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Review

Dysregulated miRNAs network in the critical COVID-19: An important clue for uncontrolled immunothrombosis/thromboinflammation

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ABSTRACT

Known as a pivotal immunohemostatic response, immunothrombosis is activated to restrict the diffusion of pathogens. This beneficial intravascular defensive mechanism represents the close interaction between the immune and coagulation systems. However, its uncontrolled form can be life-threatening to patients with the critical coronavirus disease 2019 (COVID-19). Hyperinflammation and ensuing cytokine storm underlie the activation of the coagulation system, something which results in the provocation of more immune-inflammatory responses by the thrombotic mediators. This vicious cycle causes grave clinical complications and higher risks of mortality. Classified as an evolutionarily conserved family of the small non-coding RNAs, microRNAs (miRNAs) serve as the fine-tuners of genes expression and play a key role in balancing the pro/anticoagulant and pro-/anti-inflammatory factors maintaining homeostasis. Therefore, any deviation from their optimal expression levels or efficient functions can lead to severe complications. Despite their extensive effects on the molecules and processes involved in uncontrolled immunothrombosis, some genetic agents and uncontrolled immunothrombosis-induced interfering factors (*e.g.*, miRNA-single nucleotide polymorphysms (miR-SNPs), the complement system components, nicotinamide adenine dinucleotide phosphate (NADPH) oxidases, and reactive oxygen species (ROS)) have apparently disrupted their expressions/functions. This review study aims to give an overview of the role of miRNAs in the context of uncontrolled immunothrombosis/thromboinflammation accompanied by some presumptive interfering factors affecting their expressions/functions in the critical COVID-19. Detecting,

Abbreviations: 3'-UTR, 3'-untranslated region; αIIbβ3, Integrin αIIbβ3; ACE2, Angiotensin-converting enzyme 2; ADAMTS13, A disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; AGO, Argonaute; AIS, Acute ischemic stroke; ALI, Acute lung injury; Ang II, Angiotensin II; aPC, Activated protein C; AT, Anti-thrombin; AT1R, Ang II type 1 receptor; BALF, Bronchoalveolar lavage fluid; C, Complement component; C5aR, C5a receptor; CD40L, Cluster of differentiation 40 ligand; CFA, Complete Freund's adjuvant; cfDNA, Cell-free DNA; CFH, Complement factor H; COVID-19, Coronavirus disease 2019; CRISPR, Clustered regularly interspaced short palindromic repeats; CRISPR-Cas9, CRISPR-associated protein 9; CRs, Complement receptors; CXCL12, C-X-C motif chemokine ligand 12; DGCR8, DiGeorge critical region 8; ECs, Endothelial cells; EPCR, Endothelial protein C receptor; EVs, Extracellular vesicles; FVII, Factor VII; FVIII, Factor VIII; FIX, factor IX; FX, Factor X; FXI, Factor XI; FXII, Factor XII; Fg, Fibrinogen; G2013, α-L-guluronic acid; hBD-1, Human β-defensin-1; HCC, Hepatocellular carcinoma; HIF, Hypoxia-inducible factor; HMGB1, High mobility group box 1; HS, Heparan sulfate; ICAM-I, Intercellular adhesion molecule 1; IFNs-I, Type-I interferons; IFN-γ, IFN gamma; IL, Interleukin; IL-1β, IL-1 beta; IL-6R, IL-6 receptor; IS, Ischemic stroke; LTRAs, Leukotriene receptor antagonists; M2000, β-D-mannuronic acid; Mac-1, Macrophage-1 antigen; MAC, Membrane attack complex; MASP, Mannan-binding lectin serine protease; miRNAs, MicroRNAs; miR-SNPs, miRNA-single nucleotide polymorphysms; MPO, Myeloperoxidase; mRNA, Messenger RNA; miRISC, miRNA-induced silencing complex; MMP, Matrix metalloproteinase; N, Nucleocapsid; NADPH oxidase, Nicotinamide adenine dinucleotide phosphate oxidases; NE, Neutrophil elastase; NETs, Neutrophil extracellular traps; NF-κB, Nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP3, Nucleotide-binding domain (NOD)-like receptor protein 3; NO, Nitric oxide; NSAIDs, Non-steroidal anti-inflammatory drugs; OVA, Ovalbumin; PAD4, Protein arginine deiminase 4; PAI-1, Plasminogen activator inhibitor-1; PDE, Phosphodiesterase inhibitor; PDGF-BB, Platelet-derived growth factor-BB; PEVs, Platelet extracellular vesicles; PGI2, Prostaglandin I2; PLTs, Platelets; Pre-miRNAs, Precursor miRNAs; Pri-miRNAs, Primary miRNAs; PRRs, Pattern recognition receptors; PS, Protein S; PSGL-1, P-selectin glycoprotein ligand-1; RNA pol II/III, RNA polymerase II/III; ROS, Reactive oxygen species; S, Spike; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; SIRS, Systemic inflammatory response syndrome; SLE, Systemic lupus erythematosus; SNAP23, Synaptosomal-associated protein 23; SNI, Spared nerve injury; ssRNA, Single-strand RNA; STAT3, Signal transducer and activator of transcription 3; suPAR, Soluble urokinase plasminogen activator receptor; T2DM, Type II diabetes mellitus; TAFI, Thrombin activatable fibrinolysis inhibitor; TF, Tissue factor; TFPI, Tissue factor pathway inhibitor; TLRs, Toll-like receptors; TM, Thrombomodulin; TMPRSS2, Transmembrane protease, serine 2; t-PA, Tissue plasminogen activator; TRBP, Transactivation response element RNA-binding protein; u-PA, Urokinase plasminogen activator; UL-VWF, Ultra-large von Willebrand factor; VAMP8, Vesicle-associated Membrane Protein 8; VCAM-1, Vascular cell adhesion molecule 1; VWF, Von Willebrand factor; XPO5, Exportin-5.

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monitoring, and resolving these interfering agents mafy facilitate the design and development of the novel miRNAs-based therapeutic approaches to the reduction of complications incidence and mortality in patients with the critical COVID-19.

1. Introduction

The coronavirus disease 2019 (COVID-19) is a multifaceted medical condition caused by the novel member of the *Coronaviridae* family named the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Entering through angiotensin-converting enzyme 2 (ACE2)-mediated endocytosis or fusion, this virus can clinically create a heterogeneous infection. Nearly 20% of patients develop a critical condition. Despite the discovery and production of different vaccines worldwide, SARS-CoV-2 infections and COVID-19 critical forms are still being reported (especially in poor countries). Its mutation-prone nature (more than 50 mutations only caused by the Omicron variant) necessitates adopting the novel therapeutic methods by more precise diagnosis of COVID-19 molecular-immunogenetic mechanisms. In patients with the critical COVID-19, dysregulated immune reactions and high-level production of inflammatory mediators have been observed in the circulation and

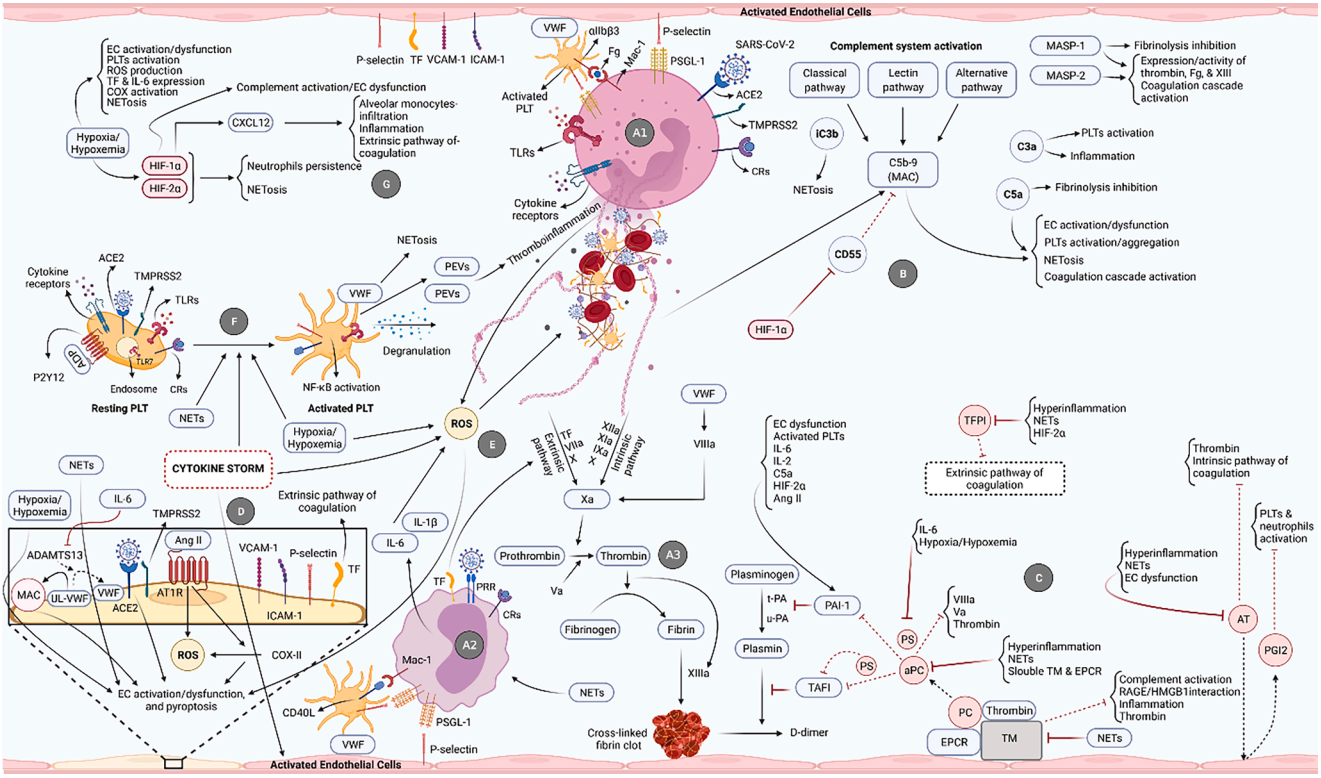

Fig. 1. The most pivotal processes/pathways involved in the development of uncontrolled immunothrombosis in the critical COVID-19. A1) SARS-CoV-2/ACE2 interaction and ligation of different receptors of neutrophils provoke their activation and NETs formation. These cells then interact with PLTs and ECs and release NETs. **A2)** Ligation of diverse receptors of monocytes (*e.g.*, pattern recognition receptors (PRRs) and CRs), their interplay with ECs and PLTs, and also released NETs cause the activation of monocytes followed by high-levels production of pro-inflammatory cytokines. **A3)** NETs are decorated with TF on the one hand and induce factor XII (FXII) on the other, respectively resulting in the activation of extrinsic and intrinsic coagulation pathways and formation of cross-linked fibrin clots. TF is also expressed on the monocytes and activates the extrinsic coagulation pathway. **B)** Activation of the complement system through all three pathways can lead to the formation of MAC, production of C3a, C5a, iC3b, etc. each of which directly and indirectly causes NETosis induction, inflammation development, and fibrinolysis inhibition. The MASP-1 and MASP-2 molecules also play key roles in the coagulation induction and fibrinolysis restraining. **C)** During the fibrinolysis process, plasminogen is converted into plasmin under the influence of t-PA and u-PA eventually leading to the breakdown of the cross-linked fibrin clots and generation of D-dimer. PAI-1 inhibits these plasminogen activators and is activated by several factors involved in uncontrolled immunothrombosis. Endogenous anticoagulants also play central roles provoking fibrinolysis and preventing the formation of the clots. In addition to the induction of some anti-inflammatory roles, TM forms a complex with thrombin and activates the PC (bound to the endothelial protein C receptor (EPCR)), whereas aPC inhibits the coagulation mediators in different ways. Another anticoagulant, PS, directly and indirectly (as an aPC's co-factor) participates in the fibrinolysis process. AT and TFPI also inhibit the coagulation pathways. In addition, AT restricts the NETosis through the induction of prostaglandin I2 (PGI2) production by the ECs. Involved in the uncontrolled immunothrombosis, multiple factors restrain the functions of anticoagulants resulting in inefficient fibrinolysis. **D)** SARS-CoV-2/ACE2 and Ang II/AT1R interactions, NETs, hypoxia/hypoxemia, and cytokine storm cause the activation/dysfunction and pyroptosis of ECs. The inhibition of ADAMTS13 by IL-6 also underlies the reduced conversion of ultra-large VWF (UL-VWF) into the normal size. This molecule then acts as a scaffold for the formation of MAC contributing to the ECs damage. The expression of TF and adhesion molecules by ECs is followed by the activation of the extrinsic coagulation pathway and NETosis. **E)** The high-levels production of ROS, induced by neutrophils, cytokine storm, hypoxia/hypoxemia, monocytes-released pro-inflammatory cytokines, etc., can provoke NETosis and ECs damage. **F)** SARS-CoV-2/ACE2 and endosomal TLR7/virus single-strand RNA (ssRNA) interactions, and also the ligation of different receptors of PLTs can cause their activation leading to the NETosis induction, PLT extracellular vesicles (PEVs) release, NF-κB pathway activation, and PLTs degranulation. The released NETs, cytokine storm, and hypoxia/hypoxemia are the other stimulants of PLTs activation. **G)** Hypoxia/hypoxemia stimulates different processes involved in the uncontrolled immunothrombosis and also mediates the production of HIF-1α and HIF-2α. These two factors perpetuate NETosis. HIF-1α also induces the activities of CXCL12 and the complement system. Therefore, it can proceed the ECs dysfunction leading to excessive NETosis, inflammation, and coagulation.

bronchoalveolar lavage fluid (BALF) causing a hyperinflammatory condition called the cytokine storm [1–8]. At the same time, accomplished assessments have shown high rates of thrombotic events in these patients leading to a hypercoagulability situation and high mortality rates [1–3,9–13]. In other words, the COVID-19 is a kind of endotheliopathy that causes hypercoagulability situation, exhausted fibrinolysis, and extensive vascular thrombosis associated greatly with a hyperinflammatory condition. According to the research evidence, there is a reciprocal correlation between the immune and coagulation systems that reinforce each other. In the critical COVID-19, the excessive immune responses have a key role in the incidence of uncontrolled immunothrombosis/thromboinflammation through the development of inflammation and induction of thrombotic factors (Fig. 1). Venous thromboembolism, ischemic stroke (IS), neurological disorders, acute coronary syndrome, and myocardial damage are among the grave clinical complications ensuing from the above-mentioned processes in patients with the critical COVID-19 [1–3,10–18]. Normally, there is a balance between the pro/anticoagulant factors and pro-/anti-inflammatory ones that would maintain homeostasis [1]. Acting as post-transcriptional regulators of gene expression, microRNAs (miRNAs) are pivotal molecules for the well-balanced inflammatory and thrombotic processes. These non-coding RNAs mostly bind to the 3′-untranslated region (3′-UTR) of their target molecules and regulate their expressions [14,19–22]. Many studies have demonstrated the role of miRNAs in the pro-inflammatory pathways, activated in the severe/critical COVID-19, which we discussed in another paper [5]. As exemplified, an investigation into the mouse model of ovalbumin (OVA)/complete Freund's adjuvant (CFA)-induced neutrophilic asthma indicates a significant elevation of the nucleotide-binding domain (NOD)-like receptor protein 3 (NLRP3)-Inflammasome level and activity in miR-223$^{-/-}$ mice [23]. Moreover, a clinical study on patients with systemic lupus erythematosus (SLE) revealed the crucial role of miR-410 in targeting the signal transducer and activator of transcription 3 (STAT3) playing a key role in interleukin (IL)-6/IL-6 receptor (IL-6R) pathway [24]. Regarding the close correlation between pro-inflammatory and procoagulant processes as well as the bilateral role of miRNAs in their balance, any disruption to the expressions or efficient functions of these small RNAs can underlie the development of excessive inflammatory or thrombotic reactions consequently followed by the intensification of another system activation. Accordingly, this review study aims to discuss the role of miRNAs in the incidence of uncontrolled immunothrombosis/thromboinflammation accompanied by some interfering factors affecting their expressions/functions in the critical COVID-19 and to propose some miRNAs-based therapeutic approaches.

2. Interaction of the immune and coagulation systems in critical COVID-19

2.1. Uncontrolled immunothrombosis/thromboinflammation

The immune and coagulation systems cooperate to restrict the diffusion of pathogens. The term "immunothrombosis", which is considered as an example of their interaction, refers to an effective endogenous process of the innate immune system induced by the pathogens and damaged cells. It can be considered a beneficial intravascular immune mechanism. However, its uncontrolled form can underpin the inflammation and immunologically-mediated microthrombi formation leading to thromboinflammation (Fig. 1). This physiological process is mostly mediated by the neutrophils and monocytes in which they release neutrophil extracellular traps (NETs) and express tissue factor (TF) on the one hand and restrain the endogenous anticoagulants on the other resulting in severe inflammation-induced coagulation [2,3,14,25] (Fig. 1-A1-A3, 1C). In particular, the myeloperoxidase (MPO) of NETs provokes the monocytes toward the pro-inflammatory M1 phenotype contributing to the thromboinflammation and endothelial cells (ECs) damage [2,26,27] (Fig. 1-A2, 1-D, 1-E). The interaction of monocytes and platelets (PLTs), which has elevated in the COVID-19 patients, is another factor for more activation of the former and subsequently higher NETs formation [28–30] (Fig. 1-A2, 1-E). The broad infiltration of neutrophils into diverse organs and uncontrolled immunothrombosis associated with the disease exacerbation have been observed in patients with the critical COVID-19 [2,3,25,31,32]. Many immunologic-hemostatic processes participate in the incidence and development of the dysregulated form of immunothrombosis (Fig. 1), something which will be discussed in the following.

2.1.1. NETosis

Several *in vitro* and *in vivo* studies have reported that neutrophils release NETs in a process called "NETosis" following the stimulation by the inflammatory mediators or pathogens and also mitochondrial dysfunction. NETs are the structures that consist of cell-free DNA (cfDNA), histones, and granular as well as cytoplasmic proteins [3,9,14,25,33–39]. Moreover, multiple investigations have observed mitochondrial DNA in the NETs, such as the ones released by isolated neutrophils of patients with the systemic inflammatory response syndrome (SIRS) and also inflammatory-stimulated neutrophils of healthy donors. [40–42] (Figs. 1-A1). During the NETosis, neutrophil elastase (NE) and MPO translocate into the nucleus and proceed decondensation of DNA. Activities of the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase complex (reactive oxygen species (ROS) production) and protein arginine deiminase 4 (PAD4) (histone citrullination) are the other important factors in the NETosis [14,25,33,39,43] (Fig. 2a-A1). In this regard, using the NADPH oxidase inhibitor can inhibit NETosis in the circulating neutrophils isolated from patients with coronary artery disease [43]. Furthermore, the inability to citrullinate the histones or form the NETs was observed in PAD4$^{-/-}$ mouse neutrophils [39]. Despite the beneficial roles of NETs (*e.g.*, inducing type-I interferons (IFNs-I) and trapping the inflammatory mediators), their excessive formation is followed by vascular occlusion, hyperinflammation, and disease exacerbation [2,3,14,25,26,33,44–48]. In addition, NETs-derived thrombosis is mostly PLTs-dependent mediated by some adhesion molecules such as P-selectin and its receptor, called P-selectin glycoprotein ligand-1 (PSGL-1) (Figs. 1-A1). Consistently, high levels of neutrophils-PLTs aggregations, excessive NETs formation, and neutrophils activation markers have been reported in the critical COVID-19 [29,30,36,49,50]. In this context, a clinical study on patients with the severe and critical forms reported the augmented NETs in plasma, tracheal aspirate, and lung autopsies tissues. Other studies have found the vast infiltration of neutrophils along with the acute capillaritis and fibrin deposition in the lung autopsies of patients with the critical COVID-19. Their neutrophils were somewhat degenerated and trapped in fibers indicating the production of NETs [36,51,52]. These findings show that SARS-CoV-2, similar to the inflammatory mediators, can provoke the neutrophils toward the NETosis in the COVID-19 patients [36,42,53]. Most importantly, NETs can activate both extrinsic and intrinsic coagulation pathways [2,14,47,54] (Figs. 1-A1, 1-A3). High levels of NETs and their components have been observed in the circulation of the patients with the critical COVID-19 positively associated with inflammation, endothelial dysfunction, and mortality [54–58]. The histones of NETs can dose-dependently increase thrombin generation and fibrin deposition through the inhibition of activated protein C (aPC) (known as an endogenous anticoagulant) and activation of PLTs [2,59–61] (Fig. 1C, F). Moreover, several studies such as the ones conducted on golden Syrian hamsters with SARS-CoV-2 and patients with SLE reported that NETs damaged the ECs leading to the fibrin clots formation [47,62–65] (Fig. 1D). Another study also found that NETs acted as a scaffold and directly induced the activation of the complement system [33,66,67] (Figs. 1-A1, 1B).

2.1.2. Complement system activation

As a humoral innate immune response, the activation of the complement system through all three classical, alternative, and lectin

pathways can play a crucial role in the development of inflammation and coagulation [9,10]. The enhanced activation of this system alongside the uncontrolled immunothrombosis was reported in the critical COVID-19. According to the research evidence, both SARS-CoV-2 proteins (*e.g.*, nucleocapsid (N) and spike (S)) and immune complexes can activate the complement cascade in these patients. Considerably, the increased levels of soluble and deposited complement component (C) 5b-9 (membrane attack complex (MAC)), C4d (caused by C4b breakdown), and mannan-binding lectin serine protease (MASP)-2 have been observed in the lung microvasculature of the patients with the critical COVID-19. The evaluation of their purpuric skin lesions resulted in similar findings. Moreover, the elevated circular levels of C5a and C5b-9 along with the high expression of the C5a receptor (C5aR) on the surface of neutrophils and monocytes were found in the patients with the critical COVID-19. The increased expression of MASP-2 was also accompanied by the enhanced coagulation [54,68–72]. The activated complement proteins play a central role in the uncontrolled immunothrombosis. They can directly (through neutrophils activation/recruitment) and indirectly (with the activation of TF, ECs, PLTs, and inflammation) provoke the NETosis [2,3,9,14,25,33,54,73–80] (Fig. 1B, F). The induction of PLTs activation/aggregation and expression of von Willebrand factor (VWF) by the activated ECs are pivotal in the development of NETosis, fibrin deposition, and dysregulated immunothrombosis [3,10,81,82]. At the same time, *in vitro* and *in vivo* studies reported that the complement factors (*e.g.*, C5a) could induce the expression of plasminogen activator inhibitor-1 (PAI-1) by different cells and inhibit fibrinolysis (Fig. 1C). In this regard, Shagdarsuren *et al.* reported the reduction of PAI-1 levels in the atherosclerosis-prone mice, treated with the C5aR antagonist. MASP-1 also activates thrombin activatable fibrinolysis inhibitor (TAFI) (known as a fibrinolysis inhibitor) [3,83–86] (Fig. 1B).

2.1.3. Exhausted fibrinolysis and inefficient endogenous anticoagulants

Following the increased formation of clots, the fibrinolysis process is activated whereby plasminogen is converted into the active plasmin under the influence of tissue plasminogen activator (t-PA) and urokinase plasminogen activator (u-PA). The active plasmin then breaks down the fibrin in the vasculature [87–89] (Fig. 1C). Being affected by different factors involved in the uncontrolled immunothrombosis (*e.g.*, NETs and ECs activation/dysfunction), exhaustion/disruption of the fibrinolytic system occurs in patients with the critical COVID-19 leading to its inefficiency [2,3,9,87,90,91] (Fig. 1C). Both hyperfibrinolysis (high levels of D-dimer) and hypofibrinolysis (plasmin consumption, its reduced fibrinolytic function, and high-level production of PAI-1) have been reported in these patients [3,87–89,92–102]. Moreover, hyperinflammation, NE, and hypoxia-inducible factor (HIF)-2α inhibit the tissue factor pathway inhibitor (TFPI), whereas MASP-1 activates TAFI resulting in the disrupted fibrinolysis [3,85,103–105] (Fig. 1B, C). The upregulated levels of D-dimer, t-PA, u-PA, soluble u-PA receptor (suPAR), and thrombin-anti-thrombin (AT) complexes have been reported in patients with the critical COVID-19 positively associated with the activation of neutrophils, NETs plasma levels, and mortality. Disruption to the functions of endogenous anticoagulants has also been observed in these patients. Based on the research evidence, activities and plasma levels of AT, PC, and protein S (PS) have been reduced in patients with the critical COVID-19 under the influence of the factors involved in the uncontrolled immunothrombosis and have negatively been associated with the disease exacerbation and mortality [2,57,87,88,98–100,102,104–116]. Furthermore, the increased soluble form (inefficient/attenuated form) of thrombomodulin (TM) (known as an anticoagulant and anti-inflammatory molecule) and its decreased tissue expression level were reported in patients with the critical COVID-19 accompanied by the disease severity [3,97,102,105,111,117].

2.1.4. ECs activation and dysfunction

Activation, dysfunction, and pyroptosis of the ECs (known as important pathological events found in the critical COVID-19) can occur directly after the SARS-CoV-2 entrance and indirectly as a result of the immunologic-hemostatic responses (Fig. 1D). Regarding the crucial role of the endothelium in the maintenance of vascular homeostasis and immune responses, its dysfunction acts as a stimulator for uncontrolled immunothrombosis [2,3,9,118–120]. Studies on the COVID-19 and severely septic patients have revealed that the interaction of the SARS-CoV-2-infected/activated ECs with neutrophils and monocytes can lead to the activation of the latter and higher levels of NETosis. The interplay between neutrophils and PLTs is another underlying factor in this process and ECs activation [53,121] (Figs. 1-A1 and 1-A2). As Nitric oxide (NO) is vital for the normal function of the ECs, the occurrence of oxidative stress and high-levels production of ROS (induced by the different factors involved in the uncontrolled immunothrombosis, and reducing NO bioavailability) are the most important mechanisms of the ECs dysfunction [26,43,118,120,122] (Fig. 1D, E). Accordingly, the decreased and increased levels of the NO and ROS have respectively been reported in the patients with the critical COVID-19 [5,123–125]. Above all, ROS provoke NETosis [25,43,118] (Fig. 1E). NETs can directly activate the ECs and induce their apoptosis [14]. The excessive production of these molecules can also damage endothelium integrity and activate the complement system resulting in the ECs dysfunction [62,66] (Figs. 1-A1, 1-D). According to *in vitro* and *in vivo* studies, angiotensin II (Ang II)/Ang II type 1 receptor (AT1R) axis and cytokine storm proceed the ECs dysfunction [2,3,9,118,120,126,127] (Fig. 1D). The elevated levels and activity of several markers related to the ECs activation/dysfunction and pyroptosis (*e.g.*, VWF, P-selectin, intercellular adhesion molecule 1 (ICAM-I), vascular cell adhesion molecule 1 (VCAM-1), and caspase-1) were observed in the patients with the critical COVID-19 positively associated with the disease severity and mortality [102,117,119,128–131]. Known as a stimulator of coagulation, complement activation, and NETosis, the VWF plays a major role in the uncontrolled immunothrombosis [132,133] (Figs. 1-A1-3, 1-D). Apparently, its increased expression is associated with the reduced activity of a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13) (known as a regulator of VWF multimers size) in the critical COVID-19. According to the research evidence, a high level of IL-6 (found in the critical COVID-19) inhibits the activity of this metalloproteinase [2,9,134,135] (Fig. 1D). The negative correlation between NETs and ADAMTS13 levels was reported in the patients with the critical COVID-19 [57,136].

2.1.5. PLTs activation

Apart from the key role of PLTs in the coagulation cascade, these cells have recently been considered the crucial and unique components of the immune system [137–139]. The immunologic functions of the PLTs are mediated by the pro-inflammatory molecules stored in their granules (degranulation) and/or newly synthesized (through the long-lived transcripts) [2,9,137,140]. Moreover, several immune-inflammatory receptors such as toll-like receptors (TLRs) 1, 2, 4, 6, 7, 9, complement receptors (CRs), and cytokine receptors are expressed by the PLTs underlying their activation, launching the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway (in a non-genomic route), and release of the pro-inflammatory mediators. The ligation of non-immune receptors of the PLTs (*e.g.*, P2Y12) also causes their activation. Most importantly, thrombocytes express the ACE2 and transmembrane protease, serine 2 (TMPRSS2) that can underpin the activation of these cells, PLTs-neutrophils interaction, and development of uncontrolled immunothrombosis [9,141–145] (Fig. 1-F). In this connection, the increased expression levels of the markers related to the PLTs activation (*e.g.*, P-selectin, VWF, and the cluster of differentiation 40 ligand (CD40L)) were reported in the critical COVID-19 [30,49,50,102,117,146,147]. Moreover, the activation of PLTs through TLR4 and TLR9 (with high expression levels in the critical COVID-19) is followed by their further interactions with neutrophils and NETosis [148–150]. According to different *in vitro* and *in vivo* studies,

NETs induce pro-inflammatory effects through the activation of TLR2, 4, 9, and PLTs activation, in turn, leading to the higher expressions of these three TLRs [25,141,151–153]. The majority of molecules released by the activated PLTs (*e.g.*, IL-1 beta (IL-1β), high mobility group box 1 (HMGB1), human β-defensin-1 (hBD-1), and complement factors) can also provoke NETosis. In this regard, it was observed that HMGB1$^{-/-}$ PLTs, isolated from the Ly5.1 C57BL/6 mice, failed to induce the generation of NETs [2,3,9,33,137,154,155] (Fig. 1F).

2.1.6. Hypoxia/hypoxemia

Hypoxia/hypoxemia is among the stimulant and supportive factors of uncontrolled immunothrombosis in the critical COVID-19 [2,9]. Following the SARS-CoV-2 infection, extensive pulmonary infiltration of the neutrophils and other immune cells causes the local consumptive hypoxia, high-level production of ROS, and excessive NETosis. Moreover, the increased permeability of the endothelium is followed by the NETs leakage into the alveolar space, disruption to the gas exchange, and the incidence of hypoxemia [53]. Hypoxia/hypoxemia also acts as a predisposing factor in the promotion of inflammation and coagulation resulting in the further production of NETs [2,3,26,27,53] (Fig. 1E, G). Under hypoxic conditions, HIFs (*e.g.*, HIF-1α and HIF-2α) are expressed by the immune cells and ECs. Although these two HIFs have been reported to be able to preclude the infection of the lung epithelial cells with the SARS-CoV-2, their inappropriate activities can be followed by the persistence of neutrophils, higher rates of the NETosis, and uncontrolled immunothrombosis [26,156] (Fig. 1G). Consistently, the significantly elevated expression of the HIF-1α was reported in the COVID-19, especially in the critical form [157,158]. The HIF-1α-induced C-X-C motif chemokine ligand 12 (CXCL12) also plays a pivotal role in the uncontrolled immunothrombosis by recruiting the leukocytes (Fig. 1G). In this context, the CXCL12-mediated transmigration of monocytes into the brain perivascular space and consequent neuroinflammation were observed in a study conducted on the spared nerve injury (SNI) mouse model [26,159]. In a preclinical study on the C57BL/10 male mice, Pandya *et al.* have reported the inhibition of CD55 by HIF-1α. Therefore, this molecule can intensify the complement-mediated ECs damage [3,27,160] (Fig. 1B, G). According to *in vitro* and *in vivo* studies, HIF-2α causes the upregulated and downregulated expressions of the PAI-1 and TFPI, respectively. Therefore, it can take part in the uncontrolled immunothrombosis [26,103,161] (Fig. 1C).

3. miRNAs

The miRNAs are classified as an evolutionarily conserved family of the small non-coding RNAs with an average length of 22 nucleotides found in diverse forms such as intracellular (nuclear, cytoplasmic, and organelic), circular/extracellular (in the biofluids), and exosomal types. The transcription of the miRNAs genes (located in the exonic, intergenic, and intronic regions) is accomplished by the RNA polymerase II/III (RNA pol II/III) leading to the formation of primary stem-loop structures called primary miRNAs (Pri-miRNAs). The breakdown of these molecules by Drosha/DiGeorge critical region 8 (DGCR8) complex is followed by the generation of hairpin molecules called precursor miRNAs (Pre-miRNAs) transported into the cytoplasm by exportin-5 (XPO5). Afterwards, the Dicer/transactivation response element RNA-binding protein (TRBP) complex does more processing on them; therefore, mature miRNAs are produced. Finally, these mature strands are loaded on the argonaute (AGO) protein leading to the formation of miRNA-induced silencing complex (miRISC) which binds to the messenger RNAs (mRNAs). The binding sites of the miRNAs are mostly located in the 3′-UTR regions of their target mRNAs. However, research evidence has shown that they can also bind to the 5′-UTR region, gene promoters, and coding areas. Every single miRNA can regulate the expressions of several target mRNAs. At the same time, the expression of every single mRNA can be controlled by several miRNAs. This represents the functional extensiveness of the miRNAs. Although the interactions between the miRNAs and their targets usually cause the translation inhibition or instability/destruction of the latter, they can be followed by the induction of the gene expression under certain conditions. The miRNAs act as a post-transcriptional gene fine-tuner. However, the regulation of a gene's expression or production of a protein can either arise from the direct interaction of a miRNA and the corresponding mRNA or targeting the mRNAs of the factors involved in the induction of a gene's expression (*e.g.*, transcription factors and receptors). In other words, the outcomes of the expression regulation of an mRNA by a miRNA can underlie the induction or repression of other genes on the transcription, post-transcription, translation, and post-translation levels depending on the role of the target mRNA (even if they are not the direct target of the considered miRNA). According to the research evidence, human miRNAs can, directly and indirectly, affect the expression of the molecules involved in the immunothrombosis [5,21,162–168]. Therefore, any disruption to their optimal expression levels or efficient functions can result in the incidence of an uncontrolled form of this process and thromboinflammation. Differential expressions of miRNAs have been reported in the COVID-19 patients [163,169–177].

3.1. miRNAs affecting neutrophils/monocytes activities and NETosis

A wide spectrum of miRNAs can affect the activities of the neutrophils. For instance, miR-146a, miR-223, and miR-17 target the IL-8 and control their recruitment. However, miR-155 acts toward their increased infiltration and NETosis through the induction of the IL-8 and PAD4 genes [178–180] (Fig. 2a-A1). The miR-223 and miR-130a restrict the NETosis and preclude the development of uncontrolled immunothrombosis through the negative regulation of NE, MPO, and prevention of the perpetuated activity of neutrophils [180–182] (Fig. 2a-A1). Receptors and adhesion molecules involved in the NETosis process are also among the target molecules of miRNAs. As exemplified, miR-15a, miR-31, and miR-let-7a reduce the expression/activation of the integrin αIIbβ3 (αIIbβ3) on the surface of the activated PLTs. The miR-26b targets the P-selectin, whereas miR-146a, miR-124, miR-223, miR-133a, miR-1, etc. target the macrophage-1 antigen (Mac-1) to limit neutrophils-/monocytes-PLTs interactions and regulate the NETs formation [138,183–186] (Fig. 2a-A1, 2a-A2). Moreover, targeting the TLR2 by miR-146a, miR-143, and miR-195, expression regulation of the TLR4 by miR-146a, miR-let-7, miR-135a, and miR-16, targeting the IL-6 by miR-223, miR-let-7, and miR-410, and expression regulation of the IL-6R by miR-205-3p, miR-299-3p, and miR-124-3p underlie the regulation of NETosis [5,181,183,187–189] (Fig. 2a-A1, 2a-A2). The negative regulation of the expression/activation of the NADPH oxidases and the production of ROS by miR-146a, miR-25, miR-218a, miR-29c-3p, miR-34a, miR-138, miR-126a, etc. are among the other factors controlling the release of NETs [168,183,190–192]. However, the miR-21, miR-155, miR-506, etc. induce the ROS production and the resultant NETs formation [191] (Fig. 2a-A1, 2a-A2). In this connection, the disrupted expression of some above-mentioned miRNAs such as miR-223, miR-17, miR-130a, miR-15a, miR-31, miR-16, miR-124, miR-146a, miR-218, miR-126-3p (reduced), and miR-155 (elevated) were reported in the circulation of patients with the COVID-19 [170,171,173–176,193–199]. The downregulated level of miR-34a was also observed in the post-mortem lung biopsy of patients with severe forms of the disease [163]. All of the miRNAs affecting the other pathways/events (*e.g.*, activation of PLTs and the complement system, in addition to hypoxia/hypoxemia) (Fig. 2b-D, 2c-E, 2c-G) also indirectly affect the neutrophils/monocytes activities and NETosis. Moreover, some miRNAs may interact with the genome of SARS-CoV-2 and regulate the expression of its genes [5,200]. Therefore, they may have some indirect impacts on the activation of neutrophils/monocytes and the generation of NETs

3.2. miRNAs affecting coagulation cascade

The extrinsic, intrinsic, and common pathways of coagulation can be

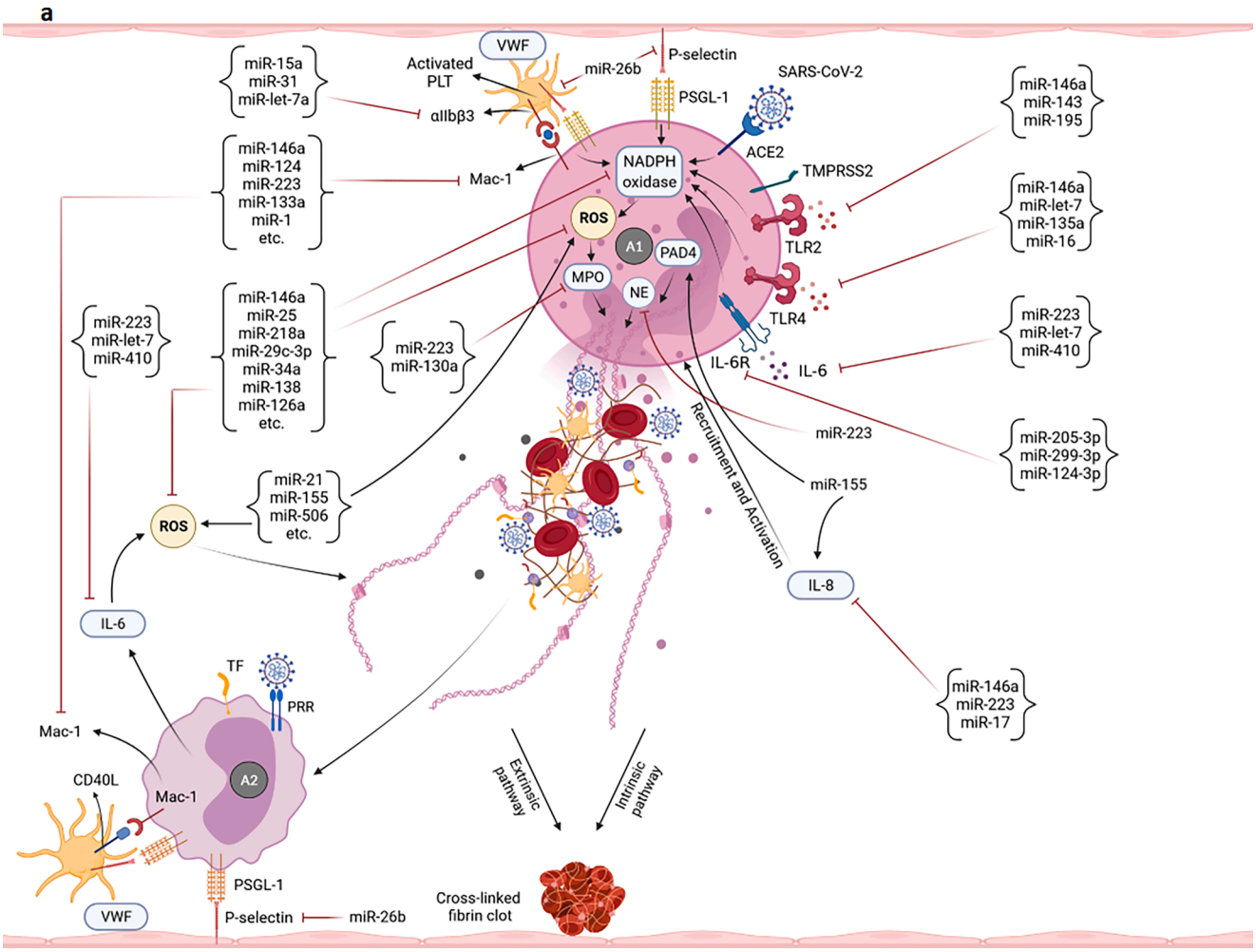

Fig. 2. Potential of miRNAs in targeting/regulation of key molecules involved in the development of uncontrolled immunothrombosis. a-A1) According to the research evidence, many miRNAs can target IL-8, ROS, and different receptors as well as enzymes participating in the NETosis process. Adhesion molecules-mediated neutrophils-PLTs and neutrophils-ECs interactions can also be affected by miRNAs. Some of these small RNAs also cause the production of ROS and induction of NETosis. The modulation of the NETosis process by miRNAs can indirectly affect some of the adverse outcomes resulting from their excessive production such as activation of monocytes, coagulation pathways, etc. **a-A2)** miRNAs can affect the interactions of monocytes with PLTs as well as ECs and control the immunothrombosis. The modulation of monocytes-released pro-inflammatory cytokines by miRNAs can also restrict the NETs formation. **b-B1)** Multiple miRNAs target the key molecules simultaneously involved in both NETosis and coagulation processes such as VWF, TF, Fg, and αIIbβ3. **b-B2)** miRNAs can also regulate the expression levels of molecules/factors with the key roles in extrinsic, intrinsic, and common pathways of coagulation leading to more control of thromboinflammation. **b-B3)** The PLTs-/ECs-monocytes interactions and TF on the surface of monocytes are targeted by miRNAs leading to the regulation of the coagulation cascade and immunothrombosis. **b-C)** Several miRNAs can affect the expression of molecules involved in the ECs activation/dysfunction and pyroptosis. Causing the ECs damage, ADAMTS13 is also targeted by some of these small RNAs. Targeting the TF on the ECs is followed by the limitation of the extrinsic coagulation pathway. **b-D)** The expression regulation of different receptors of PLTs with central roles in their activation is accomplished by miRNAs. Targeting some other molecules such as CD40L, VWF, P-selectin, SNAP23, and VAMP8 can also affect the activation and degranulation of PLTs leading to more restriction of uncontrolled immunothrombosis. **c-E)** Several miRNAs can target the complement factors and regulators. They negatively or positively regulate their expressions and affect the uncontrolled immunothrombosis. **c-F)** The negative and positive regulations of molecules involved in the fibrinolysis process are done by some miRNAs leading to the limitation of fibrin deposition and development of the uncontrolled immunothrombosis **c-G)** The expressions of hypoxia/hypoxemia-induced HIF-1α and HIF-2α are affected by several miRNAs. CXCL12 is also considered a target molecule of miRNAs affecting the uncontrolled immunothrombosis.

regulated by miRNAs. For instance, miR-145, miR-106b, miR-103-3p, miR-19b, miR-223, etc. target the TF, whereas miR-19a/b-3p, miR-134, miR-885, etc. target the factor VII (FVII) to control the extrinsic coagulation pathway [201–203] (Fig. 2b-B1-3, 2b-C). Furthermore, factor IX (FIX) is the target molecule of miR-223, miR-125, and miR-128. Studies have shown that several miRNAs such as miR-145, miR-93, miR-15b, miR-96, etc. can negatively regulate the intrinsic coagulation pathway by targeting the factor XI (FXI) [202,203] (Fig. 2b-B2). The miR-24 and miR-103-3p through targeting the factor X (FX) and VWF, miR-34a/c, miR-26b, miR-15b-3p, miR-7, miR-186, etc. by targeting the factor VIII (FVIII), and miR-18a, miR-29a/b/c, miR-211, miR-193-3p, miR-186, etc. by targeting the fibrinogen (Fg) regulate the common coagulation pathway [202–205] (Fig. 2b-B1-3, 2b-D). The non-optimal circular levels of some of these miRNAs such as miR-223, miR-93, miR-186, miR-18a (reduced), and miR-19a/b-3p as well as miR-15b (elevated) have been found in patients with the COVID-19 [170,171,174,176,197]. Decreased levels of miR-24 in ECs-derived extracellular vesicles (EVs) accompanied by more cerebrovascular complications have been reported in these patients [206]. The down-regulation of miR-34a and miR-29b-3p was also reported in the post-mortem lung biopsy of patients with the severe COVID-19 [163]. In addition, the indirect effects of the miRNAs controlling the other

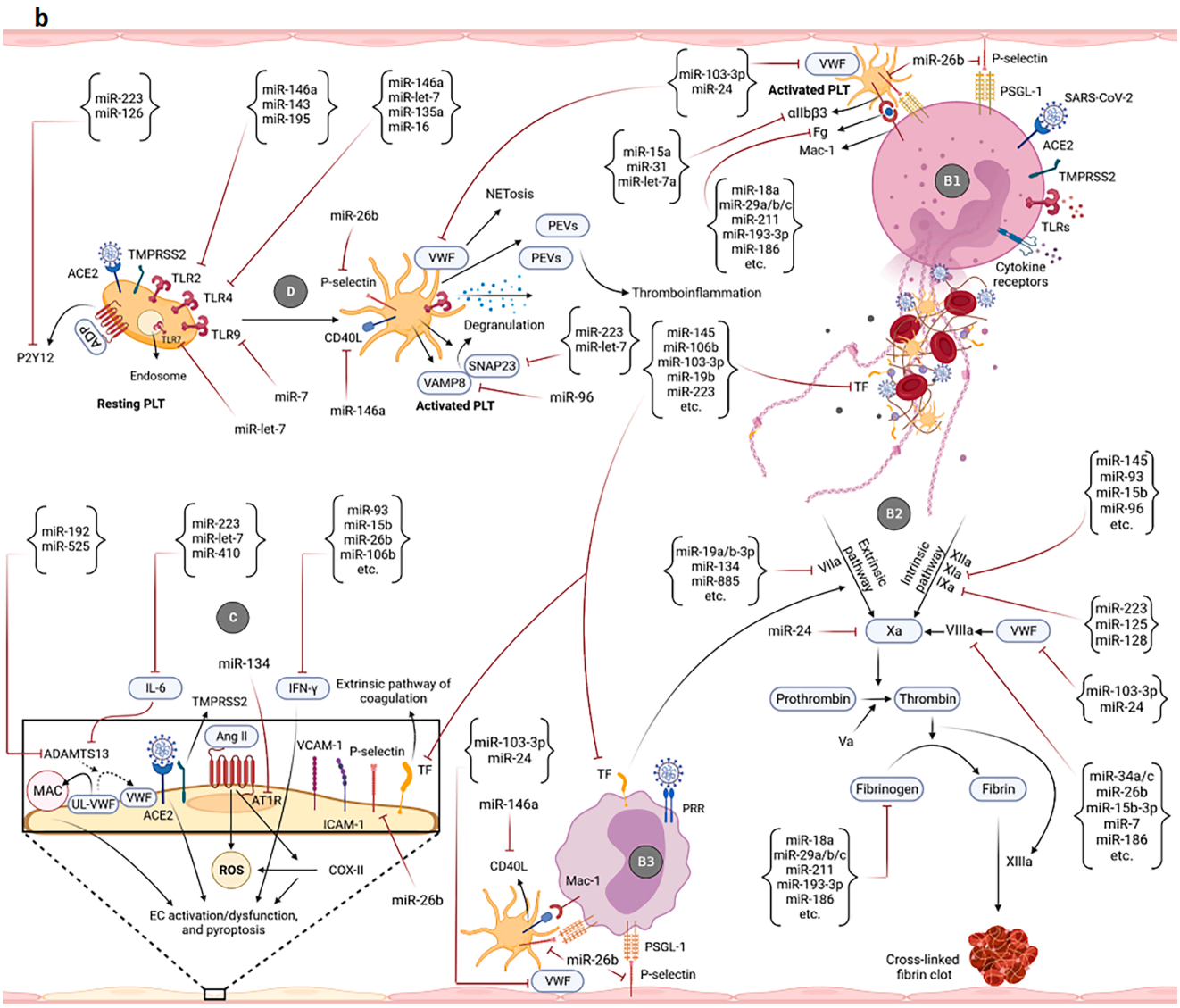

Fig. 2. (*continued*).

pathways/events (*e.g.*, neutrophils/monocytes activities, NETosis, ECs activation/dysfunction, and activation of PLTs as well as the complement system, fibrinolysis, and hypoxia/hypoxemia) (Fig. 2a, 2b-C, 2b-D, 2c-E-G) on the coagulation cascade cannot be ignored.

3.3. miRNAs affecting ECs activation/dysfunction

The miRNAs can extensively affect the activation or dysfunction of ECs. As exemplified, miR-223, miR-let-7, and miR-410 by targeting the IL-6, miR-93, miR-15b, miR-26b, miR-106b, etc. through the expression regulation of the IFN gamma (IFN-γ), and miR-134 by targeting the AT1R participate in the regulation of their activation/dysfunction and pyroptosis. Moreover, the expression regulation of the P-selectin by miR-26b, and targeting the ADAMTS13 by miR-192 and miR-525 affect those processes [5,180,181,187,202,207] (Fig. 2b-C). In this regard, the deregulated circular expression levels of some of the mentioned miRNAs such as miR-223, miR-93, miR-192, (reduced), and miR-15b (elevated) have been reported in patients with COVID-19 [176,197,198]. Moreover, the regulation of the other pathways/events (*e.g.*, neutrophils/monocytes activities, NETosis, NADPH oxidases/ROS axis, coagulation cascade, the complement activation, and hypoxia/hypoxemia) (Fig. 2a, 2b-B2, 2c-E, 2c-G) by miRNAs can also affect the ECs activation/dysfunction and pyroptosis, indirectly. As mentioned earlier, some miRNAs may target the SARS-CoV-2 genome [5,200]. Thus, they may affect the activation/dysfunction of ECs that express ACE2.

3.4. miRNAs affecting PLTs activation

The activation and degranulation of PLTs can be controlled by miRNAs. For instance, miR-146a, miR-143, miR-195, miR-let-7, miR-135a, miR-16, and miR-7 regulate the expression of the TLR2, 4, 7, 9. However, miR-146a can also target the CD40L on the surface of the PLTs [5,183,187–189,208,209] (Fig. 2b-B3, 2b-D). Their P2Y12 receptor is the target molecule of miR-223 and miR-126 [184,210] (Fig. 2b-D). Moreover, targeting the synaptosomal-associated protein 23 (SNAP23) and vesicle-associated membrane protein 8 (VAMP8) (known as the vital molecules for the PLTs degranulation) by miR-223, miR-let-7, and miR-96, expression regulation of the P-selectin by miR-26b, and targeting the αIIbβ3 molecule by miR-15a, miR-31, and miR-let-7a can affect the PLTs activation and degranulation [138,184–187,203,210–212] (Fig. 2b-B1, 2b-B3, 2b-D). Among these miRNAs, the disrupted expression patterns of miR-146a, miR-16, miR-223, miR-126-3p, miR-15a, and miR-31 (reduced) have been found in the circulation of patients with the COVID-19 [174–176,195–199]. It is remarkable that all of the miRNAs

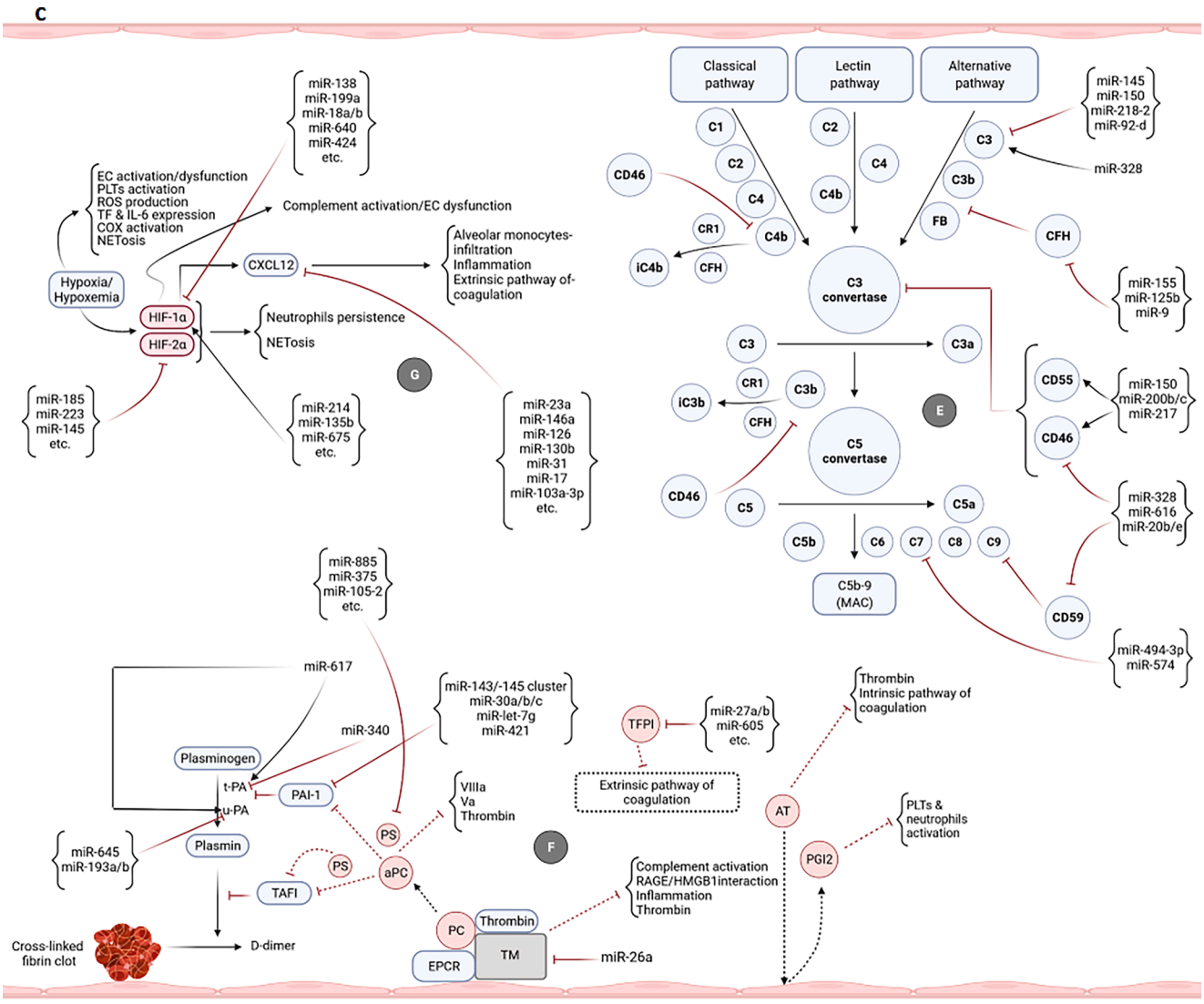

Fig. 2. (*continued*).

affecting the other pathways/events (*e.g.*, neutrophils/monocytes activities, NETosis, coagulation cascade, and hypoxia/hypoxemia) (Fig. 2a, 2b-B2, 2c-G) can also indirectly impact the PLTs activation. The predicted miRNAs (targeting the genome of SARS-CoV-2) may be involved in the activation of these cells, as PLTs express ACE2 [5,200].

3.5. miRNAs affecting complement system activation

Different complement components and regulators are among the target molecules of miRNAs. For instance, miR-145, miR-150, miR-218–2, and miR-92-d negatively regulate the C3 and miR-328 induces its deposition [213–216]. The miR-494-3p and miR-574 also target the C7 [217] (Fig. 2c-E). Moreover, CD46 and CD59 are the target molecules of miR-328, miR-616, and miR-20b/e, and at the same time, miR-155, miR-125b, and miR-9 target another regulatory factor of this system called complement factor H (CFH) all resulting in the excessive complement activation [214,218–220] (Fig. 2c-E). Several miRNAs such as miR-150, miR-200b/c, and miR-217 underpin the more regulated activity of the complement system through the positive regulation of CD46 and CD55 molecules [214,221] (Fig. 2c-E). In this regard, the non-optimal circular expression levels of some of these miRNAs such as miR-150, miR-218, miR-494-3p, miR-20b (reduced), and miR-155 (elevated) have been observed in patients with the COVID-19 [173,193,196,199,222]. Furthermore, the indirect effects of the miRNAs on the other pathways/events (*e.g.*, neutrophils/monocytes activities, NETosis, and hypoxia/hypoxemia) (Fig. 2a, 2c-G) involved in the activation of this system should be taken into consideration.

3.6. miRNAs affecting fibrinolysis process and endogenous anticoagulants

Several studies have reported that the activation of fibrinolysis process can be regulated by some miRNAs. For instance, miR-645 and miR-193a/b target the u-PA, whereas miR-340 controls the t-PA gene expression [223–225]. However, the miR-617 induces their both activations [226] (Fig. 2c-F). Multiple miRNAs such as miR-143/-145 cluster, miR-30a/b/c, miR-let-7 g, and miR-421 target the PAI-1 and regulate its expression [203,227,228] (Fig. 2c-F). Moreover, miR-27a/b, miR-605, etc. target the TFPI, miR-885, miR-375, miR-105–2, etc. regulate the expression of the PS, whereas miR-26a targets the TM to control the expression and function of the endogenous anticoagulants [202,203,229] (Fig. 2c-F). In this regard, the deregulated expression patterns of miR-340, miR-375 (reduced), and miR-27a/b (elevated) were found in patients with the COVID-19 [170,196,198,222]. Considerably, all of the miRNAs affecting the other pathways/events (*e.g.*, neutrophils/monocytes activities, NETosis, ECs dysfunction, the complement activation, and hypoxia/hypoxemia) can indirectly affect the

fibrinolysis process and endogenous anticoagulants (Fig. 2a, 2b-C, 2c-E, 2c-G).

3.7. miRNAs affecting hypoxia/hypoxemia

Some miRNAs such as miR-138, miR-199a, miR-18a/b, miR-640, miR-424, etc. can negatively regulate the HIF-1α. However, miR-214, miR-135b, miR-675, etc. can induce its gene expression [212,230–232]. The HIF-2α is a direct target of miR-185, miR-223, miR-145, etc. [232–234] (Fig. 2c-G). Moreover, miR-23a, miR-146a, miR-126, miR-130b, miR-31, miR-17, miR-103a-3p, etc. can inhibit the CXCL12 expression [183,202,235–237] (Fig. 2c-G). The non-optimal circular expression levels of miR-18a, miR-223, miR-146a, miR-126-3p, miR-31, miR-17 (reduced), and miR-199a (elevated) have been reported in patients with the COVID-19 [170,171,175,176,195–199]. Furthermore, all of the miRNAs affecting the other pathways/events (*e.g.*, neutrophils and monocytes activities) (Fig. 2a) can also indirectly impact the hypoxia/hypoxemia.

4. miRNAs and interfering factors

Although miRNAs play crucial roles in controlling immunothrombosis process, clinical manifestations and paraclinical findings of patients with the critical COVID-19 indicate that the expressions and functions of these small RNAs have largely been disrupted [163,169–177]. Various studies have demonstrated that several agents such as SARS-CoV-2-induced interfering factors can affect the expression levels and efficient functions of miRNAs which have been discussed in another paper [5]. According to *in vitro* and *in vivo* studies, the upregulated expressions of miRNAs are not always followed by their higher efficiency [238,239]. Research evidence indicates that miRNAs regulate the expressions of their target molecules in a dose-dependent manner and display their best functions at optimal levels [240,241]. The literature review revealed that several genetic agents and uncontrolled immunothrombosis-induced interfering factors could affect the expressions and functions of these non-coding RNAs (Table 1) which will be discussed in the following.

4.1. miRNA-single nucleotide polymorphisms

In fact, miRNA-single nucleotide polymorphisms (miR-SNPs) are the most rampant genetic variations in the human genome affecting the processing and expression of miRNAs (Table 1). As exemplified, the minor T allele of miR-SNP rs2431697 (located 16 kb upstream of pre-miR-146a) causes the reduced gene expression/production of mature miR-146a leading to the high-levels generation of pro-inflammatory mediators. In this regard, the *in vitro* and *in vivo* observations have revealed that the activation of neutrophils with this SNP is accompanied by more NETs formation consistent with the high plasma levels of NE found in the T allele carriers. The CC genotype of miR-SNP rs2910164 (located in the stem region opposite to mature miR-146a sequence) and the A/G genotype of miR-SNP rs57095329 (located in the promoter region of the miR-146a gene) are the two other SNPs in the miR-146a gene that can decrease its expression. The existence of the A/T allele of miR-SNP rs767649 (located in the regulation region of the miR-155 gene) can underlie the elevated transcriptional activity of this gene [183,242–247] (Table 1). Moreover, the reduced expressions of miR-143 and miR-145 have respectively been reported in the carriers of CT/TT variant of miR-SNP rs353292 (located 673 bp upstream from the start site) and C/T variant of miR-SNP rs74693964 (located 65 bp downstream of the miR-145 genomic region) [248,249] (Table 1). Accordingly, the presence of the miR-SNPs in patients with the critical COVID-19 can be followed by the disrupted functions of these miRNAs (Table 1). The correlation between miR-SNPs and the incidence of various diseases (*e.g.*, autoimmune disorders and cancers) has been proven. For instance, the downregulation of miR-146a, correlated with

Table 1
Some genetic agents and uncontrolled immunothrombosis-induced interfering factors effective on miRNAs functions/expressions that could be beneficial for the treatment of critical COVID-19.

Interfering factor	Effect	Ref	Expected results
miR-SNPs			
rs2431697 T allele	Expression reduction of miR-146a	[183,246]	Increased expression of Mac-1, TLR2, TLR4, IL-8, CD40L, and CXCL12, Upregulated activity of NADPH oxidases and excessive production of ROS, Enhanced activation of neutrophils, monocytes, and PLTs, Activation, dysfunction, and pyroptosis of ECs, Increased NETosis, Severe inflammation and coagulation, Uncontrolled immunothrombosis
rs2910164 CC genotype		[243]	
rs57095329 A/G genotype		[244]	
rs767649 A/T allele	Expression elevation of miR-155	[245,247]	Excessive production of ROS, IL-8, and PAD4, Reduced expression of CFH, Activation, dysfunction, and pyroptosis of ECs, Increased activation of neutrophils and monocytes, Higher complement activation, Enhanced NETosis, Severe inflammation and coagulation, Uncontrolled immunothrombosis
rs353292 CT/TT variant	Expression reduction of miR-143	[248]	Increased expression of TLR2 and PAI-1, Upregulated activation of neutrophils, monocytes, and PLTs, Reduced/inefficient fibrinolysis, Increased NETosis, Severe inflammation and coagulation, Uncontrolled immunothrombosis
rs74693964 C/T variant	Expression reduction of miR-145	[249]	Higher expression of TF, FXI, HIF-2α, C3, and PAI-1, Elevated complement activation, Increased neutrophils persistence and monocytes activation, Reduced/inefficient fibrinolysis, Upregulated NETosis, Severe inflammation and coagulation, Uncontrolled immunothrombosis
Complement system components			
Sublytic doses of MAC	Expression elevation of miR-328 and miR-616	[214]	Increased expression/deposition of C3, Inhibition of CD46 and CD59,

(*continued on next page*)

Table 1 (*continued*)

Interfering factor	Effect	Ref	Expected results
			Higher complement activation, Enhanced NETosis, Severe inflammation and coagulation, Uncontrolled immunothrombosis
C5a	Expression reduction of miR-193 and miR-133a	[250]	Increased production of Fg and Mac-1, Reduced u-PA and fibrinolysis regulation, Increased NETosis, Severe inflammation and coagulation, Uncontrolled immunothrombosis
	Excessive expression of miR-26b		Deviation from optimal expression level and inefficient function of this miRNA, based on the manifestations of the critical COVID-19, Reduced regulation of P-selectin, FVIII, and IFN-γ expressions, Activation, dysfunction, and pyroptosis of ECs, Increased NETosis, Severe inflammation and coagulation, Uncontrolled immunothrombosis
C3	Expression reduction of miR-145	[216]	Higher expression of TF, FXI, HIF-2α, C3, and PAI-1, Enhanced complement activation, Increased neutrophils persistence and monocytes activation, Reduced/inefficient fibrinolysis, Elevated NETosis, Severe inflammation and coagulation, Uncontrolled immunothrombosis
NADPH oxidases and ROS			
————	Expression reduction of miR-29a/b, miR-29c-3p, miR-24–2, miR-145, miR-128, miR-let-7, miR-199a, miR-125b, and miR-126a	[192,251,252,257,258]	Increased expression/ production of NADPH oxidases, ROS, Fg, VWF, TF, FIX, FX, FXI, HIF-1/2α, CXCL12, C3, PAI-1, IL-6, TLR4, TLR7, αIIbβ3, SNAP23, and P2Y12, Elevated neutrophils persistence and monocytes activation, Higher complement activation, Inefficient fibrinolysis, PLTs activation and degranulation, Activation, dysfunction, and pyroptosis of ECs, Increased NETosis, Severe inflammation and coagulation,

Table 1 (*continued*)

Interfering factor	Effect	Ref	Expected results
			Uncontrolled immunothrombosis
————	Expression elevation of miR-21, miR-146a, miR-9, and miR-143	[251,253–256,259]	Deviation from optimal expression levels and inefficient functions of these miRNAs, based on the manifestations of the critical COVID-19, Reduced regulation of Mac-1, TLR2, TLR4, IL-8, CD40L, CXCL12, and PAI-1 expressions, Upregulated activity of NADPH oxidases and excessive production of ROS, Decreased expression of CFH, Elevated activation of neutrophils, monocytes, and PLTs, Activation, dysfunction, and pyroptosis of ECs, Higher complement activation, Reduced/inefficient fibrinolysis, Increased NETosis, Severe inflammation and coagulation, Uncontrolled immunothrombosis
PAD enzymes and histone citrullination			
————	Reduced expression of miR-let-7c-2, miR-29c, and miR-16	[260,261]	Upregulated expression of IL-6, TLR4, TLR7, SNAP23, and Fg, Enhanced activity of NADPH oxidases and excessive production of ROS, PLTs activation and degranulation, Activation, dysfunction, and pyroptosis of ECs, Increased neutrophils and monocytes activation, Increased NETosis, Severe inflammation and coagulation, Uncontrolled immunothrombosis
Hypoxia/hypoxemia			
————	Expression elevation of miR-155, miR-21, miR-103, and miR-146a	[262,264–266]	Deviation from optimal expression levels and inefficient functions of these miRNAs, based on the manifestations of the critical COVID-19, Upregulated activity of NADPH oxidases and excessive production of ROS, IL-8, and PAD4, Reduced expression of CFH, Decreased regulation of VWF, TF, CXCL12, Mac-1, TLR2, TLR4,

(*continued on next page*)

Table 1 (*continued*)

Interfering factor	Effect	Ref	Expected results
			IL-8, and CD40L expressions, Higher complement activation, Enhanced activation of neutrophils, monocytes, and PLTs, Activation, dysfunction, and pyroptosis of ECs, Increased NETosis, Severe inflammation and coagulation, Uncontrolled immunothrombosis
————	Expression reduction of miR-150, miR-25, miR-15a, miR-205, and miR-34a	[267–271]	Elevated activity of NADPH oxidases and excessive production of ROS, αIIbβ3, IL-6R, and FVIII, Enhanced activation of neutrophils, monocytes, and PLTs, Activation, dysfunction, and pyroptosis of ECs, Higher complement activation, Increased NETosis, Severe inflammation and coagulation, Uncontrolled immunothrombosis
CXCL12	Inefficient function of miR-31	[237]	Increased expression of αIIbβ3 and CXCL12, Enhanced activation of neutrophils, monocytes, and PLTs, Upregulated NETosis, Severe inflammation and coagulation, Uncontrolled immunothrombosis
Coagulation and fibrinolysis mediators			
Fibrin	Expression reduction of miR-146a	[272]	Increased expression of Mac-1, TLR2, TLR4, IL-8, CD40L, and CXCL12, Upregulated activity of NADPH oxidases and excessive production of ROS, Enhanced activation of neutrophils, monocytes, and PLTs, Activation, dysfunction, and pyroptosis of ECs, Increased NETosis, Severe inflammation and coagulation, Uncontrolled immunothrombosis
PDGF-BB	Expression reduction of miR-145	[273]	Higher expression of TF, FXI, HIF-2α, C3, and PAI-1, Elevated complement activation, Increased neutrophils persistence and monocytes activation, Reduced/inefficient fibrinolysis, Upregulated NETosis,
aPC	Expression reduction of miR-199a, miR-29b, and miR-211	[275]	Severe inflammation and coagulation, Uncontrolled immunothrombosis Elevated expression of HIF-1α, Fg, and HIF-1α-induced CXCL12 Increased neutrophils persistence, Upregulated complement activation, Increased NETosis, Severe inflammation and coagulation, Uncontrolled immunothrombosis
t-PA	Expression reduction of miR-15a	[276]	Elevated expression of αIIbβ3, Enhanced activation of neutrophils, monocytes, and PLTs, Increased NETosis, Severe inflammation and coagulation, Uncontrolled immunothrombosis
	Inefficient function of miR-146a	[272]	Increased expression of Mac-1, TLR2, TLR4, IL-8, CD40L, and CXCL12, Upregulated activity of NADPH oxidases and excessive production of ROS, Enhanced activation of neutrophils, monocytes, and PLTs, Activation, dysfunction, and pyroptosis of ECs, Increased NETosis, Severe inflammation and coagulation, Uncontrolled immunothrombosis

Abbreviations: αIIbβ3, Integrin αIIbβ3; aPC, Activated protein C; C, Complement component; CD40L, Cluster of differentiation 40 ligand; CFH, Complement factor H; CXCL12, C-X-C motif chemokine ligand 12; ECs, Endothelial cells; Fg, Fibrinogen; FVIII, Factor VIII; FIX, Factor IX; FX, Factor X; FXI, Factor XI; HIF, Hypoxia-inducible factor; IFN-γ, Interferon gamma; IL, Interleukin; IL-6R, IL-6 receptor; Mac-1, Macrophage-1 antigen; MAC, Membrane attack complex; miRNAs, MicroRNAs; miR-SNPs, MicroRNA-single nucleotide polymorphisms; NADPH oxidase, Nicotinamide adenine dinucleotide phosphate oxidase; NET, Neutrophil extracellular trap; PAD, Protein arginine deiminase; PAI-1, Plasminogen Activator Inhibitor-1; PDGF-BB, Platelet-derived growth factor-BB; PLTs, Platelets; ROS, Reactive oxygen species; SNAP23, Synaptosomal-associated protein 23; TF, Tissue factor; TLR, Toll-like receptor; t-PA, Tissue plasminogen activator; u-PA, Urokinase plasminogen activator; VWF, Von Willebrand factor.

T allele of miR-SNP rs2431697, has been observed in patients with SLE, whereas higher expressions of miR-155 have been reported in patients with hepatocellular carcinoma (HCC) carrying the risk allele of miR-SNP rs767649. This can increase the risk of uncontrolled immunothrombosis in the COVID-19 patients with these comorbidities [246,247].

4.2. Complement system components

According to the research evidence, sublytic (non-lytic) doses of

MAC can affect the expression of miRNAs (Table 1). Although incomplete MAC complexes do not cause cell lysis, they activate many cellular inflammatory responses (*e.g.*, NF-κB pathway) and affect the production of pro-inflammatory cytokines, adhesion molecules, and miRNAs. Accordingly, the prompt increased expressions of miR-328 and miR-616 have been reported following the cell stimulation with sublytic doses of MAC that can have specific effects on the expression of their target molecules and consequently different cellular processes [214] (Table 1). It has also been observed that C5a can change the expression of several miRNAs in the ECs. For instance, it significantly reduces the expression of miR-193 and miR-133a and underlies the increased expression of miR-26b [250] (Table 1). The C3-mediated downregulation of miR-145 has also been found [216] (Table 1).

4.3. NADPH oxidases and ROS

The reduced expressions of miR-29b, miR-24–2, miR-145, and miR-128, as well as the elevated expression of miR-21 have been observed under the influence of NADPH oxidases and ROS (Table 1). In fact, ROS can change the expression of these small regulatory RNAs in different ways such as affecting the enzymes involved in the miRNAs biogenesis, activities of transcription factors, and epigenetic modifications. Consistently, the ROS-induced enhanced activation of the NF-κB has been reported to result in the high-level production of miR-21, miR-146a, miR-9, and miR-143 in addition to the low-level expression of miR-let-7 (Table 1). Moreover, ROS reduce the generation of miR-199a and miR-125b through the induction of their genes hypermethylation [191,251–259] (Table 1). Liu *et al.* reported that the NADPH oxidase 4 inhibitor provoked the expression of miR-29a and miR-29c-3p, and that the inhibition of NADPH oxidase 2 was followed by the induction of miR-126a expression [192] (Table 1).

4.4. PAD enzymes and histone citrullination

The PAD enzymes (*e.g.*, PAD4 playing a key role in the NETosis) affect the chromatin organization and genes expression (*e.g.*, miRNAs genes) by converting the arginine residues into the citrulline ones. According to the literature review, the expressions of miR-let-7c-2, miR-29c, and miR-16 are suppressed by the histone citrullination (Table 1), and the inhibition of PAD enzymes is accompanied by their expression restoration [260,261].

4.5. Hypoxia/hypoxemia

Research evidence has shown that hypoxia/hypoxemia can affect the gene expression of molecules involved in the miRNAs biogenesis (*e.g.*, Dicer) and also the ones participating in their functions (*e.g.*, *EIF2C4* encoding the AGO4). Accordingly, the upregulated expressions of miR-155, miR-21, miR-103, and miR-146a, as well as the reduced expressions of miR-150, miR-25, miR-15a, miR-205, and miR-34a were reported under the hypoxic condition *in vitro* and *in vivo* [231,232,262–271] (Table 1). The miR-146a elevation was hypoxia level-dependent. The higher expression of CXCL12, induced by HIF-1α, was accompanied by the disrupted function of miR-31 [237] (Table 1).

4.6. Coagulation and fibrinolysis mediators

According to the research evidence, fibrin reduced the production of mature miR-146a in the ECs, and platelet-derived growth factor-BB (PDGF-BB), whose primary source was alpha-granules of the activated PLTs, suppressed the expression of miR-145 [272–274] (Table 1). Moreover, aPC had some reducing effects on the expression of miR-199a, miR-29b, and miR-211. The high levels of t-PA decreased the miR-15a expression levels and also caused the inefficient function of miR-146a [272,275,276] (Table 1).

5. Conclusion and therapeutic perspective

Representing the close interactions between the immune and coagulation systems, uncontrolled immunothrombosis/thromboinflammation is a life-threatening event leading to the administration of anticoagulant medicines in patients with the critical COVID-19. However, the efficiency of these medications is still open to dispute. Inadequate responses and also adverse effects such as the higher risks of severe hemorrhagic complications have been reported in some cases possibly resulting from the excessive hyperinflammation and disrupted functions of PLTs or coagulation factors [1–3,88,277–282]. Moreover, preclinical and clinical studies respectively on relevant mouse models and patients with the critical COVID-19 reported the aggregated NETs-mediated vascular occlusion which is not resolved merely by anticoagulants [14,53,283]. In addition, NETs can trap the clots and impose some antifibrinolytic effects [284]. DNase and Ruxolitinib (a Janus kinase inhibitor) have respectively been utilized for the destruction of NETs and suppression of their formation [2,283,285]. However, they can remove the beneficial effects of NETs (*e.g.*, provocation of the IFNs-I release). Moreover, a high level of human cathelicidin LL-37, which is produced by neutrophils and can stabilize the NETs against DNase, has been observed in the lung tissue and also in an embedded form inside the NETs of the COVID-19 patients and has led to the inefficiency of DNase [286,287]. Cellular heparan sulfate (HS) has also been proposed as a co-receptor for the SARS-CoV-2/ACE2 interaction. Thus, exogenous heparin can affect viral attachment and infection [3,288]. Heparin may also not work efficiently or even cause resistance in patients suffering from the critical COVID-19 with a low level of free AT and functional defects of ECs [87,281]. Hence, the efficiency of anticoagulant medicines is yet to be completely confirmed in the critical COVID-19, and alternative therapeutic strategies are needed. As discussed earlier, miRNAs act as the fine-tuners of gene expression but not suppressors. Due to the extensive roles of these small RNAs in different cellular pathways, their optimal expression levels or efficient functions may underpin the homeostasis of the immune and coagulation systems rescuing the patients with the critical COVID-19. Above all, some of them (*e.g.*, miR-146a and miR-155) regulate the expressions of several key molecules involved in uncontrolled immunothrombosis accentuating their roles in the regulation of this process (Fig. 2a-2c). However, multiple factors may disrupt their normal expressions and functions (Table 1). The adoption of some therapeutic strategies for resolving the interferer factors may pave the way for the optimal expression and efficient functions of miRNAs leading to the reduction of complications incidence and mortality in patients with the critical COVID-19. In this regard, clustered regularly interspaced short palindromic repeats (CRISPR)-based therapeutic approaches (*e.g.*, CRISPR-associated protein 9 (Cas9)) can be beneficial. These are promising methods for a permanent modification of the genome. Most importantly, the novel designed web tool called SNP-CRISPR has improved the systematic study of the SNP variants and can be used for the elimination of negative effects of miR-SNPs on the expressions/functions of miRNAs [289]. Since the majority of these interfering agents result from the hyperinflammatory and hyperoxidant states, the utilization of anti-inflammatory and anti-oxidant drugs can be greatly advantageous in restraining uncontrolled immunothrombosis/thromboinflammation [3,5]. Various studies have proven the brilliant anti-inflammatory and anti-oxidant effects of a wide spectrum of medications in the COVID-19 [290–293]. In this regard, Al-kuraishy *et al.* reported that Metformin, with anti-oxidant properties, played a considerable role alleviating the severity of the COVID-19 and its complications (*e.g.*, acute lung injury (ALI) and acute IS (AIS)) through the modulation of inflammatory reactions in patients with the type II diabetes mellitus (T2DM) comorbidity [291]. The sequential combination therapy with Colchicine and Doxycycline has also been followed by the restriction of inflammation and remission of the patients with the critical COVID-19 [292]. Another study has demonstrated that the administration of Allopurinol in patients with the critical COVID-19 can lead to

a significant reduction of inflammatory factors and oxidative stress index [293]. The application of AMY-101 and Narsoplimab (C3 and MASP-2 inhibitors, respectively) has also been accompanied by attenuation of inflammation [294,295]. Not only do these medications control the hyperinflammatory/hyperoxidant states but they may also recover the efficient functions and optimal expressions of miRNAs resulting in the limitation of uncontrolled immunothrombosis/thromboinflammation. Some other groups of drugs such as anti-heart failure ones, anti-histamines, leukotriene receptor antagonists (LTRAs), the phosphodiesterase (PDE) inhibitors, etc., with confirmed anti-inflammatory and anti-oxidant roles, can also be administrated for the amelioration of miRNAs performances [17,18,296–301]. Produced in the body, some alarming agents can also be helpful. For instance, Neopterin plays a protective role against the ECs dysfunction and reduces the inflammatory pathways. The development of its agonists can be of great importance in retrieving the efficiency of the miRNAs [302]. The estrogen therapy, especially in women during the postmenopausal period, can also be prescribed due to its eminent anti-inflammatory roles [303]. Furthermore, as miRNAs display their best functions in the optimal levels [240,241], their upregulated expressions are not always followed by their higher efficiency [238,239]. Moreover, each miRNA can neutralize the functions of the other ones by affecting some target molecules (*e.g.*, induction and inhibition of IL-8 by miR-155 and miR-146a, respectively). Therefore, the identification and application of the drugs affecting the miRNAs and bringing them to the optimal levels are more efficient than the administration of the ones merely affecting a special protein molecule [5,21,162]. The drugs β-D-mannuronic acid (M2000) and α-L-guluronic acid (G2013) are the two novel members of the non-steroidal anti-inflammatory drugs (NSAIDs) family whose anti-inflammatory and immunomodulatory properties have been proven in the cellular, animal, and human levels. Interestingly, they leave some regulatory effects on the expressions and functions of miRNAs (*e.g.*, miR-146a and miR-155) [238,239,304–319]. The modulation of the production and performance of these two miRNAs (and also the other miRNAs) may simultaneously alleviate the hyperinflammation and restrict the uncontrolled immunothrombosis/thromboinflammation. As the dysfunction of ECs is correlated with the activation of endothelial matrix metalloproteinase (MMP)-2 by MMP-9 (existing in NETs), the reduction of these MMPs by M2000 can be of great importance [62,320]. Moreover, M2000 and G2013 have anti-oxidant and angioprotective properties reinforcing their positive effects on the limitation of uncontrolled immunothrombosis [321–324]. In addition, the phase III clinical trial of drug G2013 (IRCT20080901001165N64) is being conducted on patients with moderate to severe symptoms of the COVID-19. The regulatory effects of Metformin, Colchicine, and Doxycycline on the expression levels of miRNAs have also been illustrated [325–327]. Moreover, the modulation of miRNAs content of EVs (*e.g.*, exosomal ones), released by the cells with the key roles in the uncontrolled immunothrombosis (*e.g.*, activated PLTs and ECs) through drug consumption or utilization of the non-immunogenic engineered exosomes, may limit the uncontrolled immunothrombosis/thromboinflammation in patients with the critical COVID-19 [162,328].

A few studies have meticulously evaluated the roles of miRNAs in the critical COVID-19, especially in the uncontrolled immunothrombosis. Moreover, most studies have assessed the expression levels of miRNAs in the circulation of the patients. Their tissue as well as cellular expression amounts and functions have remained poorly identified. However, this review cast light on the pivotal roles of these small RNAs in the processes involved in the uncontrolled immunothrombosis and can act as a beneficial clue to design and conduct the future preclinical and clinical studies. In addition, the interfering factors, affecting the miRNAs expression/function, should be analyzed further in preclinical and clinical studies.

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SSM-J and MA collected the data following the raising the issue. SSM-J and MA then designed the figures and wrote/edited the manuscript in equal parts.

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.

Data availability

No data was used for the research described in the article.

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