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Current understanding on long non-coding RNAs in immune response to COVID-19

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Highlights

- The 2019 coronavirus (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has become a global epidemic threatening the lives and health of people worldwide. Currently, there are no effective therapies or available vaccines for COVID-19. In SARS-CoV-2 infection, lncRNAs are demonstrated to be closely related to viral infection, interferon and cytokine storm in COVID-19. LncRNA NEAT1, DANCR, MALAT1, C058791.1, TTTY15 and TPTEP1 played a role in the infection of SARS-CoV-2. LncRNAs also can modulate the expression of interferon. Inversely, interferon can stimulate the expression of lncRNAs. Besides, lncRNAs can regulate the cytokine storm by downregulating the expression of cytokines. Thus, we can speculate that developing drugs targeting some specific sites in the pathway or relation network of lncRNAs may be promising strategy to treat SARS-CoV-2 infection.

Abstract

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has become a global pandemic threatening the lives and health of people worldwide. Currently, there are no effective therapies or available vaccines for COVID-19. The molecular mechanism causing acute immunopathological diseases in severe COVID-19 is being investigated. Long noncoding RNAs (lncRNAs) have been proven to be involved in many viral infections, such as hepatitis, influenza and acquired immune deficiency syndrome. Many lncRNAs present differential expression between normal tissue and virus-infected tissue. However, the role of lncRNAs in SARS-CoV-2 infection has not been fully elucidated. This study aimed to review the relationship between lncRNAs and viral infection, interferon and cytokine storms in COVID-19, hoping to provide novel insights into promising targets for COVID-19 treatment.

Keywords: LncRNAs, COVID-19, SARS-CoV-2, viral infection, interferon, cytokine storms

Introduction

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). COVID-19 spread at an alarming rate, threatening the lives and health of the entire human race. SARS-CoV-2, a single-stranded RNA virus, is a member of the

Coronaviridae family (1). Patients with COVID-19 present with fever, dry cough and respiratory failure, combined with gastrointestinal and neurological symptoms (2). It is projected that asymptomatic dissemination is responsible for nearly half of SARS-CoV-2 transmission (3). Respiratory failure accounts for the highest mortality of patients with COVID-19 (4). SARS-CoV-2 can lead to acute respiratory distress syndrome (ARDS) mediated by proinflammatory cytokines (5). Proinflammatory cytokines can cause severe damage to vital organs and lead to multiple organ dysfunction syndrome (MODS) (6). The main therapeutic measures include convalescent plasma, remdesivir and cytokine blocker drugs (7). Specific vaccination represents a key strategy against SARS-CoV-2 infection. According to the World Health Organization (WHO), more than 360 vaccines have been developed, and 45 vaccines have been evaluated in phase III clinical trials to date (8). These COVID-19 vaccines seem to be well tolerated and display a preventive effect on the original strain and variants of SARS-CoV-2 (8). However, the regulatory mechanism of host genetic expression in response to infection remains unclear (9). It is necessary to explore viral pathogenesis and biological reactions against SARS-CoV-2 in the host.

Long noncoding RNAs (lncRNAs), a subclass of noncoding RNAs, lack an open reading frame and have a length of more than 200 nucleotides (10).

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By competing with endogenous RNA (ceRNA), lncRNA serves as a miRNA sponge, regulating the expression of target genes. LncRNA, miRNA, and mRNA were used to construct a lncRNA–miRNA-mRNA competing endogenous (ceRNA) network (11). LncRNAs are involved in a broad spectrum of biological processes, especially immunity and inflammatory reactions (12, 13). The lncRNA XIST plays a role in inflammation via the NF-κB/NLRP3 pathway (14). Chen et al. found that the lncRNA MALAT1 functions as a negative factor in inflammation in sepsis (15). It has been revealed that lncRNA SNHG14 enhances the inflammatory response by increasing the level of ROCK1 and downregulating the expression of miR-136-5p (16). Several lncRNAs have been identified in multiple viral infections, such as hepatitis and AIDS (17, 18). Notably, lncRNAs were also identified in the process of SARS-CoV-2 infection. LncRNA H19 regulates spike transcription of SARS-CoV-2 by binding to the genome of SARS-CoV-2, thereby affecting SARS-CoV-2 infection (19). However, the relationship of lncRNAs with viral infection and the antiviral inflammatory response in COVID-19 needs to be clarified.

LncRNAs in SARS-CoV-2 viral infection

Some lncRNAs, such as NEAT1 and EGOT, increase in influenza A virus and HIV infection (20). In addition, NEAT1 suppresses the replication and growth of HIV and Hantaan virus (HTNV) (21-24). Similarly, in

SARS-CoV-2 viral infection, lncRNA NEAT1 and DANCR change the level of inflammatory transcripts by regulating the expression of immune-related genes (25). Approximately 500 lncRNAs were found to be differentially expressed during SARS-CoV-2 infection (26). HOTAIRM1, PVT1 and AL392172.1 can bind to the SARS-CoV-2 genome with high affinity, suggesting the major regulatory role of lncRNAs in COVID-19 (27). Transcriptome analysis of bronchial epithelial cells in patients with SARS-CoV-2 infection showed that the lncRNA MALAT1 had significantly different expression levels. The lncRNA MALAT1 may be a potential biomarker of SARS-CoV-2 infection (28). An in silico study detected the expression levels of lncRNAs both in cell lines and lung tissue. In vitro, there were a total of 20 overexpressed lncRNAs and 4 downregulated lncRNAs during SARS-CoV-2 infection. Moreover, NEAT1 was upregulated in the lung tissue of patients with SARS-CoV-2 infection (20). Another study found that a total of 898 lncRNAs (414 overexpressed lncRNAs; 484 downregulated lncRNAs) were differentially expressed between healthy individuals and patients with SARS-CoV-2 infection. In addition, these differentially expressed lncRNAs were likely to be associated with exosomes and regulate the inflammatory process (29). Transcriptome analysis of SARS-CoV-2-infected lung tissues showed that three lncRNAs (C058791.1, TTTY15 and TPTEP1) were enriched with

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maximum target genes. These three lncRNAs interact with genes via the lncRNA–miRNA-mRNA pathway and release the mRNA for translation. The activity of AC058791.1 has not been identified; TTTY15 is involved in proteolysis and ubiquitin-dependent catabolism (30), and TPTEP1 inhibits STAT3 phosphorylation (31).

Furthermore, lncRNA H19 can bind to the 5'UTR of the SARS-CoV-2 genome and modulate the spike transcript in viral infection (19). LncRNA-based oligosequences can be candidates to combat SARS-CoV-2. Of note, these results need to be experimentally validated at the patient level. Clinically, a comprehensive profile of COVID-19-related lncRNAs in peripheral blood mononuclear cells of patients with SARS-CoV-2 infection and healthy individuals was built. More specifically, 1072 lncRNAs were differentially expressed between the two populations. The top three increased lncRNAs are ENSG00000231412 (AC005392.2), followed by ENSG00000274173 (AL035661.1) and ENSG00000231535 (LINC00278). The top decreased lncRNAs are ENSG00000229807 (XIST) and ENSG00000273160 (AL359962.2) (32). These differentially expressed lncRNAs may be potential biomarkers for the diagnosis and prognosis of patients with SARS-CoV-2 viral infection. Collectively, these COVID-19-related lncRNAs may be possible innovative candidates against SARS-CoV-2 infection. Further studies are needed to fully identify and understand the

functions of lncRNAs in COVID-19.

LncRNAs and interferon in COVID-19

LncRNAs were shown to modulate interferon-stimulated genes (ISGs) in the inflammatory process. LncRNA#32/LUARIS can combat EMCV, HBV and HCV infection by regulating the transcription factor ATF2 to alter the expression of ISG (33). Interestingly, angiotensin I converting enzyme 2 (ACE2), the receptor for COVID-19, is an ISG. SARS-CoV-2 could exploit species-specific interferon-driven upregulation of ACE2 to aggravate the host immune response and enhance infection (5). Additionally, lncRNAs can be stimulated by interferon (IFN). The expression of NRIR/lncCMPK2 can be activated by IFN and then modulated by signal transducer and activator of transcription 2 (STAT2). There was a reliable association between the expression of IFN and SARS-CoV-2 infection both in laboratory and clinical studies (28). It was observed that lncRNAs can modify ISG levels in different viral infections (33-36). In contrast, Laha et al. found that the expression of lncRNAs had no correlation with interferons. Then, they investigated the interaction between lncRNAs and heterogeneous nuclear ribonucleoproteins (hnRNPUs), a group of RNA-binding proteins. They found that several lncRNAs could be regulated by interferon regulatory factors (IRFs) and STAT in response to SARS-CoV-2 infection (20). LncRNAs might be involved in the antiviral response by regulating IFN. However, several

host lncRNAs can repress the viral immune response by downregulating type I interferons (IFN-1). In the early stage of SARS-CoV-2 viral infection in asymptomatic patients, the production of IFN, especially IFN-b, was delayed. More importantly, SARS-CoV-2 N protein can inhibit IFN production by disturbing the retinoic acid-induced gene I (RIG-I) pathway (37). Clinically, IFN-α is a common interferon for antiviral therapy in patients with COVID-19. These lncRNAs mediate IFN regulation in COVID-19 and should be validated to explore effective antiviral strategies in future studies.

LncRNAs regulate cytokine storms in COVID-19

The organ damage caused by the inflammatory reaction accounts for the high mortality and morbidity in COVID-19 (38, 39). Studies in human and animal models implied that immunopathological events might lead to the death of patients with SARS-CoV-2 viral infection (40, 41). In addition, the lung tissue of patients with SARS-CoV-2 infection displayed pathological infiltration of immune cells such as macrophages and monocytes (42). It has been validated that an inflammatory cytokine storm, an overwhelming inflammatory immune response with hyperproduction of mainly proinflammatory cytokines, such as IL-1, IL-6, IL-12, IFN-γ, and TNF-α, contributes to the development of SARS-CoV-2 infection and is the cause of severe COVID-19 (43-45). LncRNAs can target cytokines in inflammatory cytokine storms in

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COVID-19. LncRNAs with the potential to regulate the inflammatory response showed differential expression in patients with SARS-CoV-2 infection compared with healthy individuals (29). LncRNAs MALAT1 and NEAT1 may contribute to the development of inflammation in SARS-CoV-2-infected cells (27). In contrast, 22 lncRNAs bound to 10 important cytokines, and 8 of 22 lncRNAs targeted multiple cytokines. RAD51-AS1 and lnrCXCR4 each can target 3 cytokines. Notably, the lncRNA NORAD, which is activated by DNA damage, can bind with 5 cytokines, including interleukin (IL)-6, IL-10, CSF3, tumor necrosis factor (TNF)-α and CXCL10 (46). LncRNAs may target and bind important cytokine nucleotide sequences and possibly decrease the expression of cytokines, thus reducing the emergence of cytokine storms in the infection. Given the interaction between lncRNAs and inflammatory cytokines, some methods, such as viral gene therapy, RNAi knockdown, viral vectors and antisense oligonucleotides, have been used in clinical practice (47, 48). Agents targeting lncRNAs show promise in enhancing the anti-SARS-CoV-2 response by inhibiting the cytokine storm.

LncRNAs function as potential targets for COVID-19

Several functional lncRNAs involved in viral infection and cytokine storms in COVID-19 are summarized in **Table 1**. In a coexpression network analysis of human lung epithelial cell lines and bronchoalveolar

lavage fluid from patients with SARS-CoV-2 infection, four lncRNAs (WAKMAR2, EGOT, EPB41L4A-AS1, and ENSG00000271646) were upregulated. These four lncRNAs were associated with multiple cytokine pathways and overactivated inflammatory responses (49). LncRNAs can regulate the expression of IL-6 and NLRP3 through epigenetic, transcriptional, and post-transcriptional mechanisms. Agents targeting these signalling pathways have been developed. Tocilizumab, an IL-6 receptor antagonist, effectively inhibits the IL-6 receptor (IL-6R) and reduces the serum levels of C-reactive protein (CRP) and serum amyloid A (SAA) (50, 51). Similarly, BML-111, an IL-6 blocker, can increase the level of lncRNA MALAT1 and then downregulate the expression of inflammatory factors, such as monocyte chemotactic protein-1 (MCP-1) and IL-6 (52, 53). A drug perturbation analysis found that digoxin and proscillaridin can regulate gene expression levels by increasing or decreasing the expression levels of some lncRNAs. By conducting molecular docking and drug perturbations on gene expression, we found that digoxin and proscillaridin can be used to treat severe COVID-19 infections (54). Moreover, a bioinformatic analysis implied that the TGF-beta signalling pathway is interactive and involved in the network of lncRNAs, human proteins, and miRNAs. The TGF-beta signalling pathway may be a promising target for COVID-19 treatment (55). These studies suggested that lncRNAs can interact with several inflammatory

factors, including inflammatory genetic processes and cytokine release in COVID-19. LncRNAs may serve as potential therapeutic enhancers in combatting SARS-CoV-2.

Table1. A summary of functional lncRNAs involved in viral infection and cytokine storm in COVID-19.

LncRNA	Function
LncRNAs in SARS-CoV-2 viral infection	
NEAT1	Upregulated in the lung tissue of patients with SARS-CoV-2 infection (20)
MALAT1	May be a potential biomarker of SARS-CoV-2 infection(28)
HOTAIRM1/PVT1 /AL392172.1	Bind to the SARS-CoV-2 genome with the high affinity(27)
TTTY15	Regulates proteolysis, ubiquitin dependent catabolism(30)
TPTEP1	Inhibits STAT3 phosphorylation(31)
LncRNA H19	Binds to the 5'UTR of SARSCoV-2 genome and modulates the Spike transcript(19)
LncRNAs regulate cytokine storm in COVID-19	
MALAT1	Induces inflammatory responses and release of IL-6 and TNF-α(52)
DANCR	Regulates ncRNA-mRNA network in inflammation(25)
HOTAIR	Regulates activation of NF-κB and IL-6 and iNOS expression(56)
NEAT1	Promotes activation of inflammasomes in macrophages(57)
NORAD	Binds with IL-6, IL-10, CSF3, TNF-a and CXCL10(46)
RAD51-AS1	Leads to expression of pro-inflammatory cytokines(46)

Summary

In SARS-CoV-2 infection, lncRNAs have been demonstrated to be related to viral infection, interferon and cytokine storms in COVID-19 **(Figure 1)**. These lncRNAs interacted with genes of SARS-CoV-2 via the lncRNA–miRNA-mRNA pathway. LncRNAs can also modulate the expression of interferon. Conversely, interferon can stimulate the expression of lncRNAs. In addition, lncRNAs bind with important or multiple cytokine storm cytokines. LncRNAs identified in the COVID-19

cytokine storm have the potential to serve as disease markers or drug targets. Thus, we can speculate that developing drugs targeting some specific sites in the pathway or network of lncRNAs may be a promising strategy to treat SARS-CoV-2 infection. More experimental studies are needed to further confirm the regulatory mechanism of lncRNAs in COVID-19.

AUTHOR CONTRIBUTION

Jing Ding collected and reviewed the literature and wrote the manuscript. Xude Yin assisted in drawing. Jing Chen revised the manuscript. Jing zhou designed the main study and reviewed this manuscript. All authors have read and approved the final submitted manuscript.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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FIGURE CAPTIONS:

Figure1. LncRNAs are related to viral infection, interferon and cytokine storm in COVID-19.