Potential role of micro RNAs in the treatment of COVID-19(SARS-CoV-2 virus).

Sadaf Ali[1], Shiekh Amir[2], Shafat Ali[3*], Ali Mohd Yatoo[4], Sabhiya Majid[5], Adil Farooq Wali[6], Summya Rashid[7]

[1]Department of Biochemistry, Government Medical College, Srinagar, Jammu and Kashmir, India.

[2]Department of Forensic Medicine and Toxicology, Government Medical College, Srinagar, Jammu and Kashmir, India.

[3]Department of Biochemistry, Government Medical College, Srinagar, Jammu and Kashmir, India.

[4]Department of Cytogenetics and Molecular Biology Laboratory/ Centre of Research for Development, University of Kashmir, Srinagar, Jammu and Kashmir, India.

[5]Department of Biochemistry, Government Medical College, Srinagar, Jammu and Kashmir, India.

[6]Department of Pharmaceutical Chemistry, RAK College of Pharmaceutical Sciences, RAK Medical and Health Sciences University, Ras Al Khaimah, UAE.

[7]Department of Pharmacology & Toxicology, College of Pharmacy Girls Section, Prince Sattam Bin Abdulaziz University, Al-Kharj 11942, Saudi Arabia

Abstract

COVID-19 firstly erupted in China in December 2019 as an epidemic that led to a global pandemic within a short span of time. Evaluating and examining patients and after laboratory analysis of respiratory samples, a novel coronavirus was labeled as the causative agent for this disease. Micro RNAs are defined as short non-coding segments of RNAs. Almost one-third of all human protein-coding genes are regulated by micro-RNAs. The discovery of micro RNAs added a new element into a comprehensive understanding of complex networks regulated by various genes. Micro RNAs regulate the expression of genes. These mainly help in post-transcriptional regulation of the expression of various target mRNAs. It is proposed to make use of micro RNA that is responsible for the regulation of proteins at the translational level for Covid-19 vaccination. SARS-CoV2 invades its host all the way through RNA (its genetic material). During various viral infections changes in the expression of micro RNA takes place. Vaccine production is the most advanced and recent application of micro RNAs. The Discovery of miRNA use as biomarkers is needed for developing therapeutic agents and or vaccination against Covid-19. Thus, micro-RNA based therapy may be planned for the treatment of Covid-19 through suppression of the viral genome. Therefore, synthesizing in vitro micro RNA that will be specific to the SARS COV-2 RNA genome sequence may help in Covid-19 viral elimination and prevent lung damage. In this article, we have tried to depict the role of micro-RNAs for the treatment of Covid-19. This concept of micro RNAs may help us in vaccine formation or developing some therapeutic agents against Covid-19.

Keywords: Micro RNA, Covid-19, Post transcriptional regulation.

Accepted on 27 December, 2022

Introduction

COVID-19 firstly erupted in China in December 2019 as an epidemic that led to a global pandemic within a short span of time. Evaluating and examining patients and after laboratory analysis of respiratory samples, a novel coronavirus was labeled as the causative agent for this disease [1]. Humans suffered a grave threat due to a SARS COV-2 infection that causes acute damage to lungs and affects different respiratory-system outcomes. Higher pathogenic nature and rate of transmission of this virus has drawn the attention of global research communities. The complex viral proteomic structural organization, reproductive process, and its interaction with host suggests for exploring the role of host factors in the multiplication of the virus [2]. Different therapeutic agents have been suggested for the management of covid-19 that include lopinavir-ritonavir, tocilizumab, nitazoxanide, Hydroxychloroquine, and remdesivir. Additionally, several phyto-compounds are reported to demonstrate promosing anti-viral properties [3]. Ahmad et al (2020b) also suggested the clinical trials of thymoquinone for preventing SARS COV-2 infection [4]. The regulation of nitric oxide pathway can offer a promising therapy for reducing SARS CoV-2-mediated mortality [5]. Arafah et al (2020) proposed that blocking SARS

COV-2 S1-subunit and inhibiting protease simultaneously with pharmacological compounds may acts as potential therapeutic targets for covid-19 treatment [6]. At the molecular level regulation of viral replication is mainly controlled by host micro RNAs. Various possible mechanisms are responsible for the interaction of different viruses towards micro RNAs. Some micro RNAs may bind directly to viral RNA. However, it is crucial to recognize and subsequently classify miRNAs that are involved in host interactions in the case of Covid-19. COVID-19 is caused by SARS-COV-2 [7, 8]. ARDS is the most common cause of death in the case of SARS-COV-2 infection [9]. Some patients however present as mild to moderate cases of infection and many have recovered well. The expression of miRNAs is critical in determining the reaction to infections such as Covid-19 and can be used as therapeutic targeting agents in these infections [10]. Micro-RNAs (miRNAs) are defined as short non-coding segments of RNAs. Almost one-third of all human protein-coding genes are regulated by micro-RNAs [11]. Micro RNAs induce the formation of silencing complex in relation to a set of proteins and binds to 3′-UTR of a target mRNA. This association may promote translation, repression, or else even degradation of mRNA [12]. miRNAs are capable of degrading viral RNA as well as disrupting the binding of eukaryotic translation-initiating factors with the viral mRNA and thus can be used for inhibiting or suppressing viral translation [13]. According to diverse research work, miRNAs are believed to play a critical role in the development, the progression of various diseases in human beings. Different types of carcinomas may have a variation of miRNAs expression [14, 15]. Micro RNAs also influence cardiovascular diseases [16]. According to [17] due to differences in Micro RNA expression, there is the possibility of various neurological diseases. Micro RNAs are also essential for intercellular interactions [18]. According to genomic analysis done between SARS-COV and SARS-COV2, there is a phylogenetic similarity of around 79% between the two [19]. However, the genomic similarity between SARS COV2 and MERS COV was comparatively poor [20]. Additionally, the genomic homology (85.5%-92.4%) between SARS COV-2 and Pangolin-derived coronovirus has been found [21]. Choi et al (2014) [22] considered variations in micro RNA expression at some point in infection with influenza-A. Significant variations of expression were shown by several miRNAs in infected mice. These micro RNAs play a significant role in different cellular processes. Effective therapeutic action was demonstrated by respective anti-miRNAs. Micro-RNAs help in the regulation of cellular gene expression in Covid-19 infected oligodendrocytes. The length of Pri-miRNA ranges from 200 nt to several thousand nt. These possess either single or numerous different miRNAs. Inside the nucleus of a cell, pri-miRNA undergoes a step-wise dispensation. Another heterodimer that consists of Exportin 5 and the GTP-bound form of its cofactor Ran then exports the pre-miRNA into the cytoplasm of the cell. The pre-miRNA is released from the exporting complex by GTP hydrolysis, which is bound by the second RNase III enzyme; Dicer, and its cofactor. Dicer facilitates the congregation of the miRNA strand of the duplex into the RNA-induced silencing complex. The passenger strand is then set free and degraded subsequently [23].

Micro RNAs

The discovery of micro RNAs added a new element into a comprehensive understanding of complex networks regulated by various genes. Micro RNAs are defined as small, non-coding RNAs that support to regulate expression of genes. The non-coding RNA strands suppress the translation of mature mRNAs [24]. Specificity to the particular sequence is an important feature of micro-RNAs [18]. Caenorhabditis elegans was originally in the very beginning linked to the two oldest members of the micro-RNA family [14]. Afterward, different micro RNAs have been recognized within almost all genomes including mammals. Micro-RNAs are known for their varied expression patterns that help in the regulation of a variety of physiological processes [25]. Micro RNAs have shown a role in biochemical mechanisms and gene regulation [26]. In order to find the exact role of the vast majority of miRNAs in gene expression regulation, advanced research is essential. There is quite a similarity between miRNAs and siRNAs maturation, though slight differences exist between them. An exhaustive overview of specific relationships between above-mentioned RNAs and the protein components of the RNA machinery needs in-depth understanding. An essential compilation of miRNA data has been formulated in the form of a micro RNA registry. This became possible due to worldwide efforts for miRNA cloning and characterization [27].

Role of micro RNAs in immunity

Micro-RNAs are endogenous, small, non-coding RNAs. These mainly help in post-transcriptional regulation of the expression of various target mRNAs [28]. Micro-RNAs inhibit translation and or the initiation of mRNA degradation thereby modulating various cellular processes and functioning [29]. Mi RNAs modulate innate immune responses in host cells during various infections and play an important role in autophagy [26].

Micro RNAs and treatment of COVID-19

A Covid-19 vaccine is designed in order to provide acquired immunity to this deadly virus. The covid-19 vaccine should have the ability to provide protection both from SARS and MERS Cov. It is proposed to make use of micro RNA that is responsible for the regulation of proteins at the translational level. SARS-CoV2 invades its host all the way through RNA (its genetic material). RNA of SARS-COV2 is made of four ribonucleotides comprising of four nitrogen bases i.e. adenine, uracil, guanine, and cytosine. A genetic antigen against the genetic material of the SARS-CoV-2 is needed to get rid of Covid-19 infection. This may prove as helpful for the suppression of the viral genome.

Goals for treatment development of the COVID 19 require two strategies

1. Designing of a complementary micro-RNA for binding 3 UTR regions of the virus. This might be useful for the

prevention of the translation of viral RNA on the host ribosomes thereby leading to the elimination of the virus and its disintegration.

2. The neutral or acidic pH is most favorable for covid-19 and host interaction. Rising the concentration of hydrogen ion to alkaline pH might prevent the binding of viral envelop glycoproteins and the host's receptor thus preventing entry of the virus into the cells [8].

Coronavirus

Coronavirus (Figure1) is wrapped in an RNA coat, single-stranded and possesses positive polarity frequently associated with respiratory tract infections [30]. The size of the genome in these single-stranded viruses is approximately 30 kb [20]. The coronavirus family is further categorized into 4 sub-genera including α, β, Ÿ, and § coronavirus [31]. Coronaviruses lead to flu-like symptoms such as common cold and may complicate to severe respiratory distress. An ideal immunity of the host may self-limit the infection in most of the cases and thus has a low mortality rate [32]. Coronavirus nucleocapsid proteins such as OC43 have a significant role in this process [33]. Coronavirus-infected cells activate different cascades and send signals that lead to an increase in NFKB1 and miR-9 expression. These signaling cascades are essential for the resolution of this infection [34]. Pulmonary fibrosis and insufficiency are common complications of SARS-COV2 infection [35]. SARS-HcoV mainly infects broncho-alveolar stem cells. Overexpression of miR-574-5 p and miR- 214 are mainly result of corona infection. Viral nucleocapsid also produces certain proteins that down-regulate miR-223 and miR-98 expression in bronchoalveolar stem cells. This in turn regulates numerous differentiation levels and cytokine production leading to further inflammation [36].

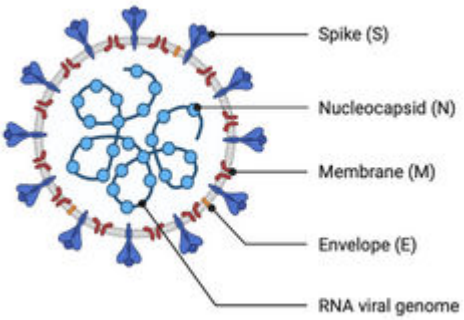

Figure 1. *Structural organization of human of SARS COV-2.*

Recent therapies on the utility of micro RNAs in vaccines

During various viral infections changes in the expression of micro-RNA take place [37]. Vaccine production is the most advanced and recent application of micro-RNAs (Fig. 2). Vaccines with attenuated viruses are made of an expression cassette that codes for an artificial miRNA. This cassette focuses on viral constitutional proteins. Vaccines that are administered intranasally confer immunity against several viral strains [38]. The most common and efficient approach for releasing small RNAs in the respiratory tract is through aerosols using a micro-sprayer [39]. This route of administration may aid in miRNA delivery in infections of the respiratory tract [40].

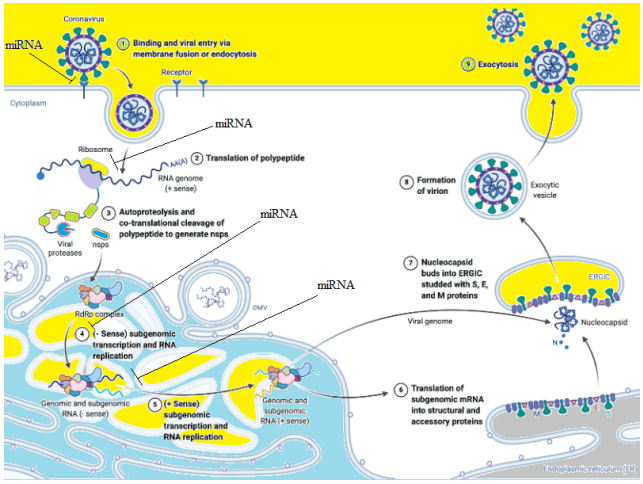

Figure 2. *Therapeutic potential of miRNAs in treating Covid-19 via blocking the replication cycle of SARS COV-2 in host cells.*

Conclusion

The discovery of miRNA use as biomarkers is needed. Also, treatment development, vaccine production in view of COVID-19 depends on the same. Thus, micro-RNA-based therapy may be planned for the treatment of COVID-19 through suppression of the viral genome. Micro RNAs take part in controlling the innate immune response in viral respiratory infections. These may favor or go against the regulation process. Regulation is based on the type of virus. Micro RNAs regulate diverse physiological processes. These influence cell differentiation, cell survival, and also the proliferation of cells thus eliminating unwanted RNAs from our body. Therefore, synthesizing in vitro micro RNA that will be specific to the SARS COV-2 RNA genome sequence may help in Covid-19 viral elimination and prevent lung damage. This concept of micro RNAs may help us in vaccine formation or developing some therapeutic agents against Covid- 19.

References

1. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The lancet. 2020; 395(10223): 497-506.
2. Manhas S, Anjali A, Mansoor S, et al. Covid-19 pandemic and current medical interventions. Archives of medical research. 2020.
3. Ahmad A, Rehman MU, Alkharfy KM, et al. An alternative approach to minimize the risk of coronavirus (Covid-19) and similar infections. European Review for Medical and Pharmacological Sciences. 2020; 24(7): 4030-4034.

4. Ahmad A, Rehman MU, Ahmad P, et al. Covid 19 and thymoquinone: Connecting the dots. Phytotherapy Research. 2020b
5. Alkharfy KM, Rehman MU, Ahmad A, et al. Nitric oxide pathway as a potential therapeutic target in COVID-19. Farmacia. 2020; 68(6).
6. Arafah A, Ali S, Yatoo AM, et al. S1 subunit and host proteases as potential therapeutic avenues for the treatment of COVID-19. Archives of medical research. 2020.
7. Zhou P, Yang XL, Wang XG, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020; 579(7798): 270-273.
8. Remuzzi A, Remuzzi, G. COVID-19 and Italy: what next? The lancet. 2020; 395(10231): 1225-1228.
9. Xu Z, Shi L, Wang Y, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. The Lancet respiratory medicine. 2020; 8(4): 420-422.
10. Mishra PK, Tandon R, Byrareddy SN, Diabetes and COVID-19 risk: an miRNA perspective. American Journal of Physiology-Heart and Circulatory Physiology. 2020; 319(3): H604-H609.
11. Nilsen TW. Mechanisms of micro-RNA-mediated gene regulation in animal cells. TRENDS in Genetics. 2007; 23(5): 243-249.
12. Carthew RW, Sontheimer EJ. Origins and mechanisms of miRNAs and siRNAs. Cell. 2009; 136(4): 642-655.
13. El-Nabi SH, Elhiti M, El-Sheekh M. A new approach for COVID-19 treatment by micro-RNA. Medical hypotheses. 2020; 143, p.110203.
14. Di Leva G, Garofalo M, Croce CM. Micro-RNAs in cancer. Annual Review of Pathology: Mechanisms of Disease. 2014; 9: 287-314.
15. Shkurnikov M, Nikulin S, Nersisyan S, et al. LAMA4-regulating miR-4274 and its host gene SORCS2 play a role in IGFBP6-dependent effects on phenotype of basal-like breast cancer. Frontiers in molecular biosciences; 2019: 6, 122.
16. Schulte C, Molz S, Appelbaum S, et al. miRNA-197 and miRNA-223 predict cardiovascular death in a cohort of patients with symptomatic coronary artery disease. PloS one. 2015; 10(12): e0145930.
17. Baranova A, Maltseva D, Tonevitsky A. Adipose may actively delay progression of NAFLD by releasing tumor-suppressing, anti-fibrotic miR-122 into circulation. Obesity Reviews. 2019; 20(1): 108-118.
18. 19. Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. The lancet. 2020; 395(10224): 565-574.
19. Xu X, Chen P, Wang J, et al. Evolution of the novel coronavirus from the ongoing Wuhan outbreak and modeling of its spike protein for risk of human transmission. Science China Life Sciences. 2020; 63(3): 457-60.
20. Lam TT, Shum MH, Zhu HC, et al. Identifying SARS-CoV-2 related coronaviruses in Malayan pangolins. Nature. 2020.
21. Choi EJ, Kim HB, Baek YH, et al. Differential micro-RNA expression following infection with a mouse-adapted, highly virulent avian H5N2 virus. BMC microbiology. 2014; 14(1): 1-13.
22. Zhang XM, Cao J. Regulation of cellular MicroRNA expression in oligodendrocytes during acute and persistent coronavirus infection. Virology and Mycology. 2015; 4(8).
23. Mirzaei R, Mohammadzadeh R, Mirzaei H, et al. Role of micro-RNAs in Staphylococcus aureus infection: Potential biomarkers and mechanism. IUBMB life. 2020; 72(9): 1856-1869.
24. Bartel DP. Micro-RNAs: genomics, biogenesis, mechanism, and function Cell. 2004; 116(2): 281-297.
25. Gantier MP, Sadler AJ, Williams BR. Fine-tuning of the innate immune response by micro-RNAs. Immunology and cell biology. 2007; 85(6): 458-462.
26. Griffiths Jones S. The micro-RNA registry. Nucleic acids research. 2004; 32(1): D109-D111.
27. Kim VN, Han J, Siomi MC. Biogenesis of small RNAs in animals, Nature reviews Molecular cell biology. 2009; 10(2): 126-139.
28. Mehta A, Baltimore D. Micro-RNAs as regulatory elements in immune system logic. Nature Reviews Immunology. 2016; 16(5): 279.
29. Al-Tawfiq JA, Zumla A, Memish ZA. Coronaviruses: severe acute respiratory syndrome coronavirus and Middle East respiratory syndrome coronavirus in travelers. Current opinion in infectious diseases. 2014; 27(5): 411-417.
30. Cheng ZJ, Shan J. 2019 Novel coronavirus: where we are and what we know. Infection. 2020; 48(2): 155-163.
31. Trombetta H, Faggion HZ, Leotte J, et al. Human coronavirus and severe acute respiratory infection in Southern Brazil. Pathogens and global health. 2016; 110(3): 113-118.
32. Huang CY, Hsu YL, Chiang WL, et al. Elucidation of the stability and functional regions of the human coronavirus OC43 nucleocapsid protein. Protein Science. 2009; 18(11): 2209-2218.
33. Lai FW, Stephenson KB, Mahony J, et al. Human coronavirus OC43 nucleocapsid protein binds micro-RNA 9 and potentiates NF-κB activation. Journal of virology. 2014; 88(1): 54-65.
34. Stark CJ, Atreya CD. Molecular advances in the cell biology of SARS-CoV and current disease prevention strategies. Virology journal. 2005; 2(1): 1-8.
35. Mallick B, Ghosh Z, Chakrabarti J. MicroRNome analysis unravels the molecular basis of SARS infection in bronchoalveolar stem cells. PloS one. 2009; 4(11): e7837.
36. Rossbach M. Small non-coding RNAs as novel therapeutics. Current molecular medicine. 2010; 10(4): 361-368.
37. Li J, Arevalo MT, Diaz-Arevalo D, et al. Generation of a safe and effective live viral vaccine by virus self-

attenuation using species-specific artificial micro-RNA. Journal of Controlled Release. 2015; 207: 70-76.

38. Rosas-Taraco AG, Higgins DM, Sánchez-Campillo J, et al. Intrapulmonary delivery of XCL1-targeting small interfering RNA in mice chronically infected with Mycobacterium tuberculosis. American journal of respiratory cell and molecular biology. 2009; 41(2): 136-145.
39. Qiu Y, Lam JK, Leung SW, et al. Delivery of RNAi therapeutics to the airways—from bench to bedside. Molecules. 2016; 21(9): 1249.

***Correspondence to:**

Dr. Shafat Ali

Department of Biochemistry, Government Medical College

Government Medical College

Jammu and Kashmir

India

E-mail: rahilshafat986@gmail.com