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New Insight of microRNAs & short interfering RNA in Treatment of COVID-19; A Narrative Review

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Abstract: Since 31 December 2019, the coronavirus disease 2019 (COVID-19) resulted in a state of hyperinflammation syndrome and multiorgan failure. In areas with pandemic outbreaks, despite several emerging vaccines, supportive treatments to mitigate fatality rates were required. Growing evidence suggests that several small RNAs such as microRNAs (miRNAs) and short interfering RNA (siRNA) could be candidates for the treatment of COVID-19 by inhibiting the expression of crucial virus genes. small RNAs by binding to the 3-untranslated region (UTR) or 5-UTR of viral RNA play an important role in COVID-19-host interplay and viral replication. In this review, the authors sought to specify the efficacy and safety of miRNAs and siRNA expressions of patients with COVID-19, which has an axial role in the pathogenesis of human diseases.

Keywords: COVID-19; miRNAs; siRNA; Treatment

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1. Introduction

Based on the last update of the National Center for Immunization and Respiratory Diseases (NCIRD) on 15 February 2020, six types of coronaviruses were known to infect the human's population, as follows: 1) 229E (-coronavirus), 2) NL63 (-coronavirus), 3) OC43 (β-coronavirus), 4) HKU1 (β-coronavirus), 5) MERS-CoV (the beta coronavirus that causes Middle East Respiratory Syndrome), and 6) SARS-CoV-1 (the beta coronavirus that causes severe acute respiratory syndrome). Coronaviruses are distributed broadly among animals and humans and cause multi-organ failure, especially in various pulmonary regions.

Similar to other coronaviruses, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) belongs to the genera β coronavirus family and primarily causes respiratory tract infections (1). Two types of the mentioned coronaviruses (SARS-CoV and MERS-CoV) caused coronavirus disease 2019 (COVID-19) pandemic in Wuhan (Hubei Province, China) since 31 December 2019 by entry into human cells. These types are highly pathogenic and rapidly spread throughout the world (approximately more than 200 countries) (2, 3), and have affected the health status of more than 21.7 million individuals with a fatality rate of around 3.5% (World Health Organization, 2020). Meanwhile, mathematical models have suggested that 40–81% of the worldwide population could be infected with COVID-19 (4, 5).

With the quick worldwide spread of COVID-19, advanced treatment for COVID-19 patients became necessary, especially in areas in need of COVID-19 vaccination to mitigate fatality rates. Carthew and Sontheimer (6) showed that microRNAs (miRNAs) and short interfering RNA (siRNA)-based regulation has direct implications for fundamental biology as well as disease etiology and treatment, such as cancers and infections (7). Nevertheless, small RNA technology for combatting COVID-19 allows specific binding and silencing of therapeutic targets by using miRNAs and siRNA molecules (8). In this review, the authors sought to specify the efficacy and safety of miRNAs and siRNA expressions of patients with COVID-19, which has an axial role in the pathogenesis of human diseases.

2. Methodology

The main aims of this narrative review were to identify new studies that describe novel results about small RNA interference mechanisms as a crucial antiviral defense system in patients with COVID-19. Authors searched WHO, MEDLINE (PubMed) and Web of Science for peer-reviewed articles from

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the earliest available dates with the help of a medical librarian. A full list of search terms and search strategies used for the study is presented in Figure 1.

3. Results

3.1. New Insight about COVID-19 Infection

Despite several emerging vaccines, there is no definitive treatment for COVID-19. The available treatments today are based on previous experience with similar viruses such as SARS-CoV, MERS-CoV, and influenza virus. COVID-19 is a single-stranded RNA-enveloped virus associated with a nucleoprotein within a capsid comprised of matrix protein (9), and a genome of nearly 30,000 nucleotides (10). Once the SARS-CoV-2 enters the cell, the viral RNA is released, polyproteins are translated from the RNA genome, and replication and transcription of the viral RNA genome occur via protein cleavage and assembly of the replicas–transcriptase complex (11). It's remarkably extensive remodeling of the intracellular environment, and its multifaceted immune evasion strategies (12). Thus, the capacity of the SARS-CoV-2 to destroy the human host cell by liberating its RNA genome is high.

Large randomized controlled trials stand as the Gold Standards for COVID-19 therapy and offer a solid scientific base on which to make treatment decisions (13). Recently, a new hypothesis presented a distinct mechanism of the possibility that SARS-CoV-2-induced respiratory damage apart from cytokine storm syndrome (CSS). CSS was earlier explained in the haemophagocytic lymphohistiocytosis process about rheumatological conditions and following Toll-like receptor immunotherapy (14). More recently, CSS has been implicated in patients with viral infections. Meanwhile, in recent days death due to COVID-19 is primarily created with a CSS, resulting in a state of hyperinflammation syndrome and multiorgan failure (16). A large cohort study relieved that the total mortality rates of COVID-19 were 2.3%, 8.1%, and 14% in ordinary, severe, and critical cases, receptively (17).

Banerjee and colleagues (17) comprehensively defined the interactions between SARS-CoV-2 proteins and human RNAs. NSP16 binds to the mRNA recognition domains of the U1 and U2 splicing RNAs and acts to suppress global mRNA splicing upon SARS-CoV-2 infection. NSP1 binds to 18S ribosomal RNA in the mRNA entry channel of the ribosome and leads to global inhibition of mRNA translation upon SARS-CoV-2 infection. Finally, NSP8 and NSP9 bind to the 7SL RNA in the signal recognition particle and interfere with protein trafficking to the cell membrane upon SARS-CoV-2 infection. Conversely, network analysis indicates that SARS-CoV-2 infection might lead to acute respiratory injury in patients with COVID-19 by affecting surfactant proteins and their regulators SPD, SPC, and TTF1 through NSP5 and NSP12 (19).

Both SARS-CoV-2 and SARS-CoV cause lethal disease in humans, characterized by an exacerbated inflammatory response, extensive lung pathology, and lethal disease in humans (20). Both types of coronaviruses utilize the same molecule, angiotensin-converting enzyme 2 as a receptor for entry into the human host cells. A typical feature of COVID-19 is the suppression of type I and III interferons (IFN)-mediated antiviral immunity. Taken together, these results indicate that the SARS-CoV-2 membrane (M) protein antagonizes type I and III IFN production by targeting RIG-I/MDA-5 signaling and subsequently impeding the phosphorylation, nuclear translocation and activation of IRF3 attenuates antiviral immunity and enhances viral replication (21). It is recommended that researchers of virology for COVID-19 treatment should have vigorous screening for various small RNAs.

3.2. Small RNAs strategies and advantages

In March 2020, the Study Group of the International Committee on Taxonomy of Viruses reported that human coronavirus infections mainly result in respiratory cells, including bronchial epithelial cells, pneumocytes, and upper respiratory tract cells (22). Due to the nature of COVID-19 (positive-sense single-stranded RNA viruses), several respiratory nucleic acids could be a candidate for treatment (like miRNAs and siRNA), which have an axial role in the pathogenesis of human diseases.

Generally, plants and all living organisms protect themselves from virus infection via the production of miRNAs (23). Meanwhile, siRNA can be delivered to the cytoplasmic space to engage the RNA-induced gene-silencing directly with minimal processing by host cells (8). miRNAs and siRNA can interact with the 3 untranslated region (3 UTR) to induce small RNA degradation and translational repression (24, 25). Thus, the review of respiratory small RNAs expressions seems necessary and could have positive beneficial effects in treating COVID-19.

Although vaccines based on either DNA/mRNA or protein have been deployed, their efficacy against emerging variants requires ongoing study, with multivalent vaccines supplanting the first-generation vaccines due to their low efficacy against new strains. RNA-based therapies offer unique opportunities to expand the range of therapeutic targets by conventional small molecules or proteins (26). Some of the previous studies reported the small RNAs to have an antiviral inhibitory effect against SARS-CoV-2, an RNA virus that was known to infect the human population around the world (23, 27, 28).

3.3. MicroRNAs (miRNAs)

miRNAs are a family of endogenous, small, 22-nucleotide long single-stranded RNAs, a non-coding RNA molecule that modulates some vital biological processes by suppressing

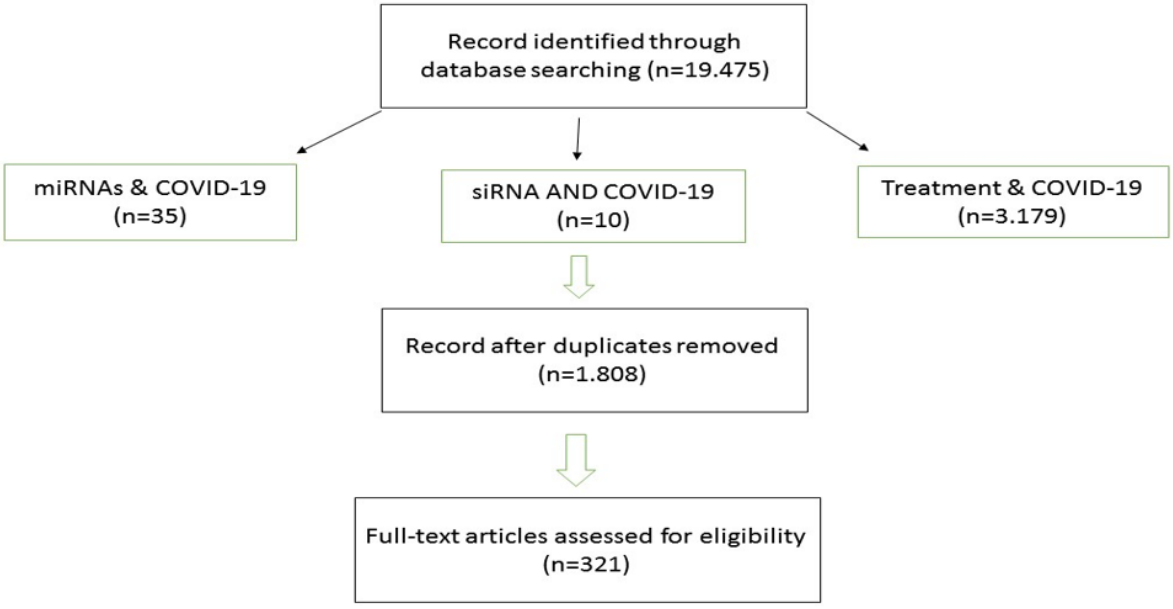

Figure 1: PRISMA flow diagram of the literature search process.

gene expression post-transcriptionally (29, 30), and regulate critical cellular pathways in a number of human disease conditions, including RNA viral infections and anti-viral defense (27). miRNAs play a significant role in gene regulation via binding to a specific region in open reading frames and/or untranslated regions to block the translation processes through either degrading or blocking mRNA resulting in knocking down or suppression of targeted genes (23). Thus, miRNAs can play an important role in COVID-19 response and represent an emerging strategy for COVID-19 therapy (31).

Growing evidence suggests that miRNAs expression profiles have an axial role in the pathogenesis of the 2020 COVID-19 pandemic. There are several targets for human miRNAs on SARS-CoV-2's RNA, most of which are in the 5' and 3' untranslated regions (32). In RNA interference (RNAi), miRNAs may bind to complementary sequences of the viral RNA strand, forming a miRNAs-induced silencing complex, which destroys the viral RNA, thereby inhibiting viral protein expression.

Increasing the expression of specific coronavirus-targeting microRNA (either therapeutically or endogenously) in lung epithelia may provide cellular defense against SARS-CoV-2 infection and propagation, conversely, low expression may confer susceptibility to infection (28). According to one study (33) published by the American Physiological Society reduced expression levels of selected miRNAs (include miR-26a-5p, miR-34a-5p, and miR-29b-3p) were observed in the lung biopsies of patients with COVID-19. Moreover, there was a significant correlation between miRNAs and inflammatory biomarkers. Thus, deregulated miRNAs expression is associated with endothelial dysfunction in post-mortem lung biopsies of patients with COVID-19.

Meanwhile, a more recent study from India (34) reported that SARS-CoV-2 infection also changes the host small RNA expression patterns by miRNAs-mediated gene silencing. Conversely, SARS-CoV-2 miRNAs target a range of genes encoding for TGF- β signaling inhibitors. These result in massive and rapid serve pulmonary fibrosis that remodels and ultimately blocks the airways leading to functional failure of the lungs and death of patients with COVID-19.

3.4. Short interfering RNA (siRNA)

siRNA or silencing RNA, 19–27 nucleotide long double-stranded RNAs, is a non-coding RNA molecule that can regulate the expression of genes, through based therapeutics that has been developed and implemented for antiviral therapy (35). Multiple siRNA effectively inhibits the SARS-CoV-2 virus by greater than 90% and is known as adjunctive therapy to current vaccine strategies (36). Wu and colleagues (37) found that siRNA directed against Spike sequences and the 3-UTR can inhibit the replication of SARS-CoV, the beta coronavirus that causes the severe acute respiratory syndrome, and is promising for the development of an effective antiviral agent against SARS-CoV. Mehta and co-workers (16), have reported siRNA sequences against conserved, essential regions of the viral genome that can prevent viral replication. Also, another study (38) recently reported siRNA is a prospective

tool of the RNAi pathway for the control of human viral infections by suppressing viral gene expression through neutralization and hybridization of target complementary miRNAs. Other researchers (39) emphasize that siRNA could be a tailored approach in managing the therapeutic potential in the current outbreak of COVID-19, and known as agents that can mitigate the viral infection symptoms in humans. Nevertheless, siRNA is effective as an antiviral agent (40). Small RNAs interact with multiple pathways and reduce inflammatory biomarkers, thrombi formation, and tissue damage to accelerate the patient outcome (41). We would like to appreciate the authors of the mentioned study for the vital insight they provide into the treatment of this COVID-19 pandemic situation.

4. Discussion

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5. Conclusion

COVID–19 disease has been a pandemic for the past two years and several companies are trying to discover effective drugs against SARS–COV–2. After different useful vaccines against coronavirus, some of the manufacturers are trying to formulate oral drugs to protect from disease. Findings that shed new insight on the possible pathogenesis of SARS-CoV-2 or an adverse effect in areas with pandemic outbreaks. small RNAs therapeutic approaches are scalable, and we hope that the ongoing controlled trials will confirm these promising results and can be administered upon the first sign of SARS-CoV-2 infection. Also, miRNAs as therapeutic goals could be achievable to formulate against COVID–19 by inhibiting the expression of crucial virus genes.

6. Appendix

6.1. Acknowledgment

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6.2. Conflict of interest

None.

6.3. Funding support

None.

6.4. Author's contributions

All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

6.5. Abbreviations

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; COVID-19: coronavirus disease 2019; miRNA: microRNAs; siRNA: short interfering RNA; CSS: cytokine storm syndrome; 3 UTR: 3 untranslated region; IFN: Interferons; RNAi: RNA interference

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