The Open COVID Journal

Content list available at: https://opencovidjournal.com

REVIEW ARTICLE

Molecular Mechanisms of Non-Coding RNAs in Modulating the Pathogenesis of SARS-Cov-2 Infection

Omid Gholizadeh[1,2], Sama Akbarzadeh[3], Zahra Yekanipour[4], Raheleh Tabatabaie[5], Somayeh Sedighi[6] and Hamed Afkhami[7,*]

[1]*Department of Bacteriology and Virology, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran*
[2]*Infectious and Tropical Diseases Research Center, Tabriz University of Medical Sciences, Tabriz, Iran*
[3]*Department of Biology, Faculty of Natural Sciences, University of Tabriz, Tabriz, Iran*
[4]*Department of Microbiology, Marand Branch, Islamic Azad University, Marand, Iran*
[5]*Department of Immunology, Medical Sciences University of Hamedan, Hamedan, Iran*
[6]*Department of Immunology, Faculty of Medicine, Medical Science of Mashhad, Mashhad, Iran*
[7]*Department of Medical Microbiology, Faculty of Medicine, Shahed University of Medical Science, Tehran, Iran*

Abstract:

The coronavirus disease 2019 (COVID-19) has been spreading worldwide since December 2019. It is a significant threat to community healthcare in all countries worldwide, so policymakers and researchers are paying close attention to it. The most significant components of non-coding RNAs (ncRNAs) are miRNAs and lncRNAs, which serve as regulatory elements. They are vital ingredients of the transcriptome, with a role in normal biological reactions and inflammatory processes, including viral infection. In the field of viral infection, microRNAs and non-coding RNAs with 19 to 25 nucleotides receive more attention as they target mRNAs to control gene expression. However, the role of many lncRNAs is yet to be discovered. In this review, we provide detailed information about the effects of host lncRNAs and viral lncRNAs, interactions between lncRNAs and their interactions with other ncRNAs, and small membrane vesicles called exosomes and microRNAs in COVID-19 infection. The profile of ncRNAs in host cells of the SARS-CoV-2 virus is altered. As a result, these changes may serve as valuable indicators for disease development and severity. Understanding these pathways will help researchers learn more about SARS-CoV-2 pathogenesis and seek more practical treatments to control cytokine storm and viral life cycle.

Keywords: COVID-19, Cytokine storm, Non-coding RNAs, IL-6, Inflammasome, MERS-CoV, Infection.

Article History	Received: April 25, 2022	Revised: August 20, 2022	Accepted: September 08, 2022

1. INTRODUCTION

The coronavirus disease 2019 (COVID-19) outbreak has been the most significant public health epidemic since 1918 and has caused many economic and health issues [1 - 3]. Therefore, learning more about its features and interactions with human host cells is essential to discover efficient therapies. MERS-CoV and SARS-CoV-1 are two additional dangerous human coronaviruses that cause moderate respiratory tract disease with a 36% and almost 10% mortality rate, respectively [4]. However, the severity of COVID-19 differs among patients. The vast majority experience common cold symptoms that develop into a mild pneumonia case, while about 14% of persistent cases express severe symptoms such as shortness of breath [5].

* Address correspondence to this author at the Department of Medical Microbiology, Faculty of Medicine, Shahed University of Medical Science, Tehran, Iran; E-mail: hamedafkhami70@gmail.com

All strains of single-stranded, positive RNA (+ssRNA) viruses make up most of coronaviruses [6], *via* an electron microscope, the presence of spike glycoproteins on the coronavirus envelope gives it a crown-like appearance (Corona is the Latin word for crown) [7, 8]. When adapting to their new human hosts, SARS-CoV-2 is susceptible to genetic evolution, with mutation development over time, resulting in variants with different features than their progenitors [2].

Nowadays, non-coding RNAs (ncRNA) are used in genomic medicine [9]. Regulatory elements such as microRNA (miRNA), long non-coding RNA (lncRNA), and circular RNA (circRNA) are non-coding RNAs that control gene expression rather than actively engaging in cell physiological activities [10]. lncRNAs are transcripts with a length of 200 nucleotides or more with various roles in cell biology [11]. The identification of lncRNAs as potential major regulators of inflammatory genes suggests that they may be required for regulating inflammatory responses [12 - 14]. Understanding the

effect of their altered expression levels and mechanism of action can have a substantial impact on immunology and infectious diseases. Scientists discovered that 500 lncRNAs interfered with the cell response to viral infection by examining SARS-CoV-infected cells [15]. They also suggest that these non-coding characters in host cells and RNAs have an essential modulating role in the antiviral innate immune system. The majority of lncRNAs associated with viral infections co-express genes involved in maintaining lung homeostasis, and they have been linked to IFN mechanistic pathways [16].

MicroRNAs are non-coding RNAs with 19 to 25 nucleotides that target mRNAs and cause translational repression or mRNA destruction to regulate gene expression. miRNA is a potent gene regulator that affects virtually every aspect of gene regulation [17, 18]. miRNA regulates gene expression by targeting the 3' and 5' untranslated regions (3' UTR and 5' UTR, respectively) (UTR) and coding regions [19 - 21]. Furthermore, microRNAs significantly impact the production of cytokines, chemokines, and growth factors [22]. Plants, animals, and viruses contain microRNAs with various biological roles [23, 24]. MicroRNA-targeted therapies have been suggested to treat malignancies, viral diseases, and other illnesses since they are essential regulators of gene expression [25]. Many miRNAs have been identified as markers in virus-infected illnesses [26]. MicroRNAs could be encoded by viral genomes, encompassing DNA and RNA viruses. MiRNAs generated from viruses may also be synthesized in host cells with a function in the life cycle of a virus as well as cellular consequences [27, 28]. On the other hand, miRNAs may attach to complementary regions on the viral RNA sequence, thus reinforcing the viral genome's silencing effect and reducing protein production [29].

With the aid of miRNA response elements, lncRNAs and circRNAs competitively attempt to bind miRNAs and form competing for endogenous RNAs (ceRNAs) [30]. CeRNAs may act as miRNA sponges, controlling the production of miRNAs that target specific mRNAs. The discovery of lncRNA/circRNA aids the development of a ceRNA network, potentially contributing to the discovery of new and effective treatment targets [31].

2. INTERPLAY BETWEEN COVID-19 AND NON-CODING RNAS

SARS-CoV-2 has produced a large epidemic with a significant mortality rate throughout the globe, and death rates are continuously increasing [32]. Understanding the relationship and effect of this virus on human host cells is critical [7]. In the coronavirus genome, spike, envelope, membrane, nucleocapsid, and all structural proteins are encoded by positive-sense RNA [32]. The rapid mutation rate in the spike nucleotide sequence has been suggested as one of the causes of SARS-CoV-2's high transmission rate [33].

Viral resistance is affected by the ncRNA network of host cells. Infection typically alters the expression patterns of ncRNA in the host, potentially increasing viral proliferation and propagation conditions. As a result, ncRNAs boosted during the infection may be efficient biomarkers for disease progress and severity [7]. Furthermore, viruses are capable of aggressive conflict against host cells to deplete their metabolic resources required for viral proliferation. They generate exogenous ncRNAs, dysregulating the expression of hundreds of host genes related to metabolism control. The ncRNAs encoded by a number of these affected genes are an essential part of the virus-induced pathogenic transcriptome in host cells [34].

LncRNA transcripts with poly(A) 3′ ends and 5′-capped terminals [21] seem incapable of encoding proteins. In the human genome, there are 16,193 lncRNAs discovered that could be transcribed from both strands, according to the most current GENCODE V30 release, but only about 3% of annotated lncRNAs have been assigned a function [35, 36]. RNA polymerase II and III are accountable for their transcription and are comparable to mRNAs in terms of evolutionary conservation. However, RNA polymerase II transcribes the bulk of them [30, 37]. LncRNAs have a role in chromosome shaping, miRNA generation, and mRNA suppression [38]. They may interact with proteins, RNA, DNA, or a combination of these molecules to mediate their activities, and their secondary structure and/or sequence might influence the lncRNAs' responsibilities (Fig. **1**) [21].

3. ROLE OF LNCRNAS IN SARS-COV-2 INFECTION

LncRNAs that moderate viral proliferation is categorized into two groups according to their origin: host-encoded lncRNAs and virus-encoded lncRNAs [20]. Host-virus lncRNA interactions typically occur in the cell's cytoplasm, nucleus, and extracellular spaces [38].

In the first stages of viral infection, host cells begin their antiviral response by evolving their lncRNA profile, and after infection, these RNAs express differently. They play a role in signaling pathways regulating the cell cycle, programmed cell death, immune response, and gene expression [21]. In addition, viruses may change the endogenous lncRNA expression of host cells. In contrast, there is no indication that SARS-CoV-2 can generate any long non-coding RNA (lncRNA) [15]. So far, most lncRNA research has been focused on cancer. Meanwhile, innate immunity research on lncRNAs has been poor, accounting for just 4% of all lncRNA articles published so far [19].

The innate immune system contributes to the formation and maturity of the adaptive immune system by acting as a relatively quick response to certain infections by inducing inflammation [39, 40]. Early in the infection process, the SARS-CoV-2 enters T lymphocyte cells and destroys them, leaving patients with severe lymphopenia. As a result, more lymphocytes target the heightened inflammatory responses of the innate and adaptive immune systems, which result in their death [41]. The regulation of the innate antiviral immune response of host cells is mediated by lncRNAs [15].

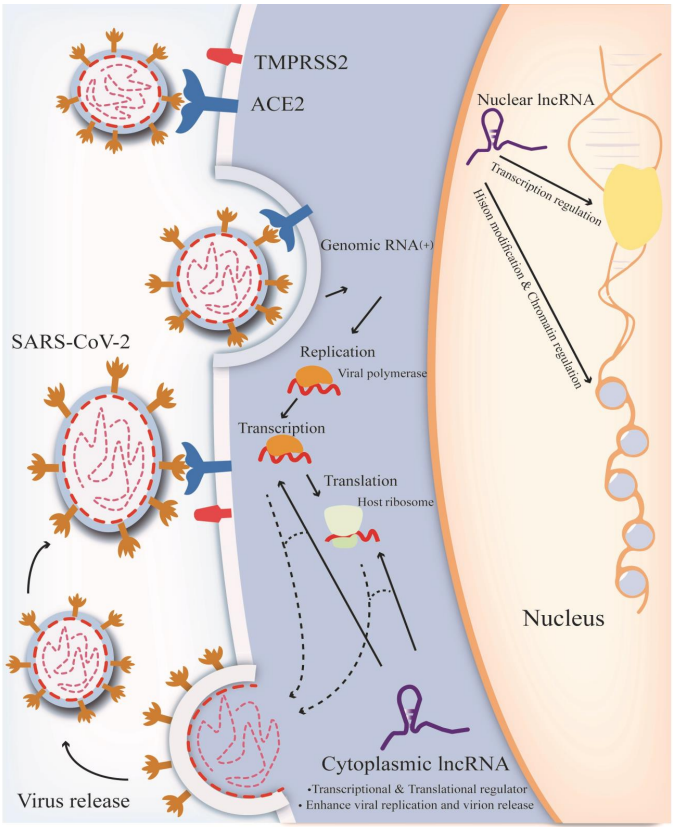

Fig. (1). Functions of nuclear and cytoplasmic lncRNAs. In the nucleus, nuclear lncRNAs interact with chromatin-modifying complexes and gene expression. In the cytoplasm, cytoplasmic lncRNAs enhance viral genome replication, gene expression, protein translation, and virus release.

The expression of lncRNAs is related to type I interferon receptor, signal transducer, and activator of transcription 1 in the same way it occurs in influenza-infected cells [15]. JAK/STAT, NF-KB, HIF-1A, and MAPK are pathways that may regulate the synthesis of interleukins through lncRNAs [32, 42, 43]. In infected cells with SARS-CoV-2, host-derived lncRNAs such as MALAT1 and nuclear-enriched autosomal transcript 1 (NEAT1) may also be used as infection biomarkers [44, 45]. Overexpression of metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) lncRNA was observed in SARS-CoV-2 infection, which is also activated in various neoplastic disorders and post-lung transplant inflammatory conditions [43]. MALAT1 silencing diminishes the occurrence of SARS-CoV-2 patients' cytokine storms by inhibiting neutrophil chemotaxis [43]. The expression of both MALAT1 and NEAT1, which are immunomodulatory lncRNAs, is altered in patients with severe symptoms. A study suggests that NEAT1, MALAT1, and an antiapoptotic lncRNA named MTRNR2L12 are significantly overexpressed in the bronchoalveolar lavage of severe patients, while their expression is suppressed in patients with mild symptoms. NEAT1 is only found in sites of inflammation and infection [46]. On the one hand, MALAT1 seems significantly expressed in CD4+ T cells of individuals with moderate symptoms, illustrating its protective role in T cells. As a vital protein for the COVID-19 virus to enter the body, cathepsin L (CTSL) may be the potential mechanism for the initiation of these lncRNA-mediated inflammatory responses [47].

Another lncRNA linked to virus-induced inflammation is DANCR, indicating a dramatic drop in inflammation-prone lung tissues [48]. It can also regulate the function of catenin beta-1, which is a protein that is linked to respiratory illnesses [49]. Generally, NEAT1 and DANCR can interact with many ncRNAs, sponge miRNAs, and transcription factors such as STAT3 to inhibit inflammation [50]. Through the IL-11/JAK2 pathway, DANCR can activate STAT3, a pro-inflammatory transcription factor [50]. STAT3 triggers IL-1b, IL-6, NFkB1, and SPI-1, which are also transcription factors interacting with TNF, DANCR, and the NEAT1-associated protein DANCR [51 - 54]. Downregulation of DANCR in infected bronchial epithelial cells is linked to a reduced ACE2 level [55].

Because lots of pathways involving miRNAs, lncRNAs, and mRNAs have been reported to have essential roles in characterizing cellular activities in the course of a viral infection, it's vital to study these connections in a unified manner to fully understand the regulatory non-coding RNA networks that underpin SARS-CoV infection [56].

4. ROLE OF MICRORNA IN SARS-COV-2 INFECTION

Viruses are dependent on host cell activity for many stages of their life cycle. The miRNA pathway is an essential part of the host's regulatory system [57]. Viruses may interact with the host miRNA in multiple ways [58]: 1) Host miRNAs that bind directly to the viral RNA and may control viral translation or other elements of the viral life cycle. Some of these miRNAs may have an antiviral impact, allowing the immune system to

combat the disease or causing the virus to enter a dormant condition. 2) The virus may alter host miRNA expression, influencing host or viral RNA targets. 3) Some virus may encode their miRNAs, which control the RNA targets of the host or virus and may alter the host's signaling pathways, allowing the virus to survive and replicate. Some viruses cause infected cells to mutate, so there are many links between viral infection and miRNA expression [59, 60].

To learn the link between miRNA and COVID-19, we must first comprehend the pathogenic mechanism of SARS-CoV-2. Inflammatory cytokines, including interleukin-6 (IL-6), TNF-α, and inflammatory complexes like the inflammasome, are produced due to ACE-mediated SARS-CoV cell entry [61, 62]. The main contributors to the inflammatory cytokine storm appear to be the inflammasome, IL-6, and NOD-like receptor protein 3 (NLRP3) [63, 64]. miRNA analogs suppress the production of proteins related to the COVID-19-mediated cytokine storm [65]. Fabbri *et al*. have discovered that miR-93-5p inhibits the IL-8 gene. They discovered that a) the miR-93-5p level is increased in the cells and b) IL-8 mRNA content and IL-8 output were significantly reduced when pre-miRNA sequences were transfected into different cell lines [66]. According to Oglesby *et al*., interleukin-8 production is reduced when miR-17 is overexpressed in airway epithelial cells [67]. According to Hong *et al*. research, polyethylenimine (PEI) was used to transport plasmid DNA encoding miR-200c into target cells, resulting in increased production of miR-200c and efficient suppression of IL-6, IL-8, and CCL-5. Hong *et al*. also discovered that miR-200c targets the 3'UTR of IL-6, IL-8, and CCL-5 [68].

5. MIRNA AND LNCRNA INTERACTION

MiRNAs can regulate lncRNAs expression. By incorrect base-pairing, RNA-induced silencing complexes (RISCs) may be used to attack lncRNAs, diminishing their morphological and chemical stability [69]. On the other hand, through specific pathways, miRNAs enhance their expression and mature cytoplasmic miRNAs reach the nucleus and influence the transcription of mRNA and ncRNAs [70]. For instance, mature miR-140 in stem cells generated from adipose tissue enhance NEAT1 expression and its stability through binding to particular sites on the NEAT1 locus [71].

Furthermore, viral miRNA can alter the host cell microenvironment by post-transcriptionally regulating many host protein-coding transcripts and lncRNAs [38]. In terms of viral infection, the lncRNA H19 can bind to the let-7 miRNA family, lowering the cell's supply of let-7 and rendering it more susceptible to infection [6]. Many forms of cancer cells have high levels of H19, making them vulnerable to viral infection [7]. The host cell transcriptome is activated during viral infection due to the infected cell's natural immunological response [72].

In turn, lncRNAs can function as miRNA sponges and may be utilized as endogenous RNA that competes with miRNA function [56]. They may bind to target miRNAs in ceRNA networks through miRNA reaction components (MREs), preventing miRNA-mediated degradation of targeted mRNAs [73]. They also produce miRNAs by splicing RNA for post-transcriptional control of mRNAs as miRNA precursors [74]. Consequently, by vying with miRNAs for particular targets, identification, and attachment to the 3'UTR of target mRNAs, lncRNAs may impede miRNA-mediated negative regulation of target mRNAs. However, the function of lncRNAs and miRNAs produced by viruses and host cells in viral infection and their competitive binding to mRNAs remains largely unknown, necessitating additional research [20].

6. CIRCRNA AND LNCRNA IN COVID-19

It has been found that immunological responses of circRNAs and lncRNAs may influence immunological tolerance and immune escape [75, 76]. In a study, authors found 898 differently expressed lncRNA in COVID-19-positive patients, of which 414 were up-regulated and 484 were down-regulated. Furthermore, among 570 circRNAs that had different expressions compared to healthy patients, 155 were up-regulated and 415 were down-regulated. Using circRNA/lncRNA as ceRNA may protect mRNA against microRNA depreciation [77]. LncRNAs affect cis-regulation in signal transduction such as Wnt/βcatenin, Ras, mTOR, and interleukin-1 mediated signaling pathways, which can affect transport, cell migration, phosphorylation of proteins, and protein transcription *via* repressing transcription factors. Furthermore, lncRNA expression in trans-regulation impacts drug metabolism. It also helps the host's natural immunity by affecting the assembly of the NLRP3 inflammasome complex [77].

7. LNCRNA AND EXOSOMES RELATIONSHIP

Studies also suggest that exosomes have a crucial function in viral infection [78]. Exosomes are small membrane vesicles that vary between 30 and 150 nm, carrying RNA and protein complexes in eukaryotic cells into the extracellular matrix [77]. Immune response, antigen presentation, cell proliferation, diversification, cancer development, and other processes may all be impacted by them, depending on the cell type from which they emerge. Exosomes can carry viral nucleic acid and proteins and can change the microenvironment, enabling diseases to propagate quickly [77]. Coronavirus-infected cells generate exosomes and may also export the SARS-CoV-2 invasion receptor (ACE2), rendering uninfected cells susceptible to virus loading [79]. CircRNA and lncRNA variants linked to exosomes were discovered in SARS-CoV-2 infected cells. Therefore, it has been proposed that exosomes might be used in COVID-19 treatment. A few studies have found that the composition of exosomes differs before and after infection, indicating that exosomes may be involved in developing new diseases. These exosomes contain 114 differently expressed circRNAs and 10 differentially expressed lncRNAs [80, 81].

8. LNCRNAS INTERACTION WITH IMMUNE SYSTEM COMPONENTS IN SARS-COV-2 INFECTION

The current SARS-CoV-2 pandemic's high morbidity and death required the development of efficient therapeutic techniques to fight the pathogenesis of SARS-CoV-2 [82, 83]. According to studies on SARS-CoV-infected humans and animals, the virus's fatal pneumonia may be linked to immune-

pathological processes [84 - 86]. The significant COVID-19 pathology and rising clinical symptoms may be due to inflammation and cytokine storm [82, 83].

Multiple studies have shown that cytokines such as IL-1, IL-6, IL-12, IL-18, TNF, IFN, and other inflammatory mediators, are released uncontrollably in "Cytokine Release Syndrome" or CRS, which is believed to be linked to severe COVID-19 [87]. It is noteworthy that the function of these components of the immune system is through non-coding RNAs such as lncRNAs [32]. The INK4 gene's antisense non-coding RNA (ANRIL), which forms an endogenous competitive RNA, has been linked to inflammatory responses [88, 89].

8.1. IL-6 secretion-related lncRNAs

IL-6, a multifunctional cytokine that promotes acute inflammatory responses, influences many cancer types as well as viral infections [90, 91]. lncRNAs regulate IL-6 synthesis through several mechanisms involving JAK/STAT, NF-κB, HIF-1, and MAPK (Fig. **2**) [92 - 95]. As an example, MALAT1 (metastasis-associated lung adenocarcinoma miRNA 1), also known as NEAT2, has been discovered to have a dual function in various signaling pathways, especially IL6 [96].

The Janus kinase/signal transducers and activators of transcription (JAK-STATA) are downstream signaling pathways that are triggered by IL-6 (STAT1,3, and 5), which affect immunological processes [97, 98]. Nuclear factor kappa-B (NF-κB) is important for IL-6 secretion and modulation of NF-κB, a major transcription factor of IL-6 that has been shown in preclinical trials to suppress SARS-CoV [99]. LncRNAs may influence IL-6 expression in a myriad of contexts, one of which is NF-κB [92 - 94]. Another long intergenic non-coding RNA (lincRNA) linked with inflammatory events through the NF-κB pathway is Gm4419 [100].

8.2. NLRP3 inflammasome Development by lncRNAs

The growing body of evidence indicates that inflammasome formation is aided by lncRNAs, which are linked to promoting severe diseases [101, 102]. The NLRP3 inflammasome is activated against infectious pathogens such as SARS-CoV-2, producing IL-1 and IL-18 [32, 62, 103]. Two different signaling pathways activate the NLRP3 inflammasome. First, pro-IL-1 and NLRP3 are enhanced by microbial compounds that recognize TLRs or cytokines and stimulate NF-κB. Pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs) activate the secondary pathway, resulting in the construction of ASC and pro-caspase-1 and, as a result, the stimulation of the NLRP3 inflammasome [104, 105]. Therefore, it's becoming apparent that anti-NLRP3 inflammasome medications may benefit patients with inflammatory illnesses by reducing inflammatory responses [106 - 108].

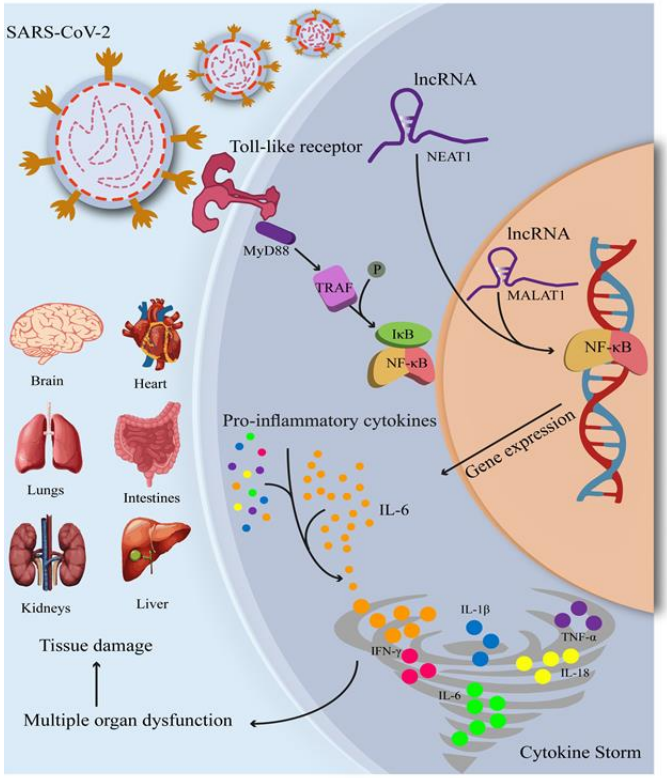

Fig. (2). This schematic illustration shows that lncRNAs such as MALAT1 and NEAT1 are involved in inflammatory responses that increase the production of IL6 and lead to cytokine storms.

NEAT1 (nuclear enriched abundant transcript 1) has been associated with several different malignancies, including cancers such as prostate, cervical, and breast cancer [109]. Furthermore, LPS-stimulated immortalized bone marrow-derived macrophages (iBMDMs) enhanced NEAT1 translocation in the nucleus and cytoplasm, resulting in inflammasome assembly, caspase one activation, and inflammatory cytokine response, highlighting NEAT1's inflammatory role [45].

9. INFLAMMATION AND CYTOKINE STORMS: THE ROLE OF MICRORNAS

Ariana Centa *et al*. believe that microRNAs are involved in endothelial function in individuals suffering from serious respiratory problems and thrombotic complications in post-mortem lung tissues. The findings of a study indicate that miR (-26a-5p,-29b-3p, and-34a-5p) recognize mRNA targets implicated in endothelial and inflammatory signaling pathways as regulators, as well as viral diseases. Based on miRNA targets, protein-protein interactions, and inflammatory indicators found in the patients, the miRNA/mRNA network showed a strong relationship between these miRNAs and endothelial activation/dysfunction. MiR-26a-5p [IL-6 and ICAM-1] and miR-29b-3p [IL-4 and IL-8] have a significant relationship with inflammatory biomarkers in COVID-19 patients. The results showed miR (-26a-5p, -29b-3p, and -34a-5p) endothelial dysfunction and inflammatory response in people infected with SARS-CoV-2, as well as the development of severe lung damage and immunothrombosis [110].

The rapid and widespread edema and fibrosis that occur during the remodeling process and eventual airway clogs are undoubtedly caused by uncontrollable and abrupt increases in TGF-β [111]. MiR-27a-3p regulates TGF function, inhibits the TGF-β /Smad pathway, and suppresses myofibroblast development by regulating Smad2 and Smad4 activity [58].

Jacopo Sabbatinelli *et al*. predicted that COVID-19 severity is related to inflammation. They analyzed samples from COVID-19 individuals with multifocal interstitial pneumonia to examine their reaction to a single intravenous infusion of tocilizumab, an anti-IL-6 receptor drug (TCZ). They evaluated a set of microRNAs that control inflammation, miR-146a-5p, miR-21-5p, and miR-126-3p, with RT-PCR and Droplet Digital PCR techniques. As a result, COVID-19 patients who did not respond to TCZ exhibited lower blood levels of miR-146a-5p and they had the poorest outcomes. These findings suggest that a blood-based biomarker like miR-146a-5p may provide insight into the molecular link between inflammation and the clinical course of COVID-19, allowing us to understand better how to use biological drug armament to fight this global health issue [112].

In nanoparticle technology, using cerium oxide nanoparticles (CNP) allows unstable medicines, such as the anti-inflammatory microRNA-146a, to be administered locally to the damaged lung without causing systemic absorption. In a study, the intrathecal injection of CNP-miR146a showed an improvement in lung biomechanics by decreasing inflammation and oxidative stress *via* modulating leukocyte recruitment and reducing collagen deposition [113].

According to recent research, the IL-6/IL-6R pathway is a significant contributor to symptom-related cytokine storms. Downregulation of miR-451a may increase IL-6R protein production. In COVID-19 patients, three up-regulated long non-coding RNAs (lncRNAs) with miR-451a binding sites may act as miRNA sponges, competing with IL-6R for miR-451a. These results help researchers identify therapeutic targets for this novel illness [114].

Dharmendra Kumar Soni *et al*. investigated the pathogenicity of SARS-CoV-2 infection by examining the function of the most potent antiviral reactions in the host and immunological and inflammatory responses. The efficacy of anti-miR-155 treatment was tested in a COVID-19 animal model (mice transgenic for human angiotensin I-converting enzyme two receptors). Their findings show that male models had higher levels of viral loads and miR-155 than female ones. Furthermore, they found that treating SARS-CoV-2-infected mice with anti-miR-155 lowers miR-155 expression and improves survival and clinical outcomes. Anti-miR-155-treated mice hACE2 infected with SARS-CoV-2 exhibited improved antiviral and anti-inflammatory cytokine responses and reduced levels of pro-inflammatory cytokines [115].

In the latest research, differentially expressed circulating miRNAs have been recognized as viable biomarkers for understanding the severity of the disease in the Brazilian population using high-throughput sequencing to detect miRNA expression levels. A total of 18 human miRNAs were expressed differently in COVID-19 patients, with 13 miRNAs being substantially elevated and 5 miRNAs being considerably downregulated. Moreover, miR (-4433b-5p, -6780b-3p, -6883-3p, -320b, -7111-3p, -4755-3p,-320c, and miR-6511a-3p) were shown to be significantly involved in the PI3K/AKT, Wnt/-catenin, and STAT3 signaling pathways, all of which are essential in viral infections. MiR-451a, -101-3p, -185-5p, -30d-5p, -25-3p, -342-3p, -30e-5p, -150-5p, 15b-5p, and 29c-3p were the most significant miRNAs found to be engaged in the Wnt/-catenin, NF- κB, and STAT3 signaling pathways, which play critical roles in immune response and inflammation. However, further studies are required to confirm these miRNAs as COVID-19 biomarkers [116].

9.1. MicroRNAs as Biomarkers for the Acute and Post-acute Phases of COVID-19

The outcomes of a real-time PCR assay were used to assess the expression level of selected miRNAs such as let-7b-3p, miR-29a-3p, -146a-3p, and 155-5p in peripheral blood mononuclear cells (PBMCs) of COVID-19 patients, in both acute and post-acute phases, and healthy controls. In COVID-19 patients, receiver operating characteristic analysis [86] was used to assess the specificity and sensitivity of miRNAs. All miRNAs were expressed at greater levels in COVID-19 patients. As a result, the expression patterns of miR-29a-3p, miR-146a-3p, and let-7b-3p were substantially different in the post-acute COVID-19 phase compared to the acute COVID-19 phase. ROC analysis recognized MiR-29a-3p, -155-5p, and -146a-3p as new biomarkers for COVID-19 diagnosis with excellent specificity and sensitivity. Furthermore, miR-29a-3p and -146a-3p may be used as novel

biomarkers to differentiate between the acute and post-acute phases of COVID-19 [117].

9.2. MicroRNAs can Regulate the Expression of ACE2 and TMPRSS2 Receptor Genes

Zhi Liu *et al*. investigate the role of miRNAs in virus-induced dysregulation. According to their results, infection-modulated miRNAs regulate two of the most important biological processes: the immune response and cytoskeleton structure [118]. The control of cellular components, molecular activities, and biological processes was used to group all of the differentially expressed miRNA target genes, as determined *via* cluster analysis. According to enrichment analyses, peptidase, protein kinases, and the ubiquitin system exhibited the highest enrichment values [119]. SARS-CoV-2 enters cells by latching on to the receptor ACE2 with the spike (S) protein *via* the host serine protease TMPRSS2, which allows viral and cellular membranes to merge (Fig. **3**) [55].

Given the significance of cellular receptors, particularly ACE2, in SARS-CoV-2 infection, Sardar *et al*. discovered that miRNA 27b controls the ACE2 receptor [120]. According to the findings of Chauhan *et al*., miRNA 200b-3p, miRNA 200c-3p, and miRNA 429 can inhibit ACE2, whereas let-7c-5p, miRNA 98-5p, let-7 f-5p, let-7 a-5p, let-7 g-5p, let-7 g-5p, let-7b-5p, miRNA 4458, let-7e-5p, let-7i-5p, let-7d-5p, and miRNA 4 can increase the expression of ACE2. Increased expression of the ACE2 receptor is observed in patients with metabolic syndrome, diabetes, and heart disease. Therefore, inhibiting the ACE2 receptor with miRNAs may be an effective treatment option for COVID-19 infection [121].

In addition to miRNAs that directly interact with the viral genome, host miRNAs that target ACE2 may play a role in regulating SARS-CoV-2 infection. In addition, a large number of miRNAs targeting the 3′-UTR of ACE2 in humans were discovered. All three online miRNA prediction algorithms found six miRNAs (miR-362-5p, miR-421, 500a-5p, 500b-5p, miR-3909, and 4766-5p). MiR-421 has already been identified as a possible ACE2 regulator, which is interesting [122].

There has been evidence of miRNA dysregulation in patients with SARS-CoV-2, which may cause changes in the genes controlled by miRNAs [41]. High-throughput sequencing was used to assess the expression levels of different miRNAs, and correlation analysis was used to discover the miRNA-primed target genes. Compared to healthy controls, 35 miRNAs were up-regulated and 38 miRNAs were downregulated in COVID-19 patients. The production of miR (6501-5p and 618) was 1.5-fold higher in COVID-19 patients as compared with healthy control donors. A 2.3-fold reduction in miR-627-5p, on the other hand, was seen in comparison to the controls. There was a 1.3-fold reduction in the expression of other miRNAs (miR-183-5p, 627-5p, and 1443-3p) compared to healthy donors. They found that hsa-miR-4661-3p, a virus-encoded miRNA, SARS-S CoV-2's gene was anticipated to be the target [118].

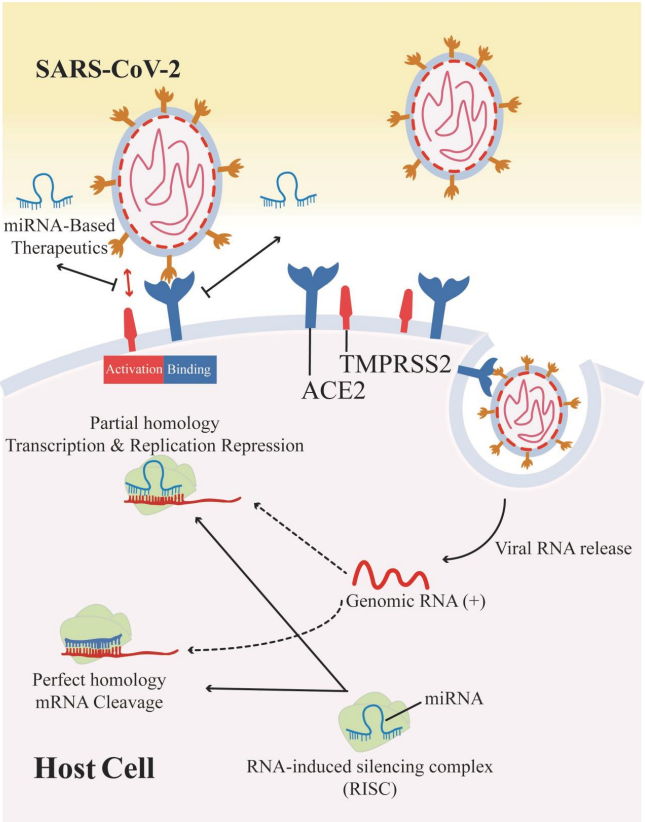

Fig. (3). Potential treatment targets for SARS-CoV-2 infection inhibition include microRNAs, which prevent viral entry and replication.

According to a study, SARS-CoV-2 needed miR-200c to connect ACE2 receptors in cardiomyocytes [123]. To identify common regions and coronavirus 2 genes linked to SARS (Severe Acute Respiratory Syndrome), Abolfazl Bahrami and Maryam Bakherad retrieved the entire genomes of all viruses identified in databases for this family (55 genomes in all) and conducted comparative genomic research on them. RELA in the viral genome and ACE2 receptors and CLEC4M genes in the host genome were the most significant genes implicated in the illness. RELA gene was reduced by hsa-miR (516b-3p, 3529-3p, and 6749-3p), ACE2 receptor was inhibited by hsa-miR (23b-5p and 769-5p), and CLEC4M gene was repressed by hsa-miR (4462 and 5187-5p). As a consequence, their findings will aid in the management and treatment of COVID-19, as well as provide fresh insight into vaccine design and miRNA therapy [124].

The NF-κB pathway activation raises the expression of miR-200c-3p, which is a key factor in ARDS. The increased miR-200c-3p expression has been linked to a reduction in ACE2 expression. In certain COVID-19 instances, reduced ACE2 expression in the lungs and upper respiratory tract may be related to decreased disease severity. As a result, it is postulated that bacterial LPS and LTA may lower ACE2 expression in COVID-19 patients' lungs *via* up-regulating miR-200c-3p [125, 126].

Transmembrane serine protease 2 (TMPRSS2) has an important role in mediating viruses, and SARS-CoV-2 employs TMPRSS2 for viral entry [127]. SARS-CoV-2 can encode miRNAs that promote TMPRSS2 overexpression, and Mir-147-3p can increase SARS-CoV-2 infection in the gut by boosting the synthesis of TMPRSS2 [118]. However, miRNAs may be used as molecular tools to prevent SARS-CoV-2 viral transmission and replication in humans since they have a strong affinity for TMPRSS2 and may block this receptor [128]. TMPRSS2 diminution mediated by miRNA for early COVID-19 prevention has been established in the laboratory for early COVID-19 prophylaxis. TMPRSS2 binding was examined in a pool of 163 miRNAs using three miRNA prediction methods, yielding 11 common miRNAs. Furthermore, negative computational energies for association confirmed miRNA-Tmprss2 interactions, while the S fold tool identified three miRNAs (hsa-miR-214, hsa-miR-98, and hsa-miR-32) based on likelihood scores of 0.8 and accessibility to the Tmprss2 target. Transfection of miRNA(s) into Caco-2 cells, quantitative differential expression analysis, and confirmation of Tmprss2 silencing with maximal gene suppression by hsa-miR-32, is a new potential function in CoV-2 pathogenesis [128].

CONCLUSION

Many of the strategic uses of non-coding RNAs to promote SARS-CoV-2 may be unrecognized. As a result of viral infections, the regulation of lncRNAs occurs irregularly, and many host functions are improperly regulated, leading to the development of viral infection. Human non-coding RNAs are influenced by viral infection as viral proteins interact intimately with their host proteome. On the other hand, A low-scale approach to studying non-coding RNAs in response to SARS-CoV-2 infection could be inappropriate in the present circumstances. We introduced many lncRNAs with altered expression levels during viral infection, which may serve as biomarkers. However, their specific role in response to the virus is yet to understand.

Furthermore, microRNAs play significant roles in COVID-19, and the presented strategies might lead to the creation of procedures for reducing the expression of critical COVID-19 "cytokine storm" components. The characteristics of lncRNA and miRNA can be employed in the treatment and diagnosis of patients with the SARS-CoV-2 virus. However, additional studies are required.

LIST OF ABBREVIATIONS

ncRNAs	=	non-coding RNAs
COVID-19	=	Coronavirus Disease 2019
ceRNAs	=	Competing for Endogenous RNAs

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

None declared.

REFERENCES

[1] Feathers L, Hinde T, Bale T, *et al.* Outbreak of SARS-CoV-2 at a hospice: terminated after the implementation of enhanced aerosol infection control measures. Interface Focus 2022; 12(2): 20210066. [http://dx.doi.org/10.1098/rsfs.2021.0066] [PMID: 35261730]

[2] Cascella M, Rajnik M, Aleem A, Dulebohn S, Di Napoli R. Features, evaluation, and treatment of coronavirus (COVID-19). StatPearls Publishing 2021.

[3] Yasamineh S, Kalajahi H G, Yasamineh P, *et al.* Spotlight on therapeutic efficiency of mesenchymal stem cells in viral infections with a focus on COVID-19. Stem Cell Research & Therapy 2022; 13(1): 257. [http://dx.doi.org/10.1186/s13287-022-02944-7]

[4] Arora S, Singh P, Dohare R, Jha R, Ali Syed M. Unravelling host-pathogen interactions: ceRNA network in SARS-CoV-2 infection (COVID-19). Gene 2020; 762: 145057. [http://dx.doi.org/10.1016/j.gene.2020.145057] [PMID: 32805314]

[5] Zimmer K. Why Some Covid-19 cases are worse than others. Scientist 2020. Available from: https://www.the-scientist.com/news-opinion/why-some-covid-19-cases-are-worse-than-others-67160

[6] Pontecorvi G, Bellenghi M, Ortona E, Carè A. microRNAs as new possible actors in gender disparities of Covid-19 pandemic.Acta Physiologica 2020; 230(1): e13538. [http://dx.doi.org/10.1111/apha.13538] [PMID: 32672403]

[7] Henzinger H, Barth D, Klec C, Pichler M. Non-coding RNAs and SARS-related coronaviruses. Viruses 2020; 12(12): 1374. [http://dx.doi.org/10.3390/v12121374] [PMID: 33271762]

[8] Ferrè F, Colantoni A, Helmer-Citterich M. Revealing protein–lncRNA interaction. Brief Bioinform 2016; 17(1): 106-16. [http://dx.doi.org/10.1093/bib/bbv031] [PMID: 26041786]

[9] Florindo HF, Kleiner R, Vaskovich-Koubi D, *et al.* Immune-mediated approaches against COVID-19. Nat Nanotechnol 2020; 15(8): 630-45.

[http://dx.doi.org/10.1038/s41565-020-0732-3] [PMID: 32661375]

[10] Zhang S, Amahong K, Sun X, *et al.* The miRNA: a small but powerful RNA for COVID-19. Brief Bioinform 2021; 22(2): 1137-49. [http://dx.doi.org/10.1093/bib/bbab062] [PMID: 33675361]

[11] Mercer TR, Dinger ME, Mattick JS. Long non-coding RNAs: insights into functions. Nat Rev Genet 2009; 10(3): 155-9. [http://dx.doi.org/10.1038/nrg2521] [PMID: 19188922]

[12] Chen J, Ao L, Yang J. Long non-coding RNAs in diseases related to inflammation and immunity. Ann Transl Med 2019; 7(18): 494. [http://dx.doi.org/10.21037/atm.2019.08.37] [PMID: 31700930]

[13] Geng H, Tan XD. Functional diversity of long non-coding RNAs in immune regulation. Genes Dis 2016; 3(1): 72-81. [http://dx.doi.org/10.1016/j.gendis.2016.01.004] [PMID: 27617274]

[14] Taft RJ, Pang KC, Mercer TR, Dinger M, Mattick JS. Non-coding RNAs: Regulators of disease. J Pathol 2010; 220(2): 126-39. [http://dx.doi.org/10.1002/path.2638]

[15] Peng X, Gralinski L, Armour CD, *et al.* Unique signatures of long noncoding RNA expression in response to virus infection and altered innate immune signaling. MBio 2010; 1(5): e00206-10. [http://dx.doi.org/10.1128/mBio.00206-10] [PMID: 20978541]

[16] Josset L, Tchitchek N, Gralinski LE, *et al.* Annotation of long non-coding RNAs expressed in Collaborative Cross founder mice in response to respiratory virus infection reveals a new class of interferon-stimulated transcripts. RNA Biol 2014; 11(7): 875-90. [http://dx.doi.org/10.4161/rna.29442] [PMID: 24922324]

[17] Alvarez-Garcia I, Miska EA. MicroRNA functions in animal development and human disease. Development 2005; 132(21): 4653-62. [http://dx.doi.org/10.1242/dev.02073] [PMID: 16224045]

[18] He L, Hannon GJ. MicroRNAs: small RNAs with a big role in gene regulation. Nat Rev Genet 2004; 5(7): 522-31. [http://dx.doi.org/10.1038/nrg1379] [PMID: 15211354]

[19] Robinson EK, Covarrubias S, Carpenter S. The how and why of lncRNA function: An innate immune perspective. Biochim Biophys Acta Gene Regul Mech 2020; 1863(4): 194419. [http://dx.doi.org/10.1016/j.bbagrm.2019.194419] [PMID: 31487549]

[20] Chen L, Zhou Y, Li H. LncRNA, miRNA and lncRNA-miRNA interaction in viral infection. Virus Res 2018; 257: 25-32. [http://dx.doi.org/10.1016/j.virusres.2018.08.018] [PMID: 30165080]

[21] Hu B, Huo Y, Yang L, *et al.* ZIKV infection effects changes in gene splicing, isoform composition and lncRNA expression in human neural progenitor cells. Virol J 2017; 14(1): 217. [http://dx.doi.org/10.1186/s12985-017-0882-6] [PMID: 29116029]

[22] Palanisamy V, Jakymiw A, Van Tubergen EA, D'Silva NJ, Kirkwood KL. Control of Cytokine mRNA Expression by RNA-binding Proteins and microRNAs. J Dent Res 2012; 91(7): 651-8. [http://dx.doi.org/10.1177/0022034512437372] [PMID: 22302144]

[23] Xiao M, Li J, Li W, *et al.* MicroRNAs activate gene transcription epigenetically as an enhancer trigger. RNA Biol 2017; 14(10): 1326-34. [http://dx.doi.org/10.1080/15476286.2015.1112487] [PMID: 26853707]

[24] Ramchandran R, Chaluvally-Raghavan P. "miRNA-mediated RNA activation in mammalian cells," RNA activation. Springer 2017; pp. 81-9.

[25] Bandiera S, Pfeffer S, Baumert TF, Zeisel MB. miR-122 – A key factor and therapeutic target in liver disease. J Hepatol 2015; 62(2): 448-57. [http://dx.doi.org/10.1016/j.jhep.2014.10.004] [PMID: 25308172]

[26] Sarkar N, Chakravarty R. Hepatitis B virus infection, microRNAs and liver disease. Int J Mol Sci 2015; 16(8): 17746-62. [http://dx.doi.org/10.3390/ijms160817746] [PMID: 26247932]

[27] Li X, Zou X. An overview of RNA virus-encoded microRNAs. ExRNA 2019; 1(1): 37. [http://dx.doi.org/10.1186/s41544-019-0037-6] [PMID: 34171007]

[28] Kincaid RP, Sullivan CS. Virus-encoded microRNAs: an overview and a look to the future. PLoS Pathog 2012; 8(12): e1003018. [http://dx.doi.org/10.1371/journal.ppat.1003018] [PMID: 23308061]

[29] Schubert S, Kurreck J. Oligonucleotide-based antiviral strategies. Handb Exp Pharmacol 2006; 173(173): 261-87.

[30] Liu W, Ding C. Roles of LncRNAs in viral infections. Front Cell Infect Microbiol 2017; 7: 205. [http://dx.doi.org/10.3389/fcimb.2017.00205] [PMID: 28603696]

[31] Ray RM, Morris KV. Long non-coding RNAs mechanisms of action in hiv-1 modulation and the identification of novel therapeutic targets. Noncoding RNA 2020; 6(1): 12. [http://dx.doi.org/10.3390/ncrna6010012] [PMID: 32183241]

[32] Paniri A, Akhavan-Niaki H. Emerging role of IL-6 and NLRP3 inflammasome as potential therapeutic targets to combat COVID-19: Role of lncRNAs in cytokine storm modulation. Life Sci 2020; 257: 118114. [http://dx.doi.org/10.1016/j.lfs.2020.118114] [PMID: 32693241]

[33] Lai CC, Shih TP, Ko WC, Tang HJ, Hsueh PR. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): The epidemic and the challenges. Int J Antimicrob Agents 2020; 55(3): 105924. [http://dx.doi.org/10.1016/j.ijantimicag.2020.105924] [PMID: 32081636]

[34] Yogev O, Henderson S, Hayes MJ, *et al.* Herpesviruses shape tumour microenvironment through exosomal transfer of viral microRNAs. PLoS Pathog 2017; 13(8): e1006524. [http://dx.doi.org/10.1371/journal.ppat.1006524] [PMID: 28837697]

[35] Derrien T, Johnson R, Bussotti G, *et al.* The GENCODE v7 catalog of human long noncoding RNAs: Analysis of their gene structure, evolution, and expression. Genome Res 2012; 22(9): 1775-89. [http://dx.doi.org/10.1101/gr.132159.111] [PMID: 22955988]

[36] Villegas V, Zaphiropoulos P. Neighboring gene regulation by antisense long non-coding RNAs. Int J Mol Sci 2015; 16(2): 3251-66. [http://dx.doi.org/10.3390/ijms16023251] [PMID: 25654223]

[37] Guttman M, Amit I, Garber M, *et al.* Chromatin signature reveals over a thousand highly conserved large non-coding RNAs in mammals. Nature 2009; 458(7235): 223-7. [http://dx.doi.org/10.1038/nature07672] [PMID: 19182780]

[38] Wower IK, Brandebourg TD, Wower J. New insights on the mobility of viral and host non-coding RNAs reveal extracellular vesicles as intriguing candidate antiviral targets. Pathogens 2020; 9(11): 876. [http://dx.doi.org/10.3390/pathogens9110876] [PMID: 33114356]

[39] Jiménez-Dalmaroni MJ, Gerswhin ME, Adamopoulos IE. The critical role of toll-like receptors - From microbial recognition to autoimmunity: A comprehensive review. Autoimmun Rev 2016; 15(1): 1-8. [http://dx.doi.org/10.1016/j.autrev.2015.08.009] [PMID: 26299984]

[40] Brubaker SW, Bonham KS, Zanoni I, Kagan JC. Innate immune pattern recognition: a cell biological perspective. Annu Rev Immunol 2015; 33(1): 257-90. [http://dx.doi.org/10.1146/annurev-immunol-032414-112240] [PMID: 25581309]

[41] Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19): a review. JAMA 2020; 324(8): 782-93. [http://dx.doi.org/10.1001/jama.2020.12839] [PMID: 32648899]

[42] Turjya RR, Khan MA, Khademul IAB. Perversely expressed long noncoding RNAs can alter host response and viral proliferation in SARS-CoV-2 infection. Future Virol 2020; 15(9): 577-93. [http://dx.doi.org/10.2217/fvl-2020-0188] [PMID: 33224264]

[43] Vishnubalaji R, Shaath H, Alajez NM. Protein coding and long noncoding RNA (lncRNA) transcriptional landscape in SARS-CoV-2 infected bronchial epithelial cells highlight a role for interferon and inflammatory response. Genes 2020; 11(7): 760. [http://dx.doi.org/10.3390/genes11070760] [PMID: 32646047]

[44] Zhan JF, Huang HW, Huang C, Hu LL, Xu WW. Long non-coding RNA NEAT1 regulates pyroptosis in diabetic nephropathy *via* mediating the miR-34c/NLRP3 Axis. Kidney Blood Press Res 2020; 45(4): 589-602. [http://dx.doi.org/10.1159/000508372] [PMID: 32721950]

[45] Zhang P, Cao L, Zhou R, Yang X, Wu M. The lncRNA Neat1 promotes activation of inflammasomes in macrophages. Nat Commun 2019; 10(1): 1495. [http://dx.doi.org/10.1038/s41467-019-09482-6] [PMID: 30940803]

[46] Huang K, Wang C, Vagts C, Raguveer V, Finn PW, Perkins DL. LncRNAs NEAT1 and MALAT1 differentiate inflammation in severe COVID-19 patients MedRxiv 21254445.2021;

[47] Bittmann S, Weissenstein A, Villalon G, Moschuring-Alieva E, Luchter E. Simultaneous treatment of COVID-19 with serine protease inhibitor camostat and/or cathepsin L inhibitor? J Clin Med Res 2020; 12(5): 320-2. [http://dx.doi.org/10.14740/jocmr4161] [PMID: 32489508]

[48] Wang N, Zhang C, Wang W, *et al.* Long noncoding RNA DANCR regulates proliferation and migration by epigenetically silencing FBP1 in tumorigenesis of cholangiocarcinoma. Cell Death Dis 2019; 10(8): 585. [http://dx.doi.org/10.1038/s41419-019-1810-z] [PMID: 31383847]

[49] Meydan C, Madrer N, Soreq H. The neat dance of COVID-19:

NEAT1, DANCR, and Co-modulated cholinergic rnas link to inflammation. Front Immunol 2020; 11: 590870. [http://dx.doi.org/10.3389/fimmu.2020.590870] [PMID: 33163005]

[50] Chen Z, Chen X, Xie R, *et al.* DANCR promotes metastasis and proliferation in bladder cancer cells by enhancing IL-11-STAT3 signaling and CCND1 expression. Mol Ther 2019; 27(2): 326-41. [http://dx.doi.org/10.1016/j.ymthe.2018.12.015] [PMID: 30660488]

[51] Hallier M, Tavitian A, Moreau-Gachelin F. The transcription factor Spi-1/PU.1 binds RNA and interferes with the RNA-binding protein p54nrb. J Biol Chem 1996; 271(19): 11177-81. [http://dx.doi.org/10.1074/jbc.271.19.11177] [PMID: 8626664]

[52] Lee H, Herrmann A, Deng JH, *et al.* Persistently activated Stat3 maintains constitutive NF-kappaB activity in tumors. Cancer Cell 2009; 15(4): 283-93. [http://dx.doi.org/10.1016/j.ccr.2009.02.015] [PMID: 19345327]

[53] Samavati L, Rastogi R, Du W, Hüttemann M, Fite A, Franchi L. STAT3 tyrosine phosphorylation is critical for interleukin 1 beta and interleukin-6 production in response to lipopolysaccharide and live bacteria. Mol Immunol 2009; 46(8-9): 1867-77. [http://dx.doi.org/10.1016/j.molimm.2009.02.018] [PMID: 19299019]

[54] Yu J, Wang Y, Yan F, *et al.* Noncanonical NF-κB activation mediates STAT3-stimulated IDO upregulation in myeloid-derived suppressor cells in breast cancer. J Immunol 2014; 193(5): 2574-86. [http://dx.doi.org/10.4049/jimmunol.1400833] [PMID: 25063873]

[55] Hoffmann M, Kleine-Weber H, Schroeder S, *et al.* SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 2020; 181(2): 271-80. [http://dx.doi.org/10.1016/j.cell.2020.02.052]

[56] Yousefi H, Poursheikhani A, Bahmanpour Z, *et al.* SARS-CoV infection crosstalk with human host cell noncoding-RNA machinery: An *in-silico* approach. Biomed Pharmacother 2020; 130: 110548. [http://dx.doi.org/10.1016/j.biopha.2020.110548] [PMID: 33475497]

[57] Umbach JL, Cullen BR. The role of RNAi and microRNAs in animal virus replication and antiviral immunity. Genes Dev 2009; 23(10): 1151-64. [http://dx.doi.org/10.1101/gad.1793309] [PMID: 19451215]

[58] Dong M, Wang X, Li T, *et al.* Mir-27a-3p attenuates bronchiolitis obliterans *in vivo via* the regulation of dendritic cells' maturation and the suppression of myofibroblasts' differentiation. Clin Transl Med 2020; 10(4): e140. [http://dx.doi.org/10.1002/ctm2.140] [PMID: 32898329]

[59] Roberts APE, Lewis AP, Jopling CL. The role of microRNAs in viral infection. Prog Mol Biol Transl Sci 2011; 102: 101-39. [http://dx.doi.org/10.1016/B978-0-12-415795-8.00002-7] [PMID: 21846570]

[60] Barbu MG, Condrat CE, Thompson DC, *et al.* MicroRNA involvement in signaling pathways during viral infection. Front Cell Dev Biol 2020; 8: 143. [http://dx.doi.org/10.3389/fcell.2020.00143] [PMID: 32211411]

[61] Conti P, Ronconi G, Caraffa A, *et al.* Induction of pro-inflammatory cytokines (IL-1 and IL-6) and lung inflammation by Coronavirus-19 (COVI-19 or SARS-CoV-2): anti-inflammatory strategies. J Biol Regul Homeost Agents 2020; 34(2): 327-31. [PMID: 32171193]

[62] Nieto-Torres JL, Verdiá-Báguena C, Jimenez-Guardeño JM, *et al.* Severe acute respiratory syndrome coronavirus E protein transports calcium ions and activates the NLRP3 inflammasome.Virology. 330-9. 2015; 485: pp. [http://dx.doi.org/10.1016/j.virol.2015.08.010]

[63] Tay MZ, Poh CM, Rénia L, MacAry PA, Ng LFP. The trinity of COVID-19: immunity, inflammation and intervention. Nat Rev Immunol 2020; 20(6): 363-74. [http://dx.doi.org/10.1038/s41577-020-0311-8] [PMID: 32346093]

[64] Tufan A, Avanoğlu Güler A, Matucci-Cerinic M. COVID-19, immune system response, hyperinflammation and repurposing antirheumatic drugs. Turk J Med Sci 2020; 50(SI-1): 620-32. [http://dx.doi.org/10.3906/sag-2004-168] [PMID: 32299202]

[65] Gasparello J, Finotti A, Gambari R. Tackling the COVID-19 "cytokine storm" with microRNA mimics directly targeting the 3'UTR of pro-inflammatory mRNAs. Med Hypotheses 2021; 146: 110415-5. [http://dx.doi.org/10.1016/j.mehy.2020.110415] [PMID: 33422363]

[66] Fabbri E, Borgatti M, Montagner G, *et al.* Expression of microRNA-93 and Interleukin-8 during *Pseudomonas aeruginosa* mediated induction of proinflammatory responses. Am J Respir Cell Mol Biol 2014; 50(6): 1144-55. [http://dx.doi.org/10.1165/rcmb.2013-0160OC] [PMID: 24433094]

[67] Oglesby IK, Vencken SF, Agrawal R, *et al.* miR-17 overexpression in cystic fibrosis airway epithelial cells decreases interleukin-8 production. Eur Respir J 2015; 46(5): 1350-60. [http://dx.doi.org/10.1183/09031936.00163414] [PMID: 26160865]

[68] Hong L, Sharp T, Khorsand B, *et al.* MicroRNA-200c represses IL-6, IL-8, and CCL-5 expression and enhances osteogenic differentiation. PLoS One 2016; 11(8): e0160915. [http://dx.doi.org/10.1371/journal.pone.0160915] [PMID: 27529418]

[69] Ballantyne MD, McDonald RA, Baker AH. lncRNA/MicroRNA interactions in the vasculature. Clin Pharmacol Ther 2016; 99(5): 494-501. [http://dx.doi.org/10.1002/cpt.355] [PMID: 26910520]

[70] Liang H, Zhang J, Zen K, Zhang CY, Chen X. Nuclear microRNAs and their unconventional role in regulating non-coding RNAs. Protein Cell 2013; 4(5): 325-30. [http://dx.doi.org/10.1007/s13238-013-3001-5] [PMID: 23584808]

[71] Gernapudi R, Wolfson B, Zhang Y, *et al.* MicroRNA 140 promotes expression of long noncoding RNA NEAT1 in adipogenesis. Mol Cell Biol 2016; 36(1): 30-8. [http://dx.doi.org/10.1128/MCB.00702-15] [PMID: 26459763]

[72] Trobaugh DW, Klimstra WB. MicroRNA regulation of RNA virus replication and pathogenesis. Trends Mol Med 2017; 23(1): 80-93. [http://dx.doi.org/10.1016/j.molmed.2016.11.003] [PMID: 27989642]

[73] Wang F, Yang H, Deng Z, Su Y, Fang Q, Yin Z. HOX antisense lincRNA HOXA-AS2 promotes tumorigenesis of hepatocellular carcinoma. Cell Physiol Biochem 2016; 40(1-2): 287-96. [http://dx.doi.org/10.1159/000452545] [PMID: 27855366]

[74] Ponting CP, Oliver PL, Reik W. Evolution and functions of long noncoding RNAs. Cell 2009; 136(4): 629-41. [http://dx.doi.org/10.1016/j.cell.2009.02.006] [PMID: 19239885]

[75] Liu W, Wang Z, Liu L, *et al.* LncRNA *Malat1* inhibition of TDP43 cleavage suppresses IRF3-initiated antiviral innate immunity. Proc Natl Acad Sci 2020; 117(38): 23695-706. [http://dx.doi.org/10.1073/pnas.2003932117] [PMID: 32907941]

[76] Ou ZL, Luo Z, Wei W, Liang S, Gao TL, Lu YB. Hypoxia-induced shedding of MICA and HIF1A-mediated immune escape of pancreatic cancer cells from NK cells: role of circ_0000977/miR-153 axis. RNA Biol 2019; 16(11): 1592-603. [http://dx.doi.org/10.1080/15476286.2019.1649585] [PMID: 31402756]

[77] Wu Y, Zhao T, Deng R, Xia X, Li B, Wang X. A study of differential circRNA and lncRNA expressions in COVID-19-infected peripheral blood. Sci Rep 2021; 11(1): 7991. [http://dx.doi.org/10.1038/s41598-021-86134-0] [PMID: 33846375]

[78] Kerr CH, Dalwadi U, Scott NE, Yip CK, Foster LJ, Jan E. Transmission of Cricket paralysis virus *via* exosome-like vesicles during infection of Drosophila cells. Sci Rep 2018; 8(1): 17353. [http://dx.doi.org/10.1038/s41598-018-35717-5] [PMID: 30478341]

[79] Wang J, Chen S, Bihl J. Exosome-mediated transfer of ACE2 (angiotensin-converting enzyme 2) from endothelial progenitor cells promotes survival and function of endothelial cell. Hindawi 2020; 2020: 1-11. [http://dx.doi.org/10.1155/2020/4213541]

[80] Wang L, Peng X, Lu X, Wei Q, Chen M, Liu L. Inhibition of hsa_circ_0001313 (circCCDC66) induction enhances the radio-sensitivity of colon cancer cells *via* tumor suppressor miR-338-3p. Pathol Res Pract 2019; 215(4): 689-96. [http://dx.doi.org/10.1016/j.prp.2018.12.032] [PMID: 30630646]

[81] Hsiao KY, Lin YC, Gupta SK, *et al.* Noncoding effects of circular RNA CCDC66 promote colon cancer growth and metastasis. Cancer Res 2017; 77(9): 2339-50. [http://dx.doi.org/10.1158/0008-5472.CAN-16-1883] [PMID: 28249903]

[82] Felsenstein S, Herbert JA, McNamara PS, Hedrich CM. COVID-19: Immunology and treatment options. Clin Immunol 2020; 215: 108448. [http://dx.doi.org/10.1016/j.clim.2020.108448] [PMID: 32353634]

[83] Zhang C, Wu Z, Li JW, Zhao H, Wang GQ. Cytokine release syndrome in severe COVID-19: interleukin-6 receptor antagonist tocilizumab may be the key to reduce mortality. Int J Antimicrob Agents 2020; 55(5): 105954. [http://dx.doi.org/10.1016/j.ijantimicag.2020.105954] [PMID: 32234467]

[84] Channappanavar R, Fehr AR, Vijay R, *et al.* Dysregulated type I interferon and inflammatory monocyte-macrophage responses cause lethal pneumonia in SARS-CoV-infected mice. Cell Host Microbe 2016; 19(2): 181-93. [http://dx.doi.org/10.1016/j.chom.2016.01.007] [PMID: 26867177]

[85] Channappanavar R, Perlman S. Pathogenic human coronavirus

infections: Causes and consequences of cytokine storm and immunopathology. Semin Immunopathol 2017; 39(5): 529-39. [http://dx.doi.org/10.1007/s00281-017-0629-x]

[86] Rockx B, Baas T, Zornetzer GA, *et al.* Early upregulation of acute respiratory distress syndrome-associated cytokines promotes lethal disease in an aged-mouse model of severe acute respiratory syndrome coronavirus infection. J Virol 2009; 83(14): 7062-74. [http://dx.doi.org/10.1128/JVI.00127-09] [PMID: 19420084]

[87] Liu B, Li M, Zhou Z, Guan X, Xiang Y. Can we use interleukin-6 (IL-6) blockade for coronavirus disease 2019 (COVID-19)-induced cytokine release syndrome (CRS)? J Autoimmun 2020; 111: 102452. [http://dx.doi.org/10.1016/j.jaut.2020.102452] [PMID: 32291137]

[88] Hu J, Wu H, Wang D, Yang Z, Dong J. LncRNA ANRIL promotes NLRP3 inflammasome activation in uric acid nephropathy through miR-122-5p/BRCC3 axis. Biochimie 2019; 157: 102-10. [http://dx.doi.org/10.1016/j.biochi.2018.10.011] [PMID: 30347231]

[89] Wahl C, Liptay S, Adler G, Schmid RM. Sulfasalazine: a potent and specific inhibitor of nuclear factor kappa B. J Clin Invest 1998; 101(5): 1163-74. [http://dx.doi.org/10.1172/JCI992] [PMID: 9486988]

[90] Kany S, Vollrath JT, Relja B. Cytokines in inflammatory disease. Int J Mol Sci 2019; 20(23): 6008. [http://dx.doi.org/10.3390/ijms20236008] [PMID: 31795299]

[91] Hunter CA, Jones SA. IL-6 as a keystone cytokine in health and disease. Nat Immunol 2015; 16(5): 448-57. [http://dx.doi.org/10.1038/ni.3153] [PMID: 25898198]

[92] Li S, Mei Z, Hu HB, Zhang X. The lncRNA MALAT1 contributes to non-small cell lung cancer development *via* modulating miR-124/STAT3 axis. J Cell Physiol 2018; 233(9): 6679-88. [http://dx.doi.org/10.1002/jcp.26325] [PMID: 29215698]

[93] Shen W, Yuan Y, Zhao M, *et al.* Novel long non-coding RNA GACAT3 promotes gastric cancer cell proliferation through the IL-6/STAT3 signaling pathway. Tumour Biol 2016; 37(11): 14895-902. [http://dx.doi.org/10.1007/s13277-016-5372-8] [PMID: 27644247]

[94] Wu J, Zhang J, Shen B, *et al.* Long noncoding RNA lncTCF7, induced by IL-6/STAT3 transactivation, promotes hepatocellular carcinoma aggressiveness through epithelial-mesenchymal transition. J Exp Clin Cancer Res 2015; 34(1): 116. [http://dx.doi.org/10.1186/s13046-015-0229-3] [PMID: 26452542]

[95] Zhang J, Chu M. Targeting of IL-6-relevant long noncoding RNA profiles in inflammatory and tumorous disease. Inflammation 2019; 42(4): 1139-46. [http://dx.doi.org/10.1007/s10753-019-00995-2] [PMID: 30825076]

[96] Tian H, Wu M, Zhou P, Huang C, Ye C, Wang L. The long non-coding RNA MALAT1 is increased in renal ischemia-reperfusion injury and inhibits hypoxia-induced inflammation. Ren Fail 2018; 40(1): 527-33. [http://dx.doi.org/10.1080/0886022X.2018.1487863] [PMID: 30277425]

[97] Johnson DE, O'Keefe RA, Grandis JR. Targeting the IL-6/JAK/STAT3 signalling axis in cancer. Nat Rev Clin Oncol 2018; 15(4): 234-48. [http://dx.doi.org/10.1038/nrclinonc.2018.8] [PMID: 29405201]

[98] Zegeye MM, Lindkvist M, Fälker K, *et al.* Activation of the JAK/STAT3 and PI3K/AKT pathways are crucial for IL-6 trans-signaling-mediated pro-inflammatory response in human vascular endothelial cells. Cell Commun Signal 2018; 16(1): 55. [http://dx.doi.org/10.1186/s12964-018-0268-4] [PMID: 30185178]

[99] DeDiego ML, Nieto-Torres JL, Regla-Nava JA, *et al.* Inhibition of NF-κB-mediated inflammation in severe acute respiratory syndrome coronavirus-infected mice increases survival. J Virol 2014; 88(2): 913-24. [http://dx.doi.org/10.1128/JVI.02576-13] [PMID: 24198408]

[100] Yi H, Peng R, Zhang L, *et al.* LincRNA-Gm4419 knockdown ameliorates NF-κB/NLRP3 inflammasome-mediated inflammation in diabetic nephropathy. Cell Death Dis 2017; 8(2): e2583-3. [http://dx.doi.org/10.1038/cddis.2016.451] [PMID: 28151474]

[101] Xue Z, Zhang Z, Liu H, *et al.* lincRNA-Cox2 regulates NLRP3 inflammasome and autophagy mediated neuroinflammation. Cell Death Differ 2019; 26(1): 130-45. [http://dx.doi.org/10.1038/s41418-018-0105-8] [PMID: 29666475]

[102] Yu S, Dong B, Tang L, Zhou S. LncRNA MALAT1 sponges miR-133 to promote NLRP3 inflammasome expression in ischemia-reperfusion injured heart. Int J Cardiol 2018; 254: 50. [http://dx.doi.org/10.1016/j.ijcard.2017.10.071] [PMID: 29407129]

[103] Shi CS, Nabar NR, Huang NN, Kehrl JH. SARS-Coronavirus Open Reading Frame-8b triggers intracellular stress pathways and activates NLRP3 inflammasomes. Cell Death Discov 2019; 5(1): 101. [http://dx.doi.org/10.1038/s41420-019-0181-7] [PMID: 31231549]

[104] Jo EK, Kim JK, Shin DM, Sasakawa C. Molecular mechanisms regulating NLRP3 inflammasome activation. Cell Mol Immunol 2016; 13(2): 148-59. [http://dx.doi.org/10.1038/cmi.2015.95] [PMID: 26549800]

[105] Kelley N, Jeltema D, Duan Y, He Y. The NLRP3 inflammasome: an overview of mechanisms of activation and regulation. Int J Mol Sci 2019; 20(13): 3328. [http://dx.doi.org/10.3390/ijms20133328] [PMID: 31284572]

[106] Dorfleutner A, Chu L, Stehlik C. Inhibiting the inflammasome: one domain at a time. Immunol Rev 2015; 265(1): 205-16. [http://dx.doi.org/10.1111/imr.12290] [PMID: 25879295]

[107] Shah A. Novel coronavirus-induced NLRP3 inflammasome activation: a potential drug target in the treatment of COVID-19. Front Immunol. 2020; 11: p. 1021.

[108] Mangan MSJ, Olhava EJ, Roush WR, Seidel HM, Glick GD, Latz E. Targeting the NLRP3 inflammasome in inflammatory diseases. Nat Rev Drug Discov 2018; 17(8): 588-606. [http://dx.doi.org/10.1038/nrd.2018.97] [PMID: 30026524]

[109] Dong P, Xiong Y, Yue J, *et al.* Long non-coding RNA NEAT1: a novel target for diagnosis and therapy in human tumors. Front Genet 2018; 9: 471. [http://dx.doi.org/10.3389/fgene.2018.00471] [PMID: 30374364]

[110] Centa A, Fonseca AS, da Silva Ferreira SG, *et al.* Deregulated miRNA expression is associated with endothelial dysfunction in post-mortem lung biopsies of COVID-19 patients. Am J Physiol Lung Cell Mol Physiol 2021; 320(3): L405-12. [http://dx.doi.org/10.1152/ajplung.00457.2020] [PMID: 33651636]

[111] Chen W. A potential treatment of COVID-19 with TGF-β blockade. Int J Biol Sci 2020; 16(11): 1954-5. [http://dx.doi.org/10.7150/ijbs.46891] [PMID: 32398962]

[112] Sabbatinelli J, Giuliani A, Matacchione G, *et al.* Decreased serum levels of the inflammaging marker miR-146a are associated with clinical non-response to tocilizumab in COVID-19 patients. Mech Ageing Dev 2021; 193: 111413. [http://dx.doi.org/10.1016/j.mad.2020.111413] [PMID: 33307107]

[113] Niemiec SM, Hilton SA, Wallbank A, *et al.* Cerium oxide nanoparticle delivery of microRNA-146a for local treatment of acute lung injury. Nanomedicine 2021; 34: 102388. [http://dx.doi.org/10.1016/j.nano.2021.102388] [PMID: 33753282]

[114] Yang P, Zhao Y, Li J, *et al.* Downregulated miR-451a as a feature of the plasma cfRNA landscape reveals regulatory networks of IL-6/IL-6R-associated cytokine storms in COVID-19 patients. Cell Mol Immunol 2021; 18(4): 1064-6. [http://dx.doi.org/10.1038/s41423-021-00652-5] [PMID: 33637960]

[115] Soni DK, Cabrera-Luque J, Kar S, Sen C, Devaney J, Biswas R. Suppression of miR-155 attenuates lung cytokine storm induced by SARS-CoV-2 infection in human ACE2-transgenic mice. BioRxiv 2020; 423130. [http://dx.doi.org/10.1101/2020.12.17.423130]

[116] de Souza Nicoletti A, Visacri MB, Vasconcelos PEdNS, *et al.* Differentially expressed circulating microRNAs in Brazilian patients with COVID-19: A preliminary study on potential biomarkers for diagnosis and severity. Mol Biol Rep 2021; 49(7): 6931-43.

[117] Donyavi T, Bokharaei-Salim F, Baghi HB, *et al.* Acute and post-acute phase of COVID-19: Analyzing expression patterns of miRNA-29a-3p, 146a-3p, 155-5p, and let-7b-3p in PBMC. Int Immunopharmacol 2021; 97: 107641. [http://dx.doi.org/10.1016/j.intimp.2021.107641] [PMID: 33895478]

[118] Liu Z, Wang J, Xu Y, *et al.* Implications of the virus-encoded miRNA and host miRNA in the pathogenicity of SARS-CoV-2 2004; arXiv:2004. 2004.04874.

[119] Li C, Hu X, Li L, Li J. Differential microRNA expression in the peripheral blood from human patients with COVID-19. J Clin Lab Anal 2020; 34(10): e23590. [http://dx.doi.org/10.1002/jcla.23590] [PMID: 32960473]

[120] Fani M, Zandi M, Ebrahimi S, Soltani S, Abbasi S. The role of miRNAs in COVID-19 disease. Future Virol 2021; 16(4): 301-6. [http://dx.doi.org/10.2217/fvl-2020-0389]

[121] Chauhan N, Jaggi M, Chauhan SC, Yallapu MM. COVID-19: fighting the invisible enemy with microRNAs. Expert Rev Anti Infect Ther 2021; 19(2): 137-45. [http://dx.doi.org/10.1080/14787210.2020.1812385] [PMID: 32814446]

[122] Lambert DW, Lambert LA, Clarke NE, Hooper NM, Porter KE,

Turner AJ. Angiotensin-converting enzyme 2 is subject to post-transcriptional regulation by *miR-421*. Clin Sci 2014; 127(4): 243-9. [http://dx.doi.org/10.1042/CS20130420] [PMID: 24564768]

[123] Lu D, Chatterjee S, Xiao K, *et al.* MicroRNAs targeting the SARS-CoV-2 entry receptor ACE2 in cardiomyocytes. J Mol Cell Cardiol 2020; 148: 46-9. [http://dx.doi.org/10.1016/j.yjmcc.2020.08.017] [PMID: 32891636]

[124] Bahrami A, Bakherad M. Comparative genomics identifies key genes and miRNAs that may be used as a strategy to control and treatment of COVID-19 trends in medicine. Oat 2020; 20: 1-17. [http://dx.doi.org/10.15761/TiM.1000253]

[125] Yang C, Li Y, Xiao S-Y. Differential expression of ACE2 in the respiratory tracts and its relationship to COVID-19 pathogenesis. E Bio Med 2020; 60: 103004. [http://dx.doi.org/10.1016/j.ebiom.2020.103004]

[126] Liu Q, Du J, Yu X, *et al.* miRNA-200c-3p is crucial in acute respiratory distress syndrome. Cell Discov 2017; 3(1): 17021. [http://dx.doi.org/10.1038/celldisc.2017.21] [PMID: 28690868]

[127] Xu L, Zhang LJ, Yang L, *et al.* Positive association of herpes simplex virus-IgG with multiple sclerosis: A systematic review and meta-analysis. Multiple Sclerosis and Related Disorders 2021; 47: 102633. [http://dx.doi.org/10.1016/j.msard.2020.102633]

[128] Kaur T, Kapila S, Kapila R, *et al.* Tmprss2 specific miRNAs as promising regulators for SARS-CoV-2 entry checkpoint. Virus Res 2021; 294: 198275. [http://dx.doi.org/10.1016/j.virusres.2020.198275] [PMID: 33359190]