



REVIEW

# Overview of COVID-19 inflammatory pathogenesis from the therapeutic perspective

Choongho Lee<sup>1</sup> · Won Jun Choi<sup>1</sup>

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**Abstract** The novel beta coronavirus (SARS-CoV-2, designated as COVID-19) that is responsible for severe acute respiratory syndrome has devastated the global economy and health care system. Since COVID-19 changed the definition of “normal” in ordinary life around the world, the development of effective therapeutics and preventive measures is desperately needed to fight SARS-CoV-2 infection and restore normalcy. A clear understanding of COVID-19 pathogenesis is crucial in providing the scientific rationale necessary to develop anti-COVID19 drugs and vaccines. According to the most recently published literature, COVID-19 pathogenesis was postulated to occur in three sequential phases: pulmonary, proinflammatory, and prothrombic. Herein, virus-host interactions, potential pathogenic mechanisms, and clinical manifestations are described for each phase. Additionally, based on this pathogenesis model, various therapeutic strategies involving current clinical trials are presented with an explanation of their modes of action and example drugs. This review is a thorough, updated summary of COVID-19 pathogenesis and the therapeutic options available for this disease.

**Keywords** Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) · Coronavirus disease 2019 (COVID-19) · Renin-angiotensin system (RAS) · Angiotensin-converting enzyme 2 (ACE2) · ACE2 deficiency · Acute respiratory distress syndrome (ARDS) · Acute lung injury (ALI) · Cytokine storm · Thrombosis · Coagulopathy · Multi-organ failure (MOF)

## Introduction

Coronavirus disease 2019 (COVID-19) has emerged as a full-fledged global pandemic after starting as an isolated infection of an unknown nature in Wuhan, China (December 2019). A new beta coronavirus strain called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was determined to be the causative agent for this unprecedented infectious disease. The COVID-19 pandemic has devastated the lives of millions of people around the world. At the same time, its negative impacts on the global economy and health care system have been unfathomable and are still ongoing. To develop effective therapeutics and preventive measures against COVID-19, an accurate and precise understanding of its pathogenesis at the molecular level is in absolute need. Based on the most recently published literature, the overall COVID-19 pathogenesis process can be summarized as three clinically distinct and potentially overlapping phases. As shown in Fig. 1, its pathological progression can be classified in chronological order as pulmonary, proinflammatory, and prothrombic phases (Domingo et al. 2020).

In the pulmonary phase, SARS-CoV-2 infects host target cells and causes interstitial pneumonia and acute respiratory distress syndrome (ARDS) through angiotensin-converting enzyme 2 (ACE2) deficiency and a subsequent renin-angiotensin system (RAS) imbalance. In the pro-inflammatory phase, infected target cells and lymphocytes further respond to SARS-CoV-2 infection by overproducing proinflammatory cytokines, which results in acute lung injury (ALI) and cytokine storm via systemic inflammation. In the final prothrombic phase, widespread platelet aggregation and thrombosis give rise to coagulopathy and multi-organ failure (MOF) at the end stage of COVID19 patients. Based on this three-step pathogenesis model, various phase-specific

✉ Choongho Lee  
choongholee@dongguk.edu

<sup>1</sup> College of Pharmacy, Dongguk University, Goyang 10326, Republic of Korea

therapeutic strategies were classified with an emphasis on their mechanisms of action with corresponding examples.

## Pulmonary phase

### *ACE2 deficiency*

SARS-CoV-2 infects alveolar epithelial cells in both the upper and lower respiratory tracts. In general, alveolar epithelial cells are composed of type 1 and 2 pneumocytes. Type 1 pneumocytes, which describes 95% of all alveolar epithelial cells, are responsible for alveolar gas exchange. On the other hand, type 2 pneumocytes produce alveolar surfactants that reduce pulmonary surface tension. They also serve as stem cell populations that can differentiate into type 1 pneumocytes.

ACE2 is a type I integral membrane protein with an enzymatic activity of mono carboxypeptidase. Its amino acid sequence exhibits 46% homology with an angiotensin-converting enzyme (ACE) (Donoghue et al. 2000; Jiang et al. 2014). ACE2 cleaves the carboxyl-terminal amino acid phenylalanine from angiotensin II to produce the vasodilator angiotensin 1–7 (Donoghue et al. 2000). Since SARS-CoV-2 uses angiotensin-converting enzyme 2 (ACE2) as the main receptor for host entry (Dhochak et al. 2020), type 2 pneumocytes are regarded as the primary target of SARS-CoV-2 infection due to their overexpression of ACE 2 (Barkauskas et al. 2013; Rico-Mesa et al. 2020). More specifically, the interaction between the receptor-binding domain of the viral spike protein with ACE2 initiates the host entry process (Fig. 2a). Once engaged with ACE2, the ACE2-bound viral spike protein undergoes proteolytic cleavage, which is catalyzed by a host membrane-anchored protein called the receptor transmembrane protease serine 2 (TMPRSS2) (Glowacka et al. 2011). This host protease-assisted digestion induces a conformational change in the spike protein that is necessary for host and virus membrane fusion. After this spike-mediated fusion process, the internalized virus particle releases its RNA genome and begins replication. The co-internalized ACE2 receptor either undergoes intracellular degradation or recycles back to the plasma membrane. As a result, the continuous infection of host target cells by SARS-CoV-2 facilitates ACE2 downregulation and ultimately leads to chronic ACE2 deficiency (Fig. 2a) (Vaduganathan et al. 2020).

### *RAS imbalance*

RAS is one of the most well-known physiological systems responsible for controlling cardiovascular dynamics through blood pressure modulation. To precisely modify this system, angiotensinogen is first converted into angiotensin I by an enzyme called renin, which is produced in the kidneys

(Fig. 2b). This newly generated angiotensin I is further processed into angiotensin II by an extracellular angiotensin-converting enzyme (ACE). ACE is metalloproteinase distinct from the previously described SARS-CoV-2 receptor, ACE2. Angiotensin II binds to the G-protein coupled receptor (GPCR) angiotensin II type 1 receptor (AT1R) to initiate its various physiological functions as shown in Fig. 2b. Generally, activation of AT1R by angiotensin II causes several physiologically important events to occur including vasoconstriction, inflammation, fibrosis, thrombosis, and reactive oxygen species (ROS) production. On the other hand, angiotensin II is further degraded into angiotensin 1–7 by the enzymatic action of ACE2 (Fig. 2b). Angiotensin 1–7 binds to another GPCR called MasR and induces physiological events that are essentially opposite to those induced by AT1R activation. They include vasodilation, anti-inflammation, anti-fibrosis, anti-thrombosis, and ROS neutralization. In essence, ACE2 plays a key role as a negative regulator in the overall RAS pathway. Therefore, ACE2 exerts protective functions in various RAS-based pathogenesis models involving acute and chronic inflammation (Banu et al. 2020). ACE2 also limits macrophages from expressing several proinflammatory cytokines. They include tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and interleukin-6 (IL-6), which are critical inflammatory components of COVID-19 pathogenesis, and they will be discussed later (Patel et al. 2016).

SARS-CoV-2-induced ACE2 downregulation and its subsequent deficiency continuously block the conversion of angiotensin II into angiotensin 1–7. As a result, excessive angiotensin II is constantly available for AT1R hyperactivation. This model is further supported by a loss of pulmonary ACE2 function associated with acute lung injury (ALI) and heart failure in other RAS-based disease models (Kuba et al. 2005, 2006; Imai et al. 2005, 2008). Moreover, angiotensin 1–7 also exhibits anti-inflammatory activities in the vascular system by decreasing levels of pro-inflammatory proteins such as vascular cell adhesion molecule 1 (VCAM-1), IL-6, and chemokine (C-C motif) ligand 2 (CCL2) (Zhang et al. 2015). Thus, SARS-CoV-2-induced ACE2 deficiency can also antagonize the anti-inflammatory properties of angiotensin 1–7. In support of this hypothesis, SARS-CoV-2-infected patients showed a significant increase in angiotensin II plasma levels. These enhanced angiotensin II plasma levels were inversely correlated with viral load (Liu et al. 2020c). As a result, ACE2 deficiency and a consequent RAS imbalance are considered one of the most clinically relevant molecular mechanisms responsible for the overall progression of COVID-19 pathogenesis (Henry et al. 2020).

Since pre-existing chronic inflammatory conditions such as hypertension, diabetes, obesity, cancer, cardiovascular disease, and autoimmune disease also activate the RAS pathway, COVID-19 patients exhibit a significant association between ACE2 deficiency and clinical severity of these

comorbidities (Verdecchia et al. 2020; Tseng et al. 2020). The reduced expression of ACE2 with age also has clinical implications for the poor prognosis of elderly COVID-19 patients. Since the ACE2 gene is located on the X chromosome, it has been hypothesized that a higher male mortality rate in COVID-19 patients may be linked to lower expression levels of the ACE2 gene in male patients. Therefore, restoring the SARS-CoV-2-induced RAS imbalance has been suggested as an ideal clinical approach to slow the early progression of COVID-19 pathogenesis.

#### *Aggravation of ACE2 deficiency*

In addition to the primary ACE2 deficiency elicited by SARS-CoV-2 infection, two other mechanistically plausible ways to enhance the SARS-CoV-2-induced RAS imbalance exist. ADAM metallopeptidase domain 17 (ADAM-17) is a TNF- $\alpha$ -converting enzyme. It activates TNF- $\alpha$  by cleaving its extracellular domain, which converts it from its inactive membrane-bound form into its active, soluble form (Fig. 2c). Since AT1R stimulation by angiotensin II indirectly induces ADAM-17 activation, ADAM-17 overactivation may be an aggravating factor in COVID-19 pathogenesis (Patel et al. 2014; Aleksova et al. 2020). ADAM-17 overactivation by angiotensin II caused by virus-induced ACE2 deficiency leads to TNF- $\alpha$  overproduction. Since TNF- $\alpha$  is a primary cytokine implicated in the pathogenesis of many chronic inflammatory diseases, it may further exacerbate inflammatory conditions of COVID-19 patients by enhancing macrophage mobilization and vascular membrane permeability (Haga et al. 2008; Glowacka et al. 2010). Furthermore, ADAM-17 can also inactivate ACE2 by digesting its extracellular domain (Aleksova et al. 2020) (Fig. 2c). Following this digestion, truncated ACE2 is released into the extracellular space, further promoting ACE2 deficiency and increasing inflammation in COVID-19 patients (Black et al. 1997; Moss et al. 1997; Gheblawi et al. 2020).

ADAM-17 also seems to play a direct role in coronavirus entry; its enzymatic activity is stimulated when SARS-CoV-2 binds to the ACE2 receptor. This enhanced proteolytic activity of ADAM-17 seems to facilitate viral entry (Haga et al. 2008). In addition to TNF- $\alpha$  activation, ADAM-17 also liberates several other membrane-bound cytokine precursors including IL-4 and interferon  $\gamma$  (IFN- $\gamma$ ) (Wang et al. 2020c). This could exert more detrimental effects on the proinflammatory reactions that are already upregulated by SARS-CoV-2 infection.

Des-arginine(9)-bradykinin (des-Arg9-BK) overproduction is another potential aggravating factor in COVID-19 pathogenesis. Des-Arg9-BK is a potent kinin-kallikrein system metabolite that increases vascular permeability. Thus, it promotes angioedema by acting on the type B1 BK receptor. This type of B1 BK receptor is, in turn, upregulated by other

inflammatory cytokines (Vickers et al. 2002). Since ACE2 is the main enzyme responsible for des-Arg9-BK's metabolic degradation (Fig. 2c) (Turner et al. 2004), SARS-CoV-2-induced ACE2 deficiency can cause increased des-Arg9-BK accumulation. This can further result in BK-B1 receptor-mediated signaling pathway overactivation (Fig. 2c). Pathologically, this could lead to increased angioedema, blood coagulation, and complementary pathway stimulation, all of which can further aggravate the proinflammation conditions induced by SARS-CoV-2 infection (Mahmudpour et al. 2020).

#### **Proinflammatory phase**

##### *Activation of innate immunity*

Pathogen-associated molecular patterns (PAMPs) recognition by host pattern recognition receptors (PRRs) is the first step in innate immune system activation against viral infection. These innate immune receptors include retinoic acid-inducible gene I (RIG-I)-like receptors, nucleotide-binding oligomerization domain (NOD)-like receptors, melanoma differentiation-associated gene 5 (MDA5), and Toll-like receptors (TLRs) (Fig. 3a). For RNA virus recognition, they directly recognize RNA virus-specific motifs such as 5'-triphosphate and double-stranded RNAs as PAMPs (Kowalinski et al. 2011; Nikonov et al. 2013). This virus-derived PAMP recognition by innate immune receptors activates a series of signaling cascades that ultimately lead to the activation of transcription factors such as nuclear factor-kappa B (NF- $\kappa$ B) and interferon regulatory factors (IRFs) (Fig. 3a). Their transcriptional activation of immune-related target genes leads to the production of type I and III IFNs and various proinflammatory cytokines and chemokines. Once secreted from cells, they exert diverse immunological effects on uninfected neighboring cells by binding to their corresponding cell surface receptors.

Endogenous self-antigens called damage-associated molecular patterns (DAMPs) also play an important role in innate immune system activation. Pyroptosis is a highly inflammatory form of programmed cell death that is commonly induced by cytopathic viruses (Fink and Cookson 2005). This unique process generates proinflammatory molecules with DAMPs. In general, DAMPs are recognized by immune receptors as endogenous danger signals induced by pathogenic microbes. This recognition also leads to the activation of NF- $\kappa$ B and IRF signaling pathways, which further drives the innate immune system to induce unscheduled cell death following microbial invasion (Fig. 3a) (Tang et al. 2012; Liu et al. 2017). In particular, NLR family pyrin domain containing 3 (NLRP3) protein (a NOD-like receptor) forms the inflammasome complex upon DAMP recognition. This DAMP recognition activates

enzymatically inactive pro-caspase 1 into its enzymatically active form. Activated caspase 1 converts IL-1 $\beta$  and IL-18 inflammatory cytokine precursors into active ones. In vitro studies have demonstrated that a SARS-CoV-1 infection can induce DAMPs-initiated intracellular stress pathways, resulting in NLRP3-dependent inflammasome activation and macrophage pyroptosis (Shi et al. 2019; Chen et al. 2019; Soy et al. 2020).

It has been hypothesized that strong recognition of SARS-CoV-2 RNA elements by various innate receptors and subsequent target gene transcriptional activation causes IFN, cytokine, and chemokine overproduction (Fig. 3a). In this regard, a diverse array of cytokines are induced by SARS-CoV-2 infection (Coperchini et al. 2020; Gao et al. 2020; Mahmudpour et al. 2020; Picchianti Diamanti et al. 2020; Ragab et al. 2020; Soy et al. 2020; Wang et al. 2020a; Ye et al. 2020). They include IL-1 $\beta$ , -2, -4, -6, -7, -8, -10, -12, -17, -18, -21, -22, and -33; tumor growth factor-beta (TGF- $\beta$ ); IFN- $\alpha$ , - $\beta$ , and - $\gamma$ ; granulocyte colony-stimulating factor (G-CSF); granulocyte-macrophage colony-stimulating factor (GM-CSF); macrophage inflammatory protein 1 alpha (MIP-1 $\alpha$ ) and beta (MIP-1 $\beta$ ); matrix metalloproteinase-1 (MMP-1) and MMP-3; TNF- $\alpha$ ; and C-reactive protein (CRP) (Scala and Pacelli 2020). A number of chemokines are also induced by SARS-CoV-2 infection (Chen and Subbarao 2007; Channappanavar and Perlman 2017; Coperchini et al. 2020; Li et al. 2020). They include chemokine (C-C motif) ligand 2 (CCL2; also known as monocyte chemoattractant protein 1, MCP1), CCL3 and 5, C-X-C motif chemokine ligand 8 (CXCL-8; also known as interferon gamma-induced protein 10, IP-10), and CXCL-9 and 10 (Chen and Subbarao 2007; Scala and Pacelli 2020). Alveolar macrophages, lung epithelial cells, and dendritic cells have been suggested as the major cell types that produce these proinflammatory cytokines and chemokines. However, an unusual lack of IFN response to SARS-CoV-2 infection was also noticed in SARS-CoV-2-infected cells in vitro (Chen and Subbarao 2007). In line with this, IFN can only be detected after SARS-CoV reached a high titer in coronavirus patients. Based on these observations, it has been postulated that SARS-CoV may delay or evade the innate immune response through early antagonism of the IFN response (Yoshikawa et al. 2010; Channappanavar et al. 2016; Channappanavar and Perlman 2017). Several studies are underway to elucidate the potential molecular mechanisms SARS-CoV-2 employs to suppress IFN activation.

### Lymphopenia

Lymphopenia is defined as a dramatic reduction in overall immune cell numbers circulating in the blood. COVID-19 patients exhibit general lymphopenia in dendritic cells,

macrophages, and T-cells (Sallenave and Guillot 2020). SARS-CoV-2 infection also reduces circulating NK cell numbers and causes an exhausted phenotype in NK cells (Market et al. 2020). The increased expression of NKG2A, programmed cell death protein 1 (PD-1), and T cell membrane protein 3 (TIM-3) further indicate viral-induced T cell and NK cell exhaustion after SARS-CoV-2 infection (Paces et al. 2020). The virus's ability to kill lymphocytes could contribute to the observed lymphopenia in coronavirus patients (Gu et al. 2005). Although lymphopenia, leukopenia, and thrombocytopenia are laboratory parameters that are consistently associated with COVID-19 (Dhama et al. 2020), a subset of other immune cells such as neutrophils, monocytes, and macrophages are significantly upregulated by SARS-CoV-2 infection (An et al. 2020; Huang et al. 2020; Liu et al. 2020c; Yang et al. 2020).

In general, monocytes are innate immune cells that participate in inflammatory responses, phagocytosis, antigen presentation, and a variety of other immune processes (Jakubzick et al. 2017). Circulating monocytes extravasate into peripheral tissues to differentiate into macrophages or dendritic cells during inflammation. (Jakubzick et al. 2017). Thus, monocyte function upregulation by SARS-CoV-2 infection may contribute to the strengthening of various proinflammatory processes that are mediated by activated monocytes.

Like monocytes, neutrophils are also recruited to the site of infection via circulation and the permeabilization of endothelial membranes adjacent to the infection site (Fig. 3a). However, due to COVID-19-induced lymphopenia, COVID-19 patients are more vulnerable to a microbial superinfection. As a result, an excessive number of neutrophils will infiltrate toward virus-infected cells owing to chemokine overproduction.

It has been hypothesized that the inability to eradicate SARS-CoV-2 infection due to its antagonism of the innate immune response hyperinflates the innate immune system (Yoshikawa et al. 2010; Kaplan and Radic 2012; Birra et al. 2020). Subsequently, this causes an excessive inflammatory cytokine release to compensate for the exhausted immune system due to SARS-CoV-2-induced lymphopenia (Fathi and Rezaei 2020). Regarding pulmonary pathogenesis, cytokine overproduction after SARS-CoV-2 infection will increase the membrane permeability of the capillary walls around the infected alveoli, resulting in pulmonary edema, dyspnea, and hypoxemia (Fig. 3b) (Imai et al. 2005; Meftahi et al. 2020). Introduction of plasma fluid into the alveoli and the loss of elasticity due to reduced surfactant production by infection of type 2 pneumocytes by SARS-CoV-2 cause ARDS and ALI in COVID-19 patients (Verdecchia et al. 2020).



### *Cytokine storm*

“Cytokine storm” was coined to describe cytokine overproduction observed during graft-versus-host disease (Ferrara et al. 1993; Clark 2007). Excessive amounts of cytokines are released into the blood, resulting in systemic inflammatory reactions. This leads to vasodilation and decreased blood pressure due to plasma loss in the entire cardiovascular system, and it is ultimately followed by an entire circulatory collapse (Allegra et al. 2020a; Coperchini et al. 2020; Ragab et al. 2020; Tufan et al. 2020). In general, proinflammatory cytokines increase the expression of cell adhesion molecules on the surface of neutrophils and endothelial cells. This promotes intercellular interactions between neutrophils and endothelial cells. Also, increasing lung endothelium permeability and reducing barrier protection attracts more neutrophils to the infection site through endothelial penetration (Fig. 3b) (Polidoro et al. 2020). This inflammatory immune response dysregulation prevents adaptive immune response activation (Manjili et al. 2020). As a consequence, these SARS-CoV-2-induced immune abnormalities can cause increased microbial infections, septic shock, and severe multiple organ dysfunction (Fig. 3c) (Yang et al. 2020).

COVID-19-induced cytokine storm resembles hemophagocytic lymphohistiocytosis (HLH; also known as macrophage activation syndrome, MAS), which has been reported in patients infected with SARS-CoV (Nicholls et al. 2003). HLH is a hyperinflammatory syndrome involving fever, cytopenias, and MOF caused by uncontrolled immune activation and excessive cytokine production (La Rosee et al. 2019). The primary HLH hallmark is the overproduction of proinflammatory cytokines such as TNF- $\alpha$ , IFN- $\gamma$ , IL-1, IL-2, and IL-6, which are released from activated macrophages and lymphocytes after several viral infections (Ramachandran et al. 2017). Regarding SARS-CoV-2 infection, cytokine overproduction and subsequent cytokine storm induce several extrapulmonary complications (Fig. 3c). They include myocardial injury, myocarditis, acute kidney injury, impaired ion transport, acute liver injury, and gastrointestinal manifestations such as diarrhea and vomiting (Gupta et al. 2020). In particular, elevated cardiac troponin levels, which are cardiac injury biomarkers, are the most commonly reported cardiac abnormality in COVID-19 patients (Bansal 2020; Imazio et al. 2020; Tomasoni et al. 2020). Myocardial injuries such as arrhythmias, acute coronary syndrome (Akhmerov and Marban 2020), heart failure, and myocardial infarction are also frequently observed in COVID-19 patients (Bandyopadhyay et al. 2020). Therefore, the cytokine storm induced by SARS-CoV-2 infection can be regarded as a self-elicited and suicidal systemic immunological reaction that can adversely affect every key organ in the body (Lippi et al. 2020). These data show the systemic detrimental effects of SARS-CoV-2 infection on the

vital functions of major organs through hyper-inflammation, and following cytokine storm, they are accountable for the relatively high mortality rate of COVID-19 patients (Gupta et al. 2020).

### **Prothrombic phase**

#### *Activation of thrombosis*

Coagulation is a natural defense mechanism that seals off damaged blood vessels and prevents local pathogens from spreading further into the systemic circulation. However, dysregulated coagulation (thrombosis) can cause pathologically detrimental effects by obstructing blood flow, which can lead to coagulation disorders with dangerous clinical consequences. In a typical blood clotting cascade, factor X is enzymatically activated by cleavage of coagulation factors from intrinsic and extrinsic pathways and tissue factor (TF)-driven platelet activation. Activated factor X converts prothrombin into thrombin. The newly generated thrombin, in turn, converts fibrinogen into fibrin. Activated fibrin initiates the self cross-linking process together with red blood cells that ultimately generates a gel-like fibrin mesh (Fig. 4).

D-dimer derives from the degradation products of this cross-linked fibrin. Therefore, the levels of D-dimer reflect both thrombin production and activation of fibrinolysis (Miesbach 2020). Interestingly, elevated D-dimer levels, prolonged prothrombin time, and low platelet count are consistently reported in COVID-19 patients (Bikdeli et al. 2020a; Zhang et al. 2020a; Zhou et al. 2020; Miesbach and Makris 2020; Salamanna et al. 2020). Also, venous thrombotic events such as pulmonary embolism are common in COVID-19 patients (Pons et al. 2020). In particular, elevated levels of D-dimer ( $> 1 \mu\text{g/L}$ ) are strongly associated with COVID-19 patient in-hospital death (Tang et al. 2020). Fibrin deposition in air spaces and lung parenchyma were also frequently found in coronavirus-induced ARDS patients (Whyte et al. 2020).

Regarding their pathogenic mechanisms, increased platelet aggregation and upregulation of coagulation-inducing factors such as the Von Willebrand factor (vWF), factor VIII, and plasminogen activator inhibitor-1 (PAI-1) are suggested to be causative factors of coagulopathy caused by SARS-CoV-2 infection (Magro 2020; Miesbach and Makris 2020; Tang et al. 2020). In particular, the induction of PAI-1 by SARS-CoV-2 infection seems to be a significant event in the pathogenesis of COVID-19 because PAI-1 can inhibit urokinase-type plasminogen activator (uPA) and tissue plasminogen activator (tPA) (Ekholm et al. 2009; Whyte et al. 2020). Since both uPA and tPA are essential for plasmin activation, plasmin-mediated fibrinolysis is suppressed by PAI-1 induction during SARS-CoV-2 infection.

Furthermore, there seem to be several additional factors that contribute to thrombosis during SARS-CoV-2 infection. Neutrophil extracellular traps (NETs) are extracellular fiber networks primarily composed of neutrophil DNA that bind to and kill extracellular pathogens while minimizing damage to host cells (Kaplan and Radic 2012). SARS-CoV-2 infection induces NET overproduction. This increased NET production by SARS-CoV-2 may facilitate thrombus formation (Kaplan and Radic 2012; Allegra et al. 2020b; Cicco et al. 2020) (Fig. 4). Since monocytes and macrophages also produce TF, monocyte, and macrophage upregulation by SARS-CoV-2 infection can also promote TF-initiated coagulation. In addition, a proinflammatory cytokine, TNF- $\alpha$ , also activates TF. In particular, IL-6 pathway activation by SARS-CoV-2 infection can induce vascular endothelial growth factor (VEGF), fibrinogen, and factor VII (Bikdeli et al. 2020b; Whyte et al. 2020). Angiotensin II also stimulates TF expression in damaged cells, increases thrombin formation, and impairs fibrinolysis (Celi et al. 2010; Miesbach 2020). As explained previously, a virus-induced chronic ACE2 deficiency results in the overactivation of AT1R receptor through the prolonged stabilization of angiotensin II. Since the increased thrombosis was one of the physiologically relevant events that were triggered by the continuous activation of the angiotensin II signaling pathway (Fig. 2b), ACE2 deficiency can further aggravate the prothrombotic state, which is already stimulated by proinflammatory conditions induced by SARS-CoV-2 infection.

## Therapeutic modulation

Based on the previously explained three-step pathogenesis model, various phase-specific therapeutic strategies can be pursued to intervene in COVID-19 progression. In line with the previously proposed three-step model for COVID-19 pathogenesis, a number of therapeutic approaches against COVID-19 that are currently in clinical trials will be classified and explained with an emphasis on their mechanisms of action along with typical examples (Table 1).

### Pulmonary phase

Pulmonary phase-specific therapeutics include RAS inhibitors, entry inhibitors, replication inhibitors, and protease inhibitors. RAS inhibitors are further divided into ACE inhibitors and angiotensin II receptor blockers (ARBs). They alleviate the RAS overactivation caused by ACE2 deficiency after SARS-CoV-2 infection. Entry inhibitors, replication inhibitors, and protease inhibitors exert direct antiviral activities by targeting specific steps of the viral life cycle.

### RAS inhibitors

RAS inhibitors such as ACE inhibitors and angiotensin II receptor blockers (ARBs) are frequently prescribed hypertensive drugs. Their use as a COVID-19 therapeutic has raised safety concerns because RAS inhibitors increase ACE2 expression in hypertensive patients (Vaduganathan et al. 2020; Aleksova et al. 2020). In theory, ACE2 upregulation caused by RAS inhibition could lead to more efficient SARS-CoV-2 entry, which makes RAS inhibitor users more vulnerable to chronic SARS-CoV-2 infection (Aleksova et al. 2020; Wang et al. 2020b). Despite these concerns, most clinical experts advise against the abrupt withdrawal of RAS inhibitors in high-risk patients, including those who have heart failure or have had a myocardial infarction because this may result in clinical instability and adverse health outcomes (Rico-Mesa et al. 2020). Until more data are available, they advised that RAS inhibitors should be continued in patients in otherwise stable conditions who are at risk for COVID-19 (Vaduganathan et al. 2020).

In general, RAS inhibitors may be beneficial to COVID-19 patients because they downregulate RAS pathways, which are overactivated by SARS-CoV-2 infection, as previously explained. Also, ACE inhibitors suppressed TMPRSS2 expression, which is an essential co-receptor for SARS-CoV-2 cell entry (Luo et al. 2020). This could help reduce new SARS-CoV-2 infections by disrupting the enzymatic digestion of the spike protein by TMPRSS2, which is necessary for membrane fusion. ACE2-mediated signaling stimulation via ACE2 gene delivery along with treatment with angiotensin 1–7 and MasR agonists was suggested as another therapeutic approach to counteract hyperactivated RAS signaling caused by ACE2 deficiency after SARS-CoV-2 infection (Verdecchia et al. 2020; Gheblawi et al. 2020).

### Entry inhibitors

Considering that ACE2 plays a central role in SARS-CoV-2 entry, SARS-CoV-2 neutralization via recombinant ACE2 protein administration has been proposed as a therapeutic modality (Crackower et al. 2002). Preliminary data suggest that the surface molecule CD147 may be an alternative pathway for the virus to enter the host cells since the spike protein of SARS-CoV-2 can bind to CD147 (Gubernatorova et al. 2020). Based on these data, the efficacy of humanized antibodies against CD147 such as meplazumab is being tested in clinical trials as a COVID-19 treatment (Drozdal et al. 2020). Also, the beneficial effects of the macrolide antibiotic azithromycin in reducing the viral load of hospitalized patients were associated with its ability to interfere with ligand/CD147 receptor interactions (Ulrich and Pillat 2020). In addition to its direct antiviral activity,

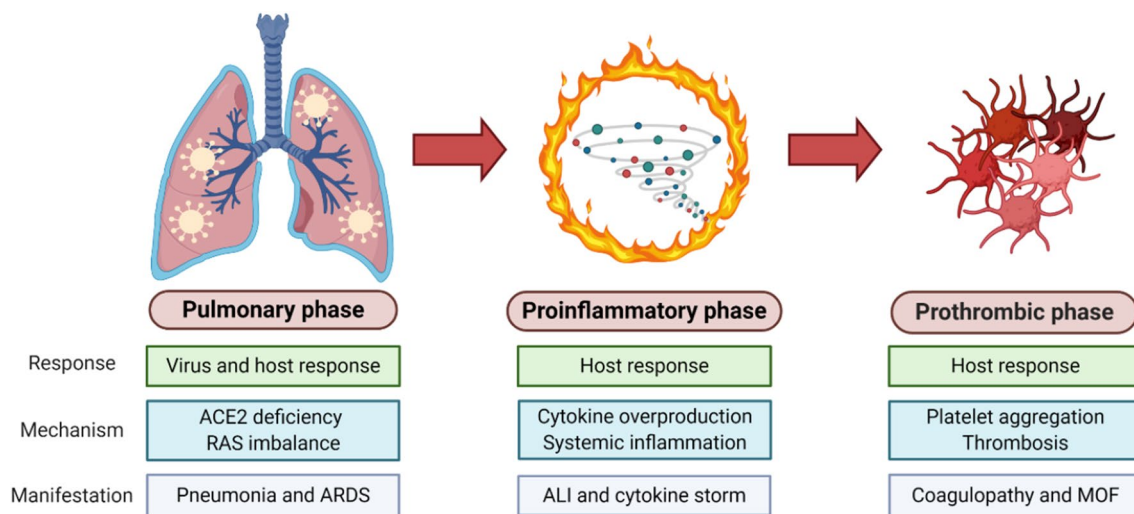
**Table 1** COVID-19 therapeutics are classified based on the pathogenesis stage

Pathogenesis stage	Class	Type	Mechanism	Example
Pulmonary phase	RAS inhibitors	ACE inhibitors	ACE inhibition	Captopril, enalapril, lisinopril, and ramipril
		Angiotensin II receptor blockers (ARBs)	Angiotensin II receptor inhibition	Azilsartan, candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, and valsartan
		ACE2 enhancers	ACE2 signaling stimulation	Gene delivery of ACE2, angiotensin 1–7, and MasR agonists
	Entry inhibitors	ACE2 blockers	ACE2 Inhibition	Recombinant ACE2 protein
		Co-receptor inhibitors	CD147 disruption	Azithromycin and meplazumab
	Replication inhibitors	RDRP inhibitors	RNA-dependent RNA polymerase (RDRP) inhibition	Remdesivir, favipiravir, and ribavirin
Proinflammatory phase	Protease inhibitors	Host protease inhibitors	TMPRSS2 protease inhibition	Nafamostat and camostat mesylate
		Virus protease inhibitors	Viral protease inhibition	Lopinavir/ritonavir
	General anti-inflammatory drugs	Corticosteroids	Inflammation inhibition	Dexamethasone, ciclesonide, budesonide, and prednisone
		NSAIDs	Prostaglandin synthesis inhibition	Naproxen
		Cytokine inhibitors	IL-6 inhibitors	IL-6 inhibition
	IL-1 $\beta$ inhibitors		IL-1 $\beta$ inhibition	Canakinumab and anakinra
	GM-CSF inhibitors		GM-CSF inhibition	Mavrilimumab (GM-CSF-R) and Gimsilumab (GM-CSF)
	IFN- $\gamma$ inhibitors		IFN- $\gamma$ inhibition	Emapalumab
	JAK-STAT signaling inhibitors	TNF- $\alpha$ inhibitors	TNF- $\alpha$ inhibition	Infliximab, adalimumab, golimumab, certolizumab, and etanercept
		VEGF inhibitors	VEGF inhibition	Bevacizumab and ranibizumab
JAK inhibitors		Janus kinase inhibition	Baricitinib, ruxolitinib, and tofacitinib	
Complement pathway inhibitors		C5 inhibitors	C5 Inhibition	Eculizumab
Immuno-modulatory drugs		Sphingosine-1 phosphate receptor regulator	T cell trafficking immunomodulation	Fingolimod (FTY720)
		Antimalaria drugs	Virus uncoating inhibition immunomodulatory activity	Chloroquine and hydroxychloroquine
Cell-based therapy		Mesenchymal stem cells	Innate immune cell restoration	N/A
Convalescent plasma therapy	Neutralizing antibody	Spike protein neutralization and entry inhibition	N/A	

**Table 1** (continued)

Pathogenesis stage	Class	Type	Mechanism	Example
Prothrombic phase	Vitamin K antagonists	Vitamin K epoxide reductase inhibitors	Vitamin K epoxide reductase inhibition	Warfarin
	Antiplatelets	ADP receptor antagonists	ADP receptor inhibition	Aspirin, ticagrelor, prasugrel, clopidogrel, and dipyridamole
	Anti-Xa agents	Heparin	Antithrombin activation	Unfractionated heparin (UFH) and molecular-weight heparin (LMHW)
		Direct thrombin inhibitors	Thrombin inhibition	Danaparoid, fondaparinux, bivalirudin, dabigatran, argatroban, apixaban, and rivaroxaban

Subtypes, potential mechanisms, and example drugs are listed for each therapeutic



**Fig. 1** COVID-19 pathogenesis model. The three phases of COVID-19 pathogenesis: pulmonary, proinflammatory, and prothrombic. Response patterns, pathogenic mechanisms, and clinical manifestations for each phase are described

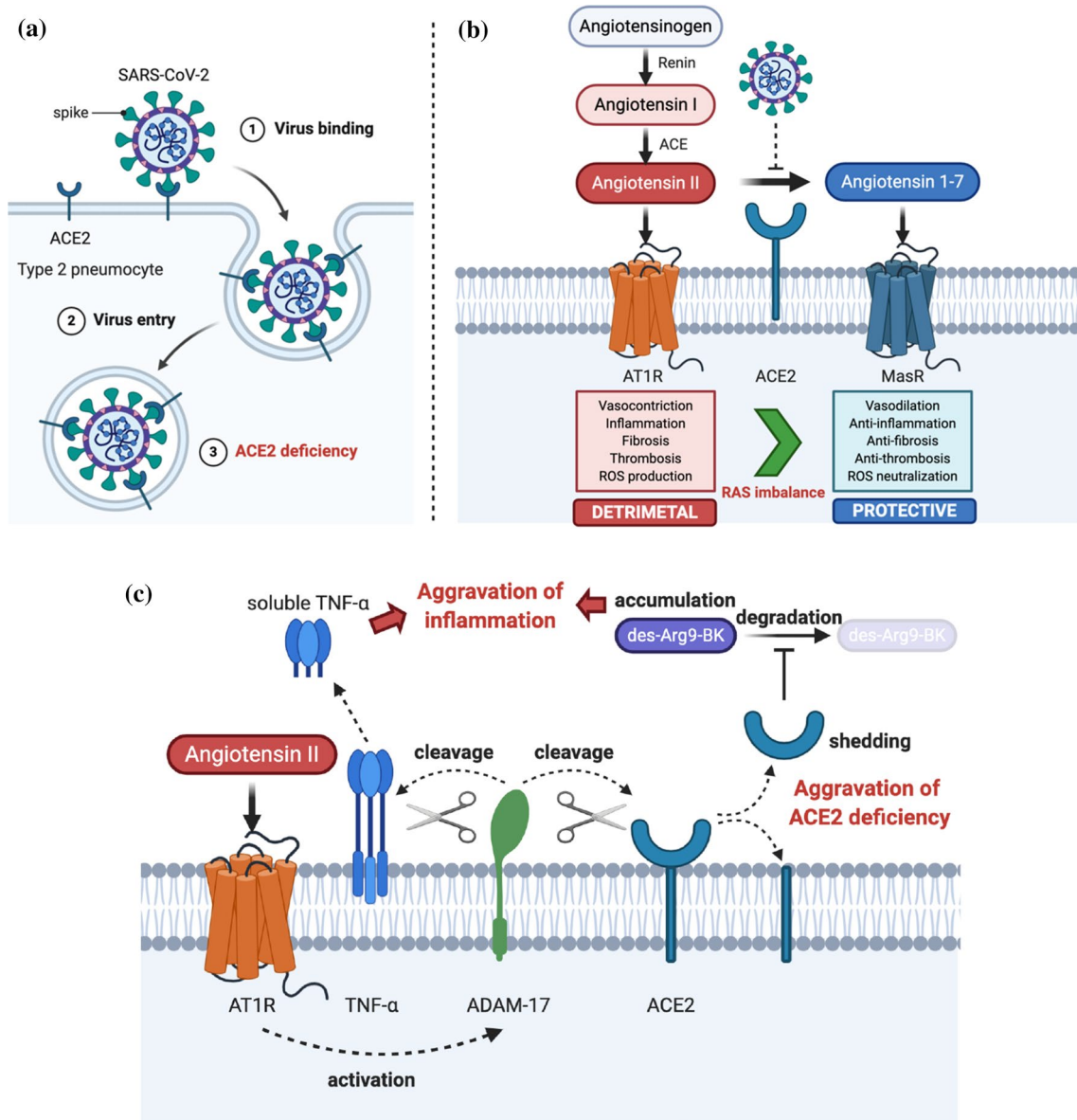
azithromycin can also influence immune parameters such as increasing antiviral interferon expression in both healthy and virus-infected cells and exerting antiviral and anti-inflammatory actions (Schijns and Lavelle 2020). These potential dual mechanisms might qualify azithromycin as a promising therapeutic candidate to be tested in the future.

#### *Replication and protease inhibitors*

Replication inhibitors suppress viral RNA genome replication by antagonizing the enzymatic activity of SARS-CoV-2 RNA-dependent RNA polymerase (RDRP). For this reason, they are called RDRP inhibitors. They include remdesivir, favipiravir, and ribavirin. Remdesivir and favipiravir were originally developed to treat the Ebola virus and influenza virus, respectively (Reina and Reina

2017; Tchesnokov et al. 2019; Shiraki and Daikoku 2020; Pardo et al. 2020). Structurally, they are nucleotide analogs that hinder the functions of endogenous nucleotides as building blocks during viral RNA synthesis. Due to their potent antiviral activity toward SARS-CoV-2, they were repurposed as a SARS-CoV-2 treatment (Cao et al. 2020; Singh et al. 2020; Pardo et al. 2020; Azevedo et al. 2020; Hashemian et al. 2020; Frediansyah et al. 2020). Remdesivir was the first drug clinically approved for the treatment of COVID-19 patients. Host protease inhibitors such as nafamostat and camostat mesylate inhibit the host TMPRSS-2 protease, which is essential for SARS-CoV-2 entry into target cells (Asakura and Ogawa 2020; Hoffmann et al. 2020; Doi et al. 2020; Hifumi et al. 2020). Therefore, these host protease inhibitors likely block virus entry. Lopinavir/ritonavir belongs to another class





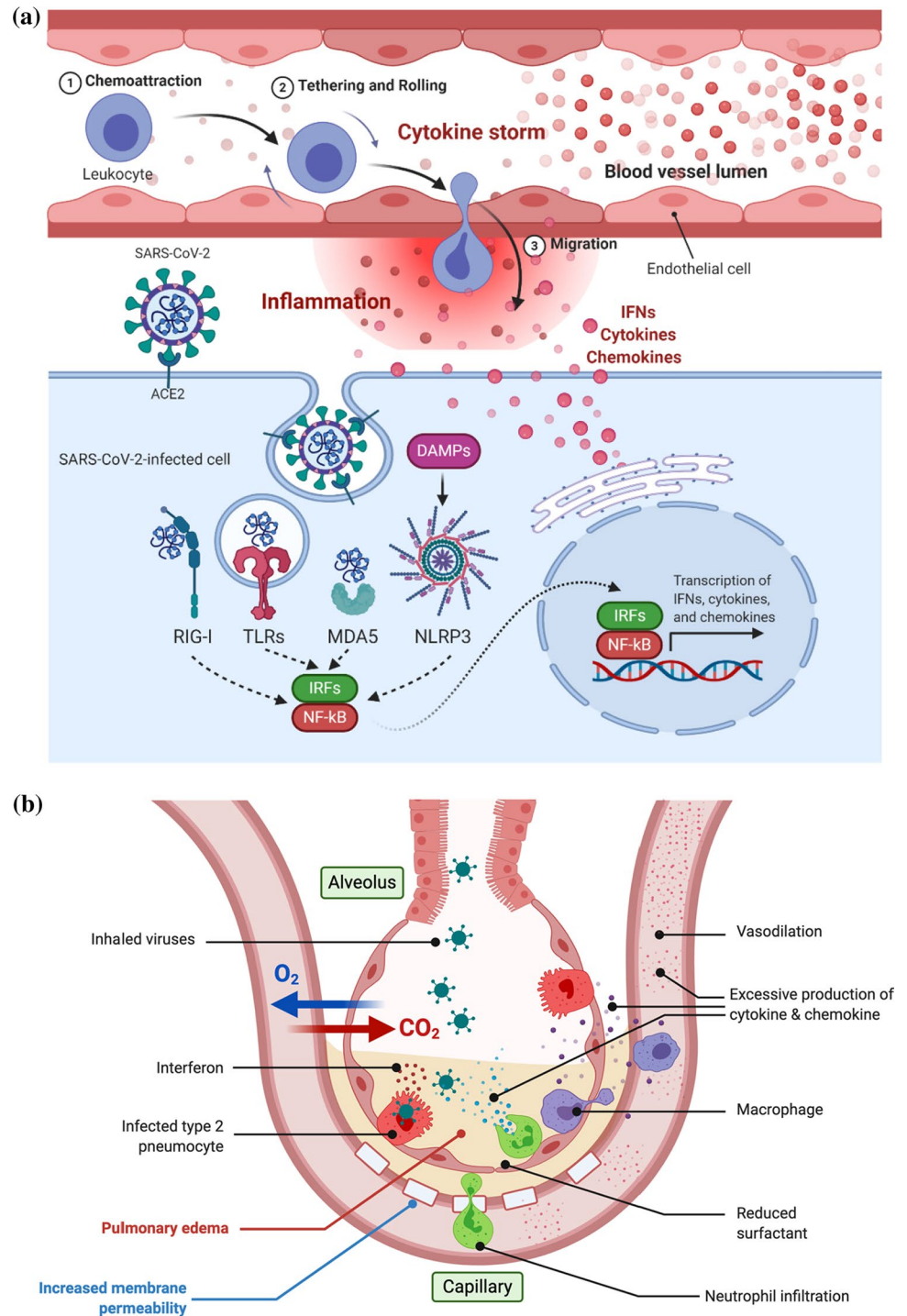
**Fig. 2** Pulmonary phase of COVID-19 pathogenesis. **a** SARS-CoV-2 enters the type 2 pneumocyte via the host receptor, ACE2. Target cell infection by SARS-CoV-2 induces ACE2 internalization, resulting in ACE2 downregulation and deficiency. **b** SARS-CoV-2-induced ACE2 deficiency decreases the conversion of angiotensin II to angiotensin 1–7 and increases angiotensin II availability. Excessive angiotensin II causes AT1R overactivation, resulting in a RAS imbalance. **c** ADAM-17 activation by AT1R promotes cleavage of both membrane-anchored TNF- $\alpha$  and ACE2. ADAM-17 truncates the ACE2 extracellular domain, which enzymatically inactivates ACE2. As a result, des-Arg9-BK degradation by ACE2 is disrupted and its abundance increases. Liberated soluble TNF- $\alpha$  and accumulated des-Arg9-BK aggravate SARS-CoV-2-induced inflammation

of virus protease inhibitors. Although it was originally developed as an anti-HIV drug, it was also repurposed due to its inhibitory activity against the coronavirus protease (Stower 2020; Doggrell 2020; Osborne et al. 2020). It should be noted that ritonavir is a pharmacokinetic booster that prevents lopinavir degradation by host cytochrome enzymes.

### Proinflammatory phase

Proinflammatory phase-specific therapeutics include general inflammatory drugs, cytokine inhibitors, JAK-STAT signaling inhibitors, complement pathway inhibitors, immunomodulatory drugs, cell-based therapy, and convalescent plasma therapy. General inflammatory drugs

**Fig. 3** Pro-inflammatory phase of COVID-19 pathogenesis. **a** After target cell entry, innate receptors such as RIG-I, TLRs, and MDA5 recognize SARS-CoV-2 RNA motifs. The NLRP3 inflammasome recognizes DAMPs, which are generated by SARS-CoV-2 infection. This virus-receptor recognition activates transcription factors such as IRFs and NF- $\kappa$ B, activating the transcription of target genes such as IFNs, cytokines, and chemokines. The secretion of these proteins induces endothelial activation by increasing blood vessel permeability. This allows leukocytes to infiltrate the site of infection. **b** SARS-CoV-2 infection of type 2 pneumocytes leads to cytokine overproduction. This increases the membrane permeability of the capillary walls around the infected alveoli, resulting in pulmonary edema. Due to this pulmonary edema, proper gas exchange is impaired in COVID-19 patients. This is clinically manifested by dyspnea, hypoxemia, and ARDS. **c** Cytokine overproduction and cytokine storm induce clinically relevant extrapulmonary effects on various key organs such as the heart, kidney, liver, and intestines

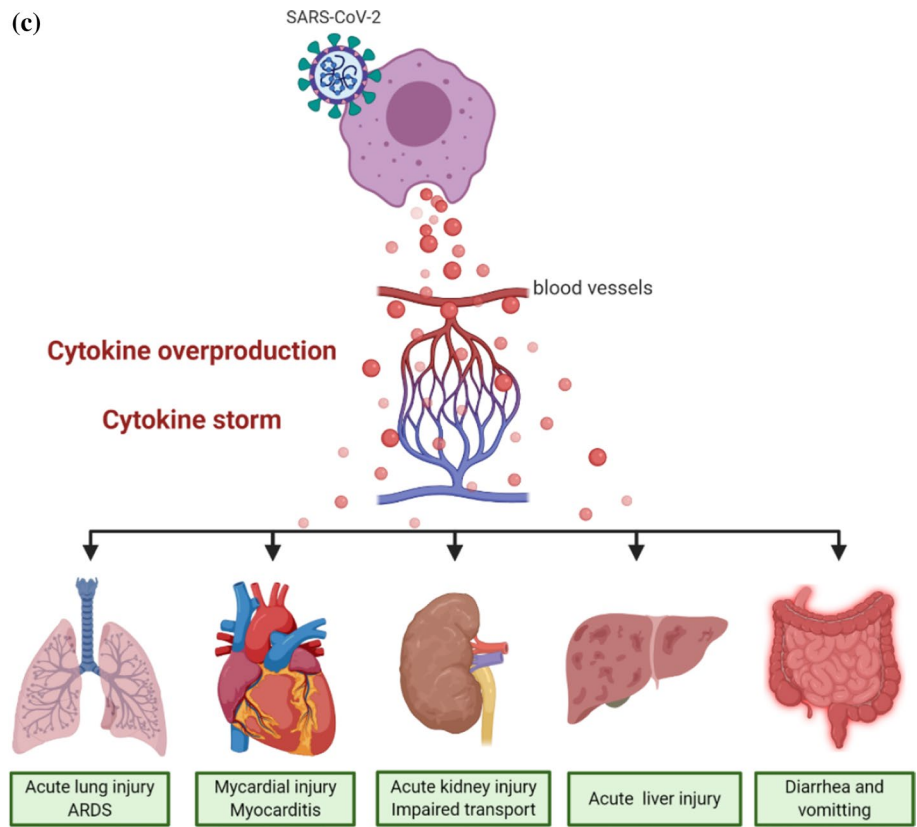


are further divided into corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs). Cytokine inhibitors target cytokines induced by SARS-CoV-2 infection. They include IL-6, IL-1 $\beta$ , GM-CSF, IFN- $\gamma$ , TNF- $\alpha$ , and VEGF.

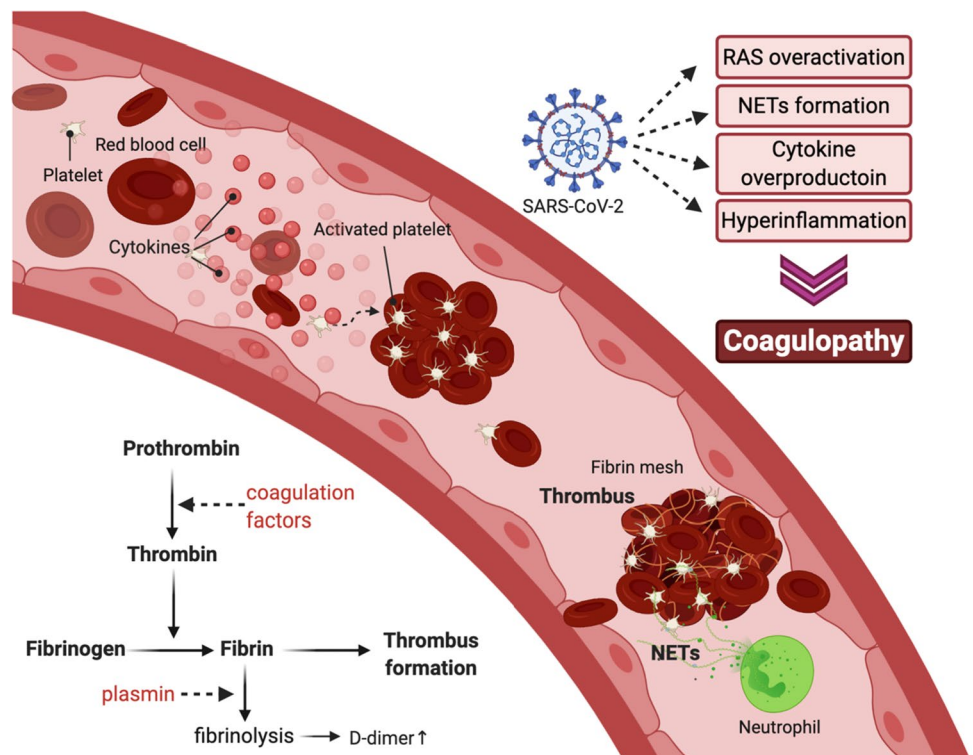
#### General anti-inflammatory drugs

Corticosteroids are a class of steroid hormones with anti-inflammatory and immunosuppressive activities. They are

Fig. 3 (continued)



**Fig. 4** Prothrombic phase of COVID-19 pathogenesis. SARS-CoV-2 infection induces RAS overactivation, NETs formation, cytokine overproduction, and hyperinflammation. These effects translate into increased risk for coagulation disorders



naturally produced in the adrenal cortex of vertebrates. Synthetic analogs include dexamethasone, ciclesonide, budesonide, and prednisone. They exert anti-inflammatory effects by blocking inflammatory mediator actions and inducing anti-inflammatory mediators. Their direct action on T-lymphocytes and subsequent suppression of delayed hypersensitivity reactions seem to be related to their immunosuppressive effects.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are frequently used to manage the early clinical symptoms of SARS-CoV-2 infection. The clinical efficacy of several corticosteroids and NSAIDs to slow down the progression of the pro-inflammatory phase of COVID-19 pathogenesis is being tested in numerous clinical trials worldwide (Hosseini-Khannazer et al. 2020; Saghazadeh and Rezaei 2020; Zhang et al. 2020b; Ye et al. 2020).

### *Cytokine inhibitors*

IL-6 is regarded as one of the most critical factors in the pro-inflammatory progression of COVID-19 pathogenesis. IL-6 was also recommended as a cytokine storm early indicator in COVID-19 patients (An et al. 2020). Therefore, antibody-based IL-6 inhibitors such as tocilizumab, sarilumab, and siltuximab were tested as pharmacological agents to reduce IL-6-mediated COVID-19 (Franco et al. 2020; Paniri and Akhavan-Niaki 2020; Gubernatorova et al. 2020; Liu et al. 2020a). Mechanistically, tocilizumab and sarilumab bind to IL-6 receptors, and siltuximab binds to IL-6, itself. As explained previously, IL-1 $\beta$ , GM-CSF, IFN- $\gamma$ , TNF- $\alpha$ , and VEGF also play critical roles in COVID-19 pathogenesis by stimulating various immune responses. Therefore, IL-1 $\beta$  inhibitors such as canakinumab and anakinra (van de Veerdonk and Netea 2020, Alijotas-Reig et al. 2020); GM-CSF inhibitors such as mavrilimumab (Lang et al. 2020; Gremese et al. 2020); IFN- $\gamma$  inhibitors such as emapalumab (Magro 2020); TNF- $\alpha$  inhibitors such as infliximab, adalimumab, golimumab, certolizumab, and etanercept (Soy et al. 2020); and VEGF inhibitors such as bevacizumab and ranibizumab (Polidoro et al. 2020) were suggested as potential COVID-19 drugs.

JAK inhibitors such as baricitinib, ruxolitinib, and tofacitinib are frequently used to treat cancers induced by JAK-STAT pathway overactivation. The JAK-STAT pathway is critical in delivering IFN, cytokine, and chemokine signals to target cells. Therefore, its inhibition by JAK inhibitors is effective against the COVID-19 proinflammatory stage pathogenesis progression induced by IFN, cytokine, and chemokine overproduction (Colafrancesco et al. 2020; Alijotas-Reig et al. 2020; Zhang et al. 2020b; Luo et al. 2020).

A complementary pathway inhibitor such as C5-targeting eculizumab was also predicted to alleviate complementary activation by SARS-CoV-2 infection (Magro 2020). The use

of immunomodulatory drugs such as a sphingosine-1 phosphate receptor regulator like Fingolimod (FTY720) was also suggested for the treatment of COVID-19 (Barzegar et al. 2020; Foerch et al. 2020).

Classic antimalarial drugs such as chloroquine and hydroxychloroquine also exhibited anti-SARS-CoV-2 activity by two mechanistically distinct activities. Their immunomodulatory properties seem to reduce the secretion of important proinflammatory cytokines such as TNF- $\alpha$  and IL-6 by peripheral blood mononuclear cells (van den Borne et al. 1997). Their ability to halt the progression from early endosome to lysosome also seems to decrease the viral replication rate (Liu et al. 2020b).

Lastly, a cell-based therapy that uses mesenchymal stem cells with immunomodulatory properties and a convalescent plasma therapy are in clinical trials to test their efficacy in alleviating COVID-19 pathogenesis progression (Wang et al. 2016).

### **Prothrombic phase**

Prothrombic phase-specific therapeutics include vitamin K antagonists, antiplatelets, and anti-Xa agents. Mechanistically, vitamin K epoxide reductase, ADP receptor, and thrombin inhibition as well as antithrombin activation suppressed COVID-19-induced coagulopathy.

#### *Vitamin K antagonists*

Warfarin is commonly used as an oral anticoagulant to treat coagulation disorders such as deep vein thrombosis and pulmonary embolism. It is also used to prevent stroke in people with heart disease. Warfarin decreases blood clotting by blocking an enzyme called vitamin K epoxide reductase. This enzyme helps reactivate vitamin K1, upon which clotting factors such as II, VII, IX, and X depend.

#### *Antiplatelets*

Adenosine diphosphate (ADP) receptor inhibitors are antiplatelet agents. They include aspirin, ticagrelor, prasugrel, clopidogrel, and dipyridamole. They are used to prevent coagulation-initiated events such as thromboembolism, myocardial infarction, and stroke. These drugs inhibit ADP from binding to the P2Y<sub>12</sub> receptor on platelets, which inhibits platelet aggregation and thrombus formation.

#### *Anti-Xa agents*

In general, anti-Xa agents are classified into heparin-related products and direct thrombin inhibitors. Heparin is a naturally occurring polysaccharide. It can activate the enzyme inhibitor antithrombin III (AT) by inducing a conformational



change. The heparin-activated AT then inactivates thrombin, factor Xa, and other proteases that are necessary for blood clot formation (Mitchell 2020). Unfractionated heparin and low molecular-weight heparin are in clinical trials to test whether their anticoagulation effects delay COVID-19 prothrombic phase pathogenesis progression (Maldonado et al. 2020; Bikdeli et al. 2020b). Direct thrombin inhibitors are another class of anticoagulants that directly inhibit the enzyme thrombin. They include danaparoid, fondaparinux, bivalirudin, dabigatran, argatroban, apixaban, and rivaroxaban.

## Conclusion and perspective

As shown in the three-step COVID-19 pathogenesis model, SARS-CoV-2 infection produces a dynamic spectrum of clinical manifestations based on complicated host and viral responses. Therefore, COVID-19 pathogenesis stage-specific therapeutics should be selected to maximize patient recovery and survival. Early therapeutic approaches should target the virus-specific or host-virus interaction steps in the virus life cycle. Early approaches should also focus on restoring RAS balance by stimulating ACE2-mediated signaling. Therapeutic strategies targeting middle to late-stage pathogenesis should focus more on alleviating exaggerated host responses to the viral infection such as cytokine overproduction, systemic inflammation, dysregulated platelet aggregation, and coagulopathy. More basic research and clinical studies will be required to find ideal drug combinations with multiple mechanisms of action against stage-specific COVID-19 pathogenesis.

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## Compliance with ethical standards

**Conflict of interest** The authors declared no conflict of interest.

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