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# Cytokine storm in the pathophysiology of COVID-19: Possible functional disturbances of miRNAs

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ABSTRACT

SARS-CoV-2, as the causative agent of COVID-19, is an enveloped positives-sense single-stranded RNA virus that belongs to the Beta-CoVs sub-family. A sophisticated hyper-inflammatory reaction named cytokine storm is occurred in patients with severe/critical COVID-19, following an imbalance in immune-inflammatory processes and inhibition of antiviral responses by SARS-CoV-2, which leads to pulmonary failure, ARDS, and death. The miRNAs are small non-coding RNAs with an average length of 22 nucleotides which play various roles as one of the main modulators of genes expression and maintenance of immune system homeostasis. Recent evidence has shown that *Homo sapiens* (hsa)-miRNAs have the potential to work in three pivotal areas including targeting the virus genome, regulating the inflammatory signaling pathways, and reinforcing the production/signaling of IFNs-I. However, it seems that several SARS-CoV-2-induced interfering agents such as viral (v)-miRNAs, cytokine content, competing endogenous RNAs (ceRNAs), etc. preclude efficient function of hsa-miRNAs in severe/critical

*Abbreviations:* 2019-nCoV, 2019 novel coronavirus; 3′-UTR, 3′-untranslated region; AA, Arachidonic acid; ACE, Angiotensin-converting enzyme; ADAM17, A disintegrin and metalloproteinase 17; AGEs, Advanced glycation end products; AGO, Argonaute; ALI, Acute lung injury; Amp, Amplifier; Ang, Angiotensin; ANRIL, Antisense noncoding RNA in the INK4 locus; AP-1, Activator protein 1; APJ, Apelin receptor; ARDS, Acute respiratory distress syndrome; ASOs, Antisense oligonucleotides; AT1R, Ang II receptor type 1; BBB, Blood-brain barrier; CatB/L, Cathepsin B/L; CCL, C-C motif chemokine ligand; CD, Cluster of differentiation; ceRNAs, Competing endogenous RNAs; CHD, Coronary heart disease; circRNAs, Circular RNAs; CNS, Central nervous system; COVID-19, Coronavirus disease 2019; COX, Cyclooxygenase; cPLA2, Cytoplasmic phospholipase A2; CRISPR, Cas13 family of clustered regularly interspaced short palindromic repeats; CSF, Colony-stimulating factor; CXCL, C-X-C motif chemokine ligand; CYLD, Cylindromatosis; DAMPs, Damage-associated molecular patterns; DCs, Dendritic cells; DIC, Disseminated intravascular coagulation; DMD, Dense matted deposits; DMVs, Double membrane vesicles; E protein, Envelope protein; EAE, Experimental autoimmune encephalomyelitis; ER, Endoplasmic reticulum; ERK, Extracellular signal-regulated kinase; FOXO3, Forkhead box O3; G-CSF, Granulocyte CSF; GM-CSF, Granulocyte-macrophage CSF; gp130, Glycoprotein 130; H3, Histone 3; HMGB1, High mobility group box protein 1; hsa, *Homo sapiens*; HSP, Heat shock protein; ICU, Intensive care unit; IFN, Interferon; IFNs-I, Type I IFNs; Ig, Immunoglobulin; IκB-ζ, Inhibitor of nuclear factor kappa B zeta; IL, Interleukin; IRF, IFN regulatory factor; ISGs, IFN-stimulated genes; JAK, Janus kinase; K, Lysine; KCNQ1OT1, KCNQ1 overlapping transcript 1; lncRNAs, Long non-coding RNAs; LOXs, Lipoxygenases; LPLs, Lysophospholipids; LPS, Lipopolysaccharide; LTs, Leukotrienes; M protein, Membrane protein; MAPK, Mitogen-activated protein kinase; MCs, Mast cells; M−CSF, Macrophage CSF; MDA5, Melanoma differentiation-associated protein 5; me2, Dimethylation; me3, Trimethylation; MEG3, Maternally expressed gene 3; MERS-CoV, Middle East respiratory syndrome coronavirus; mIL-6R, Membrane IL-6 receptor; miRISC, MicroRNA-induced silencing complex; miRNAs, MicroRNAs; MMP, Matrix metalloproteinase; MODS, Multiple organ dysfunction syndrome; mPGES-1, Microsomal prostaglandin E synthase-1; mRNA, Messenger RNA; MyD88, Myeloid differentiation factor 88; N protein, Nucleocapsid protein; NF-κB, Nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP3, NOD-, LRR- and pyrin domain-containing protein 3; NOXs, Nicotinamide adenine dinucleotide phosphate (NADPH) oxidases; nsp, Non-structural protein; ORF, Open reading frame; OxPLs, Oxidized phospholipids; PaO2/FiO2, Pressure of arterial oxygen to fractional inspired oxygen concentration; PBMCs, Peripheral blood mononuclear cells; PG, Prostaglandin; PKCα, Protein kinase C alpha; PPP2CA, Protein phosphatase 2 catalytic subunit alpha; pre-miRNAs, Precursor miRNAs; pri-miRNAs, Primary miRNAs; PRR, Pattern recognition receptor; RAGE, Receptor for advanced glycation end products; RAS, Renin-Angiotensin system; RBCs, Red blood cells; RGMB-AS1, RGMB antisense RNA 1; RhoB, Ras homolog gene family member B; RIG-I, Retinoic acid-inducible gene I; RNAi, RNA interference; RNA pol, RNA polymerase; ROS, Reactive oxygen species; S100A9, S100 calcium-binding protein A9; S protein, Spike protein; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; sIL-6R, Soluble IL-6R; siRNAs, Small interfering RNAs; SOCS3, Suppressor of cytokine signaling 3; SOFA, Sequential organ failure assessment score; Sry, Sex-determining region Y; STAT, Signal transducer and activator of transcription; TAB, Transforming growth factor β-activated kinase-1 (TAK1)-binding protein; TBK1, TANK-binding kinase 1; Th cells, T helper cells; TIMP-I, Tissue inhibitors of matrix metalloproteinases-I; TLRs, Toll-like receptors; TMPRSS2, Transmembrane serine protease 2; TNF-α, Tumor necrosis factor alpha; TNFR, TNF receptor; TRIM27, Tripartite motif-containing protein 27; TXs, Thromboxanes; v-miRNA, Viral miRNA; XPO5, Exportin-5.

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COVID-19. This subsequently leads to increased virus replication, intense inflammatory processes, and secondary complications development. In this review article, we provide an overview of hsa-miRNAs roles in viral genome targeting, inflammatory pathways modulation, and IFNs responses amplification in severe/critical COVID-19 accompanied by probable interventional factors and their function. Identification and monitoring of these interventional elements can help us in designing the miRNAs-based therapy for the reduction of complications/mortality rate in patients with severe/critical forms of the disease.

## 1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or 2019 novel coronavirus (2019-nCoV) is an enveloped virus with a positive-sense single-stranded RNA genome that belongs to the Beta-CoVs [1–4]. The disease created by this pathogen is named coronavirus disease 2019 (COVID-19) [1,2,5]. This virus induces an intense cytokine response called cytokine storm in a group of patients with severe/critical form. This event, in turn, results in serious clinical outcomes such as pulmonary failure, acute respiratory distress syndrome (ARDS), thromboinflammation, multiple organ dysfunction syndrome (MODS), and death [2–9]. Interferons (IFNs), interleukins (ILs), colony-stimulating factors (CSFs), chemokines, and tumor necrosis factor alpha (TNF-α) plus nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), Janus kinase (JAK)-signal transducer and activator of transcription (STAT) 3, activator protein 1 (AP-1), NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3)-Inflammasome, and mitogen-activated protein kinase (MAPK) are among the main components in the cytokine storm development [2,3,8,10–14] (Fig. 1a, b). Increased concentration of inflammatory mediators not only does not act toward the efficiency upregulation of antiviral responses but also underlies inefficiency/exhaustion of immune system, disease progress, and elevated risk of death [2,4]. MicroRNAs (miRNAs) are a group of endogenous non-coding RNAs performing as post-transcriptional regulators of genes expression [6,15,16]. These molecules bind to the 3′-untranslated region (3′-UTR) of their target messenger RNAs (mRNAs) and influence their expression [6,15,17,18]. Although it has been shown that some *Homo sapiens* (hsa)-miRNAs may be capable to target the SARS-CoV-2 genome, and some others can respectively regulate and augment inflammatory and type I IFNs (IFNs-I)-related pathways (Fig. 2a, b), it seems that extensive perturbations have occurred in their expression/function in severe/critical form of COVID-19 [19–21]. This can be arisen from virus-induced interfering factors (Table 1) subsequently leading to increased viral replication, continuous inflammation, and cytokine storm. Identification, monitoring, and resolution of these interferer agents in SARS-CoV-2 infection, especially in severe/critical form, may pave the way for the better management of the disease and underlie designing the miRNAs-based therapeutic protocols. Accordingly, in this review article, we aim to discuss the roles of key hsa-miRNAs in three main areas of severe/critical COVID-19 pathogenesis including targeting the viral genome, modulating the inflammatory signaling pathways, and reinforcing the IFNs responses in companion with the interfering factors with their expression/function.

## 2. SARS-CoV-2 and renin-angiotensin system

The renin-angiotensin system (RAS) is an important system for the maintenance of body homeostasis [10,22]. Angiotensin (Ang) II (a key element in this system) acts as a vascular constrictor and also causes sodium retention and blood pressure elevation [23,24]. Angiotensin-converting enzyme (ACE) 2 is an important enzyme of RAS catalysing the conversion of Ang II to Ang-(1–7) [6,10,22]. The latter exerts opposite effects of the former [22]. Various activated pathways in RAS can proceed or inhibit inflammatory processes depending on the function of diverse substrates. For instance, the ACE/Ang II/Ang II receptor type 1 (AT1R) axis performs as a pro-inflammatory pathway (Fig. 1a), whereas Apelin/Apelin receptor (APJ) axis plays an anti-inflammatory/organ protective role. Apelin is another substrate of ACE2 and counteracts the ACE/Ang II/AT1R axis [10,22] (Fig. 1a). Notably, ACE2 acts as the functional receptor for SARS-CoV-2 and its disparate expression levels (organ-specific) have been observed in diverse tissues/cells such as the heart, lungs, gastrointestinal tract, central nervous system (CNS), lymphoid organs, some immune cells, etc. [1,4,6,10,22,25,26]. Overwhelming evidence has shown that the expression of ACE2 is diminished following the SARS-CoV-2 entry into the cells and infection development leading to the reduction of Ang II breakdown into the Ang-(1–7), severe inflammation, multiple complications, and COVID-19 exacerbation [4,6,10,22,23,27].

## 3. SARS-CoV-2 entry and replication

Generally, SARS-CoV-2 genome (similar to other CoVs) consists of genes coding 4 structural proteins (spike (S), membrane (M), envelope (E), nucleocapsid (N)), 16 non-structural proteins (nsp1-16), and 9 accessory ones (open reading frame (ORF) 1a, 1b, 3a, 3b, 6, 7a, 7b, 8, 9b, 9c, 10) [1,6,22,28–30] (Fig. 1a, 2a). S protein is structurally divided into S1 and S2 functional subunits [1,10,22]. Following the virus adhesion to ACE2, priming of them is accomplished by a range of host cell proteases such as transmembrane serine protease 2 (TMPRSS2) and cathepsin B/L (CatB/L) and this facilitates virus entry into the cell [1,4,6,7,10]. The virus selects endocytosis or fusion method for entry depending on the availability rate of host proteases and type of the cell [31] (Fig. 1a). Most importantly, genomic assessments have revealed the capability of SARS-CoV-2 S protein to be cleaved by Furin protease [1,4,6,7,10]. ACE2, Furin, and TMPRSS2 are simultaneously expressed in lung macrophages, kidneys, enterocytes, adrenal stromal as well as nasal epithelial cells and strongly make the virus entry facilitated [10]. SARS-CoV-2 genome has cap structure at 5′end and Poly-A tail at 3′ end. Thus, it can act like an mRNA and be directly translated into protein on the cytoplasmic ribosomes of the host cell [22]. The virus life cycle in the host cell has 5 stages including adhesion, penetration, biosynthesis, maturation, and release [1,6]. Following the SARS-CoV-2 genome entry into the cytoplasm, a negative-sense sequence is generated from the main genomic strand by viral RNA polymerase (RNA pol). This negative-sense strand is used for replication and production of genomic positive-sense RNAs. In the next step, N protein binds to the genomic RNA and S, M, and E proteins attach to the membrane of the endoplasmic reticulum (ER). Following the assembly of viral components, the viral progeny are transported to the cell membrane by Golgi vesicles and exocytosed into the extracellular space [32].

## 4. SARS-CoV-2 and pro-inflammatory pathways

### 4.1. Receptors and sensors of the viral genome

Endosomal toll-like receptors (TLRs) (TLR3, 7, 8) and cytosolic sensors (retinoic acid-inducible gene I (RIG-I) and melanoma differentiation-associated protein 5 (MDA5)) are responsible for the detection of the viral genome following the virus entry into the target cell. Initiation of their signaling pathways leads to the production of IFNs-I (especially IFN-α/β) (Fig. 1a). The IFNs-I then bind to their receptors on the surface of immune/tissue cells consequently resulting in the expression of IFN-stimulated genes (ISGs), disruption to virus entry and replication [1,4,30,33–37] (Fig. 2b). Evidence has shown that

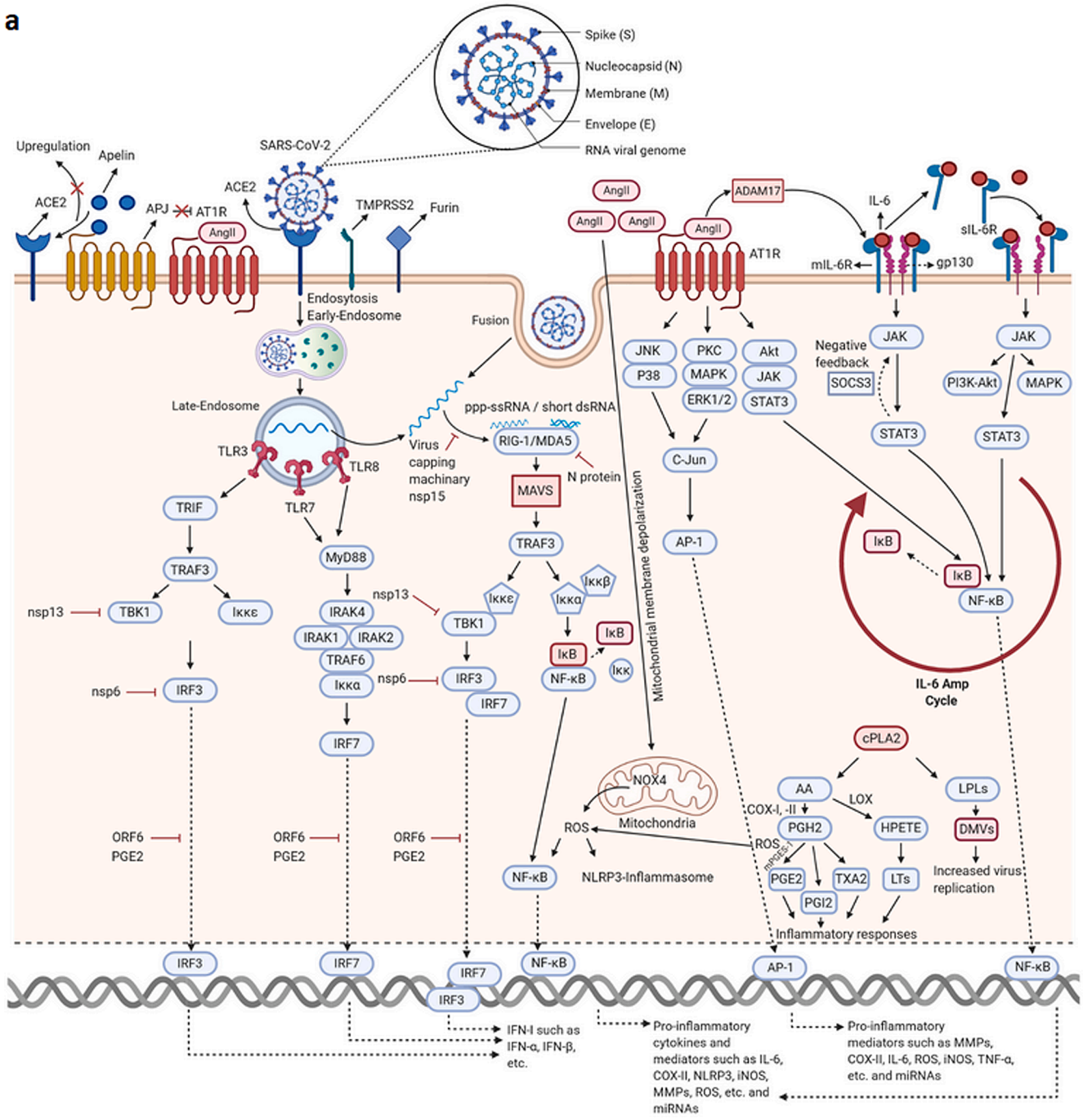


**Fig. 1. The most effective pro-inflammatory pathways on cytokine storm development in severe/critical COVID-19. a)** Following the SARS-CoV-2 entry, its genome is recognized by endosomal TLRs and cytosolic sensors. Multiple adaptor proteins are then recruited. These lead to the nuclear translocation of IRF3, IRF7, and NF-κB transcription factors accompanied by the production of IFNs-I, pro-inflammatory mediators, and miRNAs. A group of proteins, encoded by the virus or host, impede the activation of IFNs-I generation pathways. Among them, viral nsp13 and 6 inhibit the TANK-binding kinase 1 (TBK1) and IRF3, respectively. SARS-CoV-2 ORF6 and host PGE2 also prevent the nuclear translocation of IRF3 and IRF7. Moreover, viral nsp15 hinders the identification of this pathogen genome by cytosolic sensors, and its N protein inhibits them. Ang II/AT1R interaction underlies the activation of pro-inflammatory pathways, nuclear translocation of NF-κB as well as AP-1 transcription factors, and ultimately high-level production of pro-inflammatory mediators on the one hand, and causes activation of ADAM17 molecule, conversion of the mIL-6R into sIL-6R, and induction of this receptor *trans*-signaling process on the other. Several pro-inflammatory pathways are also activated downstream of IL-6R resulting in the excessive production of the pro-inflammatory mediators and IL-6 Amp cycle. The cPLA2 produces arachidonic acid (AA) and LPLs via decomposition of membrane phospholipids and the latter are predisposing factors for virus increased replication. The enzymes COX-I, -II, mPGES-1, lipoxygenases (LOXs), etc. participate in the generation pathways of eicosanoids and these lipid mediators intensify the pro-inflammatory reactions. It seems that Apelin/APJ axis undergoes some disruptions in this infection, in a way that it does not respectively induce the elevated and reduced expression of ACE2 and AT1R leading to the cytokine storm progression. **b)** Produced IFNs-I bind to the related receptors and launching their signaling pathways results in the nuclear translocation of STAT1/STAT2 heterodimers, expression of ISGs and some miRNAs. However, several viral proteins including nsp1, 6, 13, ORF3a, 7a, and M inhibit STAT1 and 2 transcription factors and decrease the activity of this pivotal antiviral pathway. In addition, SARS-CoV-2 ORF6 impedes the nuclear translocation of STAT1/STAT2 heterodimers and host PGE2 hampers the ISGs. Activation of multiple pathways and molecules including activity of nicotinamide adenine dinucleotide phosphate

(NADPH) oxidases (NOXs) in the endosome, the enzymes involved in the eicosanoids generation pathway, in the downstream of RAGE, NF-κB and AP-1 ones, and also as a consequence of mitochondrial membrane depolarization by elevated Ang II provides the basis for high-level production of ROS. This molecule provokes the activity of the NLRP3-Inflammasome complex and NF-κB pathway, both of which lead to the production of pro-inflammatory mediators and pyroptosis. The host PGE2 also stimulates the activity of the mentioned complex. The Ang II/AT1R interaction causes *trans*-activation of the cytoplasmic tail of RAGE and launching its downstream pathway on the one hand and activates ADAM17 on the other. This molecule underlies the accumulation of Ang II through ACE2 cleavage. Furthermore, ADAM17 activity is followed by high-level procreation of MMP-9 and consequently more complications. Production of mature TNF-α is the other result of ADAM17 activation. Ligation of RAGE, TNFR and TLR4 with their correspondent ligands (*e.g.* advanced glycation end products (AGEs), TNF-α, and lipopolysaccharide (LPS)) also contributes to the generation of pro-inflammatory mediators. Nuclear translocation of IRF3 and gene transcription of IFNs-I occur in the MyD88-independent pathway of TLR4 signaling. Nevertheless, SARS-CoV-2 nsp13 and 6 respectively inhibit the TBK1 and IRF3. Its ORF6 and host PGE2 also impede the IRF3 nuclear translocation resulting in the limitation of IFNs-I production in this pathway.

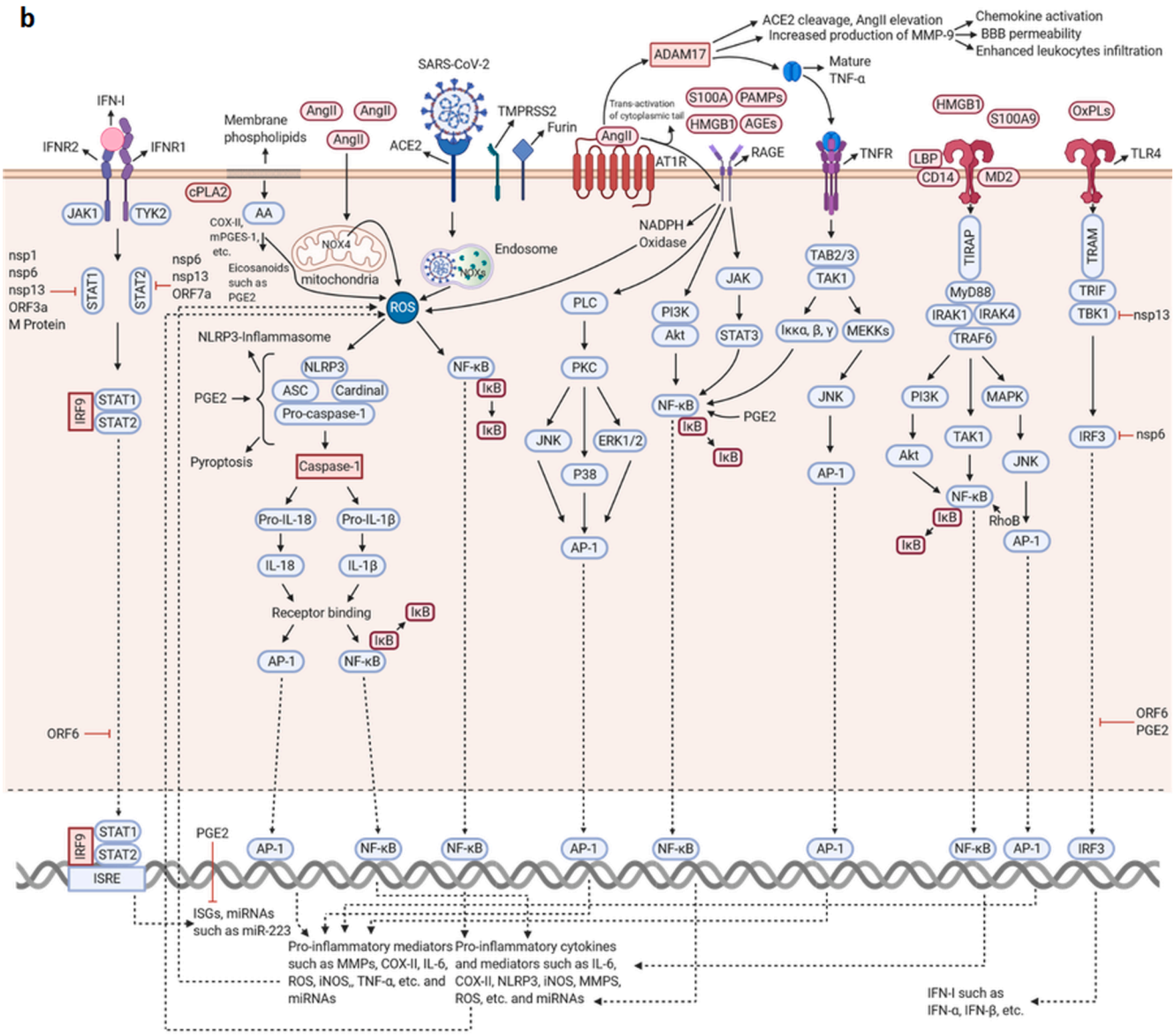


**Fig. 1.** (*continued*).

delayed production of IFNs-I (days 8–10) has occurred in a group of patients with severe/critical COVID-19. In other words, IFNs-I-related pathways (both generation and signaling) are inhibited in them contributing to upregulated viral replication. Significant reduction of IFNs-I levels and ISGs expression have been observed in these patients and this is one of the main characteristics of these types of disease. Some viral proteins (*e.g.* N, ORF6, and nsps) and also some host-produced factors (*e.g.* prostaglandin (PG) $E_2$) make the virus resistant to anti-viral responses in different ways (Fig. 1a, b). In addition, this virus (similar to other CoVs) can protect its genome from being recognized by cytosolic sensors using double-membrane vesicles (DMVs) which are made as a consequence of host cytoplasmic phospholipase A2 (cPLA2) enzyme activity [4,30,34,35,38–43] (Fig. 1a). SARS-CoV-2 evasion of IFNs-I responses leads to its perpetuated replication, high viral load in circulation, excessive activation of immune cells, elevated inflammatory responses, cytokine storm development, and disease exacerbation.

### 4.2. ACE/Ang II/AT1R axis

The binding of the Ang II to AT1R results in the increased production of inflammatory mediators including IL-6, TNF-α, cyclooxygenase-(COX-) II enzyme, eicosanoids, matrix metalloproteinases (MMPs),

reactive oxygen species (ROS) and chemokines (Fig. 1a) [1,4,7,10,23,35,44]. The Ang II/AT1R axis activates a disintegrin and metalloproteinase 17 (ADAM17) which in turn plays a vital role in the upregulation of inflammatory reactions [4,10,22,23,45] (Fig. 1a, b). Most importantly, ADAM17 converts membrane IL-6 receptor (mIL-6R) into its soluble form (sIL-6R). The sIL-6R-IL-6 complexes then bind to the

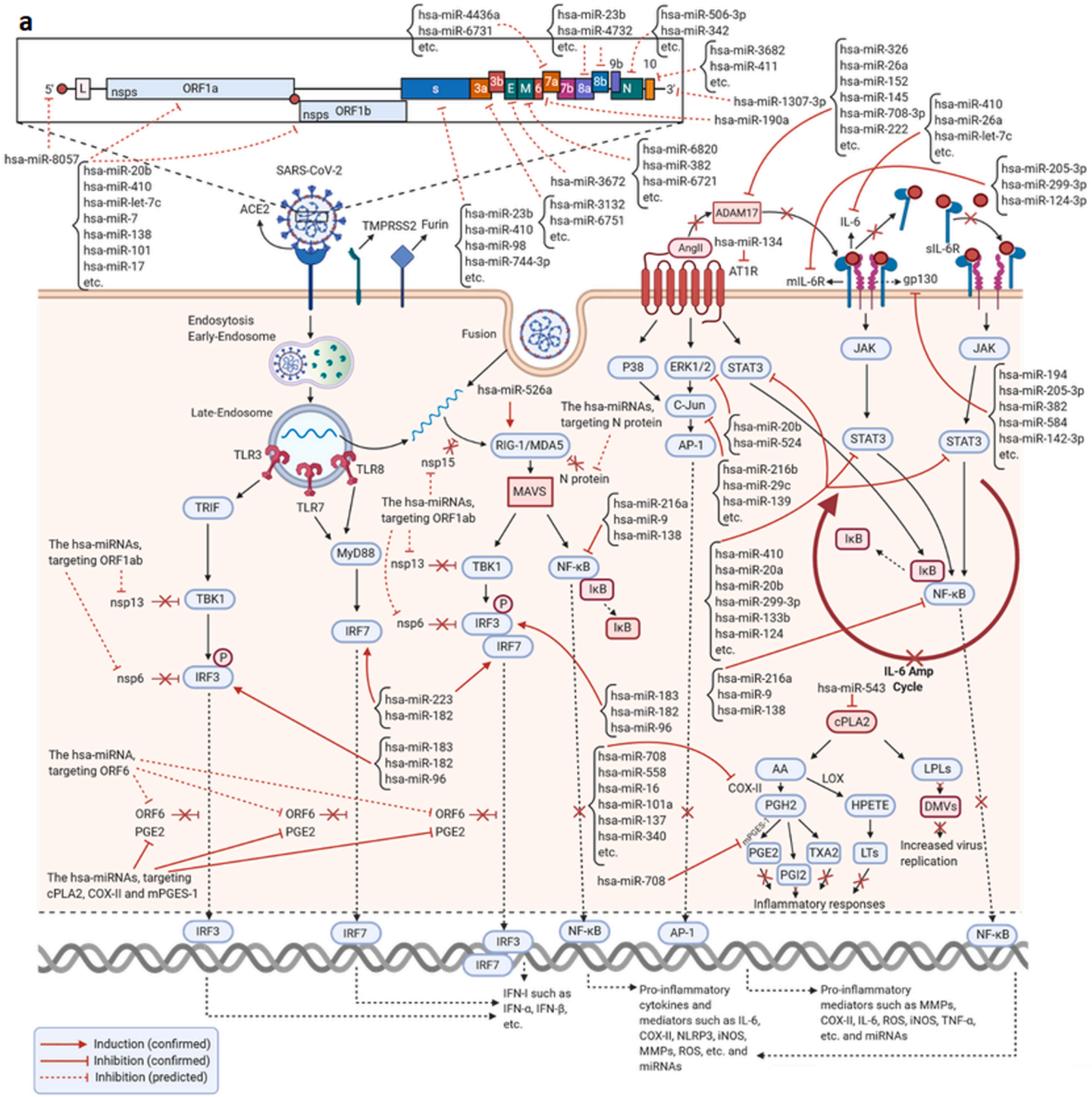


**Fig. 2. Potential of hsa-miRNAs in targeting the SARS-CoV-2 genome, modulating the pro-inflammatory pathways, and reinforcing the IFNs-I-related ones. a)** Based on the bioinformatics assessments, multiple hsa-miRNAs can preclude the generation of the viral proteins including nsps, ORFs, and structural ones through targeting the SARS-CoV-2 genome leading to the removal of their inhibitory effects on IFNs-I production pathways and augmentation of antiviral defence. Moreover, the ability of a wide spectrum of these molecules has been confirmed in binding to the pro-inflammatory mRNAs. Targeting the proteins with a central role in cytokine storm development such as ADAM17, AT1R, IL-6, IL-6R, gp130, STAT3, NF-κB, etc. by hsa-miRNAs is followed by progression reduction of pro-inflammatory events and cessation of IL-6 Amp cycle. In addition, cPLA2, COX-I, -II, and mPGES-1 can be targeted by hsa-miRNAs contributing to the reduction of pro-inflammatory responses and virus replication. Most importantly, some hsa-miRNAs can reinforce the IFNs-I generation and antiviral defence through phosphorylation induction and nuclear translocation facilitation of IRF3 and IRF7. **b)** Targeting the SARS-CoV-2 proteins-coding genes by hsa-miRNAs leads to the elimination of their inhibitory effects on IFNs-I signaling pathways, higher expression of ISGs, and subsequently strengthening the antiviral defence. Moreover, the hsa-miRNAs with the capability of targeting the enzymes, involved in the eicosanoids production pathways, cause upregulation of ISGs expression and down-regulation of ROS procreation resulting in the elevated efficiency of antiviral responses. Targeting each of pivotal pro-inflammatory molecules such as NLRP3, NF-κB, ADAM17, AT1R, TAB2 and 3, RhoB, MMP-9, etc. by hsa-miRNAs also provides the basis for abrogating the vicious cycle of pro-inflammatory reactions. Furthermore, the MyD88-independent pathway in TLR4 signaling and the production of IFNs-I are augmented following the neutralizing of the SARS-CoV-2 genome by hsa-miRNAs leading to the limitation of cytokine storm development.

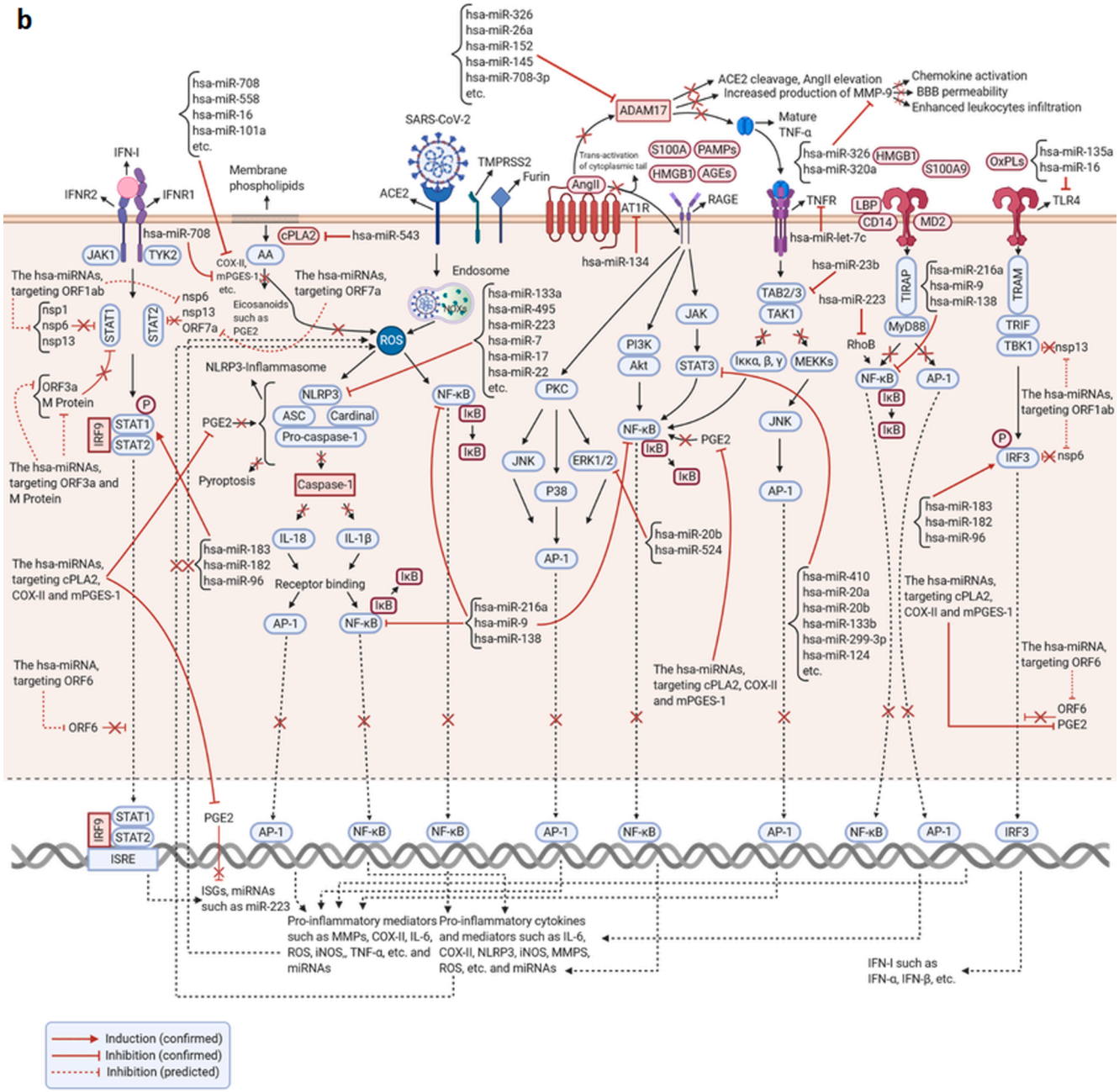


**Fig. 2.** (*continued*).

expressed glycoprotein 130 (gp130) on the surface of diverse cells (even lacking the mIL-6R) such as epithelial, endothelial, and smooth muscles cells, as well as fibroblasts underlying *trans*-signaling of this receptor. This contributes to the activation of downstream signaling pathways (*e.g.* JAK/STAT3 and NF-κB), high-level generation of pro-inflammatory mediators (*e.g.* IL-6 itself), and IL-6 amplifier (Amp) cycle (Fig. 1a). Therefore, the activity of STAT3 and NF-κB pathways and the IL-6 Amp cycle in SARS-CoV-2 infection result in a positive feedback loop of inflammation [4,7,10,23,46,47] (Fig. 1a). It should be noted that despite the activation of mIL-6R (classic pathway), *trans*-signaling pathway lacks the negative feedback loop mediated by the suppressor of cytokine signaling 3 (SOCS3) (Fig. 1a). Thus, due to the ADAM17 elevated activity, the IL-6 Amp cycle is strongly continued and causes intense inflammatory responses [10]. Trans-presentation (proximity of the soluble IL-6-mIL-6R complexes on the surface of one cell to the gp130 on the other) is another mechanism of IL-6R signaling activation resulting in inflammatory signal transduction in the second cell. This mechanism, which is necessary for T helper (Th) type 17 cells differentiation, is consistent with increased levels of IL-17, IL-23, and high frequency of Th17 cells in severe/critical form of COVID-19 [4,40,44,46–48].

### 4.3. RAGE signaling pathway

The receptor for advanced glycation end products (RAGE) is a multi-ligand pattern recognition receptor (PRR) that belongs to the immunoglobulin (Ig) superfamily [49–52] (Fig. 1b). It is continuously expressed in the lungs of healthy individuals and is also expressed on the surface of diverse cells under inflammatory circumstances. Moreover, the existence of this receptor's ligands in the extracellular space leads to its expression stimulation [49–53]. A wide spectrum of pro-inflammatory mediators (*e.g.* RAGE itself) and its ligands (*e.g.* high mobility group box protein 1 (HMGB1)) are generated as a consequence of the RAGE

**Table 1**
Some of interfering factors with hsa-miRNAs function/expression, induced by SARS-CoV-2 (Predicted).

| Interfering factor | Effect | Ref | Expected results |
|---|---|---|---|
| **Genome** | | | |
| ————— | Acting as a miRNA sponge, Prevention of the interplay of hsa-miRNAs with their targets | [15] | Uncontrolled activation of pro-inflammatory reactions, Cytokine storm development, |
| | Reprogramming of splicing events, Induction of host-related miRNA sponges (*e.g.* lncRNAs and circRNAs), Prevention of the interplay of hsa-miRNAs with their targets, Making hsa-miRNAs biogenesis disrupted | [100,188] | Infection progression, Clinical outcomes manifestation, Disease exacerbation |
| | Hijacking the hsa-miRNAs | [105] | |
| | Acting as an mRNA, Destructing the hsa-miRNAs | [22,189,190] | |
| | Developing genetic mutations, Alteration of hsa-miRNAs function, efficiency, and capacity | [19] | |
| **Proteins** | | | |
| N protein | Inhibition of hsa-miR-223 expression | [191] | Lack of IRF7 expression induction, Reduced IFNs-I production, Increased expression of NLRP3, Elevated expression of RhoB protein, Continuous activation of NF-κB signaling pathway, Increased pyroptosis, Severe inflammation, Cytokine storm development, Clinical elaboration |
| S protein | Inhibition of hsa-miR-98 expression | [191] | Lack of SARS-CoV-2 S protein inhibition, Increased expression of TMPRSS2, Enhanced virus entry, Clinical outcomes manifestation |
| **miRNAs** | | | |
| v-miR-19 v-miR-6_2 | Targeting some subunits of RNA pol II enzyme | [20] | Disruption to hsa-miRNAs biogenesis, Excessive inflammation, Clinical complications advent |
| v-miR-6_1 | Targeting STAT1 | [20] | Suppression of the IFNs-I signaling pathway, Attenuation of the anti-viral responses, Viral replication progression, Clinical outcomes development |
| v-miR-MR147-3p | | [105] | |
| | Targeting TMPRSS2, Increasing the expression of this protease | | Counteracting the hsa-miRNAs effects, Elevated virus entry/infectiousness Clinical adversity |
| v-miR-MR66-3p | Targeting TNF-α, Increasing the expression of this cytokine | [105] | Counteracting the hsa-miRNAs effects, Enhanced inflammation, Clinical outcomes manifestation |
| **Immune-inflammatory responses** | | | |
| IL-17 | Stimulation of IκB-ζ, Declining the pri-miR-23b molecules, Hindering the expression of hsa-miR-23b | [141] | Lack of SARS-CoV-2 S protein and ORF8 inhibition, Absence of TAB2/3 regulation, Increased virus entry/ infectiousness, Uncontrolled inflammatory responses, Cytokine storm development, Clinical outcomes advent |
| ADAM17 | Provocation of mature TNF-α production, Suppression of hsa-miR-145 expression | [113] | Elevated expression of ADAM17, Increased *trans*-signaling mechanism of IL-6R, Enhanced ACE2 cleavage, Ang II and MMP-9 production, Higher activation of TNFR signaling pathway, Contiguous activation of NF-κB pathway, Excessive release of pro-inflammatory mediators, Virus replication progression, Incidence of cytokine storm and clinical complications |
| IL-13 | Reducing the expression of hsa-miR-133a | [198] | Enhanced expression of NLRP3, Increased pyroptosis, Perpetuated activity of NF-κB pathway, Severe inflammation, Clinical elaboration |
| PGI2 | Downregulation of hsa-miR-7a expression | [199] | Lack of SARS-CoV-2 ORF1ab inhibition, Increased expression of NLRP3, Elevated pyroptosis Perpetuated activity of NF-κB pathway, Infection progress Severe inflammation and clinical outcomes |
| GM-CSF | Decreasing the expression of hsa-miR-223 | [155] | Lack of IRF7 expression induction, Reduced IFNs-I production, Increased expression of NLRP3, Elevated expression of RhoB |

(*continued on next page*)

**Table 1** (*continued*)

| Interfering factor | Effect | Ref | Expected results |
|---|---|---|---|
| | | | protein, Enhanced pyroptosis, Continuous activation of NF-κB signaling pathway, Cytokine storm development, Clinical complications manifestation |
| TNF-α | Declining the hsa-miR-138 expression | [200] | Lack of SARS-CoV-2 ORF1ab inhibition, Perpetuated activity of NF-κB pathway, Progression of infection, Cytokine storm development, Clinical outcomes advent |
| STAT3 | Induction of hsa-miR-384 expression | [201] | Increased differentiation of Th17 cells, Excessive inflammatory reactions, Clinical adversity |
| Some mRNAs | Degradation of some corresponding hsa-miRNAs | [189,190] | Hampering the hsa-miRNAs effects, Uncontrolled inflammation, Cytokine storm incidence, Clinical outcomes manifestation |
| Activation of multiple inflammatory pathways | Deviation of hsa-miRNAs expression levels from optimal amounts | [202] | Inappropriate function and inefficiency of hsa-miRNAs, Severe inflammation, Clinical elaboration |
| **Epigenetic modifications** | | | |
| DNA modification | Methylation of hsa-miR-495 gene promoter, Decreased expression of this hsa-miRNA, Increased expression of NLRP3 | [112] | Continuous activation of NLRP3-Inflammasome complex and NF-κB signaling pathway, Increased pyroptosis, Virus replication progression, Cytokine storm and clinical outcomes development |
| | Methylation of hsa-miR-145 gene, Decreased expression of this hsa-miRNA, Elevated expression of ADAM17 | [113] | Increased *trans*-signaling mechanism of IL-6R, Enhanced ACE2 cleavage, Ang II and MMP-9 production, Higher activation of TNFR signaling pathway, Contiguous activation of NF-κB pathway, Excessive release of pro-inflammatory mediators, Virus replication progression, Incidence of cytokine storm and clinical complications |
| Histone modification | H3K9me2/3, Downregulation of hsa-miR-182 and −183 expression | [212] | Lack of SARS-CoV-2 ORF1ab inhibition, Lack of IRF7 expression induction, Reduced phosphorylation of IRF3 and STAT1 molecules, Reduced production and signaling pathway of IFNs-I, Infection progress, Clinical elaboration |
| | H3K27me3, Decreasing the expression of hsa-miR-223 | [212] | Lack of IRF7 expression induction, Reduced production of IFNs-I Increased expression of NLRP3, Elevated expression of RhoB protein, Enhanced pyroptosis, Continuous activation of NF-κB signaling pathway, Cytokine storm and clinical outcomes development |
| **ceRNAs** | | | |
| lncRNA KCNQ1OT1 | Sponging hsa-miR-let-7c and -let-7f, Inhibiting the functions of these hsa-miRNAs | [214] | Lack of SARS-CoV-2 ORF1ab inhibition, Increased expression of IL-6, TNFR-II, and NLRP3, Enhanced pyroptosis, Elevated expression of TMPRSS2, Increased virus entry, Intense inflammation, Clinical complications manifestation |
| lncRNA ANRIL | Sponging hsa-miR-122, Inhibiting the function of this hsa-miRNA, Enhancing the expression of NLRP3 | [217] | Continuous activation of NF-κB signaling pathway, Increased pyroptosis, Virus replication progression, Cytokine storm development, Clinical outcomes advent |
| lncRNA RGMB-AS1 | Sponging hsa-miR-22, Inhibiting the function of this hsa-miRNA, Enhancing the expression of NLRP3 | [218] | |
| lncRNA MEG3 | Sponging hsa-miR-223, Inhibiting the function of this hsa-miRNA, Enhancing the expression of NLRP3 | [219] | Lack of IRF7 expression induction, Reduced production of IFNs-I, Elevated expression of RhoB protein, Enhanced pyroptosis, Continuous activation of NF-κB signaling pathway, Virus replication progression, Cytokine storm and clinical elaboration development |
| circRNA circFNDC3B<br>circRNA circCNOT1 | Binding to AGO protein, Making the hsa-miRNAs biogenesis dysregulated, Neutralizing their function | [220] | Uncontrolled activation of pro-inflammatory reactions, Infection progression, Cytokine storm development, Clinical outcomes incidence |

(*continued on next page*)

**Table 1** (*continued*)

| Interfering factor | Effect | Ref | Expected results |
|---|---|---|---|
| circRNA ciRS-7 (CDR1as) | Sponging hsa-miR-7, Inhibiting the function of this hsa-miRNA | [223,224] | Lack of SARS-CoV-2 ORF1ab inhibition, Increased expression of NLRP3, Elevated pyroptosis Progression of infection, Perpetuated activity of NF-κB pathway, Severe inflammation, Clinical adversity |
| circRNA Sry | Sponging hsa-miR-138, Inhibiting the function of this hsa-miRNA | [224] | Lack of SARS-CoV-2 ORF1ab inhibition, Perpetuated activation of NF-κB signaling pathway, Progression of infection, Cytokine storm and clinical complications development |
| circRNA_100782 | Sponging hsa-miR-124, Inhibiting the function of this hsa-miRNA | [225] | Increased expression of mIL-6R and STAT3, Continuous activation of NF-κB signaling pathway, Cytokine storm development, Clinical outcomes advent |

Abbreviations: ACE2, Angiotensin-converting enzyme 2; ADAM17, A disintegrin and metalloproteinase 17; AGO, Argonaute; Ang II, Angiotensin II; ANRIL, Antisense noncoding RNA in the INK4 locus; ceRNAs, Competing endogenous RNAs; circRNAs, Circular RNAs; GM-CSF, Granulocyte-macrophage colony-stimulating factor; H3, Histone 3; hsa-miRNAs, *Homo sapiens* microRNAs; IFNs-I, Type I interferons; IκB-ζ, Inhibitor of nuclear factor kappa B zeta; IL, Interleukin; IL-6R, IL-6 receptor; IRF, IFN regulatory factor; K, Lysine; KCNQ1OT1, KCNQ1 overlapping transcript 1; lncRNAs, Long non-coding RNAs; me2, Dimethylation; me3, Trimethylation; MEG3, Maternally expressed gene 3; MMP, Matrix metalloproteinases; mRNA, Messenger RNA; N protein, Nucleocapside protein; NF-κB, Nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP3, NOD-, LRR- and pyrin domain-containing protein 3; ORF, Open reading frame; PGI2, Prostaglandin I2; pri-miR-23b, Primary miR-23b; RGMB-AS1, RGMB antisense RNA 1; RhoB, Ras homolog gene family member B; RNA pol II, RNA polymerase II; S protein, Spike protein; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; Sry, Sex-determining region Y; STAT, Signal transducer and activator of transcription; TAB, Transforming growth factor β-activated kinase-1 (TAK1)-binding protein; Th17 cells, T helper type 17 cells; TMPRSS2, Transmembrane serine protease 2; TNF-α, Tumor necrosis factor alpha; TNFR, TNF receptor; v-miR, Viral miRNA.

ligation (a feedforward loop) resulting in inflammatory events intensification and pyroptosis. Regarding the high availability of this receptor's ligands in COVID-19 patients and also its plenitude of expression in the lungs, RAGE activation can be one of the key mechanisms of cytokine storm development [49–52]. Most importantly, a ligand-independent mechanism has recently been reported for *trans*-activation of the RAGE following the AT1R activation contributing to inflammation perpetuation [49] (Fig. 1b). Some researchers have also hypothesised that as SARS-CoV-2 S protein may bind to the cluster of differentiation (CD) 147 (produced following the RAGE activity) in addition to ACE2, the activation of this PRR may have a role in SARS-CoV-2 entry into the cell [51,54]. Among the RAGE ligands, HMGB1 has a high affinity [50,52]. This molecule can make complexes with DNA, RNA, and other damage-associated molecular patterns (DAMPs) and enter the cell through endocytosis. The HMGB1 in high concentration causes leakage of endolysosomal contents into the cytoplasm leading to inflammatory responses and pyroptosis. It is conceivable that the SARS-CoV-2 genome may also enter the cytoplasm through a facilitated transportation system mediated by the RAGE/HMGB1 axis [53].

### 4.4. Oxidative stress and NLRP3-Inflammasome complex

Oxidative stress plays a fundamental role in COVID-19 pathogenesis and exacerbation [44,48,55,56]. Overwhelming evidence has demonstrated that elevated ROS levels are considerably produced by several mechanisms during SARS-CoV-2 infection leading to cytokine storm development and viral replication [4,8,10,35,49–52,55–58] (Fig. 1a, b). Existing macrophages and dendritic cells (DCs) in the airways phagocytose the viral particles, get activated, and release high levels of inflammatory cytokines and ROS. The liberation of these molecules into the bloodstream intensifies macrophages and neutrophils activity. The occurrence of respiratory bursts in these cells causes higher levels of ROS generation. Simultaneously, activation of inflammatory pathways (*e.g.* NF-κB) happens in immune and virus-infected cells and leads to ROS and cytokines procreation. Developed cytokine storm again stimulates oxidative stress and it induces cytokine storm via stimulating the NF-κB pathway. This vicious cycle results in disease complications and complexity [55]. The ROS are also direct activators of the NLRP3-Inflammasome complex. Furthermore, NF-κB activation, which is induced by ROS themselves, causes transcription of the NLRP3 gene (Fig. 1b). Therefore, ROS, directly and indirectly, activate the NLRP3-Inflammasome pathway. This complex is one of the key elements in cytokine storm incidence and disease exacerbation in SARS-CoV-2 infection [8,55,56]. The NLRP3-Inflammasome activity also causes pyroptosis and subsequently immune-inflammatory cells recruitment [35] (Fig. 1b).

### 4.5. TLR4 signaling pathway

TLR4 is one of the innate immunity receptors that can recognize various ligands and is the only one that can be activated by myeloid differentiation factor 88 (MyD88)-dependent and -independent pathways [35,57,59–62] (Fig. 1b). Accomplished studies have shown that expression of TLR4 and its related mediators, especially the ones involved in the MyD88-dependent pathway, has significantly elevated in the patients and it has been more considerable in severe/critical form along with the disease exacerbation. It can probably be associated with altered immune responses against viral components and DAMPs [61]. The high level of S100 calcium-binding protein A9 (S100A9) (as a ligand of TLR4) has been reported in patients with severe/critical COVID-19 [61]. The HMGB1 (as another ligand of TLR4) stimulates this receptor and amplifies the inflammation [51,53]. As mentioned in part 4.4, increased oxidative stress reactions have occurred in patients with severe/critical COVID-19. This results in the production of oxidized phospholipids (OxPLs) [57,63]. Moreover, the myeloperoxidase enzyme of neutrophils, whose elevated expression has been reported in these patients, can oxidize phospholipids leading to the TLR4 signaling initiation and inflammation intensification [35,57,59,62]. Type II alveolar cells-released surfactant is physiologically one of the TLR4 blockers in the lungs. As SARS-CoV-2 damages these cells, the surfactant level is reduced and underlies severe inflammation through unblocking the TLR4 [60]. It should be mentioned that in silico and molecular docking researches have demonstrated that SARS-CoV-2 S protein has this potential to strongly bind to TLR4 and this may provide the basis for enhanced activity of this receptor and disease exacerbation [59,60,64].

### 4.6. MMPs activation

The MMPs are a group of proteases directly associated with inflammatory cytokines/chemokines (*e.g.* IL-6) [65–69]. Based on the assessments, the plasma level of MMP-9 in patients with COVID-19 has been higher than in the control group from the earliest days of hospitalization and has culminated along with the disease progress. Its level has positively been associated with neutrophils count [65]. It should be taken

into consideration that the MMP-9 is liberated by neutrophils during degranulation and this leads to injuries severity [66]. According to the evidence, IFN-β downregulates the MMP-9 generation and upregulates tissue inhibitors of matrix metalloproteinases-I (TIMP-I) (an MMP-9 inhibitor). Hence, inhibition of IFNs-I production and signaling pathways in SARS-CoV-2 infection is another predisposing factor for enhanced expression of this protease and complications [66]. MMP-3 is the other protease with a confirmed role in COVID-19 pathogenesis. Shi et al. have reported that serum level of MMP-3 in hospitalized patients is significantly higher than in the control groups positively related to IL-1β and IL-6 levels. Notably, this MMP can activate other members of the MMPs family (*e.g.* MMP-9) resulting in the disease conditions exacerbation [66,67]. As pointed before, MMPs possess proteolytic activity. Due to the dependency of the SARS-CoV-2 cell entry to proteases activation, some researchers have hypothesised that these enzymes may potentially contribute to the fusion of viral particles with the host cell membrane and facilitate viral entry into the cells [67].

### 4.7. cPLA2/COX-I, -II/Eicosanoids axis

The cPLA2 is one of the most important members of the PLA2 superfamily with a central role in COVID-19 [41,42,70–72]. This enzyme mediates the release of lipid inflammatory mediators named eicosanoids (*e.g.* PGs, thromboxanes (TXs), and leukotrienes (LTs)) and ROS (Fig. 1a, b). Produced eicosanoids then promote inflammation in various ways [70]. *In vitro* studies on SARS-CoV-2-infected cells have demonstrated that cPLA2 expression significantly increases after 6 h and culminates after 24 ones [73]. Another remarkable point about this phospholipase is its fundamental role in the facilitation and progression of CoVs reproduction through DMVs [41,71]. The cPLA2 activity-derived lysophospholipids (LPLs) are necessary for the organization of the DMVs [41] (Fig. 1a). The COX enzymes act downstream of cPLA2 activity and produce eicosanoids (Fig. 1a). According to the evidence, COX-II and PGs (in particular PGE2) play a vital role in severe/critical COVID-19 pathophysiology. Elevated expression of both COX-I and -II has been reported in peripheral blood mononuclear cells (PBMCs) of these patients [42,72,74]. Interestingly, the rates of COX-II and PGE2 production in men, elder people, and also the ones with comorbidities have been higher than in opposite groups during COVID-19 acute inflammation [75]. Enhanced PGE2 can strengthen the inflammatory responses [42,75] (Fig. 1a, b). The positive feedback loop of PGE2-NF-κB is one of the most crucial mechanisms in cytokine storm development in severe/critical forms of COVID-19 [42,76,77]. Most importantly, it has been reported that this PG can block the generation and signaling pathways of IFNs-I [78,79] (Fig. 1a, b). As mentioned in part 4.1, these two pathways are also directly inhibited by SARS-CoV-2 proteins in a group of patients with severe/critical COVID-19. Moreover, it has been observed that PGE2 stimulates NLRP3-Inflammasome activation [80] (Fig. 1b). In addition, PGE2 downregulates the differentiation of Th1 cells and induces the generation of Th17 pro-inflammatory ones, consistent with the observations in severe/critical COVID-19 [40,42]. PGI2 is another lipid inflammatory mediator performing similar activities to PGE2 to some extent [42]. Mast cells (MCs) are the other key sources of eicosanoids procreation and express ACE2. Increased number/activity of these cells has been observed in patients with severe/critical COVID-19 [25,26]. Evidence has corroborated that histamine, released by these cells, provokes the generation of the COX-II, PGE2, PGI2, and pro-inflammatory cytokines all underlying the eicosanoids release and cytokine storm development [81].

## 5. SARS-CoV-2 and clinical outcomes

SARS-CoV-2-induced cellular perturbations, cytokine storm, and IFNs-I inhibition cause serious clinical outcomes such as ARDS, thromboinflammation, MODS, and death in patients with severe/critical COVID-19 [82–84]. Reduction of ACE2 following the virus entry and also ADAM17 activity can underlie the increase of blood pressure, elevated permeability of pulmonary vessels, acute lung injury (ALI), fibrotic and thrombotic responses. [4,6,10,22,23,27,45] (Fig. 1b). Moreover, the IFNs-I reduced/delayed responses contribute to the excessive tissue infiltration of monocytes/macrophages and down-regulation of their pro-repair functions in the airways [85,86]. Reduction of these cytokines has also been reported along with the pulmonary failure progress [87]. Furthermore, each of the inflammatory mediators can in turn develop severe clinical outcomes. For instance, synthesis/release of IL-6 directly plays roles in systemic alterations (*e.g.* fever and hemodynamic effects), cardiovascular injuries (*e.g.* coronary heart disease (CHD), mitigation of myocardial contractility, and thrombosis), and pulmonary damage (*e.g.* hypoxia and ARDS) [4,82,84,88–90]. The significant negative and positive associations of IL-6 expression level have respectively been observed with the pressure of arterial oxygen to fractional inspired oxygen concentration (PaO2/FiO2) ratio and the intensive care unit (ICU) admission [91]. The significant positive relations of the IL-6, IL-8, IL-1β, TNF-α, C-X-C motif chemokine ligand (CXCL) 9, C-C motif chemokine ligand (CCL) 2, granulocyte CSF (G-CSF), macrophage CSF (M−CSF), CXCL10, etc. have been reported with the sequential organ failure assessment (SOFA) score showing their important roles in organ failure [84,90,91]. Findings from autopsy assessments of lung and kidney tissues related to patients with severe/critical COVID-19 indicate the extensive tissue injuries accompanied by vast infiltration of immune-inflammatory cells and high levels of pro-inflammatory mediators [84]. Moreover, the CCL2 chemokine has had significant negative associations with the nadir PaO2/FiO2 ratio (the lowest PaO2/FiO2 value during the hospital stay) and survival rate [92]. Based on the evidence, upregulated levels of MMPs play crucial roles in ALI, ARDS, and inflammatory demyelination [66,68]. The significant negative and positive relations of MMP-9 have respectively been reported with PaO2/FiO2 ratio and lung fibrosis/destruction [65]. This MMP is specific to type IV collagen (constructing the basal membrane around the blood–brain barrier (BBB)) and its high levels can cause BBB permeability and CNS inflammation [66] (Fig. 1b). The cPLA2 enzyme is another key inflammatory mediator in ALI and ARDS. Eicosanoids also underlie the increased vascular permeability and complications advent [41,42,70–72]. Broad perturbations occur in coagulation cascades of patients with severe/critical COVID-19 which lead to higher rates of thromboembolic events characterized by a significant increase in fibrin/fibrinogen degradation products, named D-dimer [9,55,92]. There is a mutual association between the immune and coagulation systems (a feedforward mechanism, named thromboinflammation) [9,92]. The imbalance of pro-and anti-coagulation processes (arisen from SARS-CoV-2-induced cytokine storm) causes the incidence of disseminated intravascular coagulation (DIC), microthrombosis, and MODS [9]. There is a significant positive correlation between the expression levels of IL-6, TNF-α, IL-1β, CCL2, and D-dimer levels [90,92,93]. According to the previous research, the CCL2 may develop the thromboinflammation in severe/critical COVID-19 via protein kinase C alpha (PKCα)-P38MAPK-heat shock protein (HSP) 27 pathway [94]. The liberation of ROS and pro-inflammatory cytokines into the bloodstream causes red blood cells (RBCs) damage, free iron production, and intensified oxidative stress. The free iron and oxidative stress convert the plasma soluble fibrinogen into the abnormal/enzyme-resistant fibrin clots in the form of dense matted deposits (DMD) contributing to the microthrombosis, pulmonary microcirculation, organ damage, and shock [55]. Tissue infiltration and uncontrolled activities of neutrophils also proceed the thromboinflammation [92].

Although a prompt coordinated immune response is the first line of defence against viral infections, and normal antiviral strategies require activation/interaction of multiple inflammatory pathways, dysregulated/excessive immune-inflammatory responses can cause local/systemic damage and clinical outcomes manifestation in the host leading to the disease exacerbation and complexity [2,4,95]. Most importantly, excessive production of some pro-inflammatory mediators, in turn, leads

to the inhibition of efficient antiviral molecules, extensive viral replication, and directing the patients toward the critical stage [41,42]. Homeostatically, the human body controls the activity of inflammatory pathways through various mechanisms [96]. miRNAs are one of the main factors in controlling inflammatory responses. These small RNAs play a pivotal role in the regulation of genes expression and provide the basis for the maintenance of immune system homeostasis in this way. Accordingly, we will discuss the potential roles of miRNAs and also interfering agents with their performance in severe/critical COVID-19 in the following sections.

## 6. miRNAs

The miRNAs are a class of endogenous single-stranded non-coding RNAs with an average length of 22 nucleotides discovered in the early 1990 s. These evolutionary conserved small RNAs, controlling the expression of 60% of human genes, participate in most of the biological processes including cellular proliferation, differentiation, maturation, activation, survival/apoptosis, and metabolism. miRNAs also have crucial roles in inflammatory/antiviral responses and the interaction between host and virus [6,15–17,20,97–100]. Over than 2000 miRNAs have been identified in the human, each of which has several target molecules. Furthermore, the expression of a single gene may be regulated by multiple miRNAs. Hence, these regulatory RNAs can play a fundamental role in antiviral responses [6,101,102]. miRNAs exist in diverse forms including extracellular/circular (in the body fluids), intracellular (*i.e.* cytoplasmic, nuclear, and organellic), and exosomal [17,97]. Their biogenesis is predominantly accomplished through the Canonical pathway, during which primary miRNAs (pri-miRNAs) and then precursor miRNAs (pre-miRNAs) are produced in the nucleus following the activity of RNA pol II/III and Drosha. Cytoplasmic transportation of the pre-miRNAs and their more processing are respectively done by Exportin-5 (XPO5) and Dicer. In the next step, mature miRNAs are loaded on argonaute (AGO) resulting in the formation of the miRNA-induced silencing complex (miRISC). It is then directed toward the target mRNAs and modulates their expression [17,97,103]. In most cases, miRNAs interact with the 3′-UTR of different target mRNAs. However, there are some reports about their interplay with other parts of these molecules including 5′-UTR, coding regions, and genes promoters [97,104]. Moreover, miRNAs mostly cause degradation or translation inhibition of their targets. Nevertheless based on the research evidence, the interaction of the miRNA-mRNA can lead to the genes expression activation and mRNAs positive regulation under specific circumstances [97,105–108]. On this basis, meticulous identification of these molecules and their functions in the pathophysiology of COVID-19 is of great importance.

### 6.1. hsa-miRNAs and SARS-CoV-2 genome

According to the evidence, some hsa-miRNAs can directly target the viral genomic RNA and mostly cause its degradation or translation inhibition [15,16,19,98]. Bioinformatics and in silico assessments indicate that most of the hsa-miRNAs may be able to target genome and protein-coding genes of SARS-CoV-2 (in both positive and negative strands) [15,19,20,105] (Fig. 2a). These molecules can influence the expression of genes involved in the entry, biogenesis, replication, and infectiousness of this virus [20]. For example, hsa-miR-1307-3p and hsa-miR-8057 respectively bind to the 3′- and 5′-UTR of this virus genome [20] (Fig. 2a). Most of the hsa-miRNAs (about 100) target the ORF1ab region of the SARS-CoV-2 genome where nsp proteins and essential enzymes for viral replication and translation are encoded [19–21,105]. Some of these small RNAs are: hsa-miR-20b, hsa-miR-let-7c-3p/5p, hsa-miR-410, hsa-miR-17, hsa-miR-101, hsa-miR-7, hsa-miR-138, hsa-miR-182, etc. [19–21,105] (Fig. 2a). The genes encoding SARS-CoV-2 structural proteins may also be targeted by hsa-miRNAs. For instance, hsa-miR-98, hsa-miR-744-3p, hsa-miR-410, hsa-miR-23b, etc. are potent to bind to the S protein-coding gene. In addition, hsa-miR-6820, hsa-miR-6721, hsa-miR-382, etc. may bind to the M protein-coding gene. It has been predicted that a wide spectrum of hsa-miRNAs such as hsa-miR-342, hsa-miR-6882-3p, hsa-miR-1910-3p, hsa-miR-506-3p, etc. can target the N protein-coding gene. SARS-CoV-2 E protein-coding gene can also be targeted by hsa-miR-3672 [19–21,105] (Fig. 2a). The genes encoding other accessory proteins of this virus may be targeted by hsa-miRNAs. In this connection, it has been anticipated that hsa-miR-367, hsa-miR-6751, hsa-miR-203b-3p, hsa-miR-3132, etc. can target *ORF3a*. The hsa-miR-190a may bind to *ORF6*. Besides, *ORF7a* may be targeted by hsa-miR-4436a, hsa-miR-1910-3p, hsa-miR-6866, and hsa-miR-6731, etc. The hsa-miR-4732, hsa-miR-23b, hsa-miR-3190-3p, hsa-miR-5011-3p, etc. also bind to *ORF8*, and hsa-miR-3682, hsa-miR-411, etc. target *ORF10* [19,20] (Fig. 2a).

### 6.2. hsa-miRNAs and pro-inflammatory pathways

As mentioned previously, miRNAs have an effective role in the modulation of immune responses. Several *in vitro* and *in vivo* studies have revealed disruption to the expression/function of these molecules exerting crucial effects on the pathogenesis of the diseases [17,109–119], whereas modification of these perturbations using appropriate medications has been accompanied by pathological complications reduction and improvement [110,111,120–123]. The miRNAs can target a wide spectrum of pro-inflammatory mediators (Fig. 2a, b), and may relieve the clinical outcomes caused by them. Multiple hsa-miRNAs can target the IL-6 signaling pathway as a pivotal pro-inflammatory one in severe/critical COVID-19. For example, hsa-miR-20a, hsa-miR-20b, hsa-miR-410, hsa-miR-124-3p/5p, hsa-miR-299-3p, hsa-miR-133b, etc. can target the 3′-UTR of STAT3 mRNA [124–129] (Fig. 2a). The hsa-miR-410, hsa-miR-26a, hsa-miR-let-7c, etc. have the potential to target IL-6 mRNA, and hsa-miR-205-3p, hsa-miR-124-3p, as well as hsa-miR-299-3p are among the modulators of this cytokine receptor expression [126,130–133] (Fig. 2a). Several hsa-miRNAs such as hsa-miR-382, hsa-miR-584, hsa-miR-205-3p, hsa-miR-142-3p, hsa-miR-194, etc. can also target the 3′-UTR of gp130 [126] (Fig. 2a). Moreover, the ADAM17 is a direct target of multiple hsa-miRNAs such as hsa-miR-26a, hsa-miR-152, hsa-miR-145, hsa-miR-708-3p, hsa-miR-326, hsa-miR-222, etc. [45,113,114,134–139] (Fig. 2a, b). The hsa-miR-let-7c via targeting TNF receptor- (TNFR-) II, hsa-miR-23b through binding to transforming growth factor β-activated kinase-1 (TAK1)-binding protein (TAB) 2 and 3, and hsa-miR-320a and hsa-miR-326 via targeting MMP-9 can also attenuate the inflammatory events and clinical outcomes resulting from ADAM17 activity to some extent [140–145] (Fig. 2b). The hsa-miR-134 also targets the AT1R mRNA, reduces its expression, inflammation, and complications [146] (Fig. 2a, b). It has been shown that hsa-miR-216a, hsa-miR-138, and hsa-miR-9 can inhibit the NF-κB transcription factor [96,147–149] (Fig. 2a, b). Several studies have demonstrated that the 3′-UTR of TLR4 mRNA is targeted by hsa-miR-135a and hsa-miR-16. Some others such as hsa-miR-223 prevent the excessive activation of this receptor signaling pathway through targeting Ras homolog gene family member B (RhoB) [130,150–153] (Fig. 2b). The capability of multiple hsa-miRNAs such as hsa-miR-22, hsa-miR-7, hsa-miR-17, hsa-miR-223, hsa-miR-133a, hsa-miR-495, etc. has been corroborated in targeting the NLRP3 mRNA [112,154–169] (Fig. 2b). Furthermore, several miRNAs including hsa-miR-20b and hsa-miR-524 via targeting extracellular signal-regulated kinase (ERK) 2, and hsa-miR-23b through binding to the 3′-UTR of TAB2 and 3, can control MAPK/AP-1 pathway activation. The hsa-miR-216b, hsa-miR-29c, hsa-miR-139, etc. also target the c-JUN [141,170–175] (Fig. 2a, b). According to the evidence, the hsa-miR-543 can target the 3′-UTR of cPLA2 mRNA [176] (Fig. 2a, b). The COX-II and microsomal prostaglandin E synthase-1 (mPGES-1) enzymes can be targeted by multiple hsa-miRNAs such as hsa-miR-558, hsa-miR-101a, hsa-miR-708, hsa-miR-16, hsa-miR-137, hsa-miR-340, etc. [115,177–183] (Fig. 2a, b). Based on the above-mentioned content, the efficient and accurate function of host

miRNAs can play a crucial role in the modulation of pro-inflammatory reactions, disease pathogenesis, and the rates/severity of the damage, clinical outcomes, and mortality in severe/critical COVID-19.

### 6.3. hsa-miRNAs and IFNs-I-related pathways

It has been identified that some hsa-miRNAs can, directly and indirectly, increase the production and signaling pathways of IFNs-I consequently leading to the reinforcement of antiviral defence and reduction of the clinical outcomes. For instance, Chen et al. have illustrated that hsa-miR-223, which itself is generated as a result of the IFNs-I pathways activity, elevates the expression of IFN regulatory factor (IRF) 7 and IFNs-I and subsequently reduces the viral replication and complications through targeting the 3′-UTR of forkhead box O3 (FOXO3) (a negative regulator of IRF7) [184,185] (Fig. 2a, b). In addition, *in vitro* and *in vivo* evaluations have shown that hsa-miR-182 acts as a positive regulator of IRF7 by the same mechanism as the hsa-miR-223 [186] (Fig. 2a). It has also been reported that the hsa-miR-183 cluster including hsa-miR-183, hsa-miR-182, and hsa-miR-96 upregulate both production and signaling pathways of IFNs-I via increasing the phosphorylation of IRF3 and STAT1 molecules (Fig. 2a, b). Usage of miRNA mimic belongs to each member of this cluster has led to 8-fold enhanced expression of ISGs. Mechanistically, these hsa-miRNAs straightly target the negative regulators of phosphorylation as well as activation of IRF3 and STAT1 (protein phosphatase 2 catalytic subunit alpha (PPP2CA) and tripartite motif-containing protein 27 (TRIM27)) [187]. The hsa-miR-526a is the other positive regulator of IFNs-I pathways (Fig. 2a). Based on the *in vitro* assessments, this miRNA directly targets cylindromatosis (CYLD) (a negative regulator of antiviral responses through removing lysine (K)-63-linked polyubiquitin of RIG-I), increases RIG-I ubiquitination and thereupon production of IFNs-I [109].

## 7. hsa-miRNAs and SARS-CoV-2-induced interfering factors

### 7.1. SARS-CoV-2 genome and proteins

Accomplished assessments have shown that the SARS-CoV-2-encoded sponges can potentially bind to the hsa-miRNAs and prevent their activities which can result in inflammation progress and clinical outcomes. In this process, the virus itself straightly acts as a miRNA sponge and represses the hsa-miRNAs function [15] (Table 1). Moreover, it has been observed that SARS-CoVs can stimulate the procreation of host-related miRNA sponges such as competing endogenous RNAs (ceRNAs) (*i.e.* long non-coding RNAs (lncRNAs) and circular RNAs (circRNAs)) and indirectly cause perturbations in hsa-miRNAs function contributing to enhanced viral replication and complications (Table 1). According to the evidence, SARS-CoVs can cause cytoplasmic translocation of Drosha for evasion of ISGs-mediated antiviral effects. This provides the basis for reprogramming of the splicing events, generation of ceRNAs, hindering the activity of miRNAs, an increase of viral reproduction plus the disruption of the miRNAs biogenesis pathway. Regarding the genetic resemblance of SARS-CoV-2 to other SARS-CoVs, it is conceivable that the former uses similar mechanisms for inhibiting the hsa-miRNAs [100,188] (Table 1). There are some reports around the ability of viral genomes in hijacking the host miRNAs. Application of this mechanism by SARS-CoV-2 may lead to excessive pro-inflammatory reactions and clinical outcome manifestations [105] (Table 1). As the SARS-CoV-2 genome acts as an mRNA and some target mRNAs may be capable to destruct miRNAs, the hsa-miRNAs may be affected by the genome of this virus [22,189,190] (Table 1). Occurred mutations in viral genomes are the other effective factors on the function and efficiency of host miRNAs [19] (Table 1). Furthermore, it has been demonstrated that viral proteins can influence the expression of host miRNAs. For example, N and S proteins of SARS-CoVs can respectively inhibit the expression of hsa-miR-223 and hsa-miR-98 resulting in dysregulation of their target molecules and the incidence of clinical complications [191,192] (Table 1).

### 7.2. SARS-CoV-2 miRNAs

Studies have shown that viral (v)-miRNAs can simultaneously target viral as well as host genes. Accordingly, they disrupt the immune/antiviral responses of the host on the one hand and underlie the virus evasion on the other [19,20,100,105,193]. Based on the bioinformatics assessments, several miRNAs of SARS-CoV-2 may have the potential to target host genes and then progress inflammation and clinical outcomes. Target genes of v-miRNAs can be among the components involved in the gene transcription, biogenesis, nuclear as well as cytoplasmic processing, and editing pathways of hsa-miRNAs. For instance, it has been predicted that v-miR-19 and v-miR-6_2, encoded by SARS-CoV-2, can target some subunits of the RNA pol II enzyme [20] (Table 1). The v-miRNAs may also affect the expression of key molecules in antiviral and pro-inflammatory signaling pathways. In a way that they provide the conditions for counteracting the effects of hsa-miRNAs. Among them, v-miR-6_1 of SARS-CoV-2 may be able to target STAT1 and consequently suppress the signaling pathways of IFNs-I [20] (Table 1). In addition, v-miR-MR147-3p and v-miR-MR66-3p are the other miRNAs of this new SARS-CoV which may respectively target TMPRSS2 and TNF-α, increase their expression, and cause the clinical outcomes manifestations [105] (Table 1).

### 7.3. Immune-inflammatory responses

Immune-inflammatory responses can influence the expression level and function of hsa-miRNAs leading to the diseases exacerbation and clinical outcomes development [194–197] (Table 1). For example, decreased expression of hsa-miR-23b has been observed in some inflammatory disorders. According to the evidence, IL-17 represses the gene expression of this hsa-miRNA through stimulating inhibitor of nuclear factor kappa B zeta (IκB-ζ) and also declining the pri-miR-23b molecules [40,141] (Table 1). Moreover, it has been reported that enhanced ADAM17 can suppress the expression of the hsa-miR-145 through the provocation of mature TNF-α production (Table 1) [113]. Accomplished studies on asthmatic patients have illustrated that IL-13 declines the expression of hsa-miR-133a in bronchial smooth muscle cells [198] (Table 1). Mohite et al. have reported that PGI2 can change the expression of several hsa-miRNAs such as hsa-miR-7a [199] (Table 1). Furthermore, it has been shown that granulocyte–macrophage CSF (GM-CSF) and TNF-α can respectively reduce the expression/production of hsa-miR-223 and hsa-miR-138 [155,200] (Table 1). It has also been reported that upregulated activation of STAT3 in the experimental autoimmune encephalomyelitis (EAE) model is accompanied by a higher expression level of hsa-miR-384 resulting in increased differentiation of Th17 lymphocytes [201] (Table 1). As mentioned in part 7.1, some target mRNAs can degrade the corresponding hsa-miRNAs [189,190] (Table 1). In patients with severe/critical COVID-19, many inflammatory molecules are generated in high concentration, each of which can alter the disease pathogenesis and underlie the clinical adversity by affecting the expression/function of hsa-miRNAs (Table 1). Moreover, miRNAs have a dose-dependent function and also display their most efficient performance in optimal doses. Any deviation from their optimal concentration can lead to their function disruption. In severe/critical COVID-19, multiple signaling pathways are activated provoking the transcription of various hsa-miRNAs genes. Their excessive production can be a pivotal factor in improper function and inefficiency of them leading to serious clinical outcomes [202] (Table 1).

### 7.4. Epigenetic modifications

According to the evidence, most pathogens (*e.g.* viruses) can progress their replication through exerting epigenetic modifications in host genes. Provocation of these alterations has been observed in CoVs

infections [203,204]. The gene transcription, processing, and nuclear export of miRNAs can be influenced by these alterations consequently affecting their expression level [205–211]. DNA modifications such as methylation of promoter region and also more distant areas (*e.g.* enhancer) of the hsa-miRNAs genes have already been reported. For example, studies on the ALI and renal cancer cell lines have respectively shown the methylation of the hsa-miR-495 and hsa-miR-145 genes, reduction of their expressions accompanied by high levels of their target genes (*i.e.* NLRP3 and ADAM17) leading to inflammation intensification, whereas methylation inhibition has led to reverse results [112,113] (Table 1). Moreover, based on the existing data in the EpimiR database, the expression of several hsa-miRNAs is downregulated under the influence of histone modifications [212]. For instance, it has been reported that histone 3 (H3) K9 dimethylation/trimethylation (me2/3) leads to the reduced expression of the hsa-miR-182 and hsa-miR-183. Declined expression of the hsa-miR-223 has also been observed following the H3K27me3 [212] (Table 1). Given the important role of viruses in the provocation of the epigenetic modifications, SARS-CoV-2 may alter the hsa-miRNAs genes expression through these mechanisms. In this way, the virus provides the basis for its replication progression, cytokine storm development and clinical outcomes manifestation. Furthermore, a specific profile of the hsa-miRNAs expression emerges in the complications that are happened following the SARS-CoV-2 infection (*e.g.* ALI and ARDS) and can exacerbate the disease circumstances.

### 7.5. ceRNAs

#### 7.5.1. lncRNAs

The lncRNAs are a group of non-coding RNAs with a length of over 200 nucleotides [32,213–215]. The miRNAs possess lncRNAs binding sites. Hence, they can act as a ceRNA and suppress the interaction of the hsa-miRNAs with their targets contributing to the clinical elaboration [214,216]. Accomplished bioinformatics assessments on lncRNAs in SARS-CoV-2 infection have demonstrated that these long RNAs may be capable to block several pivotal miRNAs. For instance, lncRNA KCNQ1 overlapping transcript 1 (KCNQ1OT1) can act as a miRNA sponge and hinder the functions of hsa-miR-let-7c and hsa-miR-let-7f (Table 1). In other words, increased levels of hsa-miRNAs target molecules may be protected by lncRNAs which results in the disease exacerbation and complexity [192,214]. In addition, it has been reported that lncRNAs antisense noncoding RNA in the INK4 locus (ANRIL), RGMB antisense RNA 1 (RGMB-AS1), and maternally expressed gene 3 (MEG3) elevate the NLRP3 expression, pyroptosis, inflammation severity, and clinical adversity through sponging the hsa-miR-122, hsa-miR-22, and hsa-miR-223, respectively [217–219] (Table 1). The miRNAs-lncRNAs interactions have also been observed in other SARS-CoVs infections [213]. As it has been shown that viruses utilize the cellular ceRNAs and benefit from them for increasing their reproduction, and also regarding the accomplished bioinformatics evaluations on mRNAs expression profile in SARS-CoV-infected mice [100], it is conceivable that SARS-CoV-2 also influences the human lncRNAs network and thereupon hsa-miRNAs functions leading to the development of severe/critical form of COVID-19 [213,214]. Furthermore, SARS-CoV-2-induced clinical complications can provide the basis for emerging a particular expression profile of lncRNAs and subsequently alteration of hsa-miRNAs function.

#### 7.5.2. circRNAs

The circRNAs are the other group of non-coding RNAs playing key regulatory roles. The miRNAs possess circRNAs binding sites. Hence, they can act as a ceRNA and block the interaction of the hsa-miRNAs with their targets leading to the clinical outcomes manifestation [220–224]. These molecules are named miRNA super sponge due to their high capacity for binding to miRNAs [221]. Multiple studies have shown the regulatory roles and expression disruption of circRNAs in viral infections such as CoVs ones [220]. For example, upregulated expression and activation of circRNAs circFNDC3B and circCNOT1 have been reported in the Middle East respiratory syndrome (MERS)-CoV infection. It has been observed that these two molecules possess several binding sites for AGO protein. Therefore, they can make the miRNAs biogenesis dysregulated and neutralize their functions (Table 1). Notably, their inhibition has led to reduced viral load and replication [220]. According to the evidence, circRNA ciRS-7 (CDR1as) is considered as the sponge of hsa-miR-7. In addition, circRNA mouse testicular-specific circRNA sex-determining region Y (Sry) and circRNA_100782 also hinder the function of hsa-miR-138 and hsa-miR-124, respectively [223–225] (Table 1). Based on the role of circRNAs, the extensiveness of their effects on hsa-miRNAs, and also given the accomplished bioinformatics evaluations on mRNAs expression profile in SARS-CoV-infected mice [100], it is feasible that SARS-CoV-2 infection itself and its-induced complications (*e.g.* ARDS) provoke circRNAs disrupted expression consequently resulting in the alteration of hsa-miRNAs function pattern and the disease progress.

## 8. Therapeutic perspective

Given the existence of various hsa-miRNAs with different functions toward the restriction of viral replication and infectiousness, reinforcement of IFNs-I-related pathways, and modulation of immune-inflammatory responses, it sounds that several SARS-CoV-2-induced interfering factors impede the efficient functions of these small RNAs and make them dysregulated in severe/critical COVID-19 resulting in the development of cytokine storm and clinical outcomes (Table 1). As miRNAs are multi-functional, they have the potential to be considered as therapeutic targets. Designing the miRNAs-based therapeutic methods can be even more effective than medications, merely affecting a single protein. Most importantly, miRNAs are modulators of genes expression, not suppressors, whereas direct repression of host immune mediators can preclude their homeostatic/beneficial functions leading to incidence of additional damage and complications [226–229]. Thus, interfering factors with hsa-miRNAs expression/function must be identified and obviated during SARS-CoV-2 infection, especially in severe/critical form. For instance, recognition of key v-miRNAs and inhibition of their activities using specific miRNA sponges may ameliorate the expression and function of hsa-miRNAs. Administration of appropriate anti-inflammatory drugs can also reduce the excessive inflammation and its secondary damage in patients on the one hand and underlie the hsa-miRNAs optimal expression level on the other, followed by the reduction of clinical adversity [110,111,230]. Moreover, utilizing the RNA interference (RNAi) (*e.g.* small interfering RNAs (siRNAs)), antisense oligonucleotides (ASOs), Cas13 family of clustered regularly interspaced short palindromic repeats (CRISPR) ribonucleases, and addition of nucleotides to lncRNAs binding motifs or their target molecules are important methods for degradation and inactivation of lncRNAs [231–237]. About the circRNAs, we can also benefit from the siRNAs, $m^6A$ modification, etc. and hamper their expression and function [220,238]. It has also been shown that usage of some anti-methylation drugs upregulates the efficiency of hsa-miRNAs and improves the disease circumstances through restoring the miRNAs genes expression [112]. It should be taken into account that identification and efficacy elevation of pivotal hsa-miRNAs (capable to influence the viral clearance, modulate the pro-inflammatory pathways, and strengthen the IFNs-I-related ones) are essential in patients with severe/critical COVID-19 (Fig. 2a, b). Visibly, designing and usage of the miRNAs-based therapeutic protocols should be accomplished in a combinational therapy pattern to achieve the most ideal results. According to our literature search, several hsa-miRNAs may be able to simultaneously play roles in two/three different scopes discussed in the present review article (targeting the viral genome, affecting the pro-inflammatory and IFNs-I-related pathways) (Fig. 2a, b). For example, the hsa-miR-23b is one of the most important miRNAs in severe/critical COVID-19 which may be able to target the virus S protein and ORF8 on the one hand and can cease the TNF-α signaling pathway via targeting the TAB2 and 3

molecules on the other [19–21,141] (Fig. 2a, b). However, IL-17 precludes the expression of this hsa-miRNA gene [40,141] (Table 1). In addition, the hsa-miR-223 not only can decrease the excessive inflammation via targeting the NLRP3 and RhoB molecules but also can provide the basis for the higher IRF7 expression and IFNs-I production through negative regulation of FOXO3 [154,160,162,185] (Fig. 2a). Nonetheless, the SARS-CoV-2 N protein and GM-CSF pro-inflammatory cytokine inhibit its generation. The lncRNA MEG3 also acts as a sponge of this hsa-miRNA [155,191,219] (Table 1). Furthermore, it has been anticipated that hsa-miR-138 may target the virus ORF1ab, and can negatively regulate the p65 subunit of the NF-κB transcription factor (Fig. 2a, b). However, TNF-α reduces the expression level of this miRNA and the circRNA Sry prevents its efficacy through its sponging [200,224] (Table 1). Bioinformatics assessments have predicted that hsa-miR-7 may be capable to target SARS-CoV-2 ORF1ab, and can also bind to the 3′-UTR of NLRP3 [19,20,157] (Fig. 2a, b). Nevertheless, PGI2 causes this hsa-miRNA downregulation, and the circRNA ciRS-7 (CDR1as) sponges it [199,223,224] (Table 1). According to the above-mentioned content, identification and resolution of the interfering factors with expression/function of the key hsa-miRNAs in these two forms of COVID-19 can reduce the viral load/reproduction, augment the IFNs-I-related pathways, control the pro-inflammatory reactions, and limit the cytokine storm-induced clinical outcomes through restoring these small regulatory molecules resulting in the patients' amelioration and lower mortality rate.

## 9. Conclusion

As discussed in this review article, miRNAs play a central role in the regulation of genes expression and maintenance of immune system homeostasis. Any disruption to their optimal expression level or efficient function can underlie the perturbation of multiple signaling pathways and the incidence of complications. It seems that the expression and function of a wide spectrum of hsa-miRNAs have been influenced in severe/critical COVID-19 leading to the clinical outcomes manifestation and mortality. Identification, monitoring, and resolution of these disruptive agents and also designing the miRNAs-based therapeutic protocols can be a ray of hope amid turmoil and pave the way for the better management of the infection and rescuing the patients. Furthermore, given the relative resemblance of viral infections and utilizing the evasion strategies by them, designing those protocols may be beneficial to other viral infections, as well.

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