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The Potential of MiRNA-Based Therapeutics in Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infectionmirna: The Modern Therapy for Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection

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ABSTRACT

Since the World Health Organization (WHO) designated COVID-19, a disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a pandemic in March 2020, more than 117 million individuals have been verified to have been affected throughout the world. [1] Scientists, doctors, and others are racing against the clock to discover and develop viable COVID-19 treatments. However, no effective treatment for SARS-CoV-2 infection has yet been licensed. Scientists have looked into the use of tiny RNAs like microRNAs (miRNAs) as medicines as gene therapy has become more prominent. Non-coding RNAs called miRNAs have a strong affinity for the 3'-UTRs of messenger RNAs (mRNAs)[2]. Various miRNAs may be upregulated or downregulated as a result of interactions between host cells and viral genomes. As a result, learning about the expression patterns of these miRNAs as well as their functions may help researchers figure out how to develop miRNA-based therapeutics. This study investigates the feasibility of different transfection methods and comprehensively outlines the potential targets of miRNA-based therapeutics for SARS-CoV-2 infection.

1. INTRODUCTION

MicroRNAs (miRNAs) are 19–25 nucleotide-long non-coding RNAs. In a multiprotein RNA-induced silencing complex (RISC), mature miRNAs interact with specific messenger RNAs (mRNAs) in the cytoplasm during post-transcriptional regulation. These miRNA-induced silencing complexes (miRISCs) bind with target mRNAs largely at complementary sequences in the 3′-untranslated region (3′-UTR) and reduce or enhance mRNA stability [3,4]. Complementary binding that is excellent leads in mRNA cleavage; whereas, binding that is defective results in translation failure [5]. MiRNAs were first discovered in Caenorhabditis elegans phenotype variants; through a series of experiments, it was discovered that a negative regulatory element (NRE) located at the 3′-UTR of the lin-14 gene was responsible for the observed abnormal morphology and that the element produced small RNAs molecules. Protein levels, on the other hand, did not change [3]. This unexpected discovery was later discussed, and curiosity about the phenomena grew.

Even though miRNAs are non-coding RNAs, more than 500 have been found in humans, and a single miRNA may influence hundreds of distinct mRNAs [7]. Several studies have found that a single miRNA may influence 30–60% of mammalian mRNAs [8,9]. MiRNA research has grown in popularity, with substantial emphasis on finding and characterizing miRNAs for their potential as biomarkers or in targeted therapeutics in both animal and human cells [6,10]. Epigenetic factors and dysregulation during miRNA synthesis can affect their expression, resulting in anomalies in a variety of cellular processes such as proliferation, growth, differentiation, apoptosis, cell cycle, and tissue formation [11,12]. Furthermore, numerous miRNAs have been identified to mediate changes in host defense systems associated with cellular immunity.

2. Roles of miRNAs in viral infections

Immunity is a multifaceted process. Several biochemical pathways, including miRNAs, have long been recognized to mediate the process of inflammation predominantly through immune cell regulation during an immunological response. Most pathogens, such as viruses, encode miRNAs to aid their survival, just like their hosts [14]. MiRNAs are amenable to host miRNA-mRNA co-modulation expression during infection due to their small size, lack of immunogenicity, and great functional flexibility [9]. Viruses must reproduce their genetic material utilizing the host's cellular machinery to secure their survival. Crosstalk between

host miRNAs and the viral genome can occur during this process [8,15,16]. These interactions can take place through three pathways: mRNA blocking, mRNA stabilization, and mRNA degradation via protein complexes [17]. Viruses, on the other hand, can cause changes in cellular miRNAs before infection, so facilitating pathogenesis. Although some miRNAs attach to the coding areas of viral proteins, they primarily bind to the 5′ and 3′ non-translated regions (NTRs) [18,19].

Some research has revealed that interactions between the host miRNA and the viral genome are helpful to virus survival [20]. Wang et al. [21] found that oncogenic human papillomavirus virus 16 HPV16 and HPV18 infection may inhibit the host miRNA miR-34 and disrupt the expression of the tumor suppressor p53, resulting in tumor development. Poxvirus, the human virus that causes smallpox, has been found to aid in the destruction of host miRNAs. Further research revealed that the capacity of poxvirus to bypass the host miRNA defense mechanism, as well as the binding of host miRNAs in the 3′-UTR of the viral genome, dramatically downregulated host miRNAs, enhancing infected cell proliferation.]. A miRNA from the influenza PB1 gene coding area coupled to the host miRNAs miR-323, miR-491, miR-485, miR-654, and miR-3145, causing cell destruction following viral infection [19]. When compared to non-infected cells, human epithelial type 2 (HEp-2) cells infected with respiratory syncytial virus (RSV)-green fluorescent protein (GFP) had reduced miRNA levels, and the NF-B monomers p65, p50, and p52 were dramatically changed. Even though RSV's genome does not include any miRNAs, it's binding to the host miRNA miR-146a-5p lowered its expression and decreased the expression of miR-345–5p, let-7c-5p, and miR-221. Furthermore, because the expression of p21 and the 70 kDa heat shock protein (HSP-70) was inhibited, these cells did not correctly react to and destroy the virus [9].

Some host miRNAs, on the other hand, prevent viral accumulation. MiRNAs are thought to respond to pathogenic viral activities primarily through the presence of miRNA response elements (MREs) inside the viral genome's 5′- and 3′-UTRs [22]. By engaging the RNA-mediated silencing mechanism to act on the viral proteins Tas and Bet, MiR-32 can prevent the retrovirus primate foamy virus type 1 (PFV-1) from spreading further in normal human cells [23]. During H1N1 influenza virus infection in mice, miR-144 targeted the tumor necrosis factor (TNF) receptor-associated factor 6 (TRAF6)/IRF7 signaling axis and further lowered type-1 interferon (IFN–I) levels [24]. Peng et al. [25] studied the role of hsa-miR-1-

3p in viral replication inhibition by focusing on the supporting host factor. After infection with two primary influenzas A virus (IAV) subtypes, H1N1 (PR8) and H3N2, Peng et al. [25] explored the role of hsa-miR-1-3p in viral replication suppression by targeting the supporting host factor ATP6VIA in HEK293T cells.

The increased interest in miRNA-related research is due in part to its role in understanding the mysteries of RNA, as well as the fact that they may be utilized to find targets for alternative therapeutics for diseases like COVID-19, which is caused by the severe acute respiratory syndrome-corona virus-2 (SARS-CoV-2). According to WHO epidemiological statistics [26], SARS-CoV-2 has spread to almost 200 countries and infected over 65.8 million individuals, resulting in approximately 1.5 million fatalities worldwide. SARS-CoV-2 is a virus that causes SARS. SARS-CoV-2, like SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV), is a member of the Coronaviridae (subfamily Coronavirinae) family, however, it causes less morbidity and death than the two preceding viruses [27,28]. SARS-CoV-2 is an enveloped, non-segmented, positive-sense single-stranded RNA virus [27,29] that belongs to the same lineage as SARS-CoV, which was responsible for the 2003 SARS outbreak. SARS-CoV-2 is one of seven CoV family members that can infect humans and cause diseases with a wide range of clinical manifestations by attacking the respiratory epithelial barrier and causing serious acute lung injury (ALI), sometimes acute respiratory distress syndrome (ARDS), and even death from multi-organ failure (MOF) due to massive inflammatory cell infiltration and proinflammatory cytokine/chemokine release, sometimes referred to as a "cytokine storm.

3. Host-pathogen interactions in SARS-CoV-2 infection

SARS-CoV-2 has a pleomorphic or spherical-shaped capsid envelope 150–160 nm in size, a polycistronic mRNA with a 5′ cap and 3′ poly-A-tail, and an unsegmented, positive, single-stranded RNA genome, [33], [34]]. ORF3a, ORF3b, ORF6, ORF7a, ORF7b, ORF8a, ORF8b, and ORF9b are the two major polyproteins in SARS-CoV-2; four structural proteins: spike (S), envelope (E), membrane (M), and nucleocapsid (N); and eight accessory proteins: ORF3a, ORF3b, ORF6, ORF7a, ORF7b, ORF8a, SARS-CoV-2 also doesn't have a hemagglutinin esterase gene, which is closely related to the betacoronavirus human coronavirus (hCoV) HKU1 [32,34]. ORF1ab uses papain-like protease (PLpro) and 3C-like protease (3CLpro) to cleave a total of 16 non-structural proteins (NSP) dubbed NSP1–16. ORF1ab cleaves the replicase polyprotein with the aid of papain-like protease (PLpro) and

3C-like protease (3CLpro), resulting in the expression of 16 non-structural proteins (NSP) called NSP1–16. Each NSP performs a specific function in disturbing the host cell environment while maintaining viral security. PLpro (nps3), 3CLpro (nsp5), and RNA-dependent RNA polymerase/RdRp (nsp12) are only a few of the NSPs that encode important proteins [32,35]. RdRp is involved in many aspects of the viral life cycle, and scientists believe that one of its active sites might be utilized as a therapeutic target [36]. S, E, M, and N, which are structural proteins, are required for viral assembly and have the primary function of initiating host cell infection [34]. SARS-CoV-2, like other viruses, causes a variety of issues in host cells, ranging from aberrant gene expression to complete cell death, all of which are linked to the host's immune response. Because it incorporates complicated mechanisms across the system, the molecular mechanism is still visible [37]. Because these epithelia are more sensitive to respiratory infection due to their high risk of pathogen exposure, type II pneumocytes and mucosal ciliated cells in the lung are assumed to be the main targets of SARS-CoV and IAV infection [38]. Angiotensin-converting enzyme 2 (ACE2) receptor and transmembrane protease serine 2 (TMPRSS2) are the major targets of SARS-CoV-2 in airway epithelial, alveolar epithelial, and vascular endothelial cells [39]. The S1 subunit of the surface-expressed S protein has a receptor binding domain (RBD). The S1 component of the surface-expressed S protein of SARS-CoV-2 binds to ACE2 receptors on target host cells, which starts the infection process. The S1 subunit is cleaved, while the S2 subunit, which is made up of a fusion peptide (FP) and two heptad repeat sections, HR1 and HR2, folds in on itself, joining the two heptad repetition areas. The viral genome is then unwrapped in the cytoplasm of the host cell [39].

Several inflammatory pathways have been discovered to be activated during SARS-CoV-2 infection [40]. Pattern recognition receptors (PRRs), particularly Toll-like receptor type 3 (TLR3), respond to pathogen-associated molecular patterns (PAMPS) when the innate immune system is activated, resulting in robust intercellular signaling via the Toll/IL-1R domain-containing adaptor-inducing interferon-beta (IFN-) (TRIF)-dependent pathways [14]. The transcription factor nuclear factor kappa B (NF-B) may be activated through these pathways to induce further immunological responses [14,29,41]. NF-B activation can result in the induction of downstream factors such as proinflammatory cytokines such as interleukin-6 (IL-6), interferon-alpha (IFN-), and IFN-, IL-1b, IL-6, IL-12, IL-18, IL-33, TNF-, and tumor growth factor-beta (TGF-); and chemokines such as C–C motif chemokine ligands CCL2, CCL A "cytokine storm" can occur when these cytokines are activated. Yang

et al. [43] discovered that higher levels of three proteins, IL-1 receptor antagonist, CCL7, and CXCL10, were linked to viral load and lung damage in individuals with moderate to severe COVID-19. Poor consequences, including death, were frequently unavoidable in such situations.

Antibodies to immunoglobulin M (IgM) and immunoglobulin G (IgG) were found 6–8 days after exposure [44]. At days 6–8, antibodies to immunoglobulin M (IgM) and immunoglobulin G (IgG) were detected, indicating that adaptive immunity was also activated during the infection [44]. IgM was reported to peak at 3 weeks and decline slowly, whereas IgG continued to increase and may persist beyond 7 weeks [45]. Major histocompatibility complex class 1 (MHC class 1) complexes on the cell surface help cytotoxic T lymphocytes (CTLs) or CD8+ T lymphocytes detect infected cells. Immune molecules are drawn to the cells as a result of this recognition. The SARS-CoV-2 surface glycoprotein contains five distinct CTL epitopes, three sequential B cell epitopes, and five discontinuous B cell epitopes, according to Baruah and Bose [46]. Samples taken from SARS-CoV-2-infected people, on the other hand, revealed that CD3+, CD4+, and CD8+ levels were mainly below normal, and B and NK cells were dramatically reduced. This discovery corroborated previous research that implicated direct viral death of lymphocytes as the source of large decreases in diverse immune cell types in COVID-19 patients, resulting in lymphopenia [39,47]. The presence of multiple changed genes in bronchoalveolar lavage fluid was reported by Xiong et al. [48], with one striking result: an increase in TP53I3, which is known to be important during p53 signaling-induced programmed immune cell death.

Since a study of recombinant IFN as a SARS-CoV therapy had promising results, a similar experiment for SARS-CoV-2 is underway [49]. SARS-CoV-2 patients are currently being treated with a variety of pharmaceutical therapies that have been shown to ameliorate IAV, SARS, and MERS infections. However, no particular, effective medications for COVID-19 patients have yet been approved in clinical trials [50].

4. miRNAs in SARS-CoV-2

The discovery of miRNAs as part of RNAi with antiviral properties was well documented, but its significance remained unknown. When SARS-CoV-2 binds to host receptors, it can release its genome into the cytoplasm, where it can replicate using the host machinery. Once in the cytoplasm, host endogenous miRNAs activate an antiviral defense system that

identifies short viral RNA (svRNA) [51,52]. Dicer, an RNA-ase III endonuclease that processes mature miRNAs, helps the host RNAi machinery to limit viral RNA replication by detecting the viral double-stranded RNA (dsRNA) via complementary sequence recognition. This enables the virus to avoid the antigen-specific reaction of the host to viral proteins [53]. Numerous cellular miRNAs might target the SARS-CoV-2 genome, according to an in silico analysis, with each miRNA having up to 10 target sites. As a result, these miRNAs have the potential to be used as therapeutics. However, as demonstrated by Fulzele et al. [20] in a miRNA study, miRNA activity in individuals infected with SARS-CoV-2 is age-dependent. Younger patients have more host miRNAs with viral complementary binding sites than those who are older, and hence may be better equipped to block viral replication. Research by Huan et al. [54], which found that miRNA levels in peripheral blood are related to age, supports this conclusion.

4.1. miRNA-based therapeutic approaches in SARS-CoV-2

The benefit of recognizing the characteristics of any disease, such as those caused by viral infections, is that it aids scientists in developing treatments. Potential therapy targets include nucleosides, nucleotides, viral nucleic acids, and enzymes/proteins involved in SARS-CoV-2 replication and transcription [49]. MiRNAs have a crucial association with a viral infection, since they may either promote viral activity or limit replication through a variety of mechanisms, as discussed briefly above. Several investigations of miRNA-based therapeutics have been done, and miRNAs have been shown to improve cancer survival rates [12]. MiRNA-based therapeutics are now aimed at either inhibiting or increasing miRNA activity. Modified miRNA inhibitors or oligomers, such as miRNA antisense treatment, small molecule inhibitors, locked nucleic acids (LNAs), and peptides, are used to suppress miRNA expression. MiRNA antisense treatment, small molecule inhibitors, locked nucleic acids (LNAs), peptide nucleic acids (PNAs), morpholinos, miRNA sponges, and miRNA binding site silencing employing gene-targeted single-stranded RNA (ssRNA) sequences are all examples of strategies that suppress miRNA production. MiRNA replacement treatment, on the other hand, involves transfecting synthetic mimics or miRNA-loaded lentiviral vectors into cells to increase cellular miRNA activity [55]. An antagomir is a short synthesized RNA with complementary sequences that can attach to certain genes [56]. The first synthetic oligonucleotide treatment, Antagomir miR-122 transfection, was reported to cure hepatitis C virus (HCV) infection. Following that, other investigations using the same methodology were

undertaken. MiRNA mimics, unlike antagomirs, interact with the target by forming a complex. MiRNA mimics, unlike antagomirs, interact with the target by associating with the non-distinguishable sense of actual endogenous miRNAs to cause changes in mRNA expression via miRISC (Fig. 1) [5,22]. The primary goal of miRNA mimic therapy is to restore the functional level of an underexpressed intracellular miRNA linked to illness. Several miRNA mimic medicines have shown promise, particularly in cancer, and one hepatocellular carcinoma clinical study has been undertaken. The trial was discontinued in September 2016 due to five incidences of immune-related adverse effects.

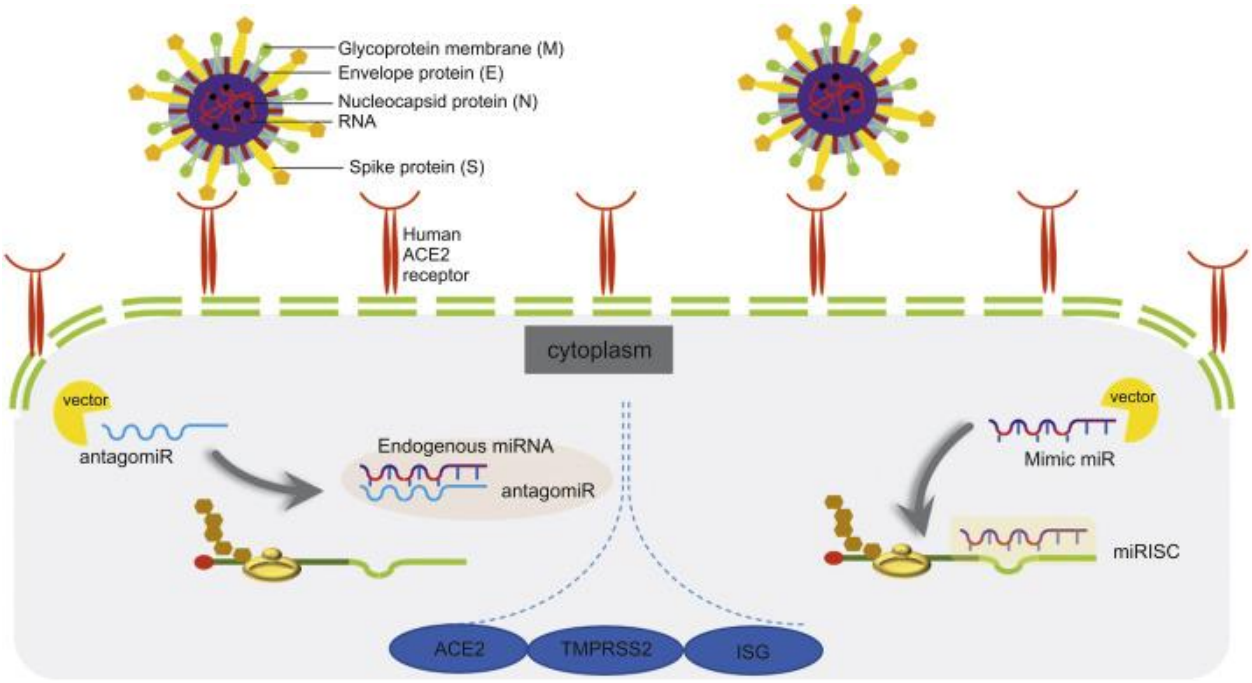

Figure no. 1. The illustration shows how transfected antagomir and miR mimic to host cell being processed intracellularly. miRNA: microRNA; antagomir: antagonist microRNA; ACE2: angiotensin-converting enzyme-2; TMPRSS2: transmembrane protease serine 2; ISG: interferon-stimulated gene; miRISC: miRNA-induced silencing complex

4.2. miRNAs that target viral proteins related to hosting binding

The spike (S) glycoprotein is thought to attach to host cells via the ACE2 receptor [29] among the structural proteins that wrap up SARS-CoV-2. The lungs and heart have a lot of ACE2 receptors, and the digestive system, testes, and kidneys have a lot of them as well. The vast range of symptoms and clinical indications of SARS-CoV-2 infection can be explained by the location of ACE2 receptors [57]. ACE2, a homolog of ACE, regulates blood pressure

and electrolyte levels in the circulatory system [58,59]. Following the S1 subunit's binding to ACE2, the S2 subunit of the S protein is anticipated to undergo conformational changes, resulting in viral-to-host attachment, which enhances viral entry, similar to SARS-CoV. SARS-CoV-2 releases its viral RNA genome into the body after internalization. Following the S1 subunit's binding to ACE2, the S2 subunit of the S protein is anticipated to undergo conformational changes, resulting in viral-to-host attachment, which enhances viral entry, similar to SARS-CoV. SARS-viral CoV-2's RNA genome is released into the cytoplasm after internalization (Fig. 1). Although peptidase activity is not required for attachment, numerous transmembrane proteinases may be implicated [59,60]. Since the SARS/MERS pandemic more than ten years ago, RNA interference (RNAi) has been routinely used to silence particular mRNAs in SARS-CoV infection. For example, Qin et al. [60] transfected the sense and antisense templates of small interfering RNAs (siRNAs) into SARS CoV-infected HEK293T cells and investigated their capacity to connect with the SARS-CoV S gene and alter its expression. Qin et al. [60] transfected the sense and antisense templates of small interfering RNAs (siRNAs) into SARS-CoV-infected HEK293T cells and investigated the capacity of the small non-coding RNAs to connect with the SARS-CoV S gene and control its degradation, resulting in host cell receptor binding failure. MiRNA-mediated RNAi, like siRNA, has sparked a lot of attention. ACE2 is hypothesized to protect the lungs from excessive inflammation that might lead to ARDS after a respiratory illness. The results of one research targeting the ACE2 receptors in the lungs during H5N1 influenza infection resulted in acute lung damage or ARDS, as indicated in Table 1 [[62], [63], [64], [65], [66]]. When the virus bound, it affected ACE2 expression in a big way, according to this study. Plasma miR-200c-3p levels were dramatically raised in a mouse model and were linked to ARDS symptoms. The animal model of pulmonary edema was effectively alleviated by antagomir miR-200c-3p administration, which upregulated ACE2 expression and promoted NF-B activation [62]. The findings of Nersisyan et al. [67] were likewise supportive of this research. When the virus bound, it affected ACE2 expression in a big way, according to this study. Plasma miR-200c-3p levels were dramatically raised in a mouse model and were linked to ARDS symptoms. The animal model of pulmonary edema was effectively alleviated by antagomir miR-200c-3p administration, which upregulated ACE2 expression and promoted NF-B activation [62]. The results of Nersisyan et al. [67], who found multiple miRs that target ACE2 and TMPRSS2 genes and are controlled by lysine-specific demethylase 5 B, such as hsa-let-7e/hsa-miR-125a and hsa-miR-141/hsa-miR-200 (JARID18). Surprisingly, Sacconi et al. [68] used bioinformatics and experimental analysis to show that patients with

head and neck cancer may be more resistant to SARS-CoV-2 infection because TMPRSS2 expression is downregulated. Further investigation revealed a close link between the two. Further investigation revealed a substantial link between miR-31–3p and miR-503–5p expression. However, investigations targeting specific miRNAs in SARS-CoV-2-infected cells are needed to corroborate this conclusion. Another study looked at the expression of multiple host miRNA targets inside SARS-CoV in bronchoalveolar stem cells (BASCs) (Table 1 [63]). The activities of not only the S glycoprotein but also the nucleotide (N) protein, matrix (M) protein, tiny envelope (E) protein, and ORF1a were discovered to be enhanced by downregulated expressions of miR-17, miR-574–5p, and miR-214 in BASCs, largely via acting on host receptor binding. As a result, upregulating these miRs and inhibiting the produced viral proteins is likely to prevent viral internalization. MiR-223 and miR-98 showed similar outcomes, with downregulation of these miRs (by 8.7 and 5.6 fold, respectively) allowing the NPC to function.

Table no 1. Examples of miRNA-based therapies for respiratory infectious diseases.

miRNA therapy	Virus	Targets	Effects	Refs.
Antagomir-miR-200c-3p	H5N1 influenza	ACE2, NF-κB upregulation	Decrease lung edema in severe pneumonia in mice model	[62]
Antagomir-200c-5p	H5N1 influenza	DUSP1	Attenuate pulmonary inflammatory responses and lung injury	[62]
miR-17 mimic	SARS-CoV	Viral S, N, E, M protein and ORF1a	Deactivate viral proteins based on microarray analysis (BASCGAP	[63]
miR-574–5p mimic				

miRNA therapy	Virus	Targets	Effects	Refs.
			consortium) in bronchoalveolar stem cells (BASC)	
miR-214 mimic				
miR-223 mimic	SARS-CoV	N and S protein	Viral entry based on microarray analysis (BASCGAP consortium) in BASC	[63]
miR-98 mimic				
miR-155 mimic	VSV	STAT1, STAT2	Phosphorylate STAT1/2 to activate ISGs transcription in murine-VSV infected ex vivo model	[64]
Inhibitor hsa-let-7e-5p	Human-Adv	NF-κB, SOC, STAT, and IFN	Viral replication in human primary lung fibroblasts (IMR-90) cells infected with HAdV5	[65,66]

Abbreviation: Antagomir: antagonist miRNA; ACE-2: angiotensin-converting enzyme-2; DUSP1: dual-specificity phosphatase 1; BASC: bronchoalveolar stem cells; BASCGAP:

bronchoalveolar stem cells genome anatomy projects; STAT1/STAT2: signal transducers and activators of transcription 1 and 2; VSV: vesicular stomatitis virus; ISG: interferon-stimulated gene; Human-Adv: human adenovirus; SOC: suppressor of cytokine; IFN: interferon; HAdV5: human adenovirus-5.

In silico studies have identified 3CLpro and RdRp as promising target candidates with exceptional outcomes. However, no research including miRNA has been able to corroborate this link. Six designed 21-mer siRNAs were able to target various areas of the SARS-CoV replicase gene in a study done by He et al. [69]. (ORF1a). Although the outcomes of this in vitro experiment were encouraging, their therapeutic use has yet to be confirmed.

4.3. Role of miRNAs in accelerating interferon-induced antiviral activity

Three studies have been published so far to identify miRNAs that are highly expressed in SARS-CoV-2 patients' lung epithelial cells. Chow and Salmena [71] discovered 11 miRNAs that were detected in all of the studies: hsa-miR-5047, hsa-miR-1301–3p, hsa-miR-125a-3p, hsa-miR-19b-2-5p, hsa-miR-141–3p, hsa-miR-19b-1-5p, hsa-miR-13 Scientists will be able to create miRNA-based therapeutics for patients with SARS-CoV-2 infection because to studies like these. Although there are no current or clinically licensed antagomirs or analogs for SARS-CoV-2, certain trials have demonstrated promising outcomes against other viral infectious illnesses, such as influenza A [25,71].

Host miRNAs that act as viral enhancers or inhibitors have been discovered through genome-wide studies. MiRNAs work as antiviral drugs by limiting viral RNA synthesis, halting viral replication, decreasing pro-viral proteins, or driving the virus to enter a dormant state [73]. Dysregulation of host miRNAs caused by viral genome interaction in SARS-CoV-2 infection disrupts TLR signaling, which is important for antiviral activities like IFN regulation and cytokine production, as well as IL, TRAF6, S1P1, estrogen receptor, protease-activated receptor (PAR), and bone morphogenetic (BMP) signaling, according to Khan et al. [74]. When a virus recognizes its host, the host's innate immunity activates the NF-B transcription factor, which modulates the production of interferon-stimulated genes (ISGs). ISGs fight viruses by expressing the genes that make type 1 interferons. Several miRNAs have been discovered to help with the regulation in this process [75]. Wang et al. [64] found that delivering miR-155 mimics to murine macrophages following ex vivo vesicular stomatitis virus (VSV) infection changed the phosphorylation of signal transducer and activator of

transcription 1 and 2 (STAT1 and STAT2). STAT1/2 is distinguished by its capacity to bind to DNA in ISG protein-coding areas. As a result, they operate as transcription promoters [73,76]. Yang et al. [77] discovered the binding site for IFN-induced NF-B in the miR-21 promoter of a complex that contained STAT3 and the p65 NF-B subunit using chromatin immunoprecipitation (ChiP) study of miR-21 in the DU145 cell line. Upregulation of miR-223 induced apoptosis in influenza virus-infected patients by repressing CREB activity and modulating NF-B activity, thereby supporting proinflammatory responses [78,79]. Upregulation of miR-223 induced apoptosis in influenza virus-infected patients by repressing CREB activity and modulating NF-B activity, thereby supporting proinflammatory responses [78,79]. Downregulation of miR-200a in the host increased ISG protein expression by targeting IFN- receptors and STAT2/4, whereas downregulation of miR-200a in the host increased ISG protein expression by targeting IFN- receptors and STAT2/4, thereby supporting MiR-9 was one of the miRNAs that upregulated NF-B expression and synergized cell sensitivity to TNF- during human coronavirus OC43 infection, according to Lai et al. [80]. MiR-9 was one of the miRNAs that upregulated NF-B expression and synergized cell sensitivity to TNF-.MiRNA may potentially have a role in the activation of T and B cells after SARS-CoV-2 infection. Several research has looked at the protective role of miRs in adaptive immune responses, such as miR-17-92, which is thought to be a major regulator of T cells growth and promotes T cell survival via BCL-2 and phosphatase and homolog-mediated tensin (PTEN) [81]. Furthermore, investigations of miR-155 in vitro and in vivo have revealed that its overexpression is linked to a higher number of activated human CD8+ T cells. MiR-155 deficiency, on the other hand, resulted in enhanced type I IFN signaling and decreased CD8+ T cell proliferation [82].

Recent computational studies have suggested that SARS-CoV-2 encodes miRNAs that may play a role in evading host immune surveillance via several signaling pathways that could be targeted indirectly, including the TLR, IL, TRAF6, autophagy, IFN-I, Wnt, and mammalian target of rapamycin (mTOR) signaling pathways [74]. This conclusion was backed up by research by Chow and Salmena [71], who found that SARS-CoV-2 may have evolved to develop a complex secondary structure including the coding area, allowing it to dodge the effects of endogenous RNAi. However, this discovery did not bring the theory to a conclusion, and further research was required to corroborate the findings. A study of the bovine leukemia virus was the first to discover miRNAs in a virus (BLV). Only when miRNAs attach to the mRNA of transcription factors can this virus replicate? Based on data

acquired utilizing HEK293T cells transfected with a plasmid encoding an EBOV pre-miRNA, and the host cell machinery stimulated viral miRNA synthesis following contact [17], the Ebola virus (EBOV) has been shown to encode multiple miRNAs.

5. MiRNA delivery systems

Because administered miRNAs may access multiple cytosolic mRNAs, systemic miRNA delivery still confronts substantial obstacles. Immunity is a double-edged sword in infections, and miRNAs have been shown to drive the innate immune response or can be rejected by cellular immunity [12,22]. Furthermore, miRNAs' physiological features, such as their short half-life, making them challenging to work with. A miRNA may be destroyed before reaching its target [83], making naked miRNA delivery unfeasible. As a result, each miRNA must be attached to a unique vehicle. When designing vectors for miRNA delivery, several factors must be addressed, including potential toxicity and the formulation of the optimum dosage to enhance bioavailability [12]. Nanocarriers may be the key to reducing potential toxicity. Nanocarriers based on organic, inorganic, lipid, protein, glycan, or synthetic components have recently been produced [84,85]. Liposome-based, nanocrystal-based, emulsion-based, and iron-carbohydrate complex-based nanocarriers are some of the carriers employed in clinical settings [86]. To ensure maximum transfection via cells, nanocarriers are frequently chemically modified with peptide-like antibodies, proteins, or small compounds [87]. Nanocarriers may be the answer to reducing the toxicity and immunogenicity issues associated with viral vectors. A nanocarrier or vector is frequently required for nucleic acid delivery methods. The use of a viral-capsid vector is still common, although it typically results in severe immunological reactions in the host [88,89].

6. CONCLUSIONS

The function of microRNAs in the pathobiology of SARS-CoV-2 has piqued researchers' curiosity. Although the broad mechanism of viral infection for SARS-CoV-2 has been adequately explained based on that of related viruses SARS-CoV and MERS-CoV, numerous uncertainties about the precise molecular signalling pathways involved remain. Several miRNA-related research have sought to investigate the link between short non-coding RNAs and mRNA expression. The fundamental viral proteins that can be targeted by host miRNAs to inhibit infection are SARS-structural CoV-2's and auxiliary envelope proteins. The degradation of the S glycoprotein, N and M proteins, and ORF1a has been found to be

induced by miR-17, miR-574–5p, and miR-214. Host immunity is initiated when the virus binds to ACE2 receptors, in an attempt to destroy the virus and prevent further reproduction. Several miRNAs, such as miR-155, would allow us to target the host's innate as well as adaptive immunity. It has also been discovered that miR-9 helps to enhance immunity by upregulating NF-B expression. Some miRNAs might be employed as diagnostic or therapeutic tools in the future. The findings of screens for miRNA imbalance can be turned into miR-inhibitors or miR-mimics for therapeutic purposes. However, significant obstacles remain, particularly in the distribution of miRNAs in a safe manner. To address this issue, a variety of solutions are being explored. We know that nonviral vectors may be utilised to transfect miRNAs with less immunogenic and harmful side effects. However, further research is needed in the near future to establish an effective and accurate delivery system for miRNAs to cure SARS-CoV-2 infection.

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