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Review

Fibrinolytic system and COVID-19: From an innovative view of epithelial ion transport

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ABSTRACT

Lifeways of worldwide people have changed dramatically amid the coronavirus disease 2019 (COVID-19) pandemic, and public health is at stake currently. In the early stage of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, fibrinolytic system is mostly inhibited, which is responsible for the development of hypofibrinolysis, promoting disseminated intravascular coagulation, hyaline membrane formation, and pulmonary edema. Whereas the common feature and risk factor at advanced stage is a large amount of fibrin degradation products, including D-dimer, the characteristic of hyperfibrinolysis. Plasmin can cleave both SARS-CoV-2 spike protein and γ subunit of epithelial sodium channel (ENaC), a critical element to edematous fluid clearance. In this review, we aim to sort out the role of fibrinolytic system in the pathogenesis of COVID-19, as well as provide the possible guidance in current treating methods. In addition, the abnormal regulation of ENaC in the occurrence of SARS-CoV-2 mediated hypofibrinolysis and hyperfibrinolysis are summarized, with the view of proposing an innovative view of epithelial ion transport in preventing the dysfunction of fibrinolytic system during the progress of COVID-19.

1. Introduction

Coronavirus disease 2019 (COVID-19) is caused by a novel β-coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that mainly acts on pulmonary endothelial and epithelial cells, triggering off viral pneumonia and acute respiratory distress syndrome (ARDS) [1–3]. The unique clinicopathological features of the latter are disseminated intravascular coagulation, venous thrombosis, and excess fibrin degradation products, which may be due to the abnormal fibrinolytic system, especially in severe and critical cases [4–6]. In the early stage or mild mild/moderate cases, virus facilitates the release of plasminogen activator inhibitor-1 (PAI-1) by binding to the angiotensin-converting enzyme 2 (ACE2) receptor, and the consequent low level of plasmin fails to cleave the fibrin sufficiently, so called hypofibrinolysis state [7]. A multicenter study in COVID-19 patients found that administration of nebulized freeze-dried plasminogen could restore lung fibrinolytic activity, and prevent disseminated intravascular coagulation developing into multiple organ failure [8]. However, at advanced stage or severe/critical cases, because of the presence of thromboembolism, elevated plasmin cleaves the excessive fibrin with increasing D-dimer, as an independent factor of COVID-19 severity and mortality [9,10].

The biopsies and autopsies reveal that diffuse alveolar damage with pulmonary edema exist in COVID-19 patients [11,12]. Epithelial sodium channel (ENaC) transports sodium ions to regulate fluid absorption, and thus a suitable target for the treatment of pulmonary edema [13]. Thus, a question is raised whether the disturbance of fibrinolytic system caused by SARS-CoV-2 infection is related with epithelial sodium channel (ENaC), which is in charge of edematous fluid clearance in the case of ARDS.

Molecular mimicry reveals SARS-CoV-2 may use the same protease that cleaves ENaC to enter human respiratory cells [14]. However, whether ENaC and spike protein are processed by identical host proteases is seldomly studied. As a core enzyme of fibrinolytic system, plasmin has been proved to cleave not only SARS-CoV-2 spike protein, but γ subunit of ENaC [9,15,16]. The occurrence of virus overwhelming

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can prevent proteolytic cleavage of ENaC, thus improving ENaC function by increasing proteolytic cleavage in pulmonary epithelium might be an appropriate strategy to treat respiratory distress with pulmonary edema formation in COVID-19 patients [17]. This review focuses on the analysis of hypofibrinolysis and hyperfibrinolysis during different stages of SARS-CoV-2 infection. Moreover, the potential relationship between fibrinolytic system and epithelial ion transport is summarized, aiming to clarify plasmin may be the identical host protease to affect ENaC-mediated SARS-CoV-2 entry, and provide a novel therapeutic schedule for the COVID-19 global pandemic.

2. Methodology

The present study reviews and filters articles concerning COVID-19 from 2020 to 2023, presented by a comprehensive document research related to fibrinolytic system and ENaC. Moreover, medical subject headings Medical Subject Headings (MeSH) controlled vocabulary were used for investigating in PubMed, Web of Science, and Elsevier ScienceDirect in order to obtain the most associated synonyms for the entered terms. Overall, 122 bibliographic references were cited in order to support and validate the information in this paper (Fig. 1).

3. Pathogensis of COVID-19

3.1. Clinical characteristics

At the end of December 2019, most initial hospitalized patients had a history of exposure to Huanan Seafood Wholesale Market in Wuhan, Hubei Province, China, where SARS-CoV-2 may be transmitted to humans through wild animals sold illegally [18–21]. It is reported that coronavirus isolated from bats and pangolins shares the high genome sequence identity with SARS-CoV-2, an enveloped, positive-sense, single-stranded RNA virus [22–24]. The respiratory tract is the major organ to be injured, and ciliated airway cells and type II alveolar cells are primary targets for SARS-CoV-2 infection [25,26]. As of February 2023, there have been over 750 million confirmed cases of COVID-19, including nearly 7 million deaths, reported by World Health Organization (https://www.who.int/emergencies/diseases/novel-coronavirus-2019).

Current evidence points that approximately 80% of COVID-19 patients develop to mild-to-moderate disease, 15% to severe stage requiring oxygen support, and the remaining 5% to critical disease [27]. During SARS-CoV-2 infection, the typical clinical symptoms are fever, dry cough, dyspnea, and up to ARDS, shock and cardiac failure [28]. The manifestations in mild and moderate cases are the typical ARDS, such as diffuse alveolar damage, pulmonary edema, and acute hypoxemic respiratory failure. When progressing to severe and critical illness, COVID-19-induced ARDS has atypical features, such as pulmonary thrombosis, thrombotic disseminated intravascular coagulation, and elevated D-dimer levels [2].

3.2. Mechanisms of SARS-CoV-2 entry

During the viral maturation process, the proprotein convertase furin in Golgi apparatus preactivates the spike protein, mediating the entry of the virus into cells [29–31]. Notably, SARS-CoV-2 is different from other β-coronaviruses, given that spike protein has a unique furin site (PRRAR|S), including the incorporation of 4 amino acid residues, P681, R682, R683, and A684, located at the boundary between the S1/S2 subunit and is indispensable to viral RNA replication/transmission [32,33]. With the emergence of various novel pathogens responsible for the COVID-19 pandemic, P681R mutation in Kappa and Delta variants, as well as P681H mutation in Omicron variant facilitates the cleavability with furin, productive membrane fusion, and a higher proportion of spike protein to bind to human ACE2 [34–37]. However, as the most heavily mutated one at present, Omicron variant only causes milder diseases, as a result of lower viral load for the mutations outside the spike protein [38,39]. In addition, during the maturation process, the extracellular host-cell proteases, including plasmin, cleave the spike protein into S1 and S2 subunits and become a prerequisite for the entry of virus into host cells [9,40]. Then the spike protein binds to human ACE2, while the dramatic conformational changes in the S1 and S2 subunits initiate membrane fusion of virus and host cells, allowing viral RNA to be released into the host cytoplasm and replication begins (Fig. 2) [41–43].

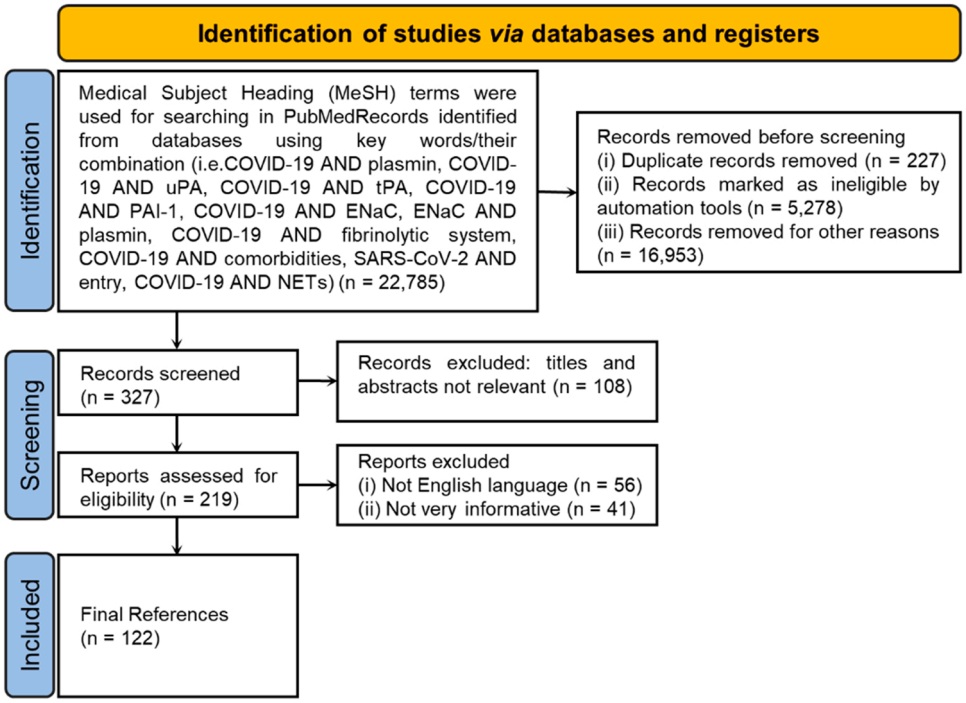

Fig. 1. The PRISMA flowchart for the selected studies.

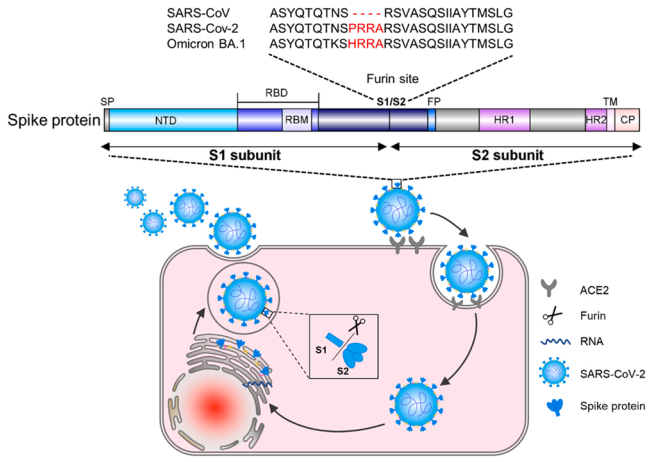

Fig. 2. Mechanisms of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) entry. The spike protein of SARS-CoV-2 binds to angiotensin-converting enzyme 2 (ACE2) and enters cells by endocytosis. Then viral RNA releases into the host cytoplasm and replication begins. Unlike other β-coronaviruses, given that spike protein of SARS-CoV-2 has a unique furin site (PRRAR|S), including the incorporation of 4 amino acid residues, P681, R682, R683, and A684, located at the boundary between the S1/S2 subunit. During the viral maturation process, the proprotein convertase furin in Golgi apparatus cleaves furin site, mediating the entry of the virus into next cells. ACE2: Angiotensin-Converting Enzyme 2, CP: C-terminal Endodomain, FP: Fusion Peptide, HR1: Hetad Repeat 1, HR2: Hetad Repeat 2, NTD: N-terminal Domain, RBD: Receptor Binding Domain, RBM: Receptor Binding Motif, SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2, SP: Signal Peptide, TM: Transmembrane Domain.

4. Involvement of fibrinolytic system in COVID-19

Plasmin is the proteolytically active form of plasminogen, which can cleave fibrin to degradation products, and is upregulated or downregulated by tissue plasminogen activator/urokinase plasminogen activator (tPA/uPA) or PAI-1, respectively [44–46]. Remarkable postmortem findings present that SARS-CoV-2 infection can give rise to diffuse alveolar damage and thromboembolism [47]. The disturbance of fibrinolytic system, including plasmin, contributes to thrombosis and causes of death in COVID-19 patients [48–50]. The reasons of thrombosis are inconsistent. Usually, thrombosis is formed during hypofibrinolysis state in COVID-19, and mainly associated with increased PAI-1 levels [51]. However, in the state of hyperfibrinolysis, plasmin can cleave fibrin into D-dimer, which is also a key factor of thrombosis [52].

Intriguingly, there is a clinical paradox that the plasmin formation can be either deleterious or beneficial in COVID-19, which comes down to timing [7]. Ongoing end-organ damage caused by SARS-CoV-2 infection, and particularly impairment leading to demise, may represent a model of hyperfibrinolysis adequate at tissue, whereas insufficient at systemic-level to avoid the excessive fibrin deposition [53]. Moreover, the decreased uPA and increased PAI-1 inhibit the formation of plasmin in the early stage, thus developing hypofibrinolysis state (Fig. 3). At advanced stage, the elevated tPA promotes the production of plasmin, resulting in hyperfibrinolysis (Fig. 4) [52,54]. There may be a possibility for a therapeutic intervention, targeting a complex interplay among the fibrinolytic system particularly plasmin upon SARS-CoV-2 infection [55]. Therefore, it is urgent to explore in detail the mechanism of fibrinolytic system in the pathogenesis of COVID-19.

4.1. Plasmin(ogen) and COVID-19

Plasmin proteolytically cleaves the furin site, resulting in the enhancement of SARS-CoV-2 virulence and infectivity [9,16]. 97% of COVID-19 patients at admission and all patients before death have an

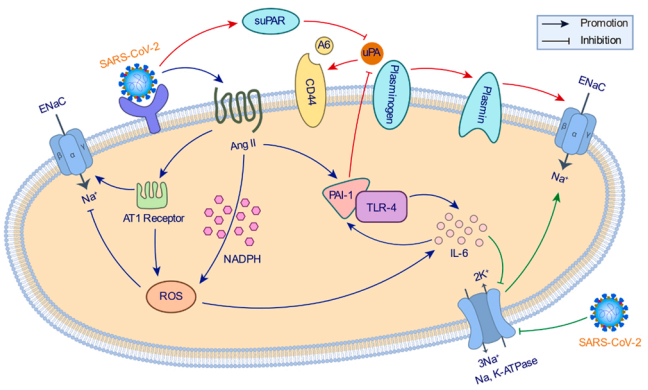

Fig. 3. The schematic diagram of hypofibrinolysis in the early stage of SARS-CoV-2 infection. Red: Reduced uPA and elevated PAI-1 inhibit plasmin to cleave γ subunit of ENa. Blue: Elevated Ang II caused by COVID-19 motivates PAI-1 protein release, triggering the secretion of IL-6, which in turn leads to the generation of PAI-1. Meanwhile, enhanced AT1 receptor can directly induce the excessive activation of ENaC and the generation of ROS, which stimulates the secretion of IL-6 and inhibits ENaC activity. Green: SARS-CoV-2 infection and the secretion of cytokines induce the downregulation of Na, K-ATPase that contributes to the attenuation of ENaC function. Ang II: Angiotensin II, AT1 Receptor: Ang II Type 1 Receptor, ENaC: Epithelial Sodium Channel, PAI-1: Plasminogen Activator Inhibitor-1, ROS: Reactive Oxygen Species, TLR-4: Toll-like Receptor-4, uPA: Urokinase Plasminogen Activator, suPAR: Soluble Urokinase Plasminogen Activator Receptor.

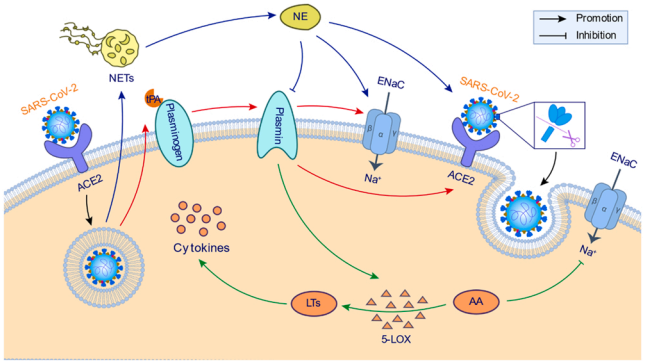

Fig. 4. The schematic diagram of hyperfibrinolysis at advanced stage of SARS-CoV-2 infection. Red: Elevated tPA boosts the generation of plasmin, which cleaves the spike protein and ENaC to accelerate virus fusion. Blue: NETs promote the excessive release of neutrophil elastase, which activates spike protein of SARS-CoV-2 and near silent ENaC by cleaveing γ subunit. Green: Plasmin is responsible for the simulation of 5-LOX following by the release of LTs and competitively suppresses the inhibition of ENaC activity. 5-LOX: 5-Lipoxygenase, AA: Arachidonic Acid, ACE2: Angiotensin-converting Enzyme 2, ENaC: Epithelial Sodium Channel, LTs: Leukotrienes, NE: Neutrophil Elastase, NETs: Neutrophil Extracellular Traps, tPA: Tissue Plasminogen Activator.

indicator of elevated plasmin, a key predisposing factor for hyperfibrinolysis [56]. Single-center case series analyzed 138 hospitalized patients with COVID-19, among which 64 suffered from one or several comorbidities that are considered as massive risk factors during the onset of COVID-19, including malignancy, diabetes, hypertension, and cardiovascular disease [19]. People with autoimmune disease and dyslipidemia were particularly susceptible to COVID-19 [57]. COVID-19-induced ARDS and cytokine storm at advanced stage may develop multiorgan failure with a hallmark of excess D-dimer by elevated plasmin in susceptible individuals who have the comorbidities.

In addition, as an antifibrinolytic drug, tranexamic acid prevents the conversion of plasminogen to plasmin and blocks plasmin production. During SARS-CoV-2 infection, tranexamic acid can attenuate the development of hyperfibrinolysis and exert a beneficial effect in

inflammation related lung injury [58,59]. However, tranexamic acid may otherwise aggravate COVID-19-induced ARDS by suppressing the effect of plasmin, which can remove fibrin and misfolded proteins, and inhibit the formation of a hyaline membrane [60,61]. The sole administration of tranexamic acid is harmful on account of fatal systemic thrombosis to COVID-19 patients, who ought to accept combined anticoagulant therapies, such as low dose warfarin, direct oral anticoagulant, and low-molecular-weight heparin [52,62,63].

4.2. tPA and COVID-19

Two retrospective studies demonstrated the levels of tPA had a gradual increase from mild to critical especially in those hospitalized patients with thrombotic diseases, suggesting severe COVID-19-induced respiratory failure was partly associated with tPA via endothelial dysfunction and pulmonary thrombosis [64,65]. Administration of tPA, an available therapeutic schedule, improves fibrin dissolution and oxygenation, as well as accelerates rehabilitation in the early stage [66,67]. While at advanced stage, the administration of tPA can hardly ameliorate hemodynamics because the efficacy of tPA is limited by the depletion of plasminogen when blood flow is needed to reestablish in clot-occluded vessels [68,69]. Hence, except for giving tPA alone, systemic thrombolytic therapy is necessary for patients who have developed into severe progression. The combination administration of tPA and heparin can accelerate dead-space ventilation and gas exchange significantly and immediately, so as to improve lung function in patients with severe COVID-19-induced respiratory failure [70,71].

4.3. uPA and COVID-19

The uPA and uPA receptor (uPAR) form a multimolecular complex anchored by glycosylphosphatidylinositol to the surface of various cell types, which can cause fibrinolysis [72,73]. The disorder of uPA/uPAR system exerts excessive proinflammatory effects and immune responses, which in turn elevates the soluble form of uPAR (suPAR) levels and prevents the transformation from plasminogen to plasmin, resulting in a hypofibrinolysis at the early stage of COVID-19 [72,74]. Moreover, experts propose that elevated suPAR can be an independent predictor for the risk of severity and mortality, admission to intensive care unit, as well as the length of hospitalization in COVID-19 patients [75–77]. A multinational observational study finds that the occurrence of venous thromboembolism during SARS-CoV-2 infection is correlated to high level of suPAR, which causes multiorgan failure and tropism in developing critical illness [78]. A double-blind, randomized controlled phase 3 trial reveals if the level of suPAR is 6 ng/ml or higher, early initiation of anakinra treatment may be suitable and significantly reduce the risk of worsening clinical outcomes [76].

4.4. PAI-1 and COVID-19

Patients with COVID-19 have higher PAI-1 levels in lung epithelial and endothelial cells, bronchoalveolar lavage fluid, as well as plasma [7,79]. After virus binds to the receptor and enters into host cells, the depletion of ACE2 promotes the generation of angiotensin II (Ang II), thereby expediting PAI-1 protein release [80–83]. The hypofibrinolytic response during SARS-CoV-2 infection is directly attributable to elevated levels of PAI-1, which inhibits plasmin generation [84]. Endothelial function can be improved by statins, which downregulate the serum PAI-1 levels [85]. In SARS-CoV-2 infected cells, overproduced PAI-1 binds to toll-like receptor-4 on macrophages and triggers the secretion of proinflammatory cytokines such as interleukin-6 (IL-6), which in turn motivates signal transducer and activator of transcription 3 to produce transforming growth factor-β, and results in a positive feedback for the PAI-1 generation [86–88]. Tocilizumab decreases PAI-1 by blocking IL-6 signaling, which can be considered as an effective treatment to blunt the cytokine release syndrome caused by COVID-19 [89,90].

5. Dysfunction of epithelial ion transport involved with fibrinolytic system of COVID-19

SARS-CoV-2 dysregulates alveolar ion and fluid transport by hijacking G protein-coupled receptor signaling pathways, as well as destroys the epithelial and endothelial function, including edema formation and low alveolar-capillary permeability [91–93]. ENaC, mainly consisting α, β, and γ subunits, is expressed in the respiratory epithelium, in charge of airway surface liquid and alveolar fluid clearance [94,95]. Plasmin cleaves both C-terminal fragment of furin site in α subunit and full-length γ subunit of ENaC proteins, which thereby become a high open-probability state [14,17,96]. Members of our group have applied single-cell RNA sequence and pseudovirus analysis and found that plasmin competitively cleaves γ subunit of ENaC, as well as the furin site at SARS-CoV-2 spike protein, which can accelerate virus entry and membrane fusion [16].

5.1. Plasmin together with neutrophil elastase boosts airway epithelial Na^+ transport

Neutrophil extracellular traps (NETs) fail to be cleared during SARS-CoV-2 infection, and promote the intravascular thrombus formation by platelet aggregation [97]. Neutrophil elastase, the metabolite of NETs, excessive release of which reduces lung permeability and cytokine storm in progression of COVID-19 [98,99]. Similar to plasmin, neutrophil elastase can cleave the furin site of spike protein and γ subunit of ENaC, resulting in the stimulation of SARS-CoV-2 entry and the reduction of airway surface liquid height, respectively [99–101]. Intriguingly, complexes consisting of neutrophil elastase and DNA from neutrophil extracellular traps can degrade plasminogen, reduce plasmin formation, and decrease fibrinolysis [102,103].

5.2. Plasmin activates arachidonic acid dependent ENaC

Proinflammatory leukotrienes remain to increase during 3–5 months of convalescent COVID-19 and are converted from arachidonic acid by using 5-lipoxygenase as a catalyst [104,105]. Arachidonic acid is also a catalyst to induce cytochrome P450 inhibiting ENaC activity [106,107]. Moreover, plasmin is responsible for the simulation of 5-lipoxygenase, whose metabolites in turn can active plasmin and release cytokines, leading to the accumulation of leukotrienes [108]. As a result, elevated plasmin stimulates arachidonic acid consumption, then actives ENaC through the arachidonic acid metabolic pathway.

5.3. SARS-CoV-2 inhibits uPA activity to reduce epithelial ion transport

Both the massive increase in PAI-1 levels and disorder of uPA/uPAR system in COVID-19 can inactivate uPA in lungs, then prevent plasmin to cleave γ subunit of ENaC with decreasing epithelial ion transport [15,109,110]. Several studies demonstrate the inhibition of epithelial ion transport attributes to the insufficient cleavage of ENaC [111,112]. Moreover, uPA facilitates self-renewal and difference of alveolar type II epithelial cells by binding to $CD44^+$ via A6 peptide and activating ENaC [111]. Consequently, decreased uPA is a key player in hypofibrinolysis state, as well as inhibits the cleavage and activity of ENaC. Several studies demonstrate the inhibition of epithelial ion transport stems from the insufficient cleavage of ENaC, evidenced in the lungs of uPA knockout mice [111,112].

5.4. SARS-CoV-2 affects Ang II related signaling pathways to regulate ENaC activity

COVID-19-induced Ang II expression releases PAI-1 protein, then deregulates plasmin and plays a crucial role in ENaC activity [15,81]. Meanwhile, NADPH oxidase is required when Ang II promotes mitochondrial reactive oxygen species, and stimulates the internalization of

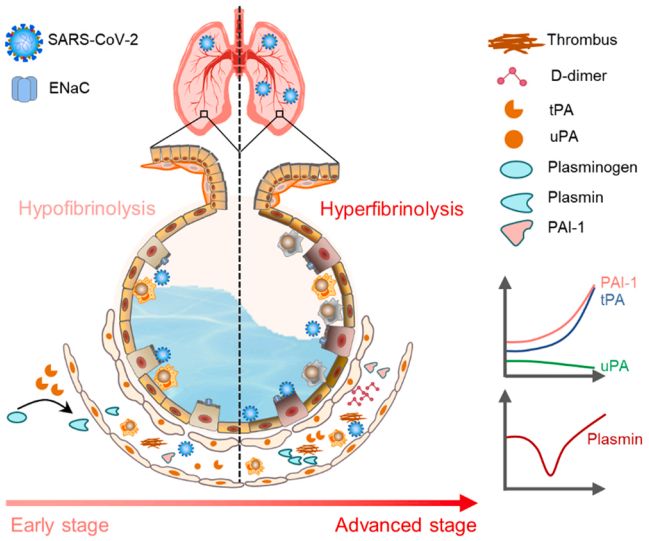

Fig. 5. The disturbance of fibrinolytic system and epithelial ion transport during SARS-CoV-2 infection. In the early stage, reduced uPA and elevated PAI-1 downregulate plasmin and ENaC, leaving the patient in a hypofibrinolytic state with thrombus. Increased tPA and plasmin cause hyperfibrinolysis with the excess D-dimer and the overactivation of ENaC at advanced stage. ENaC: Epithelial Sodium Channel, PAI-1: Plasminogen Activator Inhibitor-1, SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2, tPA: Tissue Plasminogen Activator, uPA: Urokinase Plasminogen Activator.

ENaC [113,114]. Ang II type 1 receptor serves as a catalyst for elevated Ang II caused by SARS-CoV-2 infection, to promote the excessive activation of ENaC with inadequate Na^+ reabsorption [115–117]. The spike protein gives rise to Ang II type 1 receptors mediated signaling cascade that activates nuclear factor-kappaB and activator protein-1/c-Fos via MAPK pathways, and increases IL-6 release [118]. Accordingly, the targeted therapy by blocking Ang II type 1 receptor with angiotensin receptor inhibitors, can prevent the binding of toxic angiotensin associated with cytokine storm during SARS-CoV-2 infection [119].

5.5. SARS-CoV-2 infection downregulates Na, K-ATPase

Similar to SARS-CoV, SARS-CoV-2 may upregulate activator protein-1, which binds to α1-subunit of the mineralocorticoid/glucocorticoid response element-binding sites and downregulates Na, K-ATPase [61]. In addition, COVID-19-induced hypoxia directly phosphorylates protein kinase C zeta by α1-AMP-activated protein kinase, decreasing Na, K-ATPase activity [120]. The secretion of cytokines caused by COVID-19 may also decrease Na, K-ATPase activity, further restrains alveolar clearance and aggravates ARDS deterioration [61,121,122].

6. Conclusion and perspective

To date, how to reconcile the paradox of both hyperfibrinolytic and hypofibrinolytic indicators in COVID-19 patients is still an unresolved popular topic [7,53]. As mentioned earlier, plasmin can cleave both spike protein of SARS-CoV-2 and γ subunit of ENaC. So far, researchers are increasingly interested in the studies on fibrinolytic system and ENaC in COVID-19. In the early stage, elevated PAI-1 and reduced uPA create low levels of plasmin, leaving the patient in a hypofibrinolytic state. The expression and activity of ENaC may be attenuated by SARS-CoV-2 infection, and plasmin tends to cleave the spike protein, accelerating virus entry into the host. Intriguingly, increased plasmin and tPA cause hyperfibrinolysis, and elicit the overactivation of ENaC at advanced stage (Fig. 5). However, the evidence from experimental studies is scarce to assure whether plasmin preferentially cleaves spike protein or ENaC subunit. Meanwhile, furin site is a multibasic cleavage one of SARS-CoV-2 spike protein, and can be cleaved by several cellular proteases, not limited to plasmin [40]. Until now, it has not been confirmed whether plasmin plays a crucial role among the proteases in cleavage of furin site intracellular or extracellular, which also needs to be explored furtherly.

Ethics approval and consent to participate

Not applicable.

Consent for publication

All authors approved the final manuscript and the submission to this journal.

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CRediT authorship contribution statement

Yunmei Fu: Writing – original draft, Manuscript revision, Drawing and figure making. **Hao Xue:** Writing-original draft preparation, Manuscript revision. **Tingyu Wang:** Investigation, Manuscript revision. **Yan Ding:** Drawing and figure making, Writing – review & editing. **Yong Cui:** Conceptualization, Writing – review & editing. **Hongguang Nie:** Conceptualization, Writing – original draft preparation, Writing – review & editing, Funding acquisition. All authors approved the final version of the manuscript for submission.

Declaration of Competing Interest

The authors declare no competing interests.

Data availability

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

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