Journal of Advanced Research 30 (2021) 133–145

Contents lists available at ScienceDirect

Journal of Advanced Research

journal homepage: www.elsevier.com/locate/jare

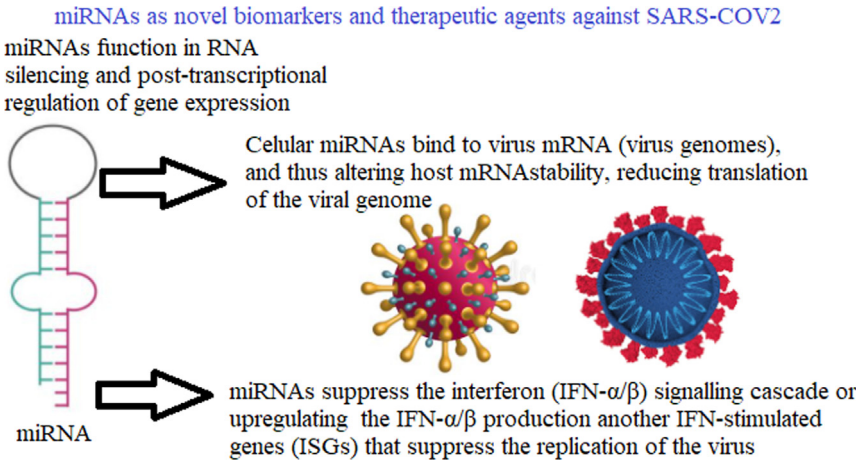
Review

Micro-RNAs in the regulation of immune response against SARS CoV-2 and other viral infections

Tareq Abu-Izneid [a], Noora AlHajri [b], Abdallah Mohammad Ibrahim [c], Md. Noushad Javed [d], Khairi Mustafa Salem [a], Faheem Hyder Pottoo [e], Mohammad Amjad Kamal [f,g,h,*]

[a] Pharmaceutical Sciences, College of Pharmacy, Al Ain University, Al Ain, Abu Dhabi, United Arab Emirates
[b] Department of Epidemiology and Population Health, College of Medicine, Khalifa University, United Arab Emirates
[c] Fundamentals of Nursing Department, College of Nursing, Imam Abdulrahman Bin Faisal University, P.O. Box 1982, Dammam 31441, Saudi Arabia
[d] Department of Pharmaceutics, School of Pharmaceutical Education and Research (SPER), Jamia Hamdard, New-Delhi, India
[e] Department of Pharmacology, College of Clinical Pharmacy, Imam Abdulrahman Bin Faisal University, P.O. Box 1982, Dammam 31441, Saudi Arabia
[f] West China School of Nursing/Institutes for Systems Genetics, Frontiers Science Center for Disease-related Molecular Network, West China Hospital, Sichuan University, Chengdu 610041, Sichuan, China
[g] King Fahd Medical Research Center, King Abdulaziz University, P. O. Box 80216, Jeddah 21589, Saudi Arabia
[h] Enzymoics, Novel Global Community Educational Foundation, 7 Peterlee Place, Hebersham, NSW 2770, Australia

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 19 September 2020
Revised 24 November 2020
Accepted 28 November 2020
Available online 2 December 2020

Keywords:
miRNAs
COVID-19

ABSTRACT

Background: Micro-RNAs (miRNAS) are non-coding, small RNAs that have essential roles in different biological processes through silencing genes, they consist of 18–24 nucleotide length RNA molecules. Recently, miRNAs have been viewed as important modulators of viral infections they can function as suppressors of gene expression by targeting cellular or viral RNAs during infection.

Aim of review: We describe the biological roles and effects of miRNAs on SARS-CoV-2 life-cycle and pathogenicity, and we discuss the modulation of the immune system with micro-RNAs which would serve as a new foundation for the treatment of SARS-CoV-2 and other viral infections.

Key scientific concepts of review: miRNAs are the key players that regulate the expression of the gene in

Peer review under responsibility of Cairo University.

* Corresponding author.
E-mail address: prof.ma.kamal@gmail.com (M.A. Kamal).

https://doi.org/10.1016/j.jare.2020.11.013

SARS-CoV-2
Viral infections
Biomarkers
Immunotherapy

the post-transcriptional phase and have important effects on viral infections, thus are potential targets in the development of novel therapeutics for the treatment of viral infections. Besides, micro-RNAs (miRNAs) modulation of immune-pathogenesis responses to viral infection is one of the most-known indirect effects, which leads to suppressing of the interferon (IFN-α/β) signalling cascade or upregulation of the IFN-α/β production another IFN-stimulated gene (ISGs) that inhibit replication of the virus. These virus-mediated alterations in miRNA levels lead to an environment that might either enhance or inhibit virus replication.

Introduction

The COVID-19 is a viral respiratory infection that is caused by the newly discovered virus SARS-CoV-2, the virus is known to have appeared initially in Wuhan wet animal market, China by December 2019 and later spread worldwide [1], it was recognized by the WHO as a pandemic in March 2020. Nowadays, the number of positive cases that are diagnosed with the disease exceeds 13 million, with over 550 thousand deaths reported which accounts for around 4% fatality rate [1]. SARS-CoV-2 is a member of the family of Coronaviridae and the subfamily Coronavirinae in which there are 4 different genera: the alphacoronavirus, betacoronavirus, gammacoronavirus, and delta coronavirus. Coronaviruses are single-stranded positive-sense RNA (+ssRNA) with a length of the genetic material of 30 kb, considering the length of its genetic material, the SARS-CoV-2 is the largest RNA virus [2]. The RNA of the virus is used for the translation first of the polyprotein 1a/1ab (pp1a/pp1ab) [2], then the polyprotein undergoes cleavage by protease and papain-like protease to form the nonstructural proteins (NSPS) [3]. The NSPS will form the replication-transcription complex (RTC) in a double-membrane vesicle (DMVs) [4]. After that, a subgenomic RNAs (sgRNAs) is formed by RTC [5]. The sgRNAs serves as templates for the production of the subgenomic mRNAs [5]. Coronavirus usually contains 10 open reading frames ORFs [6]. The first ORFs is (ORF1a/b), which is the largest and contains around two-third of the genetic material [7]. The first ORF includes the code of 16 nsps [8]. The remaining ORF encodes the four structural proteins which are: spike (S), membrane (M), envelope (E), and nucleocapsid (N) proteins. Also, it contains other accessory proteins that differ between each type of coronaviruses like 3a/b protein, and 4a/b protein, HE protein [2]. The functions of 4 structural proteins are: Homotrimers of S proteins give the spikes on the surface of the virus which serve as the attachment part to the host cell [9]. The M protein with 3 different domains gives the shape to the virus, facilitating the curvature of the membrane, and is responsible for the binding to the nucleocapsid [10]. The E protein is essential in the viral pathogenesis and has an important function for viral assembly and release [11]. The N protein has 2 different domains which can bind to RNA, it binds to nsp3 to link the viral genome to the RTC. Also it helps in the packaging of the genome into the virions. It is reported that the N protein has an antagonistic effect for the interferon, which enhances viral replication [12] (Fig. 1).

Pathophysiology of SARS-CoV-2

Transmission from person to person is via infected air droplets or direct contact; the incubation period of the virus is around 6.4 days [1]. After it enters into the respiratory system, the life cycle of the virus begins which consists of 5 stages [13], the attachment of the virus to the host cell via binding to the ACE2 through the spike protein [14]. The ACE2 receptor is found in several tissues like the lung, kidney, heart, bladder, and the GI system [15]. After the binding, the spike protein is cleaved in the two-step process to be activated. The cleavage of the S protein occurs at the S1/S2 site of the protein that would be primed and cleaved in the next step at the site S2 in order to be activated [16]. The spike protein of the coronavirus is considered unique protein among the viruses because it has several proteases to cleave it [17]. Once the spike protein is activated it will be fused with the cell membrane, which represents the second stage of the viral replication, which is the fusion or the penetration [17]. Transcription and biosynthesis of viral proteins is the third step in the replication of SARS-CoV-2, the last two steps of the virus life cycle are the viral maturation and the release of the viral particle [13].

ACE2 is found on the apical site of lung epithelium, the entry of the virus to the lung tissue causes destruction of cells and lung injury [18]. The 3 types of cells that have the initial innate immune response to viral entry are the epithelial cells, lung macrophages and the dendritic cells [19]. The phagocytosis of virally infected cells by the macrophages and dendritic cells results in presentation of the antigen to the T cells via antigen-presenting cells, which leads to T cell activation and the beginning of adaptive immune response [13]. The strong inflammatory response that is associated with the viral infection could result in Acute respiratory distress syndrome (ARDS) [20]. The mechanism that mediates the ARDS is believed to result from the cytokine storm in which a large number of cytokines and proinflammatory mediators are released by the immune cells [21].

The alveolar damage that is caused by the virus will be followed by edema of fibrin exudate, then hyperplasia of the pneumocyte type II. In some severe cases, there is a thickening of the alveolar sputum causing hyaline membrane formation. The pneumocyte type II is the target for the virus because of the expression of ACE2 receptor on its surface, those cells are responsible for the surfactant production and they share the same basement membrane with adjacent endothelial cells [22]. In severe cases, it is observed to cause acute myocardial cells injury as evidenced by an increase in cardiac troponin in 28% of the severe cases, especially if the individual has a pre-existing cardiac disease. The cause of myocardial cell injury is yet to be explained, but different theories have been proposed, it might be due to cytokine effect from the cytokine storm or direct infection by the virus although there is no evidence of signs and symptoms of myocarditis [23]. Also, Thromboembolic events are reported: DIC is found to be linked with mortality in severe COVID-19 cases, it is believed that DIC results from both arterial and venous thrombosis [24]. According to one German study, the incidence of venous thromboembolism was 27% and arterial thrombosis is 4% in cases who were admitted to ICU, half of the cases with VTE were found to develop pulmonary embolism, which complicates the respiratory status [25]. An autopsy showed large thrombosis in pulmonary vessels, the thrombosis is found in areas that have inflammatory changes [26]. The percentage of Gastrointestinal system involvement is around 17.3% according to cohort study [27], the virus can infect the epithelium of the gas-

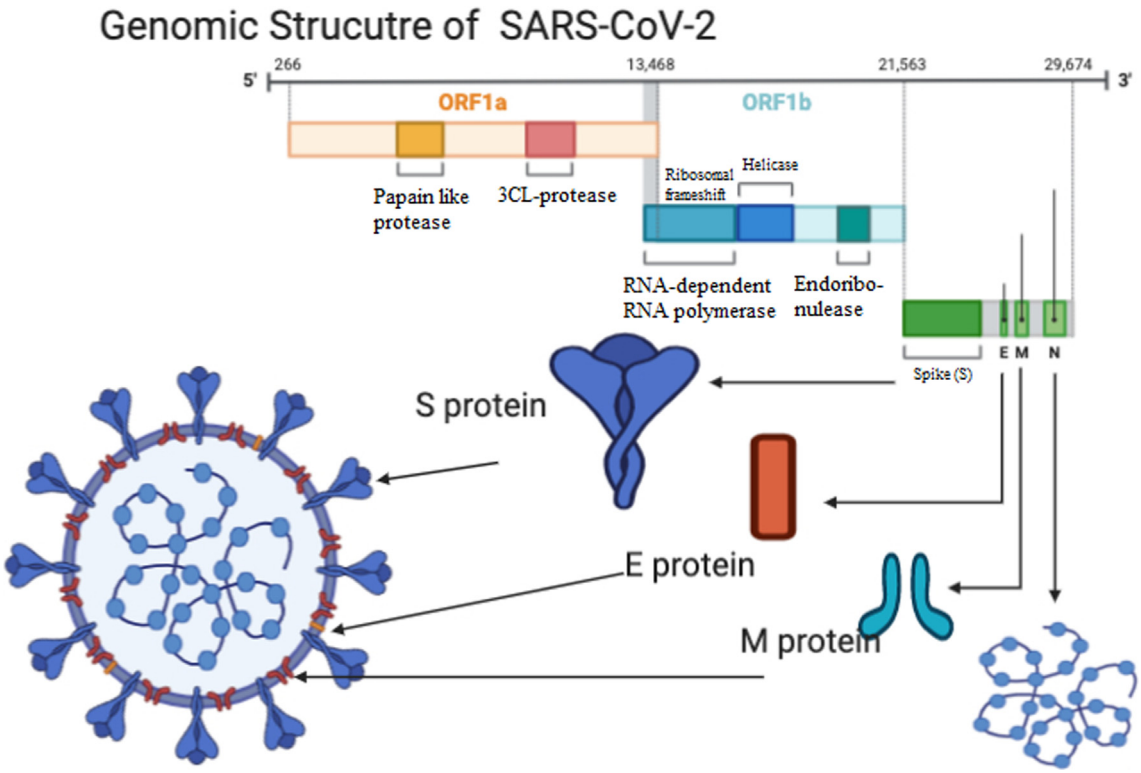


Fig. 1. Genomic structure of SARS-CoV-2 [Adapted after minor modification from open access; [136]].

trointestinal tract directly through the ACE2 receptor, GI symptoms can range from anorexia, nausea, vomiting and non-bloody diarrhea [28].

Introduction to miRNA

RNA interference or abbreviated as (RNAi) is a pathway that regulates genes [29]. microRNA (miRNAs) are small non-coding gene sequence that exists in most eukaryotes, they are 20–22 nucleotides, miRNA are part of the RNAi machinery [29,30]. The function of miRNAs is the silencing of RNA and post transcription regulation of gene expression [31,32]. miRNAs are found to have control on a wide range of genes which control biological activity like cell division, cellular differentiation, and death (apoptosis) [30]. miRNAs have a significant role in viral replication and can be utilized by the infected cells to control the replication of the virus [33]. Several viruses can express miRNAs like herpes virus and retrovirus. Recently, the identification of some genes that are regulated by viral miRNAs raised the suggestion that targeting those genes could have a role in controlling viral infection [33]. One study examined miR-122 in the treatment of chronic hepatitis c in chimpanzees, they found it causes a long-lasting suppression of the virus and improvement in the pathology [34]. Those pieces of evidence could raise the possibility that miRNAs could be a potential therapeutic option in the management of SARS-CoV-2. Several attempts have been conducted to evaluate the ability of this approach in treating and controlling COVID-19. One study used the computational approach utilizing the miR target program to match miRNA to coronavirus and evaluated the interaction between the miRNA and the mRNA of the virus using characteristics such as the free energy, the position of the binding sites in the 3′UTr and 5′UTR, and the scheme of the interaction between the nucleotides [35]. They found 7 complete complementary miRNA (cc-miRNA) that matches for SARS-CoV-2 that can bind to the location that encodes for ORF1ab, S,N [35]. They proposed that the concentration of cc-miRNA that used can suppress the viral mRNA without having a significant effect on the human genome [35]. Another paper evaluated 2565 miRNA for their ability to bind the gRNA of the coronavirus, their result revealed that miR5197-3p can bind SARS-CoV-2, interestingly, the binding site of the cc-miRNA of the coronavirus cannot target genes of the humans, which means there are fewer side effects of the translation of the human mRNA [35]. Furthermore, another computational study found that virus miRNA has greater regulation of the biological process of the immune response and the cytoskeleton, which could create a greater effect on the viral life cycle [36].

Effect of cellular/host miRNAs on viral replication and pathogenesis

Knowing fact that miRNAs play essential roles in gene regulation in mammals, therefore miRNAs directly or indirectly affecting virus ability to replicate and to cause infection [37]. During viral life cycles (Infection processes), in an infected cell with RNA viruses, cellular miRNAs are expected to bind virus mRNA (virus genomes), and thus altering host mRNA stability, reducing translation of the viral genome, and/or changing the levels of free miRNAs in the cell [38]. This effect may help the viral transcripts to be more stable and alter the host cell genome expression [39]. Several reports revealed that miRNAs are involved in viral pathogenesis process by inducing alteration in the host immune system against the virus, promoting viral replication, or altering miRNA-modulated host gene regulation [38].

It is well reported in the literature that miRNAs levels and types of expression, biogenesis and sequestration, are changed during coronavirus infection as a response from the host as well as viral manipulations. Determination and analysis of miRNA expression during coronavirus infections showed 10–100 s of miRNAs levels

are changed by different types of coronaviruses. Thus, miRNAs could be considered as potential biomarkers during coronavirus infection [37,40]. Gottwein et al. have compiled up to date data on what is known about cellular miRNAs and their effects on viral replication and pathogenicity [37]. Understanding mechanisms and functions of miRNAs during SARs-CoV-2 infections would significantly contribute to the process of developing therapeutic option based on miRNA that will act by either as; miRNA mimics and/or miRNA antagonists [41].

Effect of cellular miRNAs on the virus life cycle and pathogenesis

As discussed above, miRNAs of either cellular or viral origin could positively or negatively affect the viral life cycle and replication. They can affect host physiological processes, including the immune system [37]. Viruses generate miRNA to facilitate virus-induced cytopathy and pathogenicity [42]. Additionally, the host miRNA expression level/type was found to affected by viral infections [39]. There is evidence in the literature that cellular miRNAs can bind to various types of viral RNA and thus directly regulate viral infectious progress [38]. Given the fact that the structure of the genetic material for the positive-strand RNA viruses mimics the cellular mRNAs genomic structure, this will allow for the miRNA to bind directly to the viral RNA, and this could result in upregulation or downregulation of the viral replication. The known mechanisms of how Micro-RNAs (miRNAs) affect RNA-viruses, including SARs-CoV-2, replication are wide-ranged. They could inhibit SARs-CoV-2 replication by:

(1) Direct-Acting by Targeting Viral RNA: Host/Cellular miRNAs directly interact with the viral RNA.
(2) Indirect-acting by modulating immune-pathogenesis process/response. Affecting the IFN-α/β signalling cascade process [41].

Direct targeting of viral RNA (Direct host miRNA/viral RNA interactions)

It is reported in the literature that human miRNAs can bind indirect way to the genome of the virus in its both regions the coding and the noncoding 3′UTR regions resulting in translational repression and therefore producing antiviral effects [43]. Literature evidence also indicated that host-miRNAs bind to viral-RNA, regulating its translation, virus replication and thus affecting viral pathogenesis [38]. The underlying mechanism for host miRNAs-Viral RNA interactions is facilitated by the presence of micro-RNA Response Elements (MREs), that are in general found in the 5′UTR, coding region (CDS) and 3′UTR of the virus genetic material [41,44]. These interactions have been identified by the following outcomes that viral replication directly alters:

a) Host miRNA binds to the 3′-NTR of viral-mRNA, resulted in suppression of viral translation or enhanced RNA viral translation.
b) Host miRNA binds to the coding region of viral-mRNA, resulting in suppression of the translation of the viral genes that prevent viral replication.
c) Host miRNA binds to the 5′-NTR of viral-mRNA, resulting in stabilization of virus RNA and therefore enhancing replication (Fig. 2).

The three mechanisms regulate RNA virus replication inside certain type of cells and/or tissues [40,45]. There is a high degree of similarity that has been seen between SARS coronavirus (SARS-CoV) and SARS-CoV-2 [40].

To date, a limited number of cases where the viral infection was regulated by direct binding of miRNAs to the genome of the virus has been reported [38]. The reason behind this would most likely be justified as the virus would respond to the consequences of this interaction, and those are quickly removed. This justification was backed up by the accumulated findings which showed that most of the interaction between viral RNA and host miRNA leads to positive effects on the replication of the virus [38].

The following mi-RNAs; miR-323, miR-485, miR-491, miR-654, and miR-3145, are examples of host miRNAs which are reported to have an inhibitory effect on viral replication. This antiviral activity of these mi-RNAs was induced after they bound to the coding region of the influenza virus PB, which resulted in the degradation of the virus RNA thus suppression of viral translation and replication [43]. On the contrary, miR-122 is one of the reported miRNAs that showed a positive effect on viral replication (increased viral replication). Host miR-122 works by direct miRNA-virus interaction with the hepatotropic virus (HCV is a positive-sense ssRNA genome), leading to increased viral RNA accumulation/increase virus replication [38]. Based on this reported evidence, Fulzele et al. recently conducted *in silico* evaluation of host miRNAs targeting SARS and SAR-CoV-2. They found that 848 miRNAs could target the SARS genes and 873 miRNAs could target the SAR-CoV-2 genes. 558 miRNAs from the total number of miRNA that could target SARS (848) are commonly present in all SAR-CoV-2. Interestingly, 315 miRNAs are unique for SAR-CoV-2 and 290 miRNAs unique to SARS [43].

Viral mRNAs could go under selective pressure to avoid Host miRNA–RNA viral interactions to abundant the antiviral activity of cellular miRNAs. Therefore, the level of achievement of such interactions could be maintained or revoked according to the ability and flexibility of the viruses to rapidly change/reshape their genomic structure as a response of the selective pressure. Finally, the amount and type of the miRNA within cells which are infected is expected to indirectly change during virus infection, due to the different mechanisms/process that is used to promote or reduce viral replication and are regulated by cellular miRNAs [37]. Therefore miRNAs have been used as biomarkers that can aid in the diagnosis and the prediction of the prognosis for some diseases including cancer and viral infections.

Several reported studies, which were conducted on bronchoalveolar stem cells (BASC) infected with SARs, have demonstrated that there are significant relationships between viral effects on miRNAs expression and the immunopathogenic responses during BASC infections [46]. In another study, the use of miR-200c-3p during SARs infection (miR-200c-3 pacts by binding to the 3′-UTR-mRNA in ACE2 cells) resulted in dysregulation of angiotensin-converting enzyme ACE2 expression and therefore suppressed viral infection by SARS and by other viruses that promote acute respiratory syndromes [46].

Indirect effect by regulation of cellular mRNAs and cellular/host factors

Besides the direct action of host miRNAs, viral miRNA, in regulating viral replication, indirectly actions are also reported [47]. The indirect action of miRNAs is to increase the expression of some cellular factors (in the host cell) that are essential for one or more stages in the viral life cycle [47]. It also involves the modulation of cell-surface receptor expression that is essential for viral entry and affecting tropism, and some cofactors that are required for translation and viral replication. Finally, miRNAs also affect the immune response to the infection such as induction of apoptosis (Fig. 2).

miRNAs modulation of immune-pathogenesis responses to viral infection is one of the most-known indirect effects, which leads to suppression of the interferon (IFN-α/β) signalling cascade or upregulation of the IFN-α/β production [41]. This virus-mediated alter-

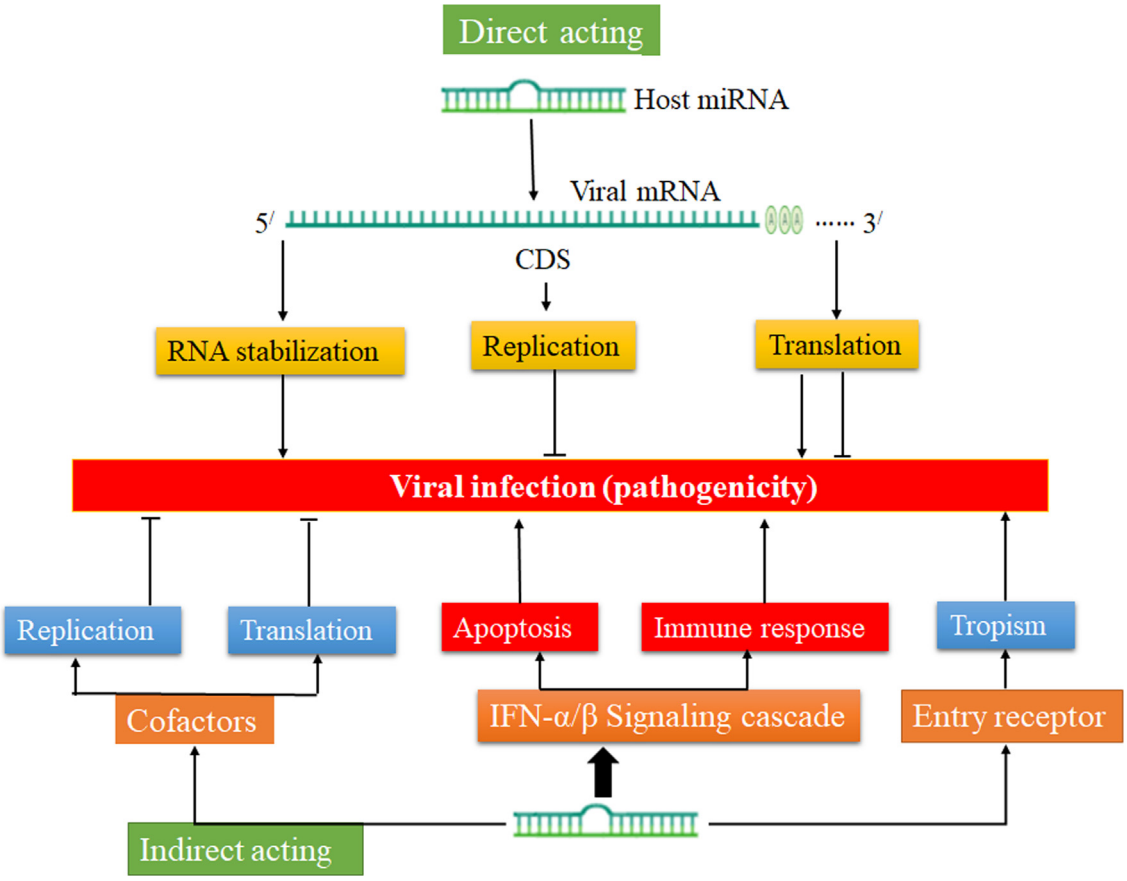


Fig. 2. Mechanism of action of miRNAs during viral infection [Adapted after minor modification from open access; [49]].

ation in miRNA levels leads to a proviral or an antiviral environment [38]. Examples on this are miR-466i and let-7b are reported to act on type I interferons, IFNα and IFNß respectively. Targeting these type I interferons by these miRNAs may cause loss of the antiviral state and some other cases prevent the translation of some pro-inflammatory cytokines such as IL6 [48]. miRNAs could also enhance or restrain the expression of some cell-surface receptors which are essential for viral entry and endocytosis such as $CD4^+$ in the case of HIV and ACE2 in the case of SAR-CoV-2 [38,49]. miRNAs are most proficient at attacking SARS-CoV-2. In conclusion, miRNAs, for both viral and cellular origin, may act by direct and/or indirect mechanisms during viral infections, and this in its turn may have positive or negative consequences on viral replication, pathogenesis and cytopathology. The understanding these mechanisms would promote miRNAs as promising and potential targets for creating miRNA-based therapeutics for the treatment of COVID-19.

Introduction to innate and adaptive immunity

The immune system is divided into two large groups: the innate immune system and the adaptive, immune system. Together they work closely and take on a wide range of tasks at different levels.

The innate immune system

The Innate immune system is the initial mechanism of defense to counter foreign pathogen and is accounted for the inciter of a series of heterogeneous inflammatory reactions [50]. These inflammatory reactions are stimulated by pattern recognition receptors (PRR) which react to pathogen-associated molecular patterns (PAMP). PRR are grouped in 5 categories of receptors: Nod-like receptors (NLR), C-type lectin receptor (CLRs), RIG-like receptors (RLRs), Toll-like receptors (TLRs), and AIM2-like receptors (ALR) [51,52]. These receptors are critical in the regulation of the innate immune system and activation of other pro-inflammatory interferons and cytokines stimulated genes [53]. Recent advances in research provide evidence that several miRNAs plays role in the control of acute inflammatory, namely miR-155, miR-146, and miR-223 subsequent to pathogen recognition (Table 1).

Adaptive immune system

The adaptive immune system is mainly characterized by stimulation and clonal expansion of T- cells and B- cells. This stimulation and expansion result in the formation of antibodies in response to infection along with cytotoxic effect or response [54]. miRNAs have been widely associated with regulating the innate and adaptive immune system by modulating series of the immune response such as the maturation, stimulation, survival, and proliferation of T-cells and B-cells [55].

miRNAs in the modulation of an immune response against viruses

miRNAs are a new class of evolutionary small non-coding RNA (snc-RNA) molecules with an estimated size of 22 nucleotides (nt) [69]. miRNAs regulate gene expression post-transcriptionally by the formation of incomplete base-pairs and attaching to sequences in the 3′ untranslated region (UTR) of genes [70]. Consequently, this could either induce gene degradation or repress gene translation thus preventing protein accumulation. Given that miR-

Table 1
Shows a list of miRNAs responsible for the activation and function of the immune system.

miRNA	Target Gene	Effect	Reference
Let-7	IL-6	Reduces the expression of IL-6	[56]
miR-24	Chitinase 3-like 1	Overexpression enhances the production of Arg-1, CCL-17, CCL-22, CD-163, and CD106, but decreases the production of phenotype markers in stimulated macrophages	[57]
miR-124	TLR	stimulate anti-inflammatory actions by downregulating TLR-6 and Myd-88	[58]
miR- 126	VCAM-1	An enhanced expression is seen as a response to hyperlipidemia treatment.	[59]
miR-132	NF-κB	Overexpression stimulates the translocation of NF-κB, acetylation of p65, and secretion of IL-8 and MCP-1	[60]
	IL-6	Related to macrophage infiltration and IL-6 levels in people with non-alcoholic liver disease	
miR-145	TNF-α	Positive effect on the secretion of TNF-α	[61]
miR-146	IL-1β	IRAK suppress miR-164 resulting in increased expression of IL-1 and control the inflammatory response in periodontal inflammation	[62,63]
	TNF-α	miR-146 is NF-κB dependent and acts as an inhibitor targeted to signalling proteins of an innate immune response	
miR-155	IL-1	During Dendritic cell maturation, it regulates the TLR/IL-1 pathway.	[64]
miR-181	NF-κB/ VCAM-1/ E-selectin	Overexpression inhibits import in a3 expression and an enriched set of NF-κB-responsive genes	[65]
miR-187	TNF-α, IL-6, and IL-2	Regulates Cytokines production	[66]
miR-221	TNF-α	Down-regulated by TNF-α	[67]
miR-222	ICAM-1	Reduces the ICAM-1 expression and prevents the interaction of cytotoxic cell to tumour cells	
miR-223	PAI-1	Prevent the accumulation of NLRP3 protein and suppress IL1b secretion from the inflammasome	[68]

NAs are capable of influencing critical proteins and molecules involved in signalling pathways and can target transcription factors with robust regulatory effect on the immune response [71,72], it was determined that miRNAs have a significant role in immune system activation and cellular differentiation. More recently, miRNAs have been shown as a novel class of regulators of various immune and biological responses such as signal transduction, apoptosis, carcinogenesis, biogenesis, cell growth and development and even responses to viral infection. Moreover, miRNAs are involved in the control of Natural Killer (NK) cells stimulation, function and survival, and has demonstrated an ability to delete Dicers or Dgcr8 conditionally [73]. More specifically, in mice, it has been shown that miR-150 is crucial in the regulation of maturation and development of NK cells, while the miR-181 is responsible for human NK cells maturation, activation and function by activating Notch signalling [74]. Further, when mouse NK cells were treated with IL-15, this resulted in an alteration in the expression of numerous miRNAs [75]. Among miRNAs, when miR-223 was down-modulated, it was found that there was an upregulation of its target gene, *granzyme B* [75]. Also, It has been shown that when miR-155 is properly regulated, it can produce protective immune effects, while when miR-155 is deregulated it could stimulate malignant transformation [76]. Significant research findings by Dickey et al. and others have suggested that miR-155 is an important oncogene in chicken lymphomas [77] and was, later on, found that it is also expressed in abundance in mammalians with hematopoietic cancers, thereafter, it was classified as immunoregulatory noncoding RNA in macrophages and B lymphocytes [78–82]. These crucial discoveries elucidated that miR-155 is regulated by and plays a significant role within heterogeneous types of the active immune cells that include different types of T and B cell types, dendritic cells and NK cells. Moreover, evidence has shown that miR-155 expression is increased during the activation of T-cells, B cells, dendritic cells, and macrophages [73]. Additionally, miR-155 regulates the expression of numerous protein and signalling molecules that have a role in controlling the immune response such as Ship1 [73] and Socs1 [83], as well as transcriptional modulators such as Jarid2 [84], Ets1 [85], PU.1 [86] and Fosl2 [87]. Corresponding to its established roles on modulating the immune response, several types of research have revealed that miR-155 is critical in activating and controlling the immune response to viruses [53,88,89].

In an experimental study done by Trotta et al. to assess the effect of miRs-155 on human NK cells that were infected by lentivirus in vivo, they observed that the NK cells which have been activated by IL-12 and IL-18 had an increased expression of miR-155, also they observed an important correlation between IL and 18 with and the levels of miR-155 and IFN-γ. Thus, it was proposed that miR-155 might play a role as a stimulator of IFN-γ production and when the miR-155 expression was down-regulated, there was a decline in IFN-γ levels. IFN-γ is a prototypic cytokine that is secreted by NK cells and they have an important role in controlling the tumour immunity and protection from inflammation. It is evident that IFN-γ deficiency can result in a greater risk of infection and/or malignancy, while overexpression of IFN-γ can result in autoimmune disorders [73].

Given miR-155 have demonstrated an important role in tailoring $CD4^+$ reactions in models of autoimmunity, thus, several papers on viruses and immune response highlighted the importance of miR-155 in intensification the responses of $CD8^+$ T cell [90–92]. Furthermore, numerous researches observed that miR-155 is essential for ample $CD8^+$ T cell activity, cytokine secretion, proliferation, and control of inflammation. The results of these reports enforce the significance of miR-155 in optimizing immune response after viral infection [90–92]. Moreover, several reports shed the light on the other aspects of the role of miRNAs as critical controls of the interaction network between host-pathogen. Although the involvement of several miRs could be part of a host defense reaction to limit the replication and proliferation of microorganism [93]. Interestingly, the host miRNAs pathway could be also manipulated by the viruses to facilitate pathogen replication and dissemination. These observations support a model where miRNAs could be used to target viral gene expression, control inflammation and modulate immune activity.

The role of miRNAs in modulating the immune system against SARS-CoV-2

In general, miRNAs are also involved in regulating several other physiological conditions and biological pathways such as cell development, maturation, differentiation, proliferation and activation [94]. miRNAs are important regulatory mechanisms by which cells can eliminate undesired or malformed mRNA. Although miRNAs can be an important anti-viral tool within the host system that can activate the innate and adaptive immune responses, it found that miRNAs can also act as a gateway for the penetration of the virus because of its non-antigenic characteristics [95]. Several studies have shown that viruses could utilize the machinery of the host to process the miRNAs and modulate host immune

response [38,96,97]. Interestingly, this can uniquely modulate cellular pathways that override the host's defense system [96]. SARS-CoV-2 belongs to coronaviridae family and have been shown to regulate the host miRNAs repertoire, henceforth, controlling the viral proliferation and dissemination [88]. Moreover, several studies hypothesized that miRNAs that were activated by the coronavirus could regulate the host's antiviral immune responses including viral sensing [98], cytokine secretion [93,99], and T-cell mediated cell killing. For instance, nucleocapsid protein of the coronavirus OC43 attaches to miR-9 and turn on Nuclear Factors light-chain- enhancer of B-cells (NF-κB), which is a prototypical proinflammatory signalling pathway that has been associated with several chronic diseases and viral illnesses when its expression is dysregulated by the invading virus [100]. Although host miRNAs could be either regulated or utilized by the invading virus. Viral miRNAs are also players in this host-pathogen interaction in which they modulate the expression of the host gene, stress genes, proliferation of cells, and expression of the virus genes [101].

Khan et al. hypothesized that genomic differences between the SARS-CoV-2 virus isolates could have contributed to variation in binding to host miRNAs and hence differences in the virus pathogenicity, symptoms and signs of the disease and the incubation period. On the contrary, viral miRNAs could differ in their effect on regulating the expression of the host gene that could be advantageous or disadvantageous to the virus or the host [102]. Given the rapid mutation rate of the virus genome in the SARS-CoV-2 samples in various global places, it is now accepted that this could have played an important role in determining the severity of the illness and mortality rate among patients infected with SARS-CoV-2.

Human miRNAs targeting SARS-CoV-2

Khan et al., identified in their experiment 106 host anti-SARS-CoV-2 miRNAs and only three (has-miR-17-5p, has-miR-20b-5p, hsa-miR323a-5p) host miRNAs against SARS-CoV-2 were found to have an antiviral effect during host infection [102]. Ace2 mRNA and Ace2 protein levels were inhibited by miR-200c in rat primary cardiomyocytes and in human iPSC-derived cardiomyocytes, thus miRNAs could reduce SARS-CoV-2 infection (as ACE2 serves as the entry gate for SARS-CoV2) [103]. Host miRNAs could also have a well-established role in preventing the viral invasion of the host system through blocking target pathways needed for viral penetration and other significant pathways for viral replication and diffusion. For instance, blocking some molecules such as - p38 MAPK signalling [104], FAK signalling pathway [105], p13K-Akt signalling pathway [106] that could be controlled by the virus for effective pre-miRNA processing and replication. Additionally, these host miRNAs can alter some of the host inflammatory responses to inhibit collateral damage to susceptible organs such as the lungs, therefore, protecting the lung from possible lung injury by targeting IGF1 signalling, VEGF signalling, PAR1 signalling, integrin signalling, and TGF-beta signalling [102]. Interestingly, there is evidence that apart from protective roles of miRNAs, some of the host miRs play an active role in the viral infection through downregulating some of the pathways intended to illicit an efficient immune response, thus supporting viral survival in infected cells by preventing early immune responses such as viral apoptosis and autophagy, thus could inhibit host immune surveillance pathways and function as a pro-viral factor. Recently, it was found that some viral miRNAs can also regulate host gene expression by mimicking cellular miRNAs or engaging in novel modulatory relationships, thus, taking advantage of predefined host regulatory pathways and therefore affecting viral replication and pathogenesis [53]. Despite that the main action initiated by host miRNAs is to inhibit the viral RNA, however, miRNAs role can be described as a double-edged sword that eases viral invasion of the host immune system by interfering with some critical immune pathways [107]. This is strikingly exemplified by the fact that host miRs can facilitate viral replication dissemination in the system, furthermore, they can suppress the expression of host miRNAs that function as a repressor of viral replication. Consistent with these data, Khan et al., highlighted several important pathways within the host immune system like- IFN-gamma signalling, TGF-beta signalling, Interleukin signalling, IGF1 signalling, TRAIL signalling pathways, that are associated with several important proinflammatory pathways that signal the release of the cytokine during viral infection [102]. Surprisingly, the authors have also documented host miRNAs are also triggered when infected with SARS-CoV-2 and may specifically suppress various Toll-Like Receptors (TLR) signalling pathways which are regarded as essential stimulatory molecules for producing host anti-viral defense system like the induction of inflammatory cytokines and other interferons. Notably, host miRNAs can also impede several receptors that are involved in signalling anti-viral responses such as uPA-UPAR signalling, TRAF6 signalling, S1P1 signalling, Estrogen receptor signalling, Protease-activated Receptor (PAR) signalling, and bone morphogenetic protein (BMP) signalling pathways, resulting in downregulation of the host anti-viral defense mechanism [102].

Nucleic acid-based therapeutics for inhibition of miRNAs function

The biological process of RNA interference (RNAi) which are defined as small complementary RNA duplexes that neutralize and interfere with certain mRNA molecules, resulting in silencing of gene translation and gene expression. There are two distinct types of RNAi molecules: small hairpin RNAs also called short hairpin RNA (shRNAs) which are synthetic RNA molecules that are synthesized in vitro with a tight hairpin turn that can be used to inhibit their target genes, thus serves as a precursor of siRNAs [108]. It is crucial to know that the shRNAs expression inside the cells can be achieved through their delivery via commercially available reagents in vitro such as bacterial or viral vectors, or plasmids [109]. miRNA is noncoding and naturally found in viruses, animal species and plants, synthetic miRNAs are developed recently to silence or restore the function of a variety of genes [110].

In contrast to miRNAs and siRNA, the antisense transcript RNA is single-stranded RNA with a sequence complementary to the messenger RNA (mRNA) rendering it the ability to hybridize and hinder protein translation. Anti-sense RNAs are either natural or synthesized, they are generally about 19–13 nucleotides [109]. Developing antisense inhibitors can be used as a restorative technique by inhibiting the overexpression of mature miRNAs sequence that is involved specifically in disease pathogenesis. With the new advancement in medical technology, it is becoming possible to artificially synthesize adjusted analogue of miRNAs as well as siRNAs that can modulate disease-related gene expression and or even block gene expression of the pathogen. Providing exogenous miRNAs can help restore the normal cell function by resetting miRNA expression [108]. Presently, mature miRNAs can be downregulated by experimentally upregulating the expression of the sites where they bind (miRs " sponges") or through giving the antisense oligonucleotides (ASO) using pharmacological approaches [111]. One of the advantages of using miRNA inhibitors is the predictable specificity of pairing the inhibitor to their target miRNA using Watson-Crick base pairing. This is an important advantage over e.g. small molecules which have unpredicted specificity to their target. As a result, designing a target for miRNAs with drugs that have nucleic acid structure presents an optimistic therapeutic

option to change the medicinal chemistry perspective of drug development, and therefore cutting down cost and time. As an example, the treatment of AntimiR-155 in a miR-155 "addicted" lymphoma case was efficient and had a higher precision to target the diseased cells compared to the current treatment [112]. Scientists found that several chemical modifications can enhance the binding of nucleotide-based miRNAs inhibitors to their target miRNAs, their stability against nucleases could reduce the cell's negative charge which inhibits penetration [113]. Nucleic acid-based inhibitors are referred to as anti-miRNAs. Despite that miRNAs inhibitions can be in vivo, however, the most challenging aspect of inhibiting miRNAs in vivo is the delivery of anti-miRNAs to the target gene. To overcome this challenge, miRNAs are conjugated to artificial carriers or are packaged into various delivery vehicles [31,32,113–115]. Artificial carriers can enhance cells uptake in vivo beside it increases the efficacy and precision for target cells and organs [116–118].

Short locked nucleic acid (LNA)- which are modified ASOs that can target miRNAs seed region, present another promising class of anti-miRNAs [119]. The LNA seed family inhibitors can block entire miRNA families and not only individual-specific miRNAs. Interestingly their bioavailability in vivo is optimal without the need for special carriers which makes them a promising class of anti-miRNAs. In a recent study, LNA- modified anti-miR-21 could suppress lupus disease in animals and psoriasis in patients with derived skin xenotransplants [120,121]. These are promising results as mice with a miR-21 deficiency do not exhibit any detectable defects proposing that there will be few to no adverse effects to inhibiting miR-21. Moreover, anti-miR-21 absorption by the skin has dramatically affected the disease outcome. This suggests that topical modes of drug delivery of anti-miRNAs readily can access the body surface (skin, eyes, oral cavity, airways, rectum and vagina) and presents an ideal substitution to overcome the challenges of systematic administration in vivo [121].

Therapeutically enhancing miRNAs expression

In contrast to the aforementioned therapeutic options, it might be intuitive to pharmacologically affect miRNAs role, either to replace lost miRNA function or to downregulate an overexpressed miRNA pathway, depending on the clinical scenario. For instance, when inducing miR-146a, it is anticipated to have suppression of certain immune pathways since it will negatively regulate various immune cells and enhance regulatory T cells role [55]. Alternatively, miR-210 which is activated in hypoxic conditions negatively regulates the T_H17 differentiation. Therefore, downregulation of T_H17-driven inflammation can be achieved by delivering miR-210 mimics [122]. Another attractive option is the induction of transcription of endogenous miRNAs instead of delivering miRNA mimics. Achieving this could be done by using CRISPR-based approaches [123]. Furthermore, targeting RNA structure or miRNAs processing is another interesting approach that has been exploring relatively. The presence of extensive miRNA secondary structures and multi-step maturation offer excellent venues for pharmacological interventions. Therefore, several strategies could be utilized to enhance miRNAs function. As an example, using a modified oligoribonucleotide termed "looptomir" to target the pre-let-7a-2 was a very successful approach [124]. Table 2. Present a summary of the development status of miRNAs based therapeutics.

miRNAs as biomarkers in COVID-19

In addition to the search for the treatment of COVID-19, the search for non-invasive COVID-19 biomarkers for diagnosis is also an urgent need, and this area of research is currently under extensive investigation and considered a rapidly growing area of research [127]. Since miRNAs have been approved to have a key role in the pathogenesis of different respiratory viral infections and to regulate host-pathogen interactions, therefore, miRNAs could serve as a potential prognostic indicator or biomarkers for respiratory virus diseases including SARS-CoV-2. In this section, we present a brief and updated review on the most updated findings in relations to the use of miRNAs overexpression and/or under-expression during different respiratory viral infections to serve as biomarkers.

Recently, several reports indicated increased or decreased amount miRNAs in circulating as a response to pathogens, this increased the potential to be as a novel tool for diagnosis [128]. Using miRNAs as diagnostic biomarkers have brought some advantages for assessment of immune-related diseases, viral infections, and cancer. These small RNAs do not only exist inside cells or tissues but also, they exist in the circulating plasma. The first miRNA was found inside the plasma was miR-21 [129,130] Later, another study detected about 91 out of 101 miRNAs exist inside the plasma, such as Let-7, miR-25, miR-192, miR-221 and miR-451 [131]. They exist either in micro-sized vesicles or bound to other content in the plasma to teleport from one tissue to another. This helps in remote communications between one tissue and another. Moreover, miRNAs expression is tissue and temporal specific [129]. The expression of miRNAs changes with the cause of the illness, as in one study, it was found that miRNAs which were highly expressed in non-small cancer lung cell were different from those expressed in colorectal cancer and type 2 diabetes [131]. Also, levels of some miRNAs were changed during some viral infections, and those miRNAs were specific to the virus which causes the infection. For example, a study found that miRNAs expressed during varicella-zoster viral infection were different from those expressed during enteroviral infection [131]. miRNAs can also help in distinguishing between active and latent infection. Expression of miRNAs was different between active TB, latent TB, and healthy individuals, meaning that it is possible to detect which stage of illness based on miRNA expression [128].

Therefore, several reports showed that miRNAs have promising potentials as diagnostic biomarkers for COVID-19 due to the following advantages; they can differentiate between an infection caused by SARS-CoV-2 from other infections that have the same manifestation like influenza, rhinoviruses or other coronaviruses. Nonetheless, miRNAs can distinguish the possibility of bad vs good disease outcomes, which have great significance in epidemic or pandemic diseases [128]. A study has found that about 34 miRNAs of positive-sense viral RNA and 45 of negative-sense viral RNA interact with specific important SARS-CoV-2 genes. It can be used to monitor different stages of the disease, assess prognosis, plan for treatment strategy, and to measure the outcome of the planned therapy. Moreover, altered expression of miRNAs can affect the levels of cytokines and chemokines, which are responsible to cause the "cytokine storm" during the SARS-CoV-2 infection. This concludes that changes in miRNAs expression can help in diagnosis and prediction of the severity of the COVID-19 infection [132].

Promises of miRNAs as the future of medical intervention

miRNAs are unique and fulfil several criteria that define good drug options, making them an attractive therapeutic target [133]. Despite their role in modulating individual target genes, the coevolution of miRNAs and their targets resulted in the modulation of an entire immune pathway. Although only recently we begin to understand little information of the full spectrum for the role of miRNAs, their involvement in the control and pathogenesis of the disease has established wide interest for their usage in the regula-

Table 2
Presents miRNA based therapeutics [47,125,126].

Company	Targeted miRNA	Disease	Mechanism	Clinical Trial Status
Regulus Therapeutics	miR-122	Hepatitis C	Anti-miR	Preclinical
	iR-10b	Glioblastoma	Anti-miR	Preclinical
	miR-221	HCC	Anti-miR	Preclinical
	miR-21	Renal fibrosis	Anti-miR	Preclinical
	miR-33	Atherosclerosis	Anti-miR	Completed preclinical
	miR-17	Autosomal dominant polycystic kidney disease	Anti-miR	Preclinical
	miR-27	Cholestatic disease	Anti-miR	Discontinued
	miR103/107	Type-II diabetes	Anti-miR	Phase-I
Santaris Plasma	miR-122	Hepatitis C	Anti-miR	Phase-IIa
Mirna therapeutics	miR-34	Primary liver cancer	Mimic	Phase-I
	miR-155	Hematological malignancies	Anti-miR	Completed preclinical
	miR-215	Cancer	Mimic	Preclinical
	miR-101	Cancer	Mimic	Preclinical
	miR-16	Cancer	Mimic	In pipeline
	let-7	Cancer	Mimic	In pipeline
miRagen therapeutics	miR-92	Peripheral artery disease	Anti-miR	Preclinical
	miR-15/195	Myocardial infarction	Anti-miR	Preclinical
	miR-155	Cutaneous T-cell lymphomas	Inhibition	Phase-I
	miR-208	Chronic heart failure	Inhibition	In pipeline
	miR-143/145	Vascular disease	Inhibition	In pipeline
	miR-29	Cardiac fibrosis	Inhibition	In pipeline
	miR-451	Abnormal red blood cell production	Anti-miR	Discovered
	miR-92	Peripheral arterial disease	Inhibition	In pipeline

tion of the immune pathways, presenting an optimistic therapeutic option for several emerging disease [134]. For a miRNA to be considered as an optimal drug target, it needs to have an expression that is specific for certain tissue. A good example will be the miR-122 that have specific expression inside hepatocyte therefore, miR-122 inhibitor will only show effects in hepatocyte [135]. Biologists believe that several different miRNAs are expressed when there is an active disease in the host system. Notably, the unusual upregulation of this specific miRNA in numerous other diseases emphasizes the importance of identifying disease biomarkers and develop strategies to create newer approaches for disease diagnosis and management.

Future perspectives and conclusion

Coronavirus disease-2019 (COVID-19) is a respiratory infection caused by a new enveloped, positive-sense, single-stranded RNA beta-coronavirus, which is currently known as SARS-CoV-2. Structurally, SARS-CoV-2 is a single strand RNA that contains crown-like spikes on its outer surface. It has four proteins that serve as structural proteins, including; spike (S) glycoprotein, small envelope (E) glycoprotein, membrane (M) glycoprotein, and nucleocapsid (N) protein, and other proteins with accessory functions. SARS-CoV-2, SARS-CoV-1 and MERS-CoV, all are coronaviruses, classified as an intracellular pathogen that utilize the host machinery system to process their genome for replication. Accordingly, SARS-CoV-2 and the host infected cells are engaged in an ever-evolving arms race to ensure their survival. The RNA molecules (including RNAs, mRNAs, miRNAs and polymerases) are under extensive investigation as potential novel therapeutics that could stop viral infection including SARS-CoV-2. Despite their role in the repression of individual target genes, coevolution of miRNAs and their targets led to regulation of entire pathways by individual miRNAs. Although we have just started to develop our insight toward the full spectrum of the role of miRNAs, their involvement in the pathogenesis of the disease has emerged wide interest for their use in regulating immune pathways, presenting an optimistic therapeutic option for several diseases. To be qualified as drug target a miRNA should be pathogenic and have the expression in certain tissues only. For example, miR-122 has a high level of specific expression in the hepatocyte, therefore, blocking miR-122 will only show action in the liver. Biologists believe that a certain number of miRNAs are upregulated in association with certain diseases or infections. Notably, the expression of these specific miRNAs in certain infectious states makes it critical to identify disease biomarkers and develop novel techniques to target viral infections like COVID-19 for diagnosis and treatment.

Compliance with Ethics Requirements

This article does not contain any studies with human or animal subjects.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Lai C-C, Shih T-P, Ko W-C, Tang H-J, Hsueh P-R. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): The epidemic and the challenges. Int J Antimicrob Agents 2020;55:. doi: https://doi.org/10.1016/j.ijantimicag.2020.105924105924.
[2] Hussain S, Pan J, Chen Y, Yang Y, Xu J, Peng Y, et al. Identification of novel subgenomic RNAs and noncanonical transcription initiation signals of severe acute respiratory syndrome coronavirus. J Virol 2005;79:5288–95. doi: https://doi.org/10.1128/JVI.79.9.5288-5295.2005.
[3] Kandeel M, Ibrahim A, Fayez M, Al-Nazawi M. From SARS and MERS CoVs to SARS-CoV-2: moving toward more biased codon usage in viral structural and nonstructural genes. J Med Virol 2020. doi: https://doi.org/10.1002/jmv.25754.
[4] Sawicki SG, Sawicki DL, Siddell SG. A Contemporary View of Coronavirus Transcription. J Virol 2007;81:20–9. doi: https://doi.org/10.1128/JVI.01358-06.
[5] Perlman S, Netland J. Coronaviruses post-SARS: update on replication and pathogenesis. Nat Rev Microbiol 2009;7:439–50. doi: https://doi.org/10.1038/nrmicro2147.
[6] Al Hajjar S, Memish ZA, McIntosh K. Middle East Respiratory Syndrome Coronavirus (MERS-CoV): a perpetual challenge. Ann Saudi Med 2013;33:427–36. doi: https://doi.org/10.5144/0256-4947.2013.427.
[7] Masters PS. The molecular biology of coronaviruses. Adv Virus Res 2006;66:193–292. doi: https://doi.org/10.1016/S0065-3527(06)66005-3.
[8] Ziebuhr J, Snijder EJ, Gorbalenya AE. Virus-encoded proteinases and proteolytic processing in the Nidovirales. J Gen Virol 2000;81:853–79. doi: https://doi.org/10.1099/0022-1317-81-4-853.

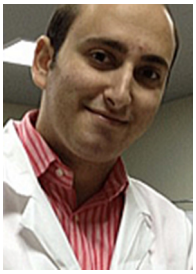
[9] Beniac DR, Andonov A, Grudeski E, Booth TF. Architecture of the SARS coronavirus prefusion spike. Nat Struct Mol Biol 2006;13:751–2. doi: https://doi.org/10.1038/nsmb1123.
[10] Nal B, Chan C, Kien F, Siu L, Tse J, Chu K, et al. Differential maturation and subcellular localization of severe acute respiratory syndrome coronavirus surface proteins S, M and E. J Gen Virol 2005;86:1423–34. doi: https://doi.org/10.1099/vir.0.80671-0.
[11] DeDiego ML, Alvarez E, Almazán F, Rejas MT, Lamirande E, Roberts A, et al. A severe acute respiratory syndrome coronavirus that lacks the E gene is attenuated in vitro and in vivo. J Virol 2007;81:1701–13. doi: https://doi.org/10.1128/JVI.01467-06.
[12] Fehr AR, Perlman S. Coronaviruses: an overview of their replication and pathogenesis. Coronaviruses 2015;1282:1–23. doi: https://doi.org/10.1007/978-1-4939-2438-7_1.
[13] Yuki K, Fujiogi M, Koutsogiannaki S. COVID-19 pathophysiology: a review. Clin Immunol 2020;215:. doi: https://doi.org/10.1016/j.clim.2020.108427108427.
[14] Li W, Moore MJ, Vasilieva N, Sui J, Wong SK, Berne MA, et al. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. Nature 2003;426:450–4. doi: https://doi.org/10.1038/nature02145.
[15] Zou X, Chen K, Zou J, Han P, Hao J, Han Z. Single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to 2019-nCoV infection. Front Med 2020;14:185–92. doi: https://doi.org/10.1007/s11684-020-0754-0.
[16] Belouzard S, Chu VC, Whittaker GR. Activation of the SARS coronavirus spike protein via sequential proteolytic cleavage at two distinct sites. Proc Natl Acad Sci USA 2009;106:5871–6. doi: https://doi.org/10.1073/pnas.0809524106.
[17] Belouzard S, Millet JK, Licitra BN, Whittaker GR. Mechanisms of coronavirus cell entry mediated by the viral spike protein. Viruses 2012;4:1011–33. doi: https://doi.org/10.3390/v4061011.
[18] Jia HP, Look DC, Shi L, Hickey M, Pewe L, Netland J, et al. ACE2 receptor expression and severe acute respiratory syndrome coronavirus infection depend on differentiation of human airway epithelia. J Virol 2005;79:14614–21. doi: https://doi.org/10.1128/JVI.79.23.14614-14621.2005.
[19] Yoshikawa T, Hill T, Li K, Peters CJ, Tseng C-TK. Severe Acute Respiratory Syndrome (SARS) Coronavirus-induced lung epithelial cytokines exacerbate SARS pathogenesis by modulating intrinsic functions of monocyte-derived macrophages and dendritic cells. J Virol 2009;83:3039–48. doi: https://doi.org/10.1128/JVI.01792-08.
[20] Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respiratory Med 2020;8:420–2. doi: https://doi.org/10.1016/S2213-2600(20)30076-X.
[21] Li X, Geng M, Peng Y, Meng L, Lu S. Molecular immune pathogenesis and diagnosis of COVID-19. J Pharm Anal 2020. doi: https://doi.org/10.1016/j.jpha.2020.03.001.
[22] Zhang H, Zhou P, Wei Y, Yue H, Wang Y, Hu M, et al. Histopathologic changes and SARS–CoV-2 immunostaining in the lung of a patient with COVID-19. Ann Intern Med 2020. doi: https://doi.org/10.7326/M20-0533.
[23] Madjid M, Safavi-Naeini P, Solomon SD, Vardeny O. Potential effects of coronaviruses on the cardiovascular system: a review. JAMA Cardiol 2020. doi: https://doi.org/10.1001/jamacardio.2020.1286.
[24] Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost 2020;18:844–7. doi: https://doi.org/10.1111/jth.14768.
[25] Klok FA, Kruip MJHA, van der Meer NJM, Arbous MS, Gommers DAMPJ, Kant KM, Kaptein FHJ, van Paassen J, Stals MAM, Huisman MV, Endeman H. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res 2020;191:145–7. doi: https://doi.org/10.1016/j.thromres.2020.04.013.
[26] Fox SE, Akmatbekov A, Harbert JL, Li G, Quincy Brown J, Vander Heide RS. Pulmonary and cardiac pathology in African American patients with COVID-19: an autopsy series from New Orleans, Lancet. Respir Med 2020;8:681–6. doi: https://doi.org/10.1016/S2213-2600(20)30243-5.
[27] Cheung KS, Hung IFN, Chan PPY, Lung KC, Tso E, Liu R, et al. Gastrointestinal manifestations of SARS-CoV-2 Infection And Virus Load In Fecal Samples From a Hong Kong Cohort: systematic review and meta-analysis. Gastroenterology 2020;159:81–95. doi: https://doi.org/10.1053/j.gastro.2020.03.065.
[28] Pan L, Mu M, Yang P, Sun Y, Wang R, Yan J, et al. Clinical characteristics of COVID-19 patients with digestive symptoms in Hubei, China: a descriptive, cross-sectional, multicenter study. Am J Gastroenterol 2020;115:766–73. doi: https://doi.org/10.14309/ajg.0000000000000620.
[29] Murchison EP, Hannon GJ. miRNAs on the move: miRNA biogenesis and the RNAi machinery. Curr Opin Cell Biol 2004;16:223–9. doi: https://doi.org/10.1016/j.ceb.2004.04.003.
[30] Reddy KB. MicroRNA (miRNA) in cancer. Cancer Cell Int 2015;15:38. doi: https://doi.org/10.1186/s12935-015-0185-1.
[31] Pottoo FH, Javed MdN, Rahman JU, Abu-Izneid T, Khan FA. Targeted delivery of miRNA based therapeuticals in the clinical management of glioblastoma multiforme. Semin Cancer Biol 2020. doi: https://doi.org/10.1016/j.semcancer.2020.04.001.
[32] Pottoo FH, Barkat MdA, Harshita, Ansari MA, Javed MdN, Sajid Jamal QM, Kamal MA. Nanotechnological based miRNA intervention in the therapeutic management of neuroblastoma. Semin Cancer Biol 2019. doi: https://doi.org/10.1016/j.semcancer.2019.09.017.
[33] Grassmann R, Jeang K. The roles of microRNAs in mammalian virus infection. Biochim Biophys Acta (BBA) - Gene Regulatory Mech 2008;1779:706–11. doi: https://doi.org/10.1016/j.bbagrm.2008.05.005.
[34] Lanford RE, Hildebrandt-Eriksen ES, Petri A, Persson R, Lindow M, Munk ME, et al. Therapeutic silencing of microRNA-122 in primates with chronic hepatitis C virus infection. Science 2010;327:198–201. doi: https://doi.org/10.1126/science.1178178.
[35] Rakhmetullina A, Ivashchenko A, Akimniyazova A, Aisina D, PyrkovaA .The miRNA Complexes Against Coronaviruses COVID-19, SARS-CoV, And MERS-CoV; 2020. https://doi.org/10.21203/rs.3.rs-20476/v1.
[36] Liu Z, Wang J, Xu Y, Guo M, Mi K, Xu R, et al. Implications of the virus-encoded miRNA and host miRNA in the pathogenicity of SARS-CoV-2, ArXiv:2004.04874 [q-Bio]; 2020. http://arxiv.org/abs/2004.04874 [accessed September 8, 2020].
[37] Gottwein E, Cullen BR. Viral and cellular MicroRNAs as determinants of viral pathogenesis and immunity. Cell Host Microbe 2008;3:375–87. doi: https://doi.org/10.1016/j.chom.2008.05.002.
[38] Trobaugh DW, Klimstra WB. MicroRNA regulation of RNA virus replication and pathogenesis. Trends Mol Med 2017;23:80–93. doi: https://doi.org/10.1016/j.molmed.2016.11.003.
[39] Wang Z, Zhao Y, Zhang Y. Viral lncRNA: a regulatory molecule for controlling virus life cycle. Non-Coding RNA Res 2017;2:38–44. doi: https://doi.org/10.1016/j.ncrna.2017.03.002.
[40] Elnabi SEH. New strategies for treatment of COVID-19 and evolution of SARS-CoV-2 according to biodiversity and evolution theory. Egypt J Basic Appl Sci 2020;7:226–32. doi: https://doi.org/10.1080/2314808X.2020.1789815.
[41] Wong RR, Abd-Aziz N, Affendi S, Poh CL. Role of microRNAs in antiviral responses to dengue infection. J Biomed Sci 2020;27:4. doi: https://doi.org/10.1186/s12929-019-0614-x.
[42] Pijlman GP, Funk A, Kondratieva N, Leung J, Torres S, van der Aa L, et al. A highly structured, nuclease-resistant, noncoding RNA produced by flaviviruses is required for pathogenicity. Cell Host Microbe 2008;4:579–91. doi: https://doi.org/10.1016/j.chom.2008.10.007.
[43] Fulzele Sadanand SB, Fulzele Sadanand SB. COVID-19 virulence in aged patients might be impacted by the host cellular MicroRNAs abundance/profile. Aging Dis 2020;11:509–22.
[44] Jopling CL, Yi M, Lancaster AM, Lemon SM, Sarnow P. Modulation of hepatitis C virus RNA abundance by a liver-specific MicroRNA. Science 2005;309:1577–81. doi: https://doi.org/10.1126/science.1113329.
[45] Duan X, Wang L, Sun G, Yan W, Yang Y. Understanding the cross-talk between host and virus in poultry from the perspectives of microRNA. Poult Sci 2020;99:1838–46. doi: https://doi.org/10.1016/j.psj.2019.11.053.
[46] Maranon DG, Anderson JR, Maranon AG, Wilusz J. The interface between coronaviruses and host cell RNA biology: novel potential insights for future therapeutic intervention. WIREs RNA 2020;11:. doi: https://doi.org/10.1002/wrna.1614e1614.
[47] Hanna J, Hossain GS, Kocerha J. The potential for microRNA therapeutics and clinical research. Front Genet 2019;10. doi: https://doi.org/10.3389/fgene.2019.00478.
[48] Leon-Icaza SA, Zeng M, Rosas-Taraco AG. microRNAs in viral acute respiratory infections: immune regulation, biomarkers, therapy, and vaccines. ExRNA 2019;1:1. doi: https://doi.org/10.1186/s41544-018-0004-7.
[49] Girardi E, López P, Pfeffer S. On the importance of host MicroRNAs during viral infection. Front Genet 2018;9. doi: https://doi.org/10.3389/fgene.2018.00439.
[50] Kawai T, Akira S. The role of pattern-recognition receptors in innate immunity: update on Toll-like receptors. Nat Immunol 2010;11:373–84. doi: https://doi.org/10.1038/ni.1863.
[51] Jang J-H, Shin HW, Lee JM, Lee H-W, Kim E-C, Park SH. An overview of pathogen recognition receptors for innate immunity in dental pulp. Mediators Inflamm 2015;2015:. doi: https://doi.org/10.1155/2015/794143e794143.
[52] Wang S, Qu X, Zhao RC. Clinical applications of mesenchymal stem cells. J Hematol Oncol 2012;5:19. doi: https://doi.org/10.1186/1756-8722-5-19.
[53] Zhang Y, Li Y. MicroRNAs in the regulation of immune response against infections. J Zhejiang Univ Sci B 2013;14:1–7. doi: https://doi.org/10.1631/jzus.B1200292.
[54] Contreras J, Rao DS. MicroRNAs in inflammation and immune responses. Leukemia 2012;26:404–13. doi: https://doi.org/10.1038/leu.2011.356.
[55] Zhang Z, Zhang C, Li F, Zhang B, Zhang Y. Regulation of memory CD8+ T cell differentiation by MicroRNAs. Cell Physiol Biochem 2018;47:2187–98. doi: https://doi.org/10.1159/000491532.
[56] Sung S-Y, Liao C-H, Wu H-P, Hsiao W-C, Wu I-H, Jinpu Yu, et al. Loss of Let-7 MicroRNA upregulates IL-6 in bone marrow-derived mesenchymal stem cells triggering a reactive stromal response to prostate cancer. PLoS ONE 2013;8:. doi: https://doi.org/10.1371/journal.pone.0071637e71637.
[57] Lian C, Lou H, Zhang J, Tian H, Ou Q, Xu J-Y, et al. MicroRNA-24 protects retina from degeneration in rats by down-regulating chitinase-3-like protein 1. Exp Eye Res 2019;188:. doi: https://doi.org/10.1016/j.exer.2019.107791107791.
[58] Ma C, Li Y, Li M, Deng G, Wu X, Zeng J, et al. microRNA-124 negatively regulates TLR signaling in alveolar macrophages in response to mycobacterial infection. Mol Immunol 2014;62:150–8. doi: https://doi.org/10.1016/j.molimm.2014.06.014.

[59] Witkowski M, Weithauser A, Tabaraie T, Steffens D, Kränkel N, Witkowski M, et al. Micro-RNA-126 reduces the blood thrombogenicity in diabetes mellitus via targeting of tissue factor. Arterioscler Thromb Vasc Biol 2016;36:1263–71. doi: https://doi.org/10.1161/ATVBAHA.115.306094.
[60] Strum JC, Johnson JH, Ward J, Xie H, Feild J, Hester A, et al. MicroRNA 132 regulates nutritional stress-induced chemokine production through repression of SirT1. Mol Endocrinol 2009;23:1876–84. doi: https://doi.org/10.1210/me.2009-0117.
[61] Lorente-Cebrián S, Mejhert N, Kulyté A, Laurencikiene J, Åström G, Hedén P, et al. MicroRNAs regulate human adipocyte lipolysis: effects of miR-145 are linked to TNF-α. PLoS ONE 2014;9:. doi: https://doi.org/10.1371/journal.pone.0086800e86800.
[62] Xie Y-F, Shu R, Jiang S-Y, Liu D-L, Ni J, Zhang X-L. MicroRNA-146 inhibits pro-inflammatory cytokine secretion through IL-1 receptor-associated kinase 1 in human gingival fibroblasts. J Inflamm 2013;10:20. doi: https://doi.org/10.1186/1476-9255-10-20.
[63] Taganov KD, Boldin MP, Chang K-J, Baltimore D. NF-κB-dependent induction of microRNA miR-146, an inhibitor targeted to signaling proteins of innate immune responses. Proc Natl Acad Sci USA 2006;103:12481–6. doi: https://doi.org/10.1073/pnas.0605298103.
[64] Taganov KD, Boldin MP, Chang K-J, Baltimore D. NF-kappaB-dependent induction of microRNA miR-146, an inhibitor targeted to signaling proteins of innate immune responses. Proc Natl Acad Sci USA 2006;103:12481–6. doi: https://doi.org/10.1073/pnas.0605298103.
[65] Sun X, Icli B, Wara AK, Belkin N, He S, Kobzik L, et al. MicroRNA-181b regulates NF-κB-mediated vascular inflammation. J Clin Invest 2012;122:1973–90. doi: https://doi.org/10.1172/JCI61495.
[66] Rossato M, Curtale G, Tamassia N, Castellucci M, Mori L, Gasperini S, et al. IL-10-induced microRNA-187 negatively regulates TNF-α, IL-6, and IL-12p40 production in TLR4-stimulated monocytes. Proc Natl Acad Sci USA 2012;109:E3101–10. doi: https://doi.org/10.1073/pnas.1209100109.
[67] Meerson A, Traurig M, Ossowski V, Fleming JM, Mullins M, Baier LJ. Human adipose microRNA-221 is upregulated in obesity and affects fat metabolism downstream of leptin and TNF-α. Diabetologia 2013;56:1971–9. doi: https://doi.org/10.1007/s00125-013-2950-9.
[68] Ojcius DM, Jafari A, Yeruva L, Schindler CW, Abdul-Sater AA. Dicer regulates activation of the NLRP3 inflammasome. PLoS ONE 2019;14:. doi: https://doi.org/10.1371/journal.pone.0215689e0215689.
[69] Chaudhary V, Jangra S, Yadav NR. Nanotechnology based approaches for detection and delivery of microRNA in healthcare and crop protection. J Nanobiotechnol 2018;16:40. doi: https://doi.org/10.1186/s12951-018-0368-8.
[70] Filipowicz W, Bhattacharyya SN, Sonenberg N. Mechanisms of post-transcriptional regulation by microRNAs: are the answers in sight?. Nat Rev Genet 2008;9:102–14. doi: https://doi.org/10.1038/nrg2290.
[71] O'Connell RM, Rao DS, Chaudhuri AA, Baltimore D. Physiological and pathological roles for microRNAs in the immune system. Nat Rev Immunol 2010;10:111–22. doi: https://doi.org/10.1038/nri2708.
[72] O'Connell RM, Baltimore D. Chapter six - MicroRNAs and hematopoietic cell development. In: Hornstein E, editor. Current topics in developmental biology. Academic Press; 2012. p. 145–74. doi: https://doi.org/10.1016/B978-0-12-387038-4.00006-9.
[73] Trotta R, Chen L, Ciarlariello D, Josyula S, Mao C, Costinean S, et al. miR-155 regulates IFN-γ production in natural killer cells. Blood 2012;119:3478–85. doi: https://doi.org/10.1182/blood-2011-12-398099.
[74] Beaulieu AM, Bezman NA, Lee JE, Matloubian M, Sun JC, Lanier LL. MicroRNA function in NK cell biology. Immunol Rev 2013;253:40–52. doi: https://doi.org/10.1111/imr.12045.
[75] Fehniger TA, Wylie T, Germino E, Leong JW, Magrini VJ, Koul S, et al. Next-generation sequencing identifies the natural killer cell microRNA transcriptome. Genome Res 2010;20:1590–604. doi: https://doi.org/10.1101/gr.107995.110.
[76] Tili E, Croce CM, Michaille J-J. miR-155: on the crosstalk between inflammation and cancer. Int Rev Immunol 2009;28:264–84. doi: https://doi.org/10.1080/08830180903093796.
[77] Dickey LL, Hanley TM, Huffaker TB, Ramstead AG, O'Connell RM, Lane TE. MicroRNA 155 and viral-induced neuroinflammation. J Neuroimmunol 2017;308:17–24. doi: https://doi.org/10.1016/j.jneuroim.2017.01.016.
[78] Dahlke C, Maul K, Christalla T, Walz N, Schult P, Stocking C, et al. A microRNA encoded by Kaposi sarcoma-associated herpesvirus promotes B-cell expansion in vivo. PLoS ONE 2012;7:. doi: https://doi.org/10.1371/journal.pone.0049435e49435.
[79] Eis PS, Tam W, Sun L, Chadburn A, Li Z, Gomez MF, et al. Accumulation of miR-155 and BIC RNA in human B cell lymphomas. Proc Natl Acad Sci USA 2005;102:3627–32. doi: https://doi.org/10.1073/pnas.0500613102.
[80] O'Connell RM, Rao DS, Chaudhuri AA, Boldin MP, Taganov KD, Nicoll J, et al. Sustained expression of microRNA-155 in hematopoietic stem cells causes a myeloproliferative disorder. J Exp Med 2008;205:585–94. doi: https://doi.org/10.1084/jem.20072108.
[81] Rodriguez A, Vigorito E, Clare S, Warren MV, Couttet P, Soond DR, et al. Requirement of bic/microRNA-155 for normal immune function. Science 2007;316:608–11. doi: https://doi.org/10.1126/science.1139253.
[82] Thai T-H, Calado DP, Casola S, Ansel KM, Xiao C, Xue Y, et al. Regulation of the germinal center response by microRNA-155. Science 2007;316:604–8. doi: https://doi.org/10.1126/science.1141229.
[83] Wang P, Hou J, Lin L, Wang C, Liu X, Li D, et al. Inducible microRNA-155 feedback promotes type I IFN signaling in antiviral innate immunity by targeting suppressor of cytokine signaling 1. J Immunol 2010;185:6226–33. doi: https://doi.org/10.4049/jimmunol.1000491.
[84] Nakagawa R, Leyland R, Meyer-Hermann M, Lu D, Turner M, Arbore G, et al. MicroRNA-155 controls affinity-based selection by protecting c-MYC+ B cells from apoptosis. J Clin Invest 2016;126:377–88. doi: https://doi.org/10.1172/JCI82914.
[85] Zhu N, Zhang D, Chen S, Liu X, Lin L, Huang X, et al. Endothelial enriched microRNAs regulate angiotensin II-induced endothelial inflammation and migration. Atherosclerosis 2011;215:286–93. doi: https://doi.org/10.1016/j.atherosclerosis.2010.12.024.
[86] Vigorito E, Perks KL, Abreu-Goodger C, Bunting S, Xiang Z, Kohlhaas S, et al. microRNA-155 regulates the generation of immunoglobulin class-switched plasma cells. Immunity 2007;27:847–59. doi: https://doi.org/10.1016/j.immuni.2007.10.009.
[87] Hu R, Kagele DA, Huffaker TB, Runtsch MC, Alexander M, Liu J, et al. miR-155 promotes T follicular helper cell accumulation during chronic, low-grade inflammation. Immunity 2014;41:605–19. doi: https://doi.org/10.1016/j.immuni.2014.09.015.
[88] Kemp V, Laconi A, Cocciolo G, Berends AJ, Breit TM, Verheije MH. miRNA repertoire and host immune factor regulation upon avian coronavirus infection in eggs. Arch Virol 2020;165:835–43. doi: https://doi.org/10.1007/s00705-020-04527-4.
[89] Zeng F-R, Tang L-J, He Y, Garcia RC. An update on the role of miRNA-155 in pathogenic microbial infections. Microbes Infect 2015;17:613–21. doi: https://doi.org/10.1016/j.micinf.2015.05.007.
[90] Dudda JC, Salaun B, Ji Y, Palmer DC, Monnot GC, Merck E, et al. MicroRNA-155 is required for effector CD8+ T cell responses to virus infection and cancer. Immunity 2013;38:742–53. doi: https://doi.org/10.1016/j.immuni.2012.12.006.
[91] Gracias DT, Stelekati E, Hope JL, Boesteanu AC, Doering TA, Norton J, et al. The microRNA miR-155 controls CD8(+) T cell responses by regulating interferon signaling. Nat Immunol 2013;14:593–602. doi: https://doi.org/10.1038/ni.2576.
[92] Ji Y, Wrzesinski C, Yu Z, Hu J, Gautam S, Hawk NV, et al. miR-155 augments CD8+ T-cell antitumor activity in lymphoreplete hosts by enhancing responsiveness to homeostatic γc cytokines. Proc Natl Acad Sci USA 2015;112:476–81. doi: https://doi.org/10.1073/pnas.1422916112.
[93] Dickey LL, Worne CL, Glover JL, Lane TE, O'Connell RM. MicroRNA-155 enhances T cell trafficking and antiviral effector function in a model of coronavirus-induced neurologic disease. J Neuroinflammation 2016;13:240. doi: https://doi.org/10.1186/s12974-016-0699-z.
[94] Kroesen B-J, Teteloshvili N, Smigielska-Czepiel K, Brouwer E, Boots AMH, van den Berg A, et al. Immuno-miRs: critical regulators of T-cell development, function and ageing. Immunology 2015;144:1–10. doi: https://doi.org/10.1111/imm.12367.
[95] Głobińska A, Pawełczyk M, Kowalski ML. MicroRNAs and the immune response to respiratory virus infections. Expert Rev Clin Immunol 2014;10:963–71. doi: https://doi.org/10.1586/1744666X.2014.913482.
[96] Ambros V. microRNAs: tiny regulators with great potential. Cell 2001;107:823–6. doi: https://doi.org/10.1016/s0092-8674(01)00616-x.
[97] Konno H, Yamamoto T, Yamazaki K, Gohda J, Akiyama T, Semba K, et al. TRAF6 establishes innate immune responses by activating NF-kappaB and IRF7 upon sensing cytosolic viral RNA and DNA. PLoS ONE 2009;4:. doi: https://doi.org/10.1371/journal.pone.0005674e5674.
[98] Li Z, Luo Q, Xu H, Zheng M, Abdalla BA, Feng M, et al. MiR-34b-5p suppresses melanoma differentiation-associated gene 5 (MDA5) signaling pathway to promote avian leukosis virus subgroup J (ALV-J)-infected cells proliferaction and ALV-J replication. Front Cell Infect Microbiol 2017;7:17. doi: https://doi.org/10.3389/fcimb.2017.00017.
[99] Mallick B, Ghosh Z, Chakrabarti J. MicroRNome analysis unravels the molecular basis of SARS infection in bronchoalveolar stem cells. PLoS ONE 2009;4:. doi: https://doi.org/10.1371/journal.pone.0007837e7837.
[100] Lawrence T. The nuclear factor NF-kappaB pathway in inflammation. Cold Spring Harb Perspect Biol 2009;1:. doi: https://doi.org/10.1101/cshperspect.a001651a001651.
[101] Haasnoot J, Berkhout B. RNAi and cellular miRNAs in infections by mammalian viruses. In: van Rij RP, editor. Antiviral RNAi: concepts, methods, and applications. Totowa, NJ: Humana Press; 2011. p. 23–41. doi: https://doi.org/10.1007/978-1-61779-037-9_2.
[102] Khan MdA-A-K, Sany MdRU, Islam MdS, Islam ABMMdK. Epigenetic regulator miRNA pattern differences among SARS-CoV, SARS-CoV-2, and SARS-CoV-2 world-wide isolates delineated the mystery behind the epic pathogenicity and distinct clinical characteristics of pandemic COVID-19. Front Genet 2020;11. doi: https://doi.org/10.3389/fgene.2020.00765.
[103] Lu D, Chatterjee S, Xiao K, Riedel I, Wang Y, Foo R, et al. MicroRNAs targeting the SARS-CoV-2 entry receptor ACE2 in cardiomyocytes. J Mol Cell Cardiol 2020;148:46–9. doi: https://doi.org/10.1016/j.yjmcc.2020.08.017.
[104] Hirasawa K, Kim A, Han H-S, Han J, Jun H-S, Yoon J-W. Effect of p38 mitogen-activated protein kinase on the replication of encephalomyocarditis virus. J Virol 2003;77:5649–56. doi: https://doi.org/10.1128/jvi.77.10.5649-5656.2003.
[105] Elbahesh H, Cline T, Baranovich T, Govorkova EA, Schultz-Cherry S, Russell CJ. Novel roles of focal adhesion kinase in cytoplasmic entry and replication of

influenza A viruses. J Virol 2014;88:6714–28. doi: https://doi.org/10.1128/JVI.00530-14.
[106] Diehl N, Schaal H. Make yourself at home: viral hijacking of the PI3K/Akt signaling pathway. Viruses 2013;5:3192–212. doi: https://doi.org/10.3390/v5123192.
[107] Bruscella P, Bottini S, Baudesson C, Pawlotsky J-M, Feray C, Trabucchi M. Viruses and miRNAs: more friends than foes. Front Microbiol 2017;8:824. doi: https://doi.org/10.3389/fmicb.2017.00824.
[108] Liu C, Zhou Q, Li Y, Garner LV, Watkins SP, Carter LJ, et al. Research and development on therapeutic agents and vaccines for COVID-19 and related human coronavirus diseases. ACS Cent Sci 2020;6:315–31. doi: https://doi.org/10.1021/acscentsci.0c00272.
[109] Zeng J, Gupta VK, Jiang Y, Yang B, Gong L, Zhu H. Cross-kingdom small RNAs among animals, plants and microbes. Cells 2019;8. doi: https://doi.org/10.3390/cells8040371.
[110] Yan B, Wang H, Tan Y, Fu W. microRNAs in cardiovascular disease: small molecules but big roles. Curr Top Med Chem 2019;19:1918–47. doi: https://doi.org/10.2174/1568026619666190808160241.
[111] Broderick JA, Zamore PD. MicroRNA therapeutics. Gene Ther 2011;18:1104–10. doi: https://doi.org/10.1038/gt.2011.50.
[112] Cheng CJ, Bahal R, Babar IA, Pincus Z, Barrera F, Liu C, et al. MicroRNA silencing for cancer therapy targeted to the tumour microenvironment. Nature 2015;518:107–10. doi: https://doi.org/10.1038/nature13905.
[113] Li Z, Rana TM. Therapeutic targeting of microRNAs: current status and future challenges. Nat Rev Drug Discov 2014;13:622–38. doi: https://doi.org/10.1038/nrd4359.
[114] Peer D. A daunting task: manipulating leukocyte function with RNAi. Immunol Rev 2013;253:185–97. doi: https://doi.org/10.1111/imr.12044.
[115] Kanasty, R., Dorkin, J., Vegas, A. et al. Delivery materials for siRNA therapeutics. Nature Mater 12, 967–977 (2013). https://doi.org/10.1038/nmat3765.
[116] Mishra S, Sharma S, Javed MN, Pottoo FH, Barkat MA, Harshita, et al. Bioinspired nanocomposites: applications in disease diagnosis and treatment. Pharm Nanotechnol 2019;7:206–19. doi: https://doi.org/10.2174/2211738507666190425121509.
[117] Sharma S, Javed MN, Pottoo FH, Rabbani SA, Barkat MA, Harshita, et al. Bioresponse inspired nanomaterials for targeted drug and gene delivery. Pharm Nanotechnol 2019;7:220–33. doi: https://doi.org/10.2174/2211738507666190429103814.
[118] Ansari MA, Badrealam KF, Alam A, Tufail S, Khalique G, Equbal MJ, et al. Recent Nano-based therapeutic intervention of Bioactive Sesquiterpenes: Prospects in cancer therapeutics. Curr Pharm Des 2020. doi: https://doi.org/10.2174/1381612826666200116151522.
[119] Obad S, dos Santos CO, Petri A, Heidenblad M, Broom O, Ruse C, et al. Silencing of microRNA families by seed-targeting tiny LNAs. Nat Genet 2011;43:371–8. doi: https://doi.org/10.1038/ng.786.
[120] Garchow BG, Bartulos Encinas O, Leung YT, Tsao PY, Eisenberg RA, Caricchio R, et al. Silencing of microRNA-21 in vivo ameliorates autoimmune splenomegaly in lupus mice. EMBO Mol Med 2011;3:605–15. doi: https://doi.org/10.1002/emmm.201100171.
[121] Guinea-Viniegra J, Jiménez M, Schonthaler HB, Navarro R, Delgado Y, Concha-Garzón MJ, et al. Targeting miR-21 to treat psoriasis. Sci Transl Med 2014;6:225re1. doi: https://doi.org/10.1126/scitranslmed.3008089.
[122] Wang H, Flach H, Onizawa M, Wei L, McManus MT, Weiss A. Negative regulation of Hif1a expression and TH17 differentiation by the hypoxia-regulated microRNA miR-210. Nat Immunol 2014;15:393–401. doi: https://doi.org/10.1038/ni.2846.
[123] Konermann S, Brigham MD, Trevino AE, Joung J, Abudayyeh OO, Barcena C, et al. Genome-scale transcriptional activation by an engineered CRISPR-Cas9 complex. Nature 2015;517:583–8. doi: https://doi.org/10.1038/nature14136.
[124] Roos M, Rebhan MAE, Lucic M, Pavlicek D, Pradere U, Towbin H, et al. Short loop-targeting oligoribonucleotides antagonize Lin28 and enable pre-let-7 processing and suppression of cell growth in let-7-deficient cancer cells. Nucleic Acids Res 2015;43:. doi: https://doi.org/10.1093/nar/gku1090e9.
[125] Chakraborty C, Sharma AR, Sharma G, Lee S-S. Therapeutic advances of miRNAs: a preclinical and clinical update. J Adv Res 2021;28:127–38. doi: https://doi.org/10.1016/j.jare.2020.08.012.
[126] Li Y, Kowdley KV. MicroRNAs in common human diseases. Genomics, Proteomics Bioinform. 2012;10:246–53. doi: https://doi.org/10.1016/j.gpb.2012.07.005.
[127] Tahamtan A, Inchley CS, Marzban M, Tavakoli-Yaraki M, Teymoori-Rad M, Nakstad B, et al. The role of microRNAs in respiratory viral infection: friend or foe?. Rev Med Virol 2016;26:389–407. doi: https://doi.org/10.1002/rmv.1894.
[128] Tribolet L, Kerr E, Cowled C, Bean AGD, Stewart CR, Dearnley M, et al. MicroRNA biomarkers for infectious diseases: from basic research to biosensing. Front Microbiol 2020;11. doi: https://doi.org/10.3389/fmicb.2020.01197.
[129] Fu Y, Chen J, Huang Z. Recent progress in microRNA-based delivery systems for the treatment of human disease. ExRNA 2019;1:24. doi: https://doi.org/10.1186/s41544-019-0024-y.
[130] Lawrie CH, Gal S, Dunlop HM, Pushkaran B, Liggins AP, Pulford K, et al. Detection of elevated levels of tumour-associated microRNAs in serum of patients with diffuse large B-cell lymphoma. Br J Haematol 2008;141:672–5. doi: https://doi.org/10.1111/j.1365-2141.2008.07077.x.
[131] Chen X, Ba Y, Ma L, Cai X, Yin Y, Wang K, et al. Characterization of microRNAs in serum: a novel class of biomarkers for diagnosis of cancer and other diseases. Cell Res 2008;18:997–1006. doi: https://doi.org/10.1038/cr.2008.282.
[132] Guterres A, de Azeredo Lima CH, Miranda RL, Gadelha MR. What is the potential function of microRNAs as biomarkers and therapeutic targets in COVID-19?. Infect Genetics Evol 2020;85:. doi: https://doi.org/10.1016/j.meegid.2020.104417104417.
[133] Gashaw I, Ellinghaus P, Sommer A, Asadullah K. What makes a good drug target?. Drug Discov Today 2011;16:1037–43. doi: https://doi.org/10.1016/j.drudis.2011.09.007.
[134] Simpson LJ, Patel S, Bhakta NR, Choy DF, Brightbill HD, Ren X, et al. A microRNA upregulated in asthma airway T cells promotes TH2 cytokine production. Nat Immunol 2014;15:1162–70. doi: https://doi.org/10.1038/ni.3026.
[135] Olive V, Minella AC, He L. Outside the coding genome, mammalian microRNAs confer structural and functional complexity. Sci Signal 2015;8:re2. doi: https://doi.org/10.1126/scisignal.2005813.
[136] Alanagreh L, Alzoughool F, Atoum M. The human coronavirus disease COVID-19: its origin characteristics, and insights into potential drugs and its mechanisms. Pathogens 2020;9:331. doi: https://doi.org/10.3390/pathogens9050331.

Dr. Tareq Abu-Izneid is an associate professor in pharmaceutical chemistry at the college of pharmacy, Al Ain University, United Arab Emirates. Dr. Tareq received his Ph.D. from the Institute for Glycomics, Griffith University, QLD, Australia, in 2005. His research interest is in pharmaceutical sciences in general, and his current focus is on studying and designing anticancer and antiviral drugs (from synthesis and natural sources). To date, he has authored many publications in various peer-reviewed journals.

Dr. Noora Alhajri is a Clinician-Scientist who received her training in the United States of America and Ireland. She earned her Doctor of Medicine (M.D.) degree from the prestigious Royal College of Surgeons of Ireland (RCSI) with first class honors (H1:1). Following her graduation, she got accepted at George Washington University where she accomplished her Master of Public Health Degree (MPH) with a GPA (4.00/4.00). During her MPH training she got accepted at the World Health Organization (WHO) where she worked with a team of international leaders and developed a tool to promote the Social Accountability of Medical Education (I-SAT). She then received a grant from the National Institute of Health (NIH) in Baltimore, Maryland, to pursue her post-doctoral fellowship training at the prestigious Johns Hopkins University (JHU) division of Vascular Surgery, and Endocrinology, Diabetes, and Metabolism. Dr. Alhajri also worked as a visiting scientist at the Division of Cardiovascular Science at the NIH. During her Post-Doc fellowship training she published several scientific papers in international peer-reviewed journals. Dr. Alhajri was recently accepted as a fellow in training at the American Heart Association (FIT-AHA). Currently she's working as a course co-director and instructor of Epidemiology and Population Health. Dr. Alhajri is interested in researching Peripheral Artery Disease in Women, the mechanism of Heart Failure, Acute Coronary Syndrome in young individuals, and topics related to Diabetic Foot Ulcers.



Mr. Abdallah Mohammad Sudqi is serving as a Lecturer in the nursing college, Imam Abdulrahman Bin Faisal University, Saudi Arabia. He holds master degree in pharmacology from university of Jordan since 2010. Interested in neuroscience, oncology, virology and genetics. To date, he has authored many publications in various peer-reviewed journals.

Dr Md. Noushad Javed is currently working in lab of Professor M. Zahid Ashraf at Jamia Millia Islamia on neuroprotective potential of TLR agonist. He has completed PhD in Pharmacy at School of Pharmaceutical Education and Research, Jamia Hamdard University, New Delhi, India (Rank #1 in Pharmacy institute as per Govt. of India). In past, he has associated with various academic and research positions which includes; Appejay Stya University; Dibrugarh University as well as consulted independent industrial assignments. He is a registered clinical pharmacist and herbalist by professional training. While, he is also a certified statistical analyst as well as an expert of international regulatory affairs and pharmaceutical patents. His interest are towards integration of holistic in-silico based approach such as computational bioinformatics; Quality by Design (QbD) and statistical approaches for validation of analytical methods and processing of novel materials; to be used as site targeted controlled release formulations for various inflammatory disorders. Till date, he has authored more than 40 publications including research and review papers in high impact peer-reviewed journals and some patent applications. Dr. Javed has also been invited for lectures and oral talks at several international conferences. He has also been awarded with various medals and best presentation awards by reputed society. He is also serving as accredited reviewer and editorial board member of some journals. While recently handled special issue in the journal Current drug metabolism (Bentham Science)

Dr. Khairi Mustafa Salem is currently working as a Professor and Dean at the Department of Pharmacy, Al Ain University of Science and Technology, United Arab Emirates. His research interests includes Pharmacy. He is serving as an editorial member and reviewer of several international reputed journals. Dr. Khairi Mustafa Salem is the member of many international affiliations. He has successfully completed his Administrative responsibilities. He has authored of many research articles/books related to Pharmacy.

Dr. Faheem Hyder Pottoo is working as an Assistant Professor, Department of Pharmacology, College of Clinical Pharmacy, Imam Abdulrahman Bin Faisal University, Saudi Arabia. He got his M.Pharm (Pharmacology) from the Department of Pharmacology, School of Pharmaceutical Education & Research, Jamia Hamdard, New-Delhi, India and PhD (Pharmacology) in 2016 from Department of Pharm. Sc, Faculty of Applied Sc. and Tech., University of Kashmir, India. His research vision is to transform the treatment of neurodegenerative diseases & cancers by modulating signalling pathways. To date, he has authored more than **75** publications in various peer-reviewed journals. The recent paper being "Targeted Delivery of miRNA Based Therapeuticals in the Clinical Management of Glioblastoma Multiforme https://pubmed.ncbi.nlm.nih.gov/32302695/" in the **Journal Seminars in Cancer Biology (IF: 11.09).** He has filed many patents and serves as a review editor in the neuropharmacology section for the journals Frontiers in Neuroscience, Frontiers in Neurology & Frontiers in Pharmacology.

Dr Mohammad Amjad Kamal is a Distinguished Adjunct Professor at the King Fahd Medical Research Center (KFMRC), King Abdulaziz University, Saudi Arabia. He is leading a highly productive global collaborative research team based on the Novel Global Community Educational Foundation (NGCEF), Australia. Prof. Kamal's biochemical research in the field of Alzheimer's disease, Type 2 diabetes and leukemia has culminated in more than **500 publications** in internationally respected journals. He was awarded a prestigious U2000 Postdoctoral Fellowship in 2000 by the University of Sydney. Amongst numerous projects, he also collaborated on the molecular biological research project "Linkage of Alzheimer's disease and Type 2 diabetes" at the University of Technology, Sydney. Moreover, he is serving as a regional/guest editor of several reputed scientific journals on an honorable basis.