, lncRNAs have been found abnormally expressed in many inflammatory and infectious diseases. It was reported that lncRNAs might regulate the expression of multiple genes and activate the signaling pathways in the development of inflammatory diseases and pathogenesis. For instance, lncRNA XLOC_010280 can modulate the inflammatory reaction of eosinophilic granulocytes and the expression of chemokine ligand 18 (CCL18), to promote the development of inflammatory polyps [4].

More importantly, emerging evidence has revealed that lncRNAs play important roles in acute lung inflammation [5], including inflammation resolution of ALI/ARDS [6]. Since that many differentially expressed lncRNAs have been identified in ALI/ARDS recently, they may potentially serve as new therapeutic strategy for acute lung inflammation [7]. This article aims to review and summarize the specific function and mechanism of lncRNAs in acute lung inflammation and further limitations.
explore their therapeutic potential in acute lung inflammation.

2. Overview of lncRNAs

Long non-coding RNA (lncRNAs) are RNAs that longer than 200 nucleotides with low coding potential. Mediated by RNA polymerase II [8], more than 90 thousand lncRNAs have been released in different databases [9,10]. Remarkably, the number of lncRNAs is increasing dramatically because of the continuous maturity of sequencing technology. However, it still lacks definitive standard for lncRNAs classification. The relatively common classification is based on the location of nearby encoded protein genes, according to which lncRNAs are divided into antisense lncRNAs, sense lncRNAs, intergenic lncRNAs, intron region lncRNAs, circRNAs and enhancer lncRNAs (eRNAs) [11]. Other reported classifications of lncRNAs include: 1) by subcellular localization or origin, e.g. mitochondrial, cytoplasmic, or nuclear; 2) by different regulatory mechanisms, e.g. scaffolding IncRNA (HOTAIR); 3) by association with specific biological processes; 4) encoded within specific DNA regulatory elements, e.g. in rRNA loci (PAPAS), centromeres, telomeres (TERRA); and 5) length, e.g. very long lncRNA (vIncRNA) [2]. As the number of functional lncRNAs increased, the categorization standard of lncRNAs is being renewed continuously.

Besides the categorization standard, the function of lncRNAs is also being updated, which denies many traditional views. For instance, lncRNAs have no protein-coding potential due to their lack of gene-specific open reading frames (ORFs) in our traditional opinion. However, this should be updated since that recent researches showed that lncRNAs also own encoding ability. For example, IncRNA 00961 was found to encode SPAR and negatively regulate mTORC1 during muscle regeneration [12]. Ruiz-Orera also identified several IncRNAs which could translate RNA into proteins [3].

3. Regulation mechanism of lncRNAs

Researchers have conducted large numbers of extensive and in-depth explorations to clarify the mechanism of lncRNAs in different diseases comprehensively. LncRNAs were found to regulate genes at three levels including the epigenetic, transcriptional and posttranscriptional levels. 1) Epigenetic level: mainly including chromatin modification, genomic imprinting and dosage compensation [13,14]. 2) Transcriptional level: binding with target proteins in cis-acting elements or in a complexes form [15]. 3) Posttranscriptional level: regulating gene expression via mRNAs degradation, splicing and translation.

Recent studies also found IncRNAs to identify and bind to specific RNA or DNA sequences via base-pairing interactions and fold into secondary or higher order structures to modulate their interaction with proteins [16]. In addition, they could exert functions in both cytoplasm and nucleus, via different mechanisms including chromosome architecture modulation, genomic regions regulation, chromat-modifying complexes interaction, nuclear domains conformation, transcriptional enhancers activation, the transcriptional machinery interference, and structural formation, nuclear bodies maintenance [17]. Of note, IncRNAs frequently acted as competitive endogenous RNAs (ceRNAs) to protect stable mRNA expression [18]. The special mechanism of ceRNAs indicated that non-coding and coding RNAs could interact via competing for miRNA binding, thus reciprocally affecting their respective expression levels. As time goes on, more advances in the regulating mechanisms of IncRNAs will be reported in the near future to help us understanding its entire regulation network.

4. Emerging research hotspots of acute lung inflammation

Acute lung inflammation is one of the main features in the pathogenesis of many acute lung diseases, such as ALL, ARDS and so on. Irrespective of the initial cause, ALI/ARDS is fundamentally characterized by severe inflammatory responses, intense epithelial/endothelial barrier damage, as well as alveolar edema [19]. Although there are some effective strategies to alleviate acute lung inflammation, the outcome of patients with acute lung inflammation has not yet improved and the underlying mechanism has not yet been clarified [16].

Multiple pulmonary cells are involved in acute lung inflammation, including epithelial cells, labocyte, macrophages, neutrophils, mononuclear cells and T cells [20,21]. Since that alveolar macrophages (AMs) play central roles in both the initiation and resolution of acute inflammatory responses, we have focused on its underlying mechanisms in acute lung inflammation. Different from classic macrophages, AMs are derived from yoke-sac procurers in fetal monocytes and comprise the majority of inflammatory cells in the lung [22]. With inflammatory invasions, bone marrow derived monocytes are recruited to the bronchoalveolar space and differentiated into AMs [23] to form the first-line host defense against infection, acting as antigen-presenting cells and releasing pro-inflammatory cytokines to propagate the inflammatory responses in ALI/ARDS [24]. The functional phenotype of AMs is modulated by different microenvironment of the lung [19], which mainly including two distinct subsets: classically activates M1 macrophages (M1) and alternatively activated M2 macrophages (M2). Accumulating evidence showed that in the early stage of acute lung inflammation, large amounts of M1 secrete molecules IL-6, TNF-α, and IL-1 to propagate inflammatory responses and mediate host defense against various bacteria or viruses, while M2 secrete biological mediators TGF-β, IL-10, and chemokines engaged in infection, immune-regulation and tissue reconstruction [25]. Notably, M2 has four subtypes (M2a, M2b, M2c, and M2d) and the regulatory macrophages (M2b) produce a lot of anti-inflammatory cytokine, such as IL-10, to control the excessive inflammation and auto-immune reactions [26]. The modulation of M1/M2 macrophage polarization has been proven to be a potential therapeutic target for acute lung inflammatory disorders.

Besides AMs, increasing reports also highlight the complexity and important function of interstitial macrophages (IMs) in lung inflammation. Like AMs, IMs are phagocytic cells and thus can be considered as the second-line defense against invading microorganisms [27]. Up to now, three distinct subpopulations of IMs, including IM1, IM2, IM3, have been identified based on their phenotypical and functional properties [28]. Recent evidence supports that IMs play a vital in the second line of defense through their antigen presentation and phagocytosis abilities in bacterial or viral lung inflammation [29]. For instance, a CD169+ IMs subset substantially located to the bronchovascular tree was recently reported to regulate lung inflammation via regulating production of inflammatory cytokines and innate immune cell infiltration [30]. Moreover, inducing metabolic and epi-genetic reprogramming of lung IMs toward an anti-inflammatory phenotype could reduce inflammatory lung injury [31] and protect from airway allergic inflammation [32]. Although our understanding of the IMs’ spatial and anatomical positioning and functions is still limited, emerging evidence suggests that they play vital roles in maintaining immune and tissue homeostasis in lung inflammation [33,34].

Multiple types of cell injury and programmed cell death were also found in acute lung inflammation, mainly includes cellular apoptosis, pyroptosis, autophagy, necrosis. Among which pyroptosis is a newly discovered type of programmed cell death. Including a typical pathway dependent on Caspase-1 activation, and an atypical pathway dependent on Caspase 4/5 (in human) and Caspase 11 (in mice) activation, pyroptosis played an important role in inflammatory resolution of acute lung inflammation [35]. Recent studies have shown that inflammasomes activation and inflammasome-dependent pyroptosis play a vital role in acute lung inflammation [36], including classical and nonclassical pathways (Fig. 1). For instance, recent studies revealed that Dihydromyricetin protected CLP-induced ALI via inhibition of Nod-like receptor protein 3 (NLRP3) inflammasomes activation and pyroptosis [1]. Another study also showed that Ang1 exerted beneficial role of phosgene-induced ALI through inhibiting NLRP3 inflammasomes activation and pyroptosis [37].

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5. Regulation of LncRNAs in acute lung inflammation

Conventional research on acute lung inflammation often involved investigations on gene expression, specific protein or protein related signaling pathways, etc. The discovery of lncRNA reveals a new insight on the pathogenesis of acute lung inflammation, which will open a new era for researchers to develop specific effective therapeutics. Several lncRNAs have been identified being involved in the procedure of acute lung inflammation, through modulating miRNAs or downstream targets or directly regulate pyroptosis [38, 39]. We concluded the regulation of reported lncRNAs in acute lung inflammation as shown in Table 1 and Fig. 2.

5.1. LncRNA MALAT1

Metastasis associated lung adenocarcinoma transcript 1 (MALAT1), a lncRNA located in more than 40 kb away on mice chromosome 19 from Neat1, is reported essential in the regulation of acute lung inflammation, especially in septic-lung injury [6]. For example, MALAT1 activates p38 MAPK/p65 NF-κB signaling pathway to evoke and intensify inflammation in septic-lung injury model [40]. Dai L et al. reported that MALAT1 was a potential biomarker to predict elevated ARDS risk and correlate with severe disease condition and raised mortality in sepsis patients [6].

MALAT1 is reported to participate in pulmonary pathogeneses via regulating aberrant macrophage activation. For example, MALAT1 upregulated in LPS-treated AMs and promoted pro-inflammatory M1 phenotype AMs activation and suppressed the alternative M2 phenotype AMs activation. Furthermore, MALAT1 knockdown attenuates pro-inflammatory activation of AMs [6], and MALAT1 overexpression aggravates LPS induced inflammatory response in murine AMs by sponging miR-146a [7].

Besides miR-146a, MALAT1 was also found to regulate acute lung inflammation via sponging or binding other miRNAs. A study showed that over expression of MALAT1 aggravating acute lung inflammation through sponging miR-425 to modulate PETN expression, and then enhance aberrant fibroblast proliferation [7] and apoptosis in LPS-induced ARDS [41]. In addition, MALAT1 binded to miR-150-5p and upregulated ICAM-1 expression to cause HPMEC apoptosis in both ARDS patients and LPS-treated HPME [41]. Similarly, MALAT1 knockdown was found to alleviate LPS induced ALI via targeting the miR 175p/FOXa1 axis [42].

Furthermore, MALAT1 can regulate acute lung inflammation through pyroptosis via different ways. A recent study showed that MALAT1 regarded as a pro-inflammatory factor in LPS-ALI model to regulate AM cell pyroptosis and inflammatory response via the miR-149/MyD88/NF-κB axis [43]. In addition, Li H et al. reported a lipoxin receptor agonist, BML-111, could significantly modulate the expression of MALAT1 and regulate the inflammatory resolution via TLR4/NF-κB/p38 MAPK signaling pathways [44], which also provided a potential target for acute lung inflammation.

Kölling M and his colleague also reported that MALAT1 knockdown could ameliorate histopathologic changes in lung injury in hypoxia-induced pulmonary hypertension [45]. All the increasing studies confirmed that MALAT1 knockdown might be potential therapeutic way to alleviate acute lung inflammation [7].

5.2. LncRNA NEAT1

Recently, lncRNA nuclear paraspeckle assembly transcript 1 (NEAT1) has grown up to be a topic of concern due to its pleiotropic function in inflammation-related diseases. It has been indicated there was positive correlation between high levels of NEAT1 and increased severity and unfavorable prognoses in patients with sepsis [46]. Groot M. also showed that high expression of NEAT1 and low expression miR-125a were associated with increased ARDS risk, higher 28-day mortality in sepsis patients and acute lung inflammation [47]. Nevertheless, the function and molecular mechanism of NEAT1 in acute lung inflammation remain elusive. In a recent study, Hongchao Zhou and his colleague confirmed that NEAT1 may modulate alveolar epithelial cells (AECs) pyroptosis and reduce inflammatory response to against LPS-induced ALI/ARDS by suppressing HMGB1/RAGE-NF-κB signaling [48]. Furthermore, NEAT1 inhibition alleviates cell apoptosis and promotes proliferation in sepsis-induced ALI. All the studies provide a theoretical basis for the therapy of NEAT1 in acute lung inflammation.

Fig. 1. Relationship between lncRNAs and pyroptosis.
LncRNAs participate in the regulation of pyroptosis by indirectly acting on miRNAs and downstream targets or directly binding to pre-caspase-1, thus regulating the pathological process of pyroptosis related diseases.
Multiple cancer types, was recently found acting as a competitive endogenous RNA that regulates AQP1 expression by sponging to miR-144-3p/PDK4 axis and exacerbate ALI in sepsis [50]. Likewise, growth arrest special candidate 9 (CASC9) was also reported to regulate miR-195-5p/PDK4 axis and induce cell apoptosis and cell death [53]. In addition, lncRNA Nkx2.1-associated noncoding intergenic RNA (NANCI) was also reported to decrease in ALI [54]. Guoyue Liu et al. found that agmatine protected hyperoxia-induced lung injury and inhibited cells apoptosis via decreasing lncRNA growth arrested DNA-damage inducible gene 7 (GADD7) to indirectly decrease MFN1 expression, due to the presence of the competitive binding of lncRNA GADD7 and MFN1 to miR-125a [55].

### 5.5. LncRNA SNHG16, SNHG14, HAGLROS

Increasing studies employed LPS-induced ALI model to confirm the role of lncRNAs in inflammatory resolution and provide potential targets for the treatment of acute lung inflammation. Take small nuclear lncRNA host gene 16 (SNHG16) as an example, it modulates IG2F expression to promote LPS-induced acute pneumonia in A549 cells by targeting miR-370-3p [56]. A recent study showed that SNHG16 regulates LPS-induced apoptosis of WI-38 cells and inflammatory response in acute lung inflammation via targeting miR-146a-5p/CCL5 expression [57]. Besides SNHG16, inhibiting small nuclear lncRNA host gene 14 (SNHG14) was found to protect against LPS-induced ALI through miRNA-34c-3p-mediated inhibition of WISP1 [58]. Down-regulation of haglr opposite strand (HAGLROS) alleviated LPS-induced inflammation in WI-38 cells through modulating miR-100/NF-kB axis to increase cell viability, inhibit apoptosis and autophagy [59].

### 5.6. LncRNA XIST, MEG3, MEG3–4

Besides HAGLROS, lncRNA X inactive-specific transcript (XIST) has also emerged as a new modulator in LPS-induced ALI. For example, it was shown that XIST deficiency alleviated LPS-induced apoptosis of WI-38 cells and inflammatory response via regulating miR-370-3p/TLR4 in acute pneumonia [60]. Li J et al. also confirmed that XIST increased IL-12A via binding to miR-21 to induce NET formation and accelerated primary graft dysfunction (PGD) after lung transplantation, which suggested that XIST and NET inhibition might be beneficial for the therapy of PGD [61]. Besides that, the lncRNA maternally expressed gene 3 (MEG3), acting as a ceRNA and sponging miRNAs, was reported to affect various cell processes such as apoptosis, proliferation and angiogenesis. A report showed that knockdown of MEG3 intensified LPS induced lung injury via miR-4262 mediated down-regulation of KLF4 [62]. Moreover, among 10 transcriptional subtypes of MEG3, transcriptional 4 (MEG3–4) encodes the least abundant subtype in the lungs of mice. It was reported that MEG3–4 acted as miRNA decoy, increasing IL-1β abundance to modulate inflammatory responses in lung cells and tissues of ALI mice via competitively binding to miR-138 [63].

### 5.7. Other newly identified lncRNAs

Many new lncRNAs have been identified to be biomarkers for clinical outcomes of ARDS/ALI. Recent evidence showed that lncRNA THRL was upregulated in patients with ARDS [47] and it was recommended as biomarker that positively correlated with mortality in sepsis-induced ARDS patients [64]. While plasma Lnc-IL7R was significantly down-regulated in ARDS patients [65], and it has been verified to negatively regulate IL7R expression to inhibit LPS-induced acute lung inflammation [66]. LncRNA A_30_P01029194 and A_30_P01029806 might also serve as candidate biomarkers in ALI [67]. Another genome-wide transcriptome analysis revealed that lncRNA NONMMUT065867,
NONMMUT064312 and NONMMUT018123 were closely related to the elevated NLRP3 expression and ARDS [68].

5.8. Promise and challenges of lncRNAs therapy in acute lung inflammation

LncRNAs have served as promising targets for acute lung inflammation by regulating miRNAs, targets or proteins, and many studies performed in LPS-induced ALI models have revealed the potential targeting lncRNAs to regulate acute lung inflammation, which provided a strong therapeutic basis for acute lung inflammation. Moreover, lncRNAs were also reported to play important roles in mesenchymal stem cells (MSCs) and MSC-derived exosomes treatment of acute lung inflammation [69–71]. However, researchers have not obtained sufficient evidence to confirm the therapeutic effects of these treatments on acute lung inflammation in clinical trials. For instance, plasma lnc-IL7R was preliminarily suggested as a biomarker in ARDS patients [72], but the sample size was small that still needs further confirmation. In addition, although numerous clinical trials of MSCs transplantation for ARDS including COVID-19 ARDS treatment have been registered and reported [73–75], whether lncRNAs are involved in the treatment still need further exploration. Moreover, before targeting the lncRNAs therapy for acute lung inflammation, several crucial challenges persist and need to be addressed. Firstly, since lncRNAs are poorly conserved among different species, it is difficult to confirm role of the selected lncRNAs in patients with acute lung inflammation in animal models, thus limits the exploration of the mechanism of lncRNAs in regulating acute lung inflammation [76]. Secondly, most current studies have focused on the role of lncRNAs as ceRNA. However, expression of most lncRNAs is generally not high in cells, in contrast to highly expressed miRNAs. It is difficult to coordinate the sponge function of ceRNAs because miRNAs offer only 1 binding site per lncRNA.

6. Conclusions and prospects

Acute lung inflammation including ALI/ARDS still lacks specific therapeutic targets. More and more lncRNAs have been found to play important roles in pathogenesis of ALI/ARDS and may serve as new diagnostic and treatment biomarkers for ALI/ARDS. Increasing evidence shows that lncRNAs can bind to microRNAs, mRNAs or proteins to regulate epigenetic modifications, transcriptional and post-transcriptional processing in epithelial cells, AMs, neutrophils and so on, which provides potential therapeutic targets for ALI/ARDS and basis for drug therapy.

However, the underlying mechanisms and therapeutic potential of lncRNAs in acute lung inflammation still need further investigation and confirmation in the future.

CRediT authorship contribution statement

CJC and YFH conceived the structure of this manuscript, drafted initial manuscript and also revised the manuscript; YWF and WLH collected all information and composed sections related to role of lncRNAs; ZQY and GJL provided the comments on this manuscript. All authors have read and approved the submission of this manuscript.

Declaration of competing interest

The authors declare that they have no competing interests.

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