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# The miRNA: a small but powerful RNA for COVID-19

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## Abstract

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a severe and rapidly evolving epidemic. Now, although a few drugs and vaccines have been proved for its treatment and prevention, little systematic comments are made to explain its susceptibility to humans. A few scattered studies used bioinformatics methods to explore the role of microRNA (miRNA) in COVID-19 infection. Combining these timely reports and previous studies about virus and miRNA, we comb through the available clues and seemingly make the perspective reasonable that the COVID-19 cleverly exploits the interplay between the small miRNA and other biomolecules to avoid being effectively recognized and attacked from host immune protection as well to deactivate functional genes that are crucial for immune system. In detail, SARS-CoV-2 can be regarded as a sponge to adsorb host immune-related miRNA, which forces host fall into dysfunction status of immune system. Besides, SARS-CoV-2 encodes its own miRNAs, which can enter host cell and are not perceived by the host's immune system, subsequently targeting host function genes to cause illnesses. Therefore, this article presents a reasonable viewpoint that the miRNA-based interplays between the host and SARS-CoV-2 may be the primary cause that SARS-CoV-2 accesses and attacks the host cells.

**Key words:** miRNA; COVID-19; immune system; virus

## Introduction

Coronavirus disease 2019 (COVID-19) pandemic presents an emerging, rapidly evolving trend and has resulted in over 71 million cases and 1.6 million deaths around 220 countries up to December 2020, and remains an increasing situation [1]. And the experts declared that the outbreak was extremely serious and would not be quelled soon. Scientists have confirmed that COVID-19 is caused by severe acute respiratory syndrome

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coronavirus 2 (SARS-CoV-2), a single-stranded RNA virus with high similarity in its genome and symptoms with SARS-CoV epidemic in 2002–04 [2]. During the early stage of SARS-CoV-2 infection, the viruses enter and kill the T lymphocyte cells, with profound lymphopenia that first occurred in the patients [3]. Meanwhile, the virus-activated inflammatory response including the innate and the adaptive immune response also attacks lymphocyte and promotes its apoptosis [3]. In the later phase of infection, with the number of virus particles accumulating, some symptoms are following, which include destructed endothelial barrier, loss of oxygen diffusion capacity and weakened alveolar-capillary oxygen transmission [3]. In severe COVID-19 individuals, the increase of systemic inflammation induced by a series of cytokines, including interleukin-6 (IL-6), IL-2 and IL-7, damages distant organs and results in multiorgan failure even death [4].

MicroRNA (miRNA) is a powerful regulator of gene expression and participates in almost all types of gene regulation [5–7], which cover conventional coding RNA (transcription factor [8], enzyme [9], etc.), non-coding RNA (ncRNA) [10] and mitochondrial transcripts [11]. Generally, miRNA controls gene expression through targeting the 3′-untranslational region (UTR) [12], 5′-UTR [13] and coding region [14] of specific mRNA or embedding in the specific gene [15, 16]. When the cells perceive changes of surrounding circumstances, they can take the necessary action to respond to these external changes by triggering a series of signaling events. In most cases, almost all the emerging signaling events are dominated by some core proteins in the current pathways, and these proteins are always controlled by their specific miRNAs. Thus, the intracellular and extracellular environments under morbid or abnormal physiologic conditions may cause deregulation of miRNAs, and some of these will ultimately contribute to the process and some will impede or delay it.

Bioinformatic methods have facilitated progresses in the field of protein functional annotation, omics studies and feature selection [17–20], and also contribute to a series of studies that indicated physiological mechanism of COVID-19. When the virus invades the host, the body may fall into a violent struggle against the virus. First, the immune system can perceive the allothigene and initiates the immune response for self-defense via activating lines of signaling pathways. However, if the virus breaks the immune barrier or eludes immunological recognition, cells will be attacked by inducing destructive cellular processes. Core proteins in these two processes are controlled by some miRNAs. In some cases, miR-130a can initiate the innate immune response via upregulating immune factors including type I interferon (IFN-$\alpha$/IFN-$\beta$), interferon-stimulated genes 15, ubiquitin-specific protease 18 and myxovirus resistance protein A during hepatitis C virus (HCV) infection [21]. MiR-146 can induce cell apoptosis by targeting son of sevenless homolog 1 in enterovirus-71 infected cells [22]. Moreover, host miRNA can also target the viral genome. MiR-122 directly binds 5′-UTR of HCV RNA thus enhancing viral replication [23–25]. Additionally, virus also produces miRNA, which, in one facet, targets human genes to induce some signaling pathways and, in another facet, targets viral genome to regulate the virus-related physiological process. For example, white spot syndrome virus (WSSV)-encoded miRNA (WSSV-miR-22) can target host signal transducer and activator of transcription (STAT) to promote the virus infection [26]. HBV-miR-3, a Hepatitis B Virus (HBV) encoded miRNA, can bind to HBV transcripts to inhibit its replication [27]. Thus, miRNAs play indispensable roles during virus infection. Bioinformatics methods have facilitated progress in the field of protein functional annotation, omics

studies and feature selection [17–20], and also contribute to a series of studies to explore physiological mechanism of COVID-19. Moreover, increasing evidence employing bioinformatics methods has discussed miRNA's role in SARS-COV-2 infection and indicated that the interplay between miRNA and its targeted biomolecules was crucial for the SARS-COV-2 development. SARS-CoV-2 can encode its miRNA, which can be transported into the host cells and be not recognized by the host's immune system as an allothigene due to its enough small size. Some of SARS-CoV-2 generated miRNAs enter the host cell, which target and inhibit immune-related genes thus triggering off paralysis of the immune system. Further, the viral miRNAs that bind to functional regions in its genomic RNA also contribute to viral infection and replication. Even worse, the vulnerable body has the incapacity to restrain the viral unscrupulous replication, leading to more severe symptoms. Besides, the cunning SARS-CoV-2 releases its RNA genome as a sponge to adsorb host functional miRNA and disturb immune system, which also provides a suitable opportunity for that SARS-COV-2 destroys host cells. In this perspective, our review summarized both host and virus miRNAs' roles during SARS-COV-2 infection.

## miRNA: small but powerful gene regulator

Most of non-coding RNAs, which include miRNA, long-noncoding RNA (lncRNA) and circular RNA (circRNA), are not directly involved in cell physiological process but severed as regulators to control gene expression. Different from other non-coding RNAs, miRNA, only containing approximately 22 nucleotides, usually regulates gene expression by directly targeting specific mRNA [12]. Some of miRNA regulatory modes have been well understood, which include (i) targeting 3′-UTR of mRNA, (ii) targeting 5′-UTR of mRNA, (iii) targeting coding region of mRNA and (iv) embedding in a specific gene. And many lncRNAs and circRNAs are indirectly involved in gene regulation via sponging miRNAs [28–30]. Thus, miRNA is a powerful and direct manipulator of gene expression. MiRNA regulates almost all protein-coding genes therefore indirectly participating in a set of signaling pathways in various pathological and physiological conditions. Knockout of miRNA in mice may lead to various degrees of phenotypes including defects in adaptive immunity, splenomegaly, postnatal death and so on [31, 32].

The available evidence suggests that miRNAs perform a crucial role in virus infection. Some miRNAs can activate immune-related signaling proteins to defend the virus. In human immunodeficiency virus type 1 (HIV-1)-infected macrophages, miR-221 and miR-222 are upregulated and reduce CD4 expression, which limits HIV-1 propagation and production [33]. A series of studies indicate that deletion of miRNAs in mice mode has a great impact on the process of viral infection and phenotypes in mice (Table 1). Besides, there are many miRNA-based interactions between host and virus (discussed in more detail below), which affect the process of viral infection in host and host's health.

## Dysregulation of host miRNA in COVID-19

As mentioned above, miRNA plays a crucial role in maintaining normal physiological function. Disorder in the internal environment of the organism is usually accompanied by abnormal synthesis or secretion of a miRNA in cell or blood. Thus, a lot of miRNAs have become recognized indicators in some diseases including cancers [34, 35], diabetes [36], cardiovascular diseases [37, 38] and virus-infected diseases [39].

**Table 1.** miRNA knockout during virus infection in mice

| miRNA | Virus | Phenotypes | Reference |
|---|---|---|---|
| miR-155 | WNV | Increased morbidity and mortality after infection with a lethal strain. 100% mortality after infection with a non-lethal strain; Sharp reduction of interleukin (IL)-1$\beta$, IL-12, IL-6, IL-15 and GM-CSF abundance during WNV infection | [107] |
| | HSV-1 | Enhanced resistance to herpetic stromal keratitis; Remarkable reduction of T helper cells type 1 and 17 in number in the ocular lesions and the lymphoid organs during HSV-1 infection; Decreased stromal keratitis lesion severity | [108] |
| | HSV-1 | Increased susceptibility to ocular infection with HSV-1; Higher mortality after infection with HSV-1 | [109] |
| | NV | No obvious phenotype | [110] |
| | JHMV | Increased morbidity and mortality during JHMV infection; Loss of the ability of T cell responses during JHMV infection | [111] |
| | MHV-68 | Reduced efficient MHV-68 reactivation | [112] |
| | Flu | Faster recovery capability from influenza infection; Low level of inflammation and endoplasmic reticulum stress in lung during influenza infection | [113] |
| | CVB3 | Decreased mortality and alleviative viral myocarditis; Reduced abundance of IFN-$\gamma$ and increased expression IL-4 and IL-13 in heart; Decreased inflammation and CD45(+) leukocytes in heart | [114] |
| miR-17-92 | LMCV | Impaired humoral response during LMCV infection; Reduced virus-specific TFH and Th1 cells during LMCV infection | [115] |
| miR-150 | LMCV | Enhanced recall response in memory CD8+ T cells; Accelerated differentiation of memory cells | [116] |
| miR-21-5p | HCV | Reduced steatosis during HCV infection | [117] |
| miR-22 | LMCV | Maintained platelet in number during LMCV infection; Sharply decreased red blood cells and hemoglobin | [118] |
| miR-34a | HIV | Enhanced resistance to HIV; Reduced antiretroviral agents and HIV-Tat protein-induced senescence during HIV infection | [119] |

WNV, West Nile virus; HSV-1, Herpes simplex virus 1; NV, norovirus; JHMV, neurotropic JHM strain of mouse hepatitis virus; MHV-68, murine gammaherpesvirus; Flu, influenza; LMCV, lymphocytic choriomeningitis virus.

The available evidence suggests that deregulation of some miRNAs emerges in SARS-CoV-2 infectious patients. A miRNA's high-throughput sequencing analysis in peripheral blood of 10 COVID-19 patients and 4 control donors indicated 35 upregulated and 38 downregulated miRNAs, in which changes of miR-16-2-3p and miR-183-5p are most remarkable in the upregulated and downregulated list, respectively [40]. And further enrichment analysis using targets of these miRNAs identified that Ras GTPase binding and protein kinases were captured [40]. Another study performed transcriptome sequencing of both whole blood noncoding RNAs and mRNAs for six moderate and six severe COVID-19 patients as well as and four healthy donors, in which (i) miR-146a-5p, miR-21-5p and miR-142-3p were consistently downregulated, (ii) miR-3605-3p was consistently upregulated, (iii) miR-15b-5p, miR-486-3p and miR-486-5p were upregulated only in severe COVID-19 patients compared with the healthy donors and (iv) miR-181a-2-3p, miR-31-5p and miR-99a-5p were downregulated only in severe COVID-19 cases [41]. The data supported that these miRNAs would be a potential indicator to recognize COVID-19 or severe COVID-19 patients [41]. Besides, functional enrichment analysis for predicted targets of miRNAs signifies that processes including virus binding, virus process and defense response to the virus may require the involvement of these miRNAs [41]. Thus, changes of these circular miRNAs may sever as indicators to recognize whether a person suffers from COVID-19 and the symptom is moderate or severe.

## The role of host miRNA in COVID-19

Dysregulation of miRNA has been presented in COVID-19 patients, which would lead to the change of the genes that are regulated by the miRNAs. Angiotensin-converting enzyme 2 (ACE2), a receptor in the cell membrane, can receive viral structural spike(S) protein and facilitate SARS-CoV-2 cell entry by coordinating transmembrane serine protease 2 (TMPRSS2) [3]. The close connection between COVID-19 and cardiovascular disease is already indisputable, because of that some cases reported COVID-19 patients also suffered from cardiac disease [42–44]. Research showed that miR-200c was essential for SARS-CoV-2 entry to the receptor ACE2 in cardiomyocytes [45]. The overexpression of miR-200c can reduce mRNA and protein expressions of ACE2, and the specific mechanism indicated that miR-200c could target 3′-UTR of its mRNA [45]. And another study identified that miR-98-5p can inhibit TMPRSS2 expression via binding its 3′-UTR in human endothelial cells [46]. Besides, Nersisyan *et al.* [47] used bioinformatic analysis to uncover that lysine-specific demethylase 5B (JARID1B) can regulate ACE2 and TMPRSS2 via transcriptional repression of let-7e/ miR-125a and miR-141/miR-200, which directly target 3′-UTR of these two receptors, and the expression of JARID1B was necessary for these two receptors. Thus, these miRNAs are crucial for the function of ACE2 and TMPRSS2 receptors. Our established therapeutic target database (TTD) provides drugs for treating COVID-19 in clinical trials and corresponding targets [48–50]. We consider that miRNA regulation for gene expression is ubiquitous and nonselective. In the current study, available miRNAs that regulate drug targets for treating COVID-19 in clinical trials are summarized in Table 2.

In addition to binding to host genes, host miRNAs also interact with the genome of SARS-CoV-2. In one facet, host miRNAs bind to the viral genome to affect viral replication or infection. In turn, the viral genome can be a magnet to adsorb host functional miRNAs thus interfering host's normal physiological function.

For a canonical case, miR-122, a liver-specific miRNA, interacts with 5′-UTR of the HCV RNA genome, enhancing viral replication [24]. A set of reports performed the prediction of interaction between human miRNA and SARS-CoV-2 genome. Research predicted miRNAs that can target functional RNAs of SARS-CoV-2 including S (Spike) protein, E (Envelope) protein, M (Membrane)

**Table 2.** miRNAs regulate the clinical targets of SARS-CoV-2 in TTD

| Target | miRNA | Description | Reference |
|---|---|---|---|
| DHODH | miR-502 | MiR-502 directly regulates DHODH through binding to the position 245 to 251 in 3′-UTR of its mRNA in colon cancer cells. | [120] |
| VCP | miR-129-5p | MiR-129-5p downregulates the expression of VCP by binding to two sites located at its 3′-UTR in hepatocellular carcinoma cells. | [121] |
| AGTR1 | miR-410 | MiR-410 suppresses the expression level of AGTR1 by two binding sites in the 3′-UTR of AGTR1 mRNA in pancreatic cancer. | [122] |
| TMEM97 | miR-152-3p | MiR-152-3p downregulates TMEM97 through interacting with 3′-UTR of TMEM97 mRNA in prostate cancer. | [123] |
| OPRS1 | miR-297 | MiR-297 regulates Sig-1R expression via directly targeting its 3′-UTR during cardiomyocyte hypertrophy. | [124] |
| MRC1 | miR-27a-3p | MiR-27a can mediate the process of phagocytosis by regulating CD206 expression on monocytes. | [125] |
| mTOR | miR-99a | MiR-99 inhibits the expression of mTOR by targeting its 3′-UTR in a post-transcriptional manner in esophageal squamous cell carcinoma. | [126] |
| JAK-2 | miR-124 | MiR-124 reduces the expression of JAK2 via binding to its UTR in non-small-cell lung carcinoma cells. | [127] |
| IMPDH2 | miR-34a-5p | MiR-34a can target and downregulate IMPDH2 by binding to its exon 7 of IMPDH2. | [128] |
| IMPDH1 | miR-19a-3p | MiR-19a could reduce gene expression of IMPDH1 through targeting its 3′-UTR in breast cancer. | [129] |
| CSK2 | miR-1228-3p | MiR-1228∗ can target 3′-UTR of CK2A2 and inhibit its expression in gastric cancer. | [130] |
| BRD2 | miR-143-3p | MiR-143-3p directly targets BRD2 by binding to its 3′-UTR in gastric cancer. | [131] |
| BAR | miR-19a-3p | MiR-19a suppresses ADRB1 expression by directly interacting with its 3′-UTR. | [132] |
| JAK-1 | miR-299-3p | MiR-299-3p targets 3′-UTR of JAK1 mRNA and inhibits its expression. | [133] |
| IL6R | miR-451a | MiR-451can negatively regulate IL6R by interacting with 3′-UTR in IL6R mRNA in umbilical vein endothelial cells. | [134] |
| IL1R1 | miR-21 | MiR-21 negatively regulates the IL1R1 at the level of translation through binding to 3′-UTR of L1R1. | [135] |
| IL6 | miR-665 | MiR-665 interacts and downregulates IL6 by targeting its 3′-UTR in adipose-derived stem cells. | [136] |
| GAK | miR-206 | MiR-206 downregulates GAK via target 3′-UTR of its mRNA in renal cell cancer. | [137] |
| VEGF | miR-125 | MiR-125 inhibits the expression of VEGF through interacting with 3′-UTR of VEGF mRNA in the colorectal cancer cells. | [138] |
| IFNG | miR-16-5p | MiR-15b regulates IFNG through binding to the sites at IFNG's 3′-UTR in natural killer cells. | [139] |
| TLR6 | miR-494-3p | MiR-494-3p remarkably downregulates the level of TLR6 through targeting its 3′-UTR. | [140] |
| TLR2 | miR-344b-1-3p | MiR-344b-1-3p targets and downregulates TLR2 by interaction with the site of TLR2 3′-UTR. | [141] |
| PIK3CG | miR-1976 | MiR-1976 interacts with PIK3CG and reduces PIK3CG expression through binding the site at PIK3CG 3′-UTR in triple-negative breast cancer. | [142] |
| PIK3CD | miR-30a | MiR-30a downregulates the expression of PIK3CD via directly binding to the 3′-UTR of PIK3CD mRNA in colorectal carcinoma. | [143] |
| IL8 | miR-203 | MiR-203 can directly target 3′-UTR of IL8 and reduce the expression of IL8 in nasopharyngeal carcinoma. | [144] |
| CCR5 | miR-455-5p | MiR-455-5p negatively regulates CCR5 by binding to the 3′-UTR of CCR5 mRNA in the prostate cancer cells. | [145] |
| CAPN2/CAPNS1 | miR-223 | MiR-223 targets CAPN2 by binding to the 3′-UTR of CAPN2. | [146] |
| CAPN1/CAPNS1 | miR-124-3p | MiR-124-3p inhibits the expression of CAPN1 in the human neural cell line. | [147] |
| BTK | miR-346 | Mir-346 inhibits BKT by targeting binding to its 3′-UTR. | [148] |
| ACE2 | Let-7b | Let-7b downregulates ACE2 through directly targeting the coding sequence of ACE2. | [149] |
| ANG-2 | miR-125b-5p | MiR-125b reduces the expression level of ANGP2 through binding to the 3′-UTR of Angpt2 mRNA. | [150] |
| TLR3 | miR-146a | MiR-146a negatively regulates TLR3 via binding to its 3′-UTR during coxsackievirus B infection. | [151] |
| BSG | miR-22-3p | MiR-22 represses the level of BASI through directly targeting its 3′-UTR in breast cancer. | [152] |
| TNF | miR-17-5p | MiR-17 can decrease TNFA expression via binding to TNFA 3′-UTR in the leukemia cells. | [153] |

**Table 2.** Continued

| Target | miRNA | Description | Reference |
| --- | --- | --- | --- |
| RIPK1 | miR-24-3p | MiR24-3p suppresses RIPK1 expression through binding to its 3′-UTR during myocardial ischemia/reperfusion injury. | [154] |
| PTGES2 | miR-146a | MiR-146a negatively regulates PTGES-2 via binding to its 3′-UTR in bone marrow stem cells. | [155] |
| TBK1 | miR-199a | MiR-199a suppresses the expression level of TBK1 by targeting 3′-UTR of TBK1 in *Mycobacterium bovis* infected cell. | [156] |
| ABCC1 | miR-7-5p | MiR-7-5p downregulates ABCC1 expression by binding to its 3′-UTR in hepatocellular carcinoma. | [157] |
| MARK2 | miR-190a-5p | MiR-190a targets PAR-1 and reduce its expression through binding to its 3′-UTR in breast cancer. | [158] |
| LOX | miR-200b-3p | MiR-200 suppresses LOX expression by binding to 3′-UTR of LOX mRNA in breast cancer. | [159] |
| LH2 | miR-26b-5p | MiR-26b-5p downregulates PLOD2 through binding to 3′-UTR of PLOD2 in bladder cancer. | [160] |
| LDH | miR-200c | MiR-200c directly binds to 3′-UTR of LDHA and inhibits LDHA expression in non-small cell lung cancer. | [161] |
| LARP1 | miR-374a | MiR-374a negatively regulates LARP1 by the binding site in the 3′-UTR of LARP1 mRNA in non-small cell lung carcinoma cells. | [162] |
| IL10 | miR-106a-5p | MiR-106a directly binds 3′-UTR of IL-10 mRNA and downregulates its expression. | [163] |
| IL1B | miR-21-5p | MiR-21-5p inhibits IL1B expression by binding the 3′-UTR of IL1B in estrogen receptor-positive breast carcinoma cell. | [164] |
| HDAC2 | miR-500a-5p | MiR-500a-5p directly regulates the expression of HDAC2 by binding to HDAC2 3′-UTR in colorectal cancer. | [165] |
| DNMT1 | miR-152 | MiR-152 can decrease the expression of DNMT1 by binding to the 3′-UTR of its transcript in the bladder cancer cells. | [166] |
| CUL2 | miR-154-5p | MiR-154-5p targets and inhibit CUL2 by binding to the 3′-UTR of CUL2 in cervical cancer. | [167] |
| CSNK2A2 | miR-1228-3p | MiR-1228∗ directly binds to 3′-UTR of CK2A2 mRNA and inhibits its expression in gastric cancer cell. | [130] |
| BRD4 | miR-200a | MiR-200a negatively regulates BRD4 expression by binding to the BRD4 3′-UTR in the prostate cancer cells. | [168] |

DHODH, dihydroorotate dehydrogenase; VCP, valosin-containing protein p97; AGTR1, type-1 angiotensin II receptor; TMEM97, sigma intracellular receptor 2; OPRS1, opioid receptor sigma 1; MRC1, mannose receptor; mTOR, mammalian target of rapamycin; JAK-2, janus kinase 2; IMPDH2, inosine-5′-monophosphate dehydrogenase 2; IMPDH1, inosine-5′-monophosphate dehydrogenase 1; CSK2, casein kinase II; BRD2, bromodomain-containing protein 2; BAR, beta adrenergic receptor; JAK-1, janus kinase 1; IL6R, interleukin 6; GAK, cyclin G-associated kinase; VEGF, vascular endothelial growth factor; IFNG, interferon gamma; TLR6, toll-like receptor 6; TLR2, toll-like receptor 2; PIK3CG, PI3-kinase gamma; PIK3CD, PI3-kinase delta; IL8, interleukin 8; CAPN2/CAPNS1, calpain-2/calpain small subunit 1 dimer; CAPN1/CAPNS1, calpain-1/calpain small subunit 1 dimer; BTK, bruton tyrosine kinase; ANG-2, angiopoietin-2; TLR3, toll-like receptor 3; BSG, basigin; RIPK1, receptor-interacting protein 1; PTGES2, prostaglandin E synthase 2; TBK1, NF-kappa-B-activating kinase; ABCC1, multidrug resistance-associated protein 1; MARK2, microtubule affinity regulating kinase 2; LOX, lysyl oxidase; LH2, lysyl hydroxylase 2; LDH, L-lactate dehydrogenase; LARP1, La-related protein 1; IL10, interleukin-10; IL1B, interleukin-1 beta; HDAC2, histone deacetylase 2; DNMT1, DNA [cytosine-5]-methyltransferase 1; CUL2, cullin-2; CSNK2A2, casein kinase II alpha prime; BRD4, bromodomain-containing protein 4.

protein, N (nucleocapsid) protein, ORF1ab, ORF3a, ORF8, ORF7a, ORF10 and ORF6 [51]. For example, 67 miRNAs including miR-447b are predicted to bind to RNA of S protein, which interacted with ACE2 for viral entry to host cell [52]; miR-3672 binds to RNA of E protein, which was integral membrane protein and forms cation-selective ion channels for viral morphogenesis and assembly [53]; 10 miRNAs including miR-325 bind to RNA of M protein, which played crucial roles for virus assembly through interaction with itself, S protein and N protein [54]. Conclusively, each of the viral 10 genes was predicted to bind to a series of miRNAs, which probably affect the function of these genes [51]. In addition to these translational regions, another study identified that host miRNAs also interact with 3′-UTR and 5′-UTR in the SAS-CoV-2 genome by bioinformatics approach [55]. Further, the researchers used 67 SARS-CoV-2 isolates from 24 different countries and found that 24 host miRNAs can bind differentially across these isolates [55]. A total of 18 miRNAs consistently were presented to interact with the genome of these isolates [55]. Pathway enrichment analysis of host miRNAs can capture some immune-related signaling pathways, which provided new insight that the virus adsorbed host immune-related miRNA and participated in the maladjustment of host's immune systems, thus affecting viral infection [55]. In this perspective, Bartoszewski *et al.* [56] also validated the hypothesis by bioinformatics approach and reckoned that SAS-CoV-2 acts as a sponge or magnet through adsorbing host functional miRNAs that were crucial for the host's immune system.

The responsibility of miRNA for viral infection is more than as discussed above. When the body is attacked by viruses, some miRNAs will be called upon and initiate the immune response through targeting and regulating immune-related genes. miR-221 and miR-222 can target the CD4 viral receptor and reduce its expression, thus activating host response and restraining HIV-1 entry to macrophage [57]. Inducing of miR-103 and 107 by interleukin-1$\beta$-mediated p53 reduced C-C chemokine receptor type 5 (CCR5) expression and HIV-1 infection of macrophages [58]. Oppositely, some deregulating miRNAs also exacerbate the process of viral infection and then destroy vulnerable host cells. In HBV-infected liver cells, increased miR-328-3p targets the forkhead box protein O4 gene, an endogenous inhibitor of the nuclear factor-$\kappa$B, and leads to hepatocyte injury by inducing cellular inflammatory response [59]. In enterovirus 71 infected

human epidermoid carcinoma cells, reduced miR-30a can mediate the abundance of Beclin-1, a key autophagy-promoting gene, thus enhancing host cellular autophagy activity and viral replication [60].

## The role of viral miRNA in COVID-19

Viruses also encode their own miRNAs [61], which have high similarities in structure and function with human miRNAs. Virus-produced miRNAs execute their function generally via two manners.

The first is to interact with specific regions of their own genome or transcript. The interaction in the functional gene or gene's regulatory region can result in changed gene expression, usually downregulation, to affect viral replication and infection. MiR-N367, a miRNA produced by HIV-1 infected T cells, can target the viral nef gene, which is important for HIV-1 replication, and block its stability and translation [62]. Besides, DNA viruses also synthesize miRNAs. WSSV, a DNA virus, produces WSSV-miR-66 and WSSV-miR-68, which can target and inhibit wsv094 and wsv177 genes as well as wsv248 and wsv309 via binding to their 3′-UTR [63]. The four genes play suppressive roles in WSSV infection, so the increase of both WSSV-miR-66 and WSSV-miR-68 will enhance the process of the virus infection [63]. A study identified 27 SARS-CoV-2-encoded miRNAs that can bind to the genomic region of the virus [64]. Most of target sites were located at ORF1ab gene and some sites were at 5′-UTR of the virus genome and the S gene [64]. Moreover, the virus-encoded miRNA binding to the region of genome could affect virus replication and entry to the host [64].

The second is that viral miRNAs can be transported to host cells and bind to host miRNAs and genes during virus infection, which generally represses the expression of these functional miRNAs or genes and triggers intracellular signaling pathways. Viruses could not produce too many kinds of miRNA due to limited genome in size [65], and the Rhesus lymphocryptovirus encodes the largest miRNAs in number, 68 miRNAs [66]. The release of viral miRNAs in host cells is more beneficial for the viral infection rather than proteins, because the smaller miRNA molecules are easier to be ignored or not recognized by the host's immune system [65]. Therefore, interactions between viral miRNAs and host genes may be crucial approaches by which virus infects host. Interleukin-1 receptor 1 (IL1R1), a cytokine receptor that binds interleukin 1 (IL-1), can recruit immune-related protein activating the signaling of host immune response during viral infection [67]. MiR-BHRF1-2-5p, a miRNA encoded by Epstein–Barr Virus, can target 3′-UTR of the host's IL1R1 gene and reduce its mRNA and protein expression, which disrupts the triggering of IL-1 signaling events and following pro-inflammatory cytokine signaling [68]. In fact, miRNA has no marked preference for sequences that it binds to. Complementary base pairing, generally 10–20 bases, is the only basis for maintaining this interaction. MiRNA can target all types of RNA, including CDS or UTR of mRNA, even miRNA, circRNA and lncRNA, whereas, in addition to UTR of mRNA and miRNA, miRNA binding to these RNAs could not degrade them or affect their functions. A research used miRNAFold software and predicted six SARS-CoV-2 miRNAs that can target human miRNAs, and further used miRbase database and identified target genes of these human miRNAs [69]. Enrichment analysis of target genes found some immune-related genes, which may indicate that viral miRNAs interact with human miRNAs targeting immune genes and result in cytokine storm [69]. Cytokine storm is a physiological phenomenon that innate

immune system is uncontrolled and hyper-activated and presents excessive release of pro-inflammatory cytokines [70]. The disorder of the immune system can lead to organ damage and death [70]. A study of Merino *et al.* [71] also discovered the SARS-CoV-2 encoded miRNAs by using deep learning. Target genes of these miRNAs were closely related to respiratory diseases and viral infection, particularly, some of which have been reported to be surely morbigenous genes that induced SARS-CoV-1 and SARS-CoV-2 [71]. Besides, another study further explored the function of SARS-CoV-2 encoded miRNAs in detail [64]. And Liu and colleagues used a computational approach and identified the function of a series of viral miRNAs [64]. Lines of facts indicated that SARS-CoV-2 encoded miRNAs may regulate host's immune system and inflammatory response during virus infection, which including MR385-3p binding to 5′-UTR of TGFBR3 (a key receptor of immune system), MR147-5p binding to the enhancer of CXCL16 and ARRB2 (two inflammation-related proteins), MR66-3p binding to the enhancer of tumor necrosis factor (TNF)-*α* (an important cytokine in the cytokine storm), MR147-3p binding to the enhancer of TMPRSS2 (a receptor collaborating ACE2 responsible for virus entry to host), MR198-3p act on the enhancer of ADAR (a IFN system response-related gene), and MR359-5p and MR328-5p relative to MYH9 and RARA (two viral infection-related proteins), respectively [64]. MD2-5p and MR147-3p targeted apoptosis-related proteins CHAC1 and RAD9A, respectively, which were probably involved in the apoptosis process caused by virus infection-induced afflictions of host cells [64].

The patients with COVID-19 were fell into the status under dysregulated physiological function, which included the emergence of excessive inflammatory response [43], impairment of lymphopoiesis [3], increase of lymphocyte apoptosis [3] and disruption of endothelial barrier [3]. Mechanistically, the cooperation or crosslink of signaling pathways induced by COVID-19, for typical cases, release of proinflammatory factors such as IL-6 [72], hyperactivation of JAK/STAT pathway [73] and enhance of Akt/mTOR/HIF-1 signaling [74] contributes to the emergence of these symptoms. SARS-CoV-2-produced miRNAs attached the criss-crossed pathway network as interactors to control the key protein expression, which are responsible for turning up or down flux of these pathways to modulate the process of virus infections. Therefore, the interactome between the viral miRNAs and host pathway network is a crucial approach in which SARS-CoV-2 infects the host and results in multiple clinical symptoms during COVID-19 infections [75, 76].

## Tools and databases for analyzing or predicting human miRNAs adsorbed by SARS-CoV-2

Bioinformatics-based methods have benefited the fields of omics study [19, 77–80] and drug design [81–85]. As discussed above, the RNA genome of SARS-CoV-2 can adsorb human functional miRNAs as a sponge, which can force the host into a susceptible state. Therefore, the acquisition of these miRNAs plays a decisive role in the understanding of the process of virus infection. Human miRNAs interacted with the genome of SARS-CoV-2 can be captured or obtained from current available bioinformatics tools or platforms. And some timely studies that focus on miRNA's role in COVID-19 have used these databases, servers and algorithms to acquire these interacted miRNAs. These tools mainly provide analyzing or predicting interaction between the miRNAs and targeted RNA sequences (Table 3).

**Table 3.** Tools of studies that focus on miRNAs role in COVID-19

| Studies | Contents | Tools | URL | Description of the tool | Reference |
|---|---|---|---|---|---|
| Khan's study [55] xs | RNA–RNA interactions for viral miRNA-host mRNA and the host miRNA-viral genome | IntaRNA 2.0 | http://rna.informatik.uni-freiburg.de/IntaRNA | An algorithm for prediction of RNA–RNA interaction | [169] |
| | | microRNA.org | http://www.microrna.org | A database containing knowledge of miRNA target prediction | [170] |
| | | psRNATarget | http://plantgrn.noble.org/psRNATarget/ | A server for analysis of miRNA target | [171] |
| | Identification of host miRNA targets | Funrich | http://www.funrich.org/forum | A software for functional enrichment analysis (containing information of experimentally validated targets of host miRNAs) | [172] |
| | | miRTarBase | http://miRTarBase.cuhk.edu.cn/ | A database containing experimentally validated microRNA-target interaction | [173] |
| Fulzele's study [174] | Identification of human miRNAs targeting the SARS-CoV-2 genome | miRDB | http://mirdb.org | A database for prediction of miRNA targets | [175] |
| Bartoszewski's study [56] | Prediction of interaction between host miRNA and coronaviruses | RNA22 v2 | https://cm.jefferson.edu/rna22/Interactive/ | A method for miRNA binding sites and their corresponding microRNA/mRNA complexes | [176] |
| Tang's study [41] | Identification of host miRNA-mRNA interaction | multimiR | http://multimir.ucdenver.edu | A R package for miRNA-target interaction | [177] |
| Satyam's study [69] | Prediction of viral miRNA targeted host gene | miRanda v3.3 | http://www.microrna.org | An algorithm for prediction of miRNA target genes | [178] |
| Sardar's study [179] | Resource of antiviral host miRNAs (experimentally verified) and their targets | VIRmiRNA | http://crdd.osdd.net/servers/virmirna | A database containing experimentally validated viral miRNAs and their targets | [180] |
| | Prediction of host miRNA targeting virus genome | miRanda v3.3 | http://www.microrna.org | An algorithm for prediction of miRNA target genes | [178] |
| | | psRNATarget | http://plantgrn.noble.org/psRNATarget/ | A server for analysis of miRNA target | [171] |

## Conclusion and future remark

MiRNA is a type of direct and powerful manipulator of gene expression. MiRNA controls gene expression by binding any regions suitable for the interaction that can be located in DNA and RNA even proteins. MiRNA-based regulation (i) spreads over almost all categories of genes, which cover conventional coding RNA (transcription factor [8], enzyme [9], etc.), nuclear ncRNA [10], mitochondrial transcripts [11], via interactions with mRNA (3′-UTR, 5′-UTR and coding sequence), ncRNA [10], promoter DNA [86–88], non-Ago protein [89] and embedding in specific gene [15]; (ii) frequently participates in a variety of biological processes, including cell differentiation [90], proliferation [91], cell death [92], innate immunity [93] and migration [94] and (iii) governs the development of a number of diseases, such as cancer [34], diabetes [36], cardiovascular disease [37] and virus-infected disease [39]. The interplay between miRNA and other biomolecules is responsible for the homeostasis of a living organism. Either deprivation or forcing of the interplay may lead to disorder of physical function or the occurrence of disease. The absence of some miRNAs may result in severe symptoms even death in mice models.

Now COVID-19 has been affecting us for nearly 1 year and remains the trend of worsening in many countries. Attention to miRNA has increased the understanding of the pathogenesis and mechanism of SARS-COV-2 infection. Bioinformatics-based studies including omics-based analyses [95–97], establishment of databases [98–100] and web servers [101–105] have provided a tremendous assistance for a series of diseases research. Considering the risk and infectivity of the coronavirus, bioinformatics serves for the study of COVID-19 as a fast and effective tool and contributes to a number of emerging researches that focus on the connection between the ncRNAs and the virus infection. Based on these online RNA–RNA interaction tools, there are emerging studies that explored the role of RNA molecules interplays between virus and host in COVID-19.

Although many types of ncRNAs including miRNA, lncRNA and circRNA are involved in intracellular physiological processes and cellular signal pathways in various diseases, miRNA received more attention to the field of COVID-19 than other ncRNAs when the virus disease is developing. For one aspect, most of miRNA regulation to gene expression is direct, which may indicate that miRNA can regulate cellular signal pathways more directly and efficiently. For another, miRNA is the smallest RNA among these ncRNAs, which makes virus-releasing miRNAs unperceived by host's immune system and might facilitate the process of virus entering to host.

An interesting hypothesis is that SARS-CoV-2 genome adsorbing host functional miRNAs leading to the host's immune system in dysfunction has been verified by computational approach. A few timely studies have predicted and analyzed human miRNAs that interacted with the genome RNA of SARS-CoV-2 and target genes of these miRNAs were related to immune system, inflammatory response and cytokine storm in virus infection. According to the experience of previous knowledge in virus infection, the thought is reasonable that virus particles of SARS-CoV-2 may elude immunological recognition through depriving the host immune related miRNAs. In turn, host miRNAs targeting some function region of SARS-CoV-2 could result in an accelerated process of virus infection. Most of the therapeutic targets of COVID-19 in clinical are regulated miRNAs, which may provide the thought that the virus controls entry to cell and damaged processes by manipulating these functional miRNAs. SARS-CoV-2 also produces its own miRNAs.

Available evidence suggests that SARS-CoV-2 encoded miRNAs also can target host genes that are related to immune system, inflammatory response and cytokine storm. Most of the findings above are based on bioinformatics techniques despite lack of experimental verification, however, which reasonably explains the cause why the SARS-COV-2 infection was not recognized by host's immune system and the fact how SARS-CoV-2 destroyed the cell through control functional genes. During SARS-COV-2 infection, host-generated and virus-generated miRNAs are involved in the process of escaping immunological recognition, triggering the inflammatory response and mediating cytokine storm via interaction with related genes. Some altered miRNA expressions also can be acted as indicators of SARS-COV-2 infection in different phages.

Conclusively, the interplay of miRNA and other molecules during SARS-COV-2 infection may be a crucial manner to permit virus entry to the host. In one facet, due to the low molecular mass of miRNA, the function miRNA released by SARS-CoV-2 is not recognized by the host's immune system and interacted with human genes, which provides a suitable opportunity for SARS-COV-2 infection. In another facet, adsorption of SARS-CoV-2's RNA genome for human function miRNAs also traps the host in weakened immune protection status. Thereby, interactions between miRNA and other molecules may be a feasible strategy for the prevention and cure of COVID-19.

Although plenty of researches have reported that understanding the role of SARS-CoV-2- and host-generated miRNA presented the guiding role in the pathological causes and development of COVID-19, the contributions are not enough to provide substantial and direct assistance for the prevention and treatment of COVID-19 due to that they are still in the theoretical stage. Because COVID-19 is developing and found for just around 1 year, little experiment-based mechanistic studies are made to further explain how miRNAs regulate gene expression to affect the processes of the virus infection and replication.

However, the studies about the miRNA in other viruses may be worthy references to apply to SARS-CoV-2 that knocking down of some virus- or host-produced miRNAs resulted in the decreased copies of the viruses [27, 63, 106]. It may mean that inhibition of miRNA can effectively block RNA–RNA interaction between host and virus to suppress virus infection and replication. Considering that the property of host miRNAs with multiple targets could lead to unanticipated disorder of physiological function in host cells, these clues may indicate that SARS-CoV-2 produced miRNAs might be potential targets of the COVID-19's prevention and treatment. Therefore, the further exploring of SARS-CoV-2 encoded miRNAs is urgently needed to investigate their targetability for COVID-19.

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**Key Points**

- Bioinformatics technology contributes to a number of timely and significant studies for understanding miRNA's role in SARS-COV-2 infection.
- Genomic RNA of SARS-CoV-2 adsorbs host immune-related miRNAs to disturb immune system, which provides a suitable opportunity for SARS-CoV-2 entry and infection to host.
- SARS-CoV-2 produces and releases its own miRNAs in the host, which target host functional genes and affect subsequent signaling pathways including immune protection, inflammatory response and so on.

- Host generated miRNAs target functional genes in the SARS-CoV-2 genome further leading to the severe progression of SARS-CoV-2 infection.

## Data availability statement

All data in the manuscript are collected and available in PubMed database and Therapeutic Target Database.

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