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Review Article

miRNAs: Key Molecules in the Immunopathogenesis of Betacoronaviruses

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Abstract

A series of patients hospitalized with acute respiratory disease was reported in Wuhan, Hubei Province, China, in December 2019. Many patients have had direct or indirect links with the Huanan Seafood Wholesale Market, Wuhan. Millions of people worldwide have been impacted by the 2019 coronavirus disease (COVID-19) in numerous nations. The pandemic has once again drawn public attention to the coronaviruses that developed epidemics in China (2002) and Saudi Arabia (2012). Given the structural and phylogenetic similarity of the 2019 novel coronavirus (2019-nCoV) with the severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV), the results of recent studies have been combined with new findings to complete one of the strangest pneumonia puzzles in human history. Coronaviruses establish extremely complex interactions with the immune system, especially in order to evade immune responses. Undoubtedly, increasing our knowledge of the immunopathogenesis of diseases caused by these viruses will eventually lead to more effective treatment and diagnosis. Non-coding RNAs (ncRNAs) are among the leading immune response regulators. MicroRNAs (miRNAs) play an important role in the expression and regulation of both innate and adaptive immune responses and in many immune disorders from autoimmunity to cancer and allergies. Our understanding of the functions of human and viral miRNAs in the pathogenesis of many viruses has increased in recent years. Accordingly, the present review article aims to review studies evaluating the role of miRNAs in the pathogenesis of other betacoronaviruses. The results of these studies, given the similarity of viruses within the family Coronaviridae, could be helpful for future research on SARS-CoV2.

Keywords: COVID19; SARS-CoV2; miRNA; SARS-CoV; MERS-CoV

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Introduction

The appearance of a solar corona, with its club-shaped spikes on its surface, inspired the name coronavirus. These viruses are potential pathogens for humans and vertebrates. They can infect the respiratory system, the gastrointestinal tract, the liver, and the central nervous system of humans, livestock, birds, bats, mice, and many other wild animals (1). Alpha- and Betacoronaviruses commonly infect mammals. In contrast, gam-

ma- and delta-coronaviruses infect birds and fish. These viruses can impose a huge economic burden because of their ability to infect livestock and pets (1). A bat coronavirus known as HKU2 caused the Swine Acute Diarrhea Syndrome coronavirus (SADS-CoV) in 2016, causing a large-scale outbreak and a deadly disease in pigs in southern China that eventually resulted in the loss of more than 24,000 pigs (2). Before 2019, there were only six coronavirus strains known to infect humans and cause respiratory diseases. HCoV-229E, HCoV-OC43, HCoV-NL63, and HKU1 only cause mild upper respiratory disease, and some of them can rarely cause severe infection in infants, children, and adults (3). In addition, SARS-CoV and MERS-CoV can infect the lower respiratory tract and develop severe acute respiratory syndrome in humans (4). A series of acute respiratory diseases was reported in Wuhan, Hubei Province, China, in December 2019. Many patients have had direct or indirect links with the Huanan Seafood Wholesale Market, Wuhan, which is believed to be the primary source for the outbreak of the 2019 novel coronavirus (2019-nCoV) (5). The novel coronavirus was identified by the Chinese Center for Disease Control and Prevention (China CDC) as the cause of the disease, initially called severe acute respiratory syndrome coronavirus 2 (SARS-CoV2). The World Health Organization (WHO) has now named the disease as Coronavirus Disease 2019 (COVID-19) (6). The novel Coronavirus 2019 belonging to Betacoronaviruses is capable of causing severe respiratory syndrome by engaging the lower respiratory system (6). Most patients deceased from COVID-19 in China were over 60 years old with a history of underlying diseases such as abdominal mass, chronic liver disease, myocarditis, renal dysfunction, and cardiovascular disease (7). Clinically, the disease is accompanied by symptoms such as fever, cough, myalgia, fatigue, diarrhea pneumonia, and even death in severe cases (8-10). According to the phylogenetic tree, the SARS-CoV2 is closer to bat coronaviruses such as CoV ZC45 and SL-CoV ZXC21 and was more distant from SARS-CoV (11). The novel coronavirus sequencing shows that the SARS-CoV2 genome sequence is 96% homogeneous with the bat coronavirus. Sequence analysis indicates that the novel coronavirus has the typical genomic structure of coronaviruses and belongs to Betacoronaviruses, including the bat corona viruses of SL-ZC45, Bat-SL ZXC21, SARS-CoV and MERS-CoV (11). **(Figure 1)**

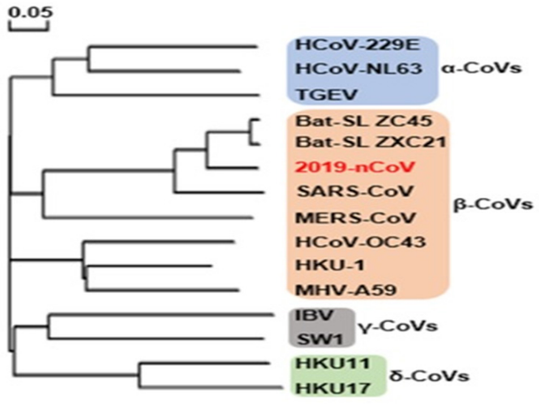

Figure1. 2019-nCoV is highlighted in red. Genomic sequence analysis indicates that the novel coronavirus has the typical genomic structure of coronaviruses and belongs to Betacoronaviruses, including the bat coronaviruses of SL-ZC45, Bat-SL ZXC21, SARS-CoV, and MERS-CoV. According to the phylogenetic tree, 2019-nCov is closer to bat coronaviruses such as SL-ZC45 and SL-ZXC21 (with structural similarity up to 89%) and is more distant from SARS-CoV. Adapted from Chen, et al. Journal of Medical Virology 2020. (12).

Genomic structure and proliferation of coronaviruses

The genome of coronaviruses contains a positive-sense single-stranded RNA (+ssRNA) with ~30 kb in length and a 5' cap structure along with a 3' poly (A) tail. The viral genome has at least six ORFs. The first ORF (ORF1a / b) comprises two-thirds of the viral genome encodes 16 non-structural proteins of the virus. Other ORFs are near the 3' ends of the virus genome encoding spike (S), membrane (M) envelope (E), and nucleocapsid (N) proteins. In addition to the four major structural proteins, various coronaviruses encode specific structural and additional proteins such as HE protein, 3a / b protein, and 4a / b protein. In the genome of various coronaviruses, the regions encoding non-structural proteins (NSPs) have 58% overlap, and the genomic regions encoding structural proteins have up to 43% overlap. This suggests that NSPs are more conserved, whereas structural proteins have more diversity to adapt to novel hosts. Since the mutation rate in RNA viruses is much higher than that of DNA viruses, the genomes of RNA viruses are usually less than 10 kb in length but coronaviruses are more than 30 kb in length. Thus, the coronavirus is the largest RNA virus ever known. Coronaviruses are different from all RNA viruses because of their so-called proof-reading properties, which is due to the ability of the 3'-5 'exoribonucleases of these viruses (11).

The penetration of the virus into host cells

Penetration into host cells is an essential step in the transmission of various strains of coronavirus, especially for betacoronaviruses. All coronaviruses encode the spike (S) glycoprotein. Part of the S protein that interacts with the host cell surface protein is called the receptor-binding domain. Upon receptor binding, the adjacent host cell protease cleaves the viral S protein, which releases the S fusion peptide and facilitates virus penetration (13). Receptors of betacoronaviruses known so far include Angiotensin-converting enzyme-2 (ACE2) for the SARS virus and dipeptidyl peptidase-4 or CD26 for MERS virus, which binds to host cell receptors and mediates viral penetration. The 2019-nCov receptor is also ACE2 (13, 14). The affinity of 2019-nCov is higher than that of SARS-CoVs. On the other hand, unlike the previous virus, 2019-nCov utilizes a unique furin-dependent mechanism previously seen for HIV and Ebola viruses, which could be a justification for much higher infectivity (15, 16).

Immunopathogenesis of Betacoronaviruses

Studies have shown that important betacoronaviruses, such as MERS-CoV, SARS-CoV, and SARS-CoV2 have extensive but complex interactions with the immune system (17-19). Studies have shown that the betacoronaviruses are able to disrupt IFNI-dependent antiviral responses (20). These viruses prevent IFNI production by blocking the identification of their PAMPs by innate immune-specific PRRs such as RIG1 and MDA5, on the other hand, and by utilizing their NSPs to block the signaling pathways of these cytokines from IFNIR receptor to downstream transcription factors of IRF and STAT1 (20). In addition, betacoronaviruses have been shown to increase cell resistance to IFNI (20). Examination of specimens from patients with SARS-CoV and MERS-CoV reveals an accumulation of macrophages in the lung tissue (9). These viruses, by infecting macrophages on the one hand and stimulating inflammasome and other inflammatory response pathways on the other hand, impair the function of macrophages and enhance the production of proinflammatory cytokines such as TNF, IL6, and IL1, as well as overexpress the inflammatory chemokines such as CXCL10, CCXL10 and, CCL5 and CCL8 on their surface (21, 22). Studies have shown that T lymphocytes are significantly reduced in the peripheral blood of patients infected with SARS-CoV2 and Findings reported severe lymphopenia in patients with COVID-19. The lymphopenia has been reported to be much more severe in the ICU patients with severe forms of the infection. In contrast, it has been found that the T-cell counts increase and return to their normal levels in patients who are in the recovery phase (7, 8).

SARS-CoV directly infects T lymphocytes and causes lymphopenia, splenic atrophy, and lymph node atrophy. It has also been shown that MERS-CoV is capable of activating intrinsic and extrinsic apoptotic pathways in T lymphocytes. The virus appears to not only develop lymphopenia but also impair the function of normal T lymphocytes. A study reported that the T lym-

phocytes in the patients with COVID-19 were over-controlled and over-activated, confirmed by the high proportion of lymphocytes expressing the HLA-DR (CD4 3.47) and CD38 (CD8 39.4) markers (23). This over-activation process appears to result in T-lymphocyte exhaustion in the patients, as a study examined 522 Chinese patients in Wuhan for the expression of T-cell exhaustion markers such as PD-1 and Tim-3 using flow cytometry (24). The results showed that their expression was significantly increased in patients with COVID-19 compared to controls. The increased expression of these markers is associated with the shift of disease to symptomatic stages. Even if no antigen is present, the memory CD4+ and CD8+ T cells can persist for four years in a number of subjects recovered from SARS-CoV infection and be able to perform T cell proliferation, DTH response, and IFN-γ production. Six years after SARS-CoV infection, the SARS-CoV S peptide-specific T-cell responses were detected in 14 of 23 patients recovered from SARS (25). In summary, recent studies have shown that SARS-CoV2 reduces, over-activates, and eventually exhausts the T lymphocytes; however, memory lymphocytes also seem to remain in the patient's body for years.

Finally, the cytokine storm is one of the reported causes of mortality in patients with COVID-19. Therefore, the use of the anti-rheumatoid drug Actemra in China has already shown promising results in the treatment of patients with COVID-19. MERS-CoV, SARS-CoV, and 2019-nCOV are able to widely modify the process of developing immune responses, which is undoubtedly caused by changes in gene expression profiles or, in other words, changes in gene expression regulation. In recent years, more than ever it has been shown that epigenetic modifications play an undeniable role in the regulation and homeostasis of immune responses (26). The ncRNAs also possess a prominent function (27).

Thus, the function of these types of ncRNAs is being seriously studied in a variety of immune disorders such as autoimmune diseases, cancers, autoinflammatory syndromes, allergies, and infectious diseases to understand more precisely mechanisms of pathogenesis and ultimately their more effective diagnosis and treatment (28-30).

The miRNA and immune system

The ncRNAs act as regulatory molecules and do not encode a protein. Studies revealed that only 2% of mammalian genomes contain protein-coding genes and a large percentage of genomes account for the ncRNAs (31). The miRNAs are a major class of ncRNAs that are short in length (19-23 nucleotides) and regulate a wide range of bioactivities in the body. The synthesis of miRNAs is a complex and multistep process (32) . Reportedly, the miRNAs play a central role in immune cell plasticity, especially the differentiation of T helper cells, such as TH17 and TH1, TH2, TH9, TH35, and Treg (33) . The regulation of producing cytokines and their signaling pathways, including IFNI and proinflammatory cytokines that play important roles in the pathogenesis of coronaviruses, are all regulated by epigenetic modifications such as miRNAs (34). Studies have shown well that the differentiation and function of macrophages M1, M2, and Mreg depend on alterations in miRNA expression (35). Given the widespread interaction of MERS-CoV, SARS-CoV, and 2019-nCov with the immune system, this review article aimed to investigate the studies investigating changes in miRNAs in the pathogenesis of these diseases. Given the similarity of viruses in the family Coronaviridae, the results of these studies could be helpful for future research into the 2019-nCoV.

The miRNAs in coronavirus infections

There have been few in vivo studies on the role of miRNAs in coronavirus infections, but this issue has been investigated in HCoV-OC43 in the in vitro condition. In addition, the role of miRNAs in SARS-CoV and MERS-CoV has been investigated using bioinformatics tools. The OC43 virus causes the common cold around the world (36). The Coronavirus N protein is one of the structural proteins of the virus that binds to genomic RNA to facilitate virus proliferation as well as to form a helical capsid. It acts as a potent stimulus by binding to the negative inhibitor of NF-κB, miR-9. NF-kB is one of the most important transcription factors in the immune system. It is not yet clear whether NF-kB activation is beneficial or harmful to the virus, whether it is directly beneficial for viral proliferation, and whether it is a random effect that ultimately limits the viral pathogenicity. However, the low pathogenicity of OC43 can be investigated in other respects. Accordingly, the reduction in OC43 pathogenicity, which is associated with more limited clinical symptoms, may result in increased contact between infected and non-infected individuals, resulting in the spread of the virus in a population when compared with coronaviruses with higher pathogenicity (37). This finding is important because the binding of virus proteins to host miRNAs and altering gene expression may be a clever strategy for coronaviruses to evade immune responses more effectively (38). Importantly, understanding the mechanisms of escape from immune responses can also help to treat COVID-19 more effectively. Previous studies in patients with COVID-19 show well the high ability of SARS-CoV2 to inhibit antiviral responses and avoid their damage. Coronaviruses take advantage of the reduced rate of proliferation within cells infected with the virus at the onset of infection as a strategy to evade immune responses so that they can infect more cells. In the cells affected by the coronavirus, the involvement of PRRs such as RIG1 and MDA5 provokes intracellular signaling cascades, thereby enhancing the expression of NFKB1 and miR-9. It should be noted that the miR-9 targets the NFKB1 mRNA and thus inhibits the translation of NFKB; however, this outcome is inhibited by the activity of OC43, which binds to miR-9 and consequently increases the translation of NFKB1. The translation of NFKB1 itself further leads to higher expression of proinflammatory cytokines (37), whose over-expression is one of the major contributing factors to the immunopathogenesis of ARDS in patients. It should be noted that the occurrence of the cytokine storm is one of the major pathological and detrimental events in SARS-CoV and 2019-nCoV. High levels of proinflammatory and suppressive cytokines such as IL-2, IL-7, G-CSF, IP-10, MCP-1, MIP-1A, and TNFα have been reported in the acute cases of the disease, which is termed the cytokine storm. In the patients with COVID-19 induced by SARS-CoV2, a study published in the authoritative journal of Lancet reported that the deaths of 6 out of 41 patients were due to cytokine storm, subsequently the ARDS and ultimately the dysfunction of several vital organs of these patients. Accordingly, the use of Actemra in China has already shown promising results in the treatment of patients with COVID-19. Roche Company is working with the FDA to start a randomized, double-blind, placebo-controlled clinical trial to study more closely the efficacy of Actemra in hospitalized patients with COVID-19. Therefore, can intervention of the virus mechanism in the case of miR9 slightly reduce the intensity of the cytokine storm? Does SARS-CoV2 also target miR9? Bioinformatics and empirical studies can answer all of these questions.

Effect of SARS-CoV on the expression of miRNA in Bronchoalveolar stem cells (BASCs)

Bronchoalveolar stem cells (BASCs, including Sca-1+ CD34+ CD45- Pecam-) are among the cells targeted and infected with SARS-CoV. The viruses can downregulate miR-223 and miR-98 in BASCs, thereby controlling several different stages of their differentiation and production of their anti-inflammatory cytokines. Viral nucleocapsid and spike proteins appear to downregulate miR-223 and miR-98 in the BASCs, simultaneously, to control different stages of BASC differentiation, activation of inflammatory chemokines, and ACE2 inhibition. These expression changes in the miRNAs by the virus actually play a dual role because, on the one hand, these changes facilitate easier viral cell-to-cell transmission, and on the other hand, disrupt the BASCs to drastically reduce the ability of affected lung tissue regeneration. Taken together, this study demonstrates yet another clever strategy of the virus in how it utilizes host cell miRNAs for its advantage (39).

SARS-CoV and the expression of svRNA

Three svRNAs including nsp3 (svRNA-nsp3.1 and -nsp3.2) and N (svRNA-N) were obtained from the genomic regions of SARS-CoV. The biogenesis of CoV svRNAs is independent of RNase III, cell type and host species, but is dependent on the rate of viral proliferation. The inhibition of svRNA-N using Antagomir tools significantly correlated with a decrease in lung pathology and proinflammatory cytokine expression. Taken together, these data suggest that the svRNAs contribute to the pathogenesis of SARS-CoV and therefore their inhibition by Antagomir could be a potential therapeutic approach in the infection with these viruses (40). As previously described, SARS-CoV2 is phylogenetically and structurally

more than 80% similar to SARS-CoV and to a lesser extent similar to MERS-CoV. Therefore, it is not out of the question that multiple svRNAs could be used as effective factors in the pathogenesis and invasion of SARS-CoV2 and ultimately in the worsening status of COVID19 patients. Currently, more than 110 clinical trials in China and other countries are evaluating the efficacy of a variety of drugs, monoclonal antibodies, vaccines and immune cell therapy in COVID19, so why should we not test our chances of evaluating the inhibition of svRNAs in SARS-CoV2 infection.

The miRNAs in porcine hemagglutinating encephalomyelitis virus (PHEV) infection

The porcine hemagglutinating encephalomyelitis virus (PHEV) is another Betacoronaviruse that causes neurological and / or digestive disease in pigs. The PHEV was the first coronavirus identified in and isolated from pigs and is the only neurotropic virus ever identified in pigs so far. The first epidemic caused by the virus was reported in 1957 in Ontario, Canada. Studies have shown that the miRNAs also play a prominent role in the pathogenesis of the virus (**Table 1**) (41). A study found that miR-10a-5p suppresses the downstream Syndecan 1 gene and acts as an antiviral mechanism in PHEV-induced disease. The Syndecan 1 is a cell surface proteoglycan that interacts with extracellular matrix molecules and growth factors to maintain epithelial cell morphology, anchor protein-dependent growth, and invasive inhibition in cell culture (42). Another study reported a significant increase in the expression level of miR-21a-5p in the rat brain as well as PHEV-infected N2a cells and a consequent decrease in the expression of CASK-interacting protein 1 (Caskin1). It should be noted that the miR-21 regulates the expression of target genes involved in several cellular processes such as cell proliferation, migration, invasion and metastasis. The role of miR-21 in the viral infection process has been confirmed in a number of studies and can be used as a target for the treatment of viral diseases. Overexpression of miR-21a-5p or deletion of Caskin1 in the host significantly contributes to PHEV proliferation. In contrast, the miR-21a-5p silencing by miR-21a 5p inhibitors results in viral suppression. Altogether, the results of this study indicate that the Caskin1 gene is a direct target of miR-21a-5p, and helps to increase virus proliferation by suppressing the Caskin expression. This illustrates well how a high-virulence beta-coronavirus is using miRNA to overwhelm the host immune system, and this raises the possibility of replicating such a strategy in the pathogenicity of other coronaviruses, especially SARS-CoV2, which we are now seeing as its pandemic, and these findings may help to develop strategies for therapeutic applications (43).

The miR-221-5p in porcine epidemic diarrhea virus (PEDV) infection

The porcine epidemic diarrhea virus (PEDV), the causative agent of porcine epidemic diarrhea, causes significant economic burden to the pig industry around the world. The researchers found that overexpression of miR-221-5p inhibits the dose-dependent PEDV proliferation and interestingly reduced expression of miR-221-5p increases PEDV proliferation. It was subsequently found that the miR-221-5p directly targets the genomic RNA of PEDV and in turn activates the NFKB signaling pathway (44). The results of this study are certainly amazing. The host miRNA directly targets the betacronavirus RNA and simultaneously alters one of the major intracellular signaling pathways involved in the exacerbation of inflammation. These findings raise some key questions: Are miRNAs similarly able to target directly the genomic RNA of SARS-CoV2 in the human body? And prevent its proliferation? And at the same time affect key signaling pathways in the emergence of immune responses? What changes does the virus make in the expression level of this miRNA? Ultimately, the existence of such a strategy can lead to the development of extremely effective treatment strategies.

Table 1. Deregulation of miRNA expression in PHEV and PEDV

Coronavirus	miRNA	Target genes	Functional activity	Ref
PHEV	miR-142a-3p	miR-142a-3p bind directly bound to the 3'UTR of Rab3a	miR-142a-3p promotes PHEV proliferation by directly targeting Rab3a mRNA.	(41)
PHEV	miR-10a-5p	Syndecan 1, a cell surface proteoglycan	miR-10a-5p leads to downstream suppression of Syndecan 1, and it functions as an antiviral mechanism in the PHEV-induced disease.	(42)
PHEV	miR-21a-5p	Caskin1	Over-expression of miR-21a-5p or Caskin1 knockdown in the host significantly contributes to PHEV proliferation.	(43)
PEDV	miRNA-221-5p	NF-kappaB-inhibitor alpha and suppressor of cytokine signaling 1.	miR-221-5p directly targets the 3' UTR of PEDV genomic RNA to inhibit PEDV proliferation.	(47)

Bioinformatics studies of miRNAs in coronaviruses

Bioinformatics studies on the interaction of viral mRNA and miRNA have suggested the idea that SARS-CoV may evade immune responses by increasing the expression of miR-17, miR-574-5p, and miR-214 and subsequently reducing their proliferation at the onset of infection. It should be noted that these host miRNAs target all four structural proteins of the virus called spike (S), nucleocapsid (N), envelope (E), and matrix (M) proteins (45). These results demonstrate how SARS-CoV may alter host miRNA expression profiles. In another study, bioinformatics studies have shown that some miRNAs such as miR-628-5p, miR-6804-3p, miR-4289, miR-208a-3p, miR-510-3p, miR-18a-3p miR-329-3p, miR-548ax, miR-3934-5p, miR-4474-5p, miR-7974, miR-6865-5p, and miR-342-3p were strongly similar in hairpin structure to the MERS-CoV genome. Therefore, all of these miRNAs may possibly help the virus to evade the immune response and eventually infect more cells by reducing virus proliferation within the infected cell (46). In addition, in vitro studies should be performed to evaluate the inhibitory effect on viral proliferation through the effect of specific human miRNAs. Let us just not forget that it is only three months since the SARS-CoV2 came out. Therefore, the role of host miRNAs as well as the virus and the complex interaction between them and the immune system must be carefully evaluated, which will definitely help to better understand the immunopathogen-

Betacoronaviruses have posed serious challenges to the healthcare systems of the international community in recent years. Previously, SARS-CoV and MERS-CoV have caused widespread epidemics that have imposed heavy financial burdens on national healthcare systems, but SARS-CoV2 is undoubtedly one of the most complex viruses that has ever challenged mankind. Although it is only about three months since the birth of SARS-CoV2, it has caused a pandemic and involved more than 150 countries, infecting more than 250,000 people and killing tens of thousands of people. The promising point is that SARS-CoV2 is structurally similar to its other counterparts in the family Coronaviridae. The 96% similarity with bat Betacoronaviruses and the 80% similarity with SARS-CoV has led many of the drugs previously evaluated in acute respiratory diseases developed by MERS and SARS to be rapidly evaluated today to control SARS-CoV2 in over 105 clinical trials. Approximately 40 large and small pharmaceutical companies are currently trying to evaluate a variety of therapies, from immune cell therapy to the use of nucleoside analogues and protease inhibitors, and monoclonal antibodies. Although the genome sequence of the novel coronavirus has been rapidly determined, the mechanism of its pathogenesis remains unknown. Undoubtedly, a better understanding of immunopathogenesis and the interaction between the immune system and the virus can be extremely useful in this regard. Understanding the immune responses in patients with severe forms of COVID-19 may lead to significant progress in the development of effective therapies. The miRNAs are the regulators of immune responses. The most prominent feature of the human immune system is plasticity and specialized function, and this can only be achieved by rigorous regulation while also being flexible in gene expression through a variety of epigenetic mechanisms, especially miRNAs. These small but extremely effective non-coding RNAs play an important role in the interaction between the immune system and infectious agents. There is currently no disease in which the key role of miRNAs has not been investigated and detected. Therefore, investigating the role of host miRNAs as well as svRNAs that are specifically involved in regulating immune responses should be prioritized for a

deep and accurate understanding of SARS-CoV2 infection. Can one imagine that evading the virus from immune responses, such as disruption of the antiviral system of type I interferon, initiation of destructive cytokine storm, induction of severe lymphopenia, and T-lymphocyte exhaustion through increased expression of Tim3 and LAG3 on them, recruitment of macrophages and dendritic cells and impaired lymphocyte differentiation, could be practically without extensive alterations of miRNAs? Therefore, the current review article presents the role of miRNAs in the pathogenesis and immunopathogenesis of other pathogenic betacoronaviruses in humans and other species, and how the virus uses miRNAs to overcome immune system and exacerbate its infectivity, as well as how alterations in miRNA expression can alter virus infection. Therefore, in situations where excessive costs are spent on clinical trials to find effective treatments and vaccines for SARS-CoV2, research on the role of miRNAs in pathogenicity, and in particular virus-host interactions, could lead to effective treatment strategies or adjunctive therapies in patients with COVID-19. Studies in recent years have focused on identifying miRNAs as therapeutic targets for viral diseases, and there are promising clinical trials, including antagomirs that target host miRNAs such as miR-122 in hepatitis C. However, it should be kept in mind that changes in the level of the host cell miRNA can cause multiple abnormalities in different biological pathways due to the multiple regulatory roles of the miRNA. However, small RNAs have been identified in the genomes of coronaviruses such as SARS-CoV2, which are able to target important human genes and can be a therapeutic target in these viruses.

Conclusion

The inhibitors of viral miRNAs can be considered as effective antiviral therapies. Targeting viral miRNAs with Antagomirs specifically in the infected cell can be a therapeutic candidate in this field. In spite of all the promising evidence, in vivo, in vitro, and ex vivo studies are necessary to evaluate the efficacy of miRNAs as targeted therapy in coronaviruses. Increasing levels of viral miRNAs in the host may alter conditions favoring the immune system for virus control. Undoubtedly increasing our understanding of the molecular details governing the viral life cycle and immune response can help accelerate access to novel antiviral therapies.

Conflict of Interest

The authors declare that they have no conflict of interest.

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