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REVIEW

The role of microRNAs in COVID-19 with a focus on miR-200c

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ABSTRACT

Objective: Epigenetics is a quickly spreading scientific field, and the study of epigenetic regulation in various diseases such as infectious diseases is emerging. The microribonucleic acids (miRNAs) as one of the types of epigenetic processes bind to their target messenger RNAs (mRNAs) and regulate their stability and/or translation. This study aims to evaluate non-coding RNAs (ncRNAs) with a focus on miR-200c in COVID-19. In this review, we first define the epigenetics and miRNAs, and then the role of miRNAs in diseases focusing on lung diseases is explained. Finally, in this study, we will investigate the role and position of miRNAs with a focus on miR-200c in viral and severe acute respiratory syndrome–related coronavirus (SARS-CoV2) infections.

Methods: Systematic search of MEDLINE, PubMed, Web of Science, Embase, and Cochrane Library was conducted for all relative papers from 2000 to 2021 with the limitations of the English language. Finally, we selected 128 articles which fit the best to our objective of study, among which 5 articles focused on the impact of miR-200c.

Results: Due to the therapeutic results of various drugs in different races and populations, epigenetic processes, especially miRNAs, are important. The overall results showed that different types of miRNAs can be effective on the process of various lung diseases through different target pathways and genes. It is likely that amplified levels of miR-200c may lead to decreased angiotensin-converting enzyme-2 (ACE2) expression, which in turn may increase the potential of infection, inflammation, and the complications of coronavirus disease.

Conclusion: miR-200c and its correlation with ACE2 can be used as early prognostic and diagnostic markers.

Keywords: Covid-19, Epigenetic, Lung diseases, miR-200c, miRNAs

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Introduction

Epigenetics is defined as hereditary changes in gene expression without altering the deoxyribonucleic acid (DNA) sequence (1). Methylation of cytosine in the DNA sequence and the biochemical changes of histones are two critical mechanisms in the epigenetics that play an important role in gene regulation, differentiation, and carcinogenicity (2-5). Another mechanism that affects epigenetics and the gene expression is microribonucleic acids (miRNAs). miRNAs are non-coding endogenous RNAs with a length of 20 to 25 nucleotides. These molecules can bind to untranslated 3' regions (UTRs) and suppress the expression of messenger RNAs (mRNAs) at the posttranscriptional level by pairing a specific base sequence (6,7). miRNAs bind to their target mRNAs and regulate their stability and/or translation. If miRNAs bind completely to their target sequence on the

mRNA, they can lead to degradation; but in case of binding incorrectly, translational suppression of their target genes occurs by a mechanism that has not yet been fully understood (8). Each miRNA is predicted to have multiple gene targets and each mRNA may be regulated by more than one miRNA (9,10). The miRNAs play a vital role in many important biological processes, including cell proliferation (11), growth (12), differentiation (13), apoptosis (14), metabolism (15), aging (16), signal transduction (17), and viral infections (18). It is estimated that about one-third of genes and their pathways are regulated and controlled by miRNAs. Briefly, miRNAs have a remarkable effect on the genomic and epigenetic mechanisms (19,20).

The role of miRNAs in diseases focusing on lung diseases

The miRNAs involve in the development, progression, prognosis, diagnosis, and evaluation of therapeutic response in human diseases (21). In recent years, altered expression of the miRNAs has been identified in many human cancers (22), cardiac hypertrophy and failure (23), metabolic disorders (24), immune system–related diseases, and inflammation (9). Also, the miRNAs have been studied in lung homeostasis, functional development, and various pulmonary diseases including asthma, chronic obstructive pulmonary disease (COPD), cystic fibrosis (CF), idiopathic pulmonary fibrosis (IPF), and lung cancer (25) (Tab. I).

In recent years, an increasing amount of research has shown the impact of miRNAs in the progress of pulmonary diseases (43). Our knowledge of the role of miRNAs in lung diseases has developed step by step. The role of miRNAs in the unique pulmonary cells is thought to be essential in understanding the mechanism of lung function and disease pathogenesis (25). More recently, many studies have begun to report the effects of miRNA transfer via extracellular vesicles. In lung diseases, this transfer was indicated to be facilitated via the intercellular communication between many types of cells in the respiratory system including endothelial cells (44), bronchial epithelial cells (45), mesenchymal stem cells, and others (46).

TABLE I - Relationship between miRNA types and their target genes in different lung diseases

Disease	miRNA	Gene target	Expression in disease	Sample	Measurement type	Ref
Asthma	miR-145	RUNX3	Up	PB	Quantitative PCR	(26,27)
	miR-21	IL-12	Up	Serum	qRT-PCR	(49)
	miR-133a	RhoA	Down	hBSMCs	qRT-PCR	(50)
	mir-19a	TGFβR2	Up	BEC	RT-PCR	(28)
	miR-155	IL-13Ra1	Up	Macrophages—monocytes	RT-PCR	(48)
COPD	miR-15b	SMAD7	Up	Lung	qRT-PCR	(29)
	miR-146a	COX-2	Down	PLF	RT-PCR/Northern Blot	(30)
	miR-24-3p	BIM	Down	Lung	RT-PCR	(31)
	miR-93-5	NFKBIA	Up	PBMCs	High-throughput microarray	(32)
CF	miR-126	TOM1	Down	Lung	RT-PCR	(33)
	miR-145	CFTR	Up	Cell line	qRT-PCR	(34)
	miR-138	SIN3A	Down	Cell culture	Quantitative PCR	(61)
	miR-9	ANO1	Up	Bronchial tissues	RT-PCR	(35)
IPF	let-7d	HMGA2	Down	Lung	Microarrays	(36)
	miR-21	Smad, Smad7	Up	Lung	miRNA array/Northern blotting	(37)
	miR-200c	TGF-β1	Down	HLT	miR Array	(38)
	miR-199a-5p	TGF-β	Up	Serum	TaqMan miRNA assay	(39)
Lung cancer	miR-137	SLC22A18	Down	Lung	Bioinformatics analysis and luciferase reporter assay	(40)
	mirRNA-34a	TGFβR2	Down	Tissues	qRT-PCR and Western blot	(41)
	miR-449a	E2F3	Down	Lung cancer tissue	RT-PCR	(42)
	miR-200	ZEB1	Down	Tissue	RT-PCR	(55)

BEC = human bronchial epithelial cells; CF = cystic fibrosis; CFTR = Cystic Fibrosis Transmembrane Channel; COPD = chronic obstructive pulmonary disease; HLT = human lung tissue; IPF = idiopathic pulmonary fibrosis; miRNA = microribonucleic acid; PB = peripheral blood; PLF = primary lung fibroblast; qRT-PCR = quantitative reverse transcription polymerase chain reaction; PBMC = peripheral blood mononuclear cell; hBSMC = Human Bronchial Smooth Muscle Cells.

The miRNAs in Asthma

Asthma is a chronic inflammatory disease of the lungs that is often associated with clinical features such as airway hyperresponsiveness (AHR), airflow obstruction, excessive mucus secretion, and airway wall structural changes (remodeling) (47). Interleukin (IL)-13 and transcription factor signal transducer-and-activation-of-transcription-6 (STAT6)-operated pathways have been shown to play a significant role in regulating the prominent asthma features, for example, AHR and remodeling. miR-155 has been shown to be upregulated in order to target directly the transcription of the IL-13 receptor a1 (IL13Ra1) in human macrophages, reducing the levels of IL13Ra1 protein and decreasing the levels of activated STAT6, which is vital in regulating the IL-13 signaling pathway (48). Inhibition of miR-21 leads to a decrease in Th2 cytokine levels (IL-4, IL-5, and IL-13), the number of inflammatory airway leukocytes and AHR (49). Downregulation of miR-133a was followed by an increased expression of RhoA and subsequently increased bronchial hyperactivity in a murine model of asthma (50). Elevated expression of the miR-155 has also been indicated in murine models of asthma. Additionally, by using antagomir against miR-145, the mucus secretion, Th2 cytokine production, and eosinophil infiltration in the airways decreased (51).

The miRNAs in lung cancer

Dysfunction of miRNAs is often identified in malignancies, including lung tumor. Lung cancer is the leading cause of cancer-related mortality worldwide and to date the roles of miRNAs in lung cancer have been specified and reviewed widely along with the other diseases. Histologically, lung cancer can be mostly divided into small cell (SCLC) and non–small cell lung cancer (NSCLC). The latter is more common and is subclassified into squamous, adenocarcinoma, and large-cell carcinoma (52). Recent sequencing studies have exposed a very large number of targets for each single miRNA. By regulating the posttranscriptional gene expression, miRNAs strongly involved in wide-ranging pathways with the main effect are on the progressive and carcinogenesis routes (53,54). Concisely, various miRNAs that are recognized as either oncogenes or tumor suppressors in lung cancer are also involved in the immune system response, for instance, the miR-200 family. The low expression of the miR-200 family members in human early-stage lung adenocarcinomas has been correlated with upregulation of PD-L1 (55) and $CD8^+$ T-cell immunosuppression and metastasis, which resulted in the reduction of tumor load. This finding greatly supported the role of miR-200 as a tumor suppressor.

The miRNAs in COPD

COPD is an inflammatory progressive lung disease that is prompted by chronic inflammation exposure of the airways to stimuli including cigarette smoking and other noxious gases. An increasing number of studies have demonstrated that injured cells such as endothelial and epithelial cells participate seriously in the pathogenesis of COPD (56). The exposure of the respiratory epithelial cells to the harmful agents like cigarette smoke leads to the release of proinflammatory and inflammatory cytokines such as IL-1, IL-6, IL-8, and tumor necrosis factor (TNF)-α (57,58).

The miRNAs and CF

In the Caucasian community, CF is the most frequent deadly hereditary disease. It is caused by a recessive mutation in the CFTR (Cystic Fibrosis Transmembrane Channel) gene, which codes for a chloride channel (59). miRNAs can target CFTR directly or indirectly for regulating CF. Several miRNAs can complementarily and directly regulate CFTR expression such as miR-145 (via SMAD3 and TGF-β), miR-223 (via CFTR mRNA), miR-9 (via Anoctamin 1), and miR-494 (via Solute Carrier family 12Member 2 (SLC12A2)), alone or together. However, miR-509-3p and miR-494 downregulate CFTR expression (60). Some miRNAs like miR-138 can also repress the biosynthesis intermediary actors, such as the transcription factor SIN3A (SIN3 transcription regulator family member A) and CFTR (61).

The miRNAs and infections

Recent advances in molecular mechanisms point to the importance of miRNAs in the lung and respiratory infections. Acute viral respiratory infections (AVRIs) are the most common causes of acute respiratory symptoms (62). Changes in the regulation of miRNA expression in the epithelial cells of human rhinovirus (hRV), influenza (IV), human metapneumovirus, human coronavirus, and respiratory syncytial virus infections are associated with the pathogenesis of acute respiratory diseases (63). For example, the expression of host miRNAs changes in response to IV stimulation. These miRNAs directly or indirectly target viral and host genes to regulate virus replication, stimulate or suppress innate immune responses and cell apoptosis during the viral infection (64,65). IV increases the expression of miR-4276 by upregulating two proteins involved in the apoptotic pathway, Cas9 and Cocx6c (74), and eventually leads to increased virus replication and apoptosis. Furthermore, a number of specific cellular miRNAs in IV-infected cells including miR-323, mir-491, and miR-654 target the protected region of viral PB1 gene to prevent the virus from replicating in MDCK cells (76).

Another mechanism in IV infection is the altered expression of cellular miRNAs and their effect on important signaling pathways associated with the immune system (66). In hRV infections, miRNAs result in antiviral responses by modulating the immune response (miR-128 and miR-155) as well as controlling virus entry into the infected lung cells (miR-23b) (67).

RSV causes viral respiratory disease in infants and young children (68), modulating the expression of host cell miRNAs for antiviral responses and virus replication similar to the miRNAs mentioned above (69,70). For instance, miR-125a regulates nuclear factor kappa B (NF-κB) signaling pathway by suppressing A20 inhibitor protein (CCL5) as an important cytokine in both innate and compatible immune systems (71). Coronaviruses cause a wide range of respiratory infections, from mild upper respiratory tract infections to severe lower respiratory tract infections (72). Table II shows the four major

TABLE II - Relationship between different types of miRNAs and their target genes in well-known viral lung infections

Viral disease		miRNA	Gene target	Effects on gene regulation	Pathways	Ref
Influenza virus		– ***miRNA-4276***	– COX6C	– Up	– Inhibits COX6C and caspase-9 and promoting viral replication	**(74)**
		– ***miR-323, miR-491***	– PB1	– Up	– Inhibits replication of virus	**(75)**
		– ***let-7c***	– M1	– Up	– Reduces virus replication by degrading M1 mRNA	**(76)**
		– ***miR-146a-5***	– TRAF6	– Up	– Negatively regulates innate immune and inflammatory responses	**(77)**
		– ***miR-576-3p***	– AP1G1	– Down	– Regulates virus entry	**(78)**
		– ***miR-21-3p***	– HDAC8	– Down	– Suppresses IAV replication	**(79)**
		– ***miR-132, miR-200c***	– MAPK3, IRAK1	– Up	– Regulates antiviral response	**(64)**
Rhinoviruses		– ***miR-128 , miR-155***	– SMAD2, EGFR	– Up	– Regulates the immune response against RV-1B and inhibits virus replication	**(80)**
		– ***miR-23b***	– VLDLR	– Up	– Prevents viral infection by decreasing the VLDLR	**(81)**
RSV		▪ ***let-7f***	CCL7, SOCS3	– Up	– Antiviral host response	**(82)**
		▪ ***miR-30, let-7i***	– IL-13, TLR4, RUNX2	– Up	– Induces miRNAs to involve in the immune response pathways such as NF-kB and type I IFNs	**(83-85)**
		▪ ***miR-221***	– NGF, TrkA	– Down	– Promotes viral replication	**(86)**
		▪ ***miR-125a***	– TNFAIP3	– Down	– Inhibits NF-κB signaling pathway and results in reducing macrophage activation	**(87)**
Coronavirus	**OC43**	***miR-9***	– NF-kB	Up	N protein of virus binds to miR-9 and modulates NF-kB expression	**(88)**
	SARS	***miR-17, miR-574-5p, miR-214***	– Virulent proteins, including N, S, M, and E	Up	– Suppresses viral replication that may aid evasion of immune surveillance until successful infection of other cells	**(89,90)**
	MERS	▪ ***miR-16-1-3p, miR-26a-1-3p, miR-425-5p, miR-1275, miR-2277-5p , miR-500b-5p, miR627-5p, miR-1257, miR-1275***	– MAP3K9, MYO15B, SPOCK1	Up	– miRNA-mRNA network significantly impacts MERS-CoV replication	**(91)**
	MERS	***miR628-5p, miR-18a-3p, hsa-miR332-3p***	– Viral mRNA	Up	– These miRNAs may downregulate viral gene expression resulting in the inhibition of viral replication	**(92)**
	SARS-CoV2	▪ ***miR-146a-5p***	IL-6	Down	– Acts as a negative regulator of NF-κB as the transcription factor of the IL-6 gene	**(93)**
		▪ ***miR-200c***	ACE2	Up	– Overexpression of miR-200c induces downregulation of ACE2 in human cells	
		▪ ***miR-1202***	SARS-CoV2 ORF1a/b	Up	– Targets SARS-CoV2 genome	**(94)**
		let-7d-5p	– TMPRSS2	Up	– Expression of let-7d-5p negatively correlates with TMPRSS2 expression 91	**(95)**

IL = interleukin; MERS = Middle East respiratory syndrome; miRNA = microribonucleic acid; NF-κB = nuclear factor kappa B; RSV = respiratory syncytial virus; SARS-CoV = severe acute respiratory syndrome–related coronavirus; IAV = Influenza A viruses.

categories of the pulmonary virus families and some of the most important miRNAs that change the expression of the genes involved in infections with these viruses. Severe acute respiratory syndrome coronaviruses (SARS-CoV) use host cell miRNAs to escape removal by the immune system (89).

In Middle East respiratory syndrome coronavirus (MERS-CoV) infection, cellular miRNAs act as an antiviral therapeutic agent (92). The functional mechanisms of miRNAs in SARS-CoV2 as the causative agent of COVID-19 are diverse. For example, increased miR-200c expression in the disease downregulates the expression of angiotensin-converting enzyme (ACE2) protein that is the receptor essential for the virus entry into the cell (73).

Association of miR-200c with the genes involved in inflammation (ACE2, IL-6)

miR-200c-3p is a member of the miR-200 family with two clusters miR-200a/b/429 and miR-200c/141. The miR-200c-3p is one of the most important miRNAs of the second cluster. Studies on the miR-200 family have shown that it has a variety of roles in cancer progression, drug resistance, and oxidative stress (96,97). The results of various studies have revealed the crucial role of the miR-200c epithelial-mesenchymal transmission, proliferation, metastasis, apoptosis, autophagy, and therapeutic resistance in several types of cancer (98). The miR-200c is also measured as a biomarker to predict disease progression, diagnosis, and response to therapy in several cancers, both in tissues and in body fluids (blood, urine) (96).

Studies using miRNAs can contribute not only to the understanding of virus-host interactions but also to the stratification of the different severities of COVID-19. In this sense, miR-200c-3p, which has been associated with viral infections, including influenza A, offers itself as a candidate for the study of COVID-19. The analysis of its expression in groups of patients presenting different levels of disease aggressiveness could contribute to a better screening of patients affected by SARS-CoV2. Thus, in Pimenta's study, which aimed to analyze the expression of miR-200c-3p in saliva samples from patients with COVID-19, the results showed that the expression pattern of miR-200c-3p increased with disease severity (99).

Furthermore, the significant impact of miR-200c-3p in acute respiratory distress syndrome (ARDS) was discovered, which proposes it as a potential factor in SARS-COV-2 research and is considered as a potential diagnostic agent for SARS-COV-2 studies (100). In a study of the H5N1 avian influenza virus (AIV) ACE, serum levels of miRNA-200c-3p were found to increase in the virus causing acute pulmonary injury and ARDS. This miRNA binds to the 3'-UTR locus of the ACE2 gene, and inhibits the expression of this protein and thus exacerbates the disease (100-102).

The ACE2 gene was first identified from complementary DNA in the left ventricle of the human heart (102). ACE2 inactivates angiotensin II (Ang II) by cleavage and produces Ang 1-7 (103).

Ang II binds to type 1 and type 2 Ang II receptors with high affinity and is involved in regulating blood pressure, body fluid balance, inflammation, cell proliferation, hypertrophy, and fibrosis (104-106). ACE2 has been shown to neutralize the development of severe ARDS caused by AIV, coronavirus, and sepsis in mice (106). ACE2 has also been reported as a receptor for the SARS-CoV2 virus to enter the pneumocytes (107).

The role of miR-200c in lung inflammation and lung diseases

MiR-200c, alongside with miR-141, is placed in the intragenic zone of chromosome 12. MiR-200c family has beneficial effects on preventing drug resistance, cancer development, and oxidative stress. It consists of two clusters: (1) miR-200c/141 cluster including miR-141-3p and miR-141-5p, miR-200c-3p, miR-200c-5p on chromosome 12p13.31; (2) miR-200a/b/429 cluster including miR-200a-3p, miR-200a-5p, miR-200b-3p, miR-200b-5p, and miR-429 on chromosome 1p36.33 (108).

miR-200, like ACE2, is greatly expressed in the epithelial cells of the pneumocytes, mainly in type II alveolar epithelial cells. The expression of miR-200 has a crucial role in the differentiation of type II alveolar epithelial cells in fetal lungs, which are important components of the renin-angiotensin system signaling pathway all over the body. miR-200 displays several important effects in the body such as anti-remodeling, anti-inflammatory, and anti-proliferative through reduction of angiotensin II levels (Fig. 1) (109). Remarkable points in this issue are about controlling COVID-19 patients' mortality rates and disease severity, by upregulating ACE2 levels with using angiotensin receptor blockers or ACE2 blockers (110). miR-200 is the exact and direct target of ACE2 at 3'-UTR of ACE2 mRNA which by binding to its locus results in the depression of ACE2 expression as a receptor responsible for ARDS incidence. Normally, ACE2 catalyzes the conversion of AgII to Ag1-7. Later, Ag1-7 binds to mitochondrial assembly (MAS) receptors resulting in Ag1-7 protective effects including anti-proliferation, anti-necrotic and anti-hypertrophic as well as vasodilation and declining of proinflammatory cytokine secretion. SARS-CoV2 inhibits this pathway and worsens AgII adverse effects on lung tissue during the acute phase of the disease. It was reported that SARS-CoV2 induces the secretion of IL-6, TNF-α, IL-1β (102,111-113). Activation of NF-κB pathway, an important factor in ARDS pathogenesis, is one of the noticeable pathways leading to the upregulation of miR-200c-3p. Increased expression of miR-200c-3p occurred when the ACE2 expression decreased (100) (Fig. 1).

These mechanisms include increased mir-200c expression, inhibition of ACE2 expression, by affecting ACE2 protein outside the cell, and by inhibition of other anti-inflammatory functions, all of which are shown in the figure. (1) increased miR-200c expression that SARs-CoV-2 inhibit ACE2 indirectly by regulating miR-200c and directly inhibiting ACE2 expression, (2) by affecting the ACE2 gene, (3) ACE2 protein outside the cell, and (4) by inhibiting other anti-inflammatory functions, all of which are shown in the figure. In addition, miR-200c can also reduce ace2 expression, thereby reducing ACE2 expression and reducing its function. According to research results, the reduction in disease severity in COVID-19 patients associates with the correlation between low expression of ACE2 and high levels of miR-200c-3p in the lungs and the upper respiratory tract (114,115).

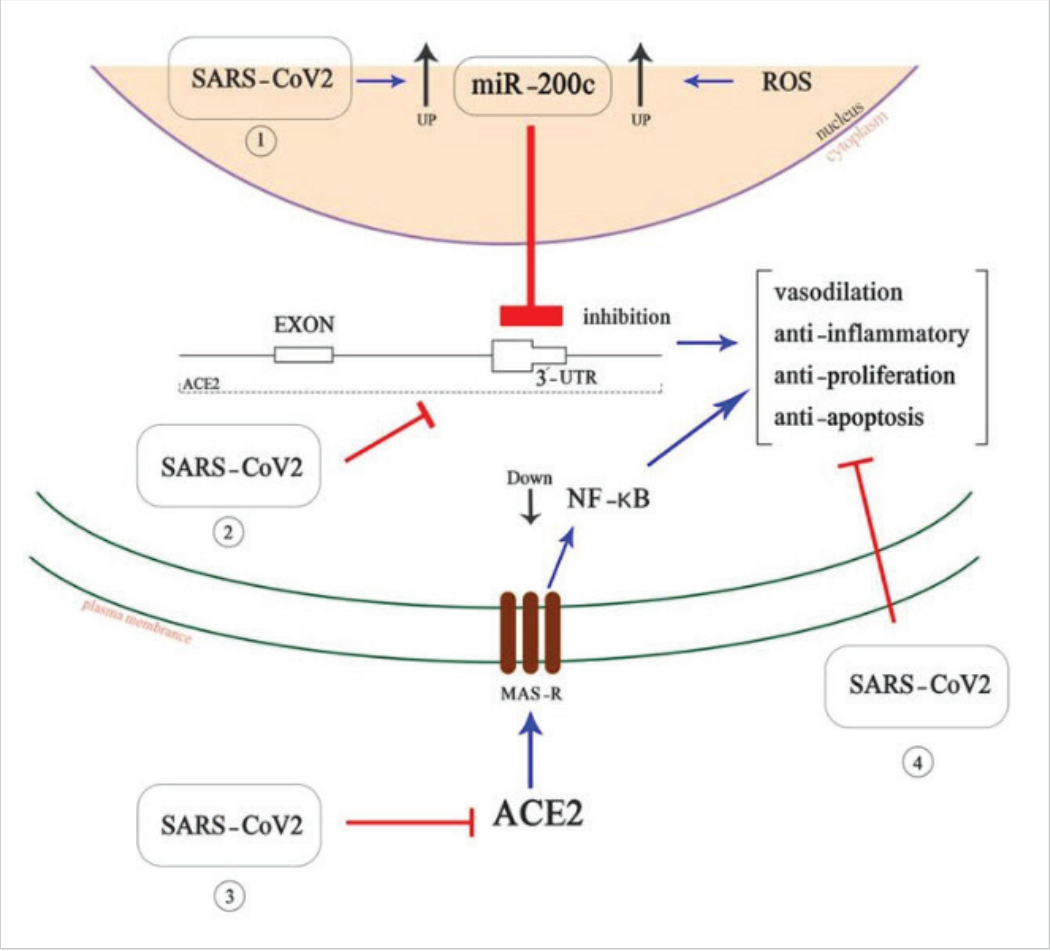

Fig. 1 - MiR-200c and ACE2 mechanism of function in the pathogenesis of COVID-19. SARS-CoV2 induces inflammation and severe ARDS through four mechanisms: (1) virus indirectly leads to ACE2 downregulation by enhancing miR-200c expression. (2) Virus directly inhibits ACE2 gene expression. (3) SARS-CoV2 inhibits binding of ACE2 protein to its receptor on the lung cells. (4) SARS-CoV2 inhibits the anti-inflammatory effects of ACE2. ACE2 = angiotensin-converting enzyme-2; ARDS = acute respiratory distress syndrome; COVID = coronavirus; SARS-CoV = severe acute respiratory syndrome–related coronavirus.

Recent studies about the entrance of SARS-CoV-2 to the host cells imply that some miRNAs can actually control the expression of ACE2 and TMPRSS2, which are potentially of high effect in SARS-COV-2 pathogenesis (116).

Several pathways have been studied about the effect of epigenetics on the regulation of ACE2/TMPRSS2 expression levels in respiratory diseases. The epigenetic repression of miRNA transcription can control their regulatory regions. For instance, Lysine-specific demethylase 5B (JARID1B, encoded by the KDM5B gene) was displayed to suppress the transcription of miR-200 family including miR-141, miR-200a, miR-200b, miR-200c, and miR-429. Hsa-miR-125a/hsa-let-7e miRNAs inhibit the transcription of miR-200 family through stimulating H3K4me3 histone, which demethylases the miRNAs of this family. Therefore, hsa-miR-125a-5p via binding to miR-200 family pursues 3'-UTR of ACE2 mRNA and results in the enhancement of ACE2 gene expression while 3'-UTR of the TMPRSS2 is targeted by hsa-let-7e-5p. Concludingly, JARID1B epigenetic activity doesn't directly regulate the expression of ACE2 and TMPRSS2 (116). Scientists have investigated if promoting H3K4me3 demethylation is caused by repression of the transcription of the let-7e and miR-125a via JARID1B gene (117); for example, the upregulation of JARID1B in lung cancer cell line A549 concluded threefold depression of miR-200a and miR-200c expression, while JARID1B knockdown enhanced 1.5-fold their conserved and stable levels (118).

The experimental data show the presence of controlling network containing miR-125a/let-7e/miR-200 families, ACE2/TMPRSS2 as well as histone demethylase JARID1B, and further point a new way for signaling pathway for ACE2 expression. In one report, the single-cell RNA sequencing data analysis sharply indicated that in the majority of human cells ACE2 and TMPRSS2 are not expressed without JARID1B. So, for better understanding, the viral infection pathogenesis needs to be investigated in the regulatory network related to the expression of JARID1B, ACE2, and TMPRSS2 in human respiratory epithelial cells (116).

According to cellular ontologies research on 24 miRNAs, for evaluating the miRNAs targeting SARS-CoV-2 host cell receptor ACE2, it was revealed that miR-429, miR-200a-3p, miR-210-3p, miR-200b-3p, and miR-200c-3p were highly expressed in the respiratory epithelial cells and miR-200c-3p exists abundantly in the cells including endo-epithelial cell, epithelial cells, respiratory epithelial cells, leukocytes, hematopoietic cells, and myeloid leukocytes. Also, miR-200b

and miR-200c were discovered to be extremely conserved (119).

In clinical trials, miR-200 and its correlation with ACE2 can be used as early prognostic and diagnostic markers. Its location on the upstream of ARDS signaling pathways may reduce the morbidity and mortality rates of COVID-19 via epigenetic procedures, which can be so beneficial for human survival.

Conclusion

At present, there is no exact treatment for COVID-19. Due to the importance of miRNAs in pulmonary diseases, mainly the infectious viral diseases as well as SARS-COV-2, they can be potential candidates of targeted therapy in SARS-COV-2 in order to reduce the morbidity and mortality rates of this disease as miR-200c and its correlation with ACE2 can be used as early prognostic and diagnostic markers. However, further research must be carried out to reveal the exact effect of miR-200c in the pathogenesis of COVID-19 in order to be used clinically.

Authors' contributions

HS was responsible for the largest share in writing the article. SA and SG-GA conceptualized and wrote the article and article design. However, SA share has been higher. SA contributed in review and editing of final submitted version. MHKA and RA contributed in Methodology, Data validation and Writing original draft of this article.

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