Coronavirus Disease 2019: The Role of the Fibrinolytic System from Transmission to Organ Injury and Sequelae

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An initial cluster of severe viral pneumonia was discovered in early December 2019 in Wuhan, China. It was found to be caused by a newly identified coronavirus, later named by the World Health Organization and the Coronavirus Study Group of the International Committee as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the disease as coronavirus disease 2019 (COVID-19).[1–4] The disease rapidly spread globally and was then declared as a pandemic. The most notable characteristic of SARS-CoV-2 is its high infectivity. As a result, much attention has been paid to its mode of transmission. The major route of infection is the binding of the spike protein of the virus to its natural receptor angiotensin-converting enzyme (ACE 2) on the surface of the host cells.[2] ACE2 is present in tissues and is particularly abundantly expressed in the lung in the alveolar (type II) cells. This is clinically correlated as the lung is the major organ affected by the viral infection, leading to acute respiratory failure and acute respiratory distress syndrome (ARDS). Many aspects of COVID-19 are similar to those seen in the SARS and in the Middle East respiratory syndrome (MERS),[5,6] including ACE2 being the receptor for the virus.[7] Impaired fibrinolysis was observed in post-SARS complications.[8,9] Impairedfibrinolysis[10,11] is present in pneumonia and acute lung injuries; accordingly, this commentary is devoted to reviewing evidence for possible involvement of the fibrinolytic system in transmission, pulmonary complications, and sequelae of COVID-19. Several possible drug targets that alter the activity of components of the fibrinolytic system are also discussed.

Transmission

One common characteristic that SARS-CoV-2 shares with SARS-CoV and MERS-CoV is its high infectivity, which gives the propensity to spread rapidly through the population. The spike protein on the viral envelop attaches to ACE2 on the surface of the host cells[12–14] (►**Fig. 1**). ACE2 is an integral component of the renin–angiotensin–aldosterone system (RAAS).[15] RAAS regulates blood pressure and aldosterone secretion.[15–17] It is present in both circulation and tissues,[18] particularly in the kidney, heart, and blood vessels. As shown in ►**Fig. 1**, the plasma protein angiotensinogen is hydrolyzed by an aspartic protease renin in the kidney to angiotensin I. Angiotensin I is then converted to angiotensin II by ACE. Angiotensin II is further cleaved to angiotensin 1-7 and catalyzed by ACE2, a homolog of ACE.[19] ACE2 is present in lung, kidney, heart, gastrointestinal system, and lymphocytes, and expressed on cell membranes. ACE2 acts as the receptor for SARS-CoV-2 as well as for other coronaviruses such as SARS-CoV.[20–22] ACE2 is abundant in type II alveolar cells and thus renders the lung highly susceptible to the attachment of SARS-CoV-2. Following binding of the virus, ACE2 is downregulated, leaving angiotensin II in excess. Angiotensin II binds to another receptor, causing lung injury.[23,24] Our understanding of the role of the RAAS system in COVID-19 leads to the potential use of inhibitors of ACE and of angiotensin receptor blockers in the treatment of COVID-19.[14]

Components of the fibrinolytic system are also regulated by RAAS.[25] Angiotensin II induces the expression of plasminogen activator inhibitor-1 (PAI-1) in the endothelial cells.[26] An ACE inhibitor quinapril was shown to lower PAI-1 level in healthy subjects,[27,28] whereas another inhibitor of ACE, ramipril, was found to lower the circulating PAI-1 level in patients with acute myocardial infarction.[29] In healthy subjects, the status of fibrinolysis in the endothelium are kept in balance between tissue plasminogen activator (tPA) and PAI-1. As ACE is downregulated following the attachment of SARS-CoV-2, this balance is shifted to an excess of uncleaved angiotensin II, which, in turn, increases PAI-1 (►**Fig. 1**). Another component of the fibrinolytic system, tPA, is upregulated by the kinin-

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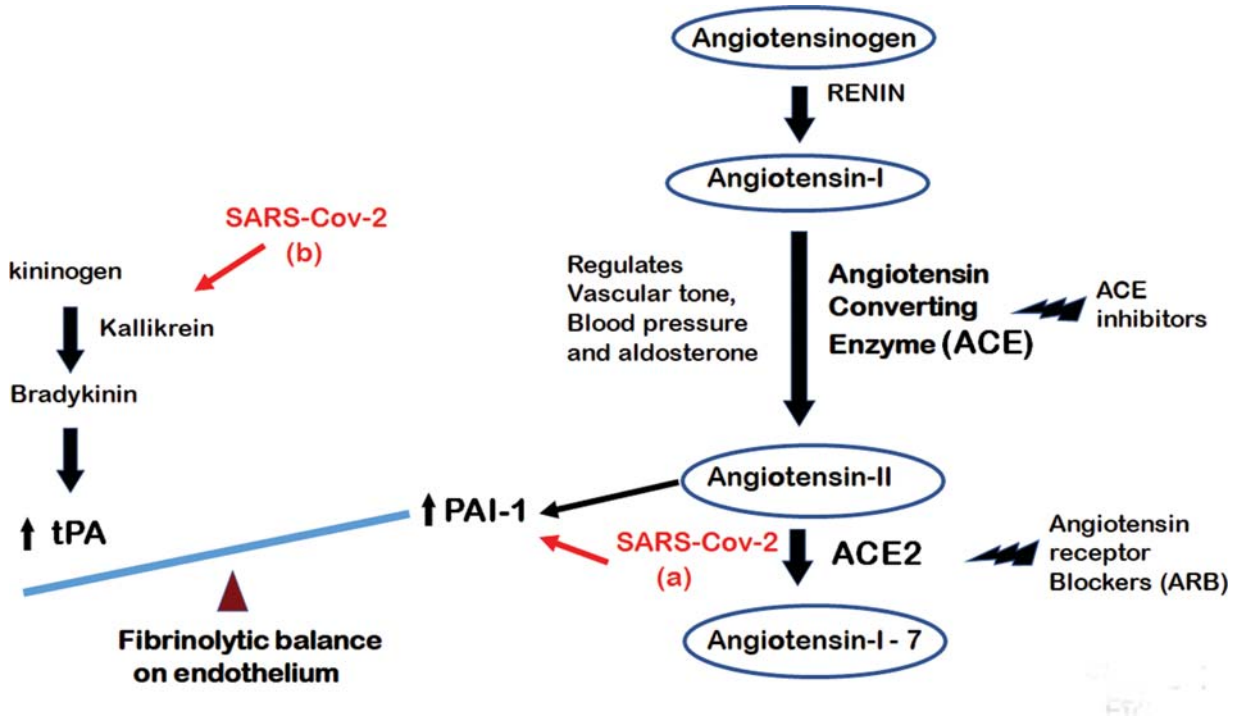

Fig.1 Effect of SARS-CoV-2 on the fibrinolytic balance of the endothelium through its actions on the renin–angiotensin–aldosterone system. By binding to ACE2, angiotensin II is prevented from breaking down to angiotensin 1-7 (a). The accumulated excess of angiotensin II enhances a greater expression of PAI-1 in the endothelium. SARS-CoV-2 evokes an acute inflammatory response with increase in bradykinin, which induces tPA expression in the endothelium, but insufficient to counterbalance the PAI-1 (b). ARB, angiotensin receptor blocker; ACE2, angiotensin-converting enzyme 2; PAI-1, plasminogen activator inhibitor-1; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; tPA, tissue plasminogen activator.

bradykinin pathway.[30] The severe acute inflammatory response in COVID-19, with increased bradykinin, would favor increased tPA but is not sufficient to counterbalance the effect of increased PAI-1.

The result of high PAI-1 in the prothrombotic state in the lung may thus explain the unresolved fibrin deposits in the alveoli, which is a dominant feature of ARDS. The results of a clinical trial of tPA (discussed in the next section) will be crucial in supporting this concept. An alternate therapeutic approach is the use of inhibitor against PAI-1.

Lung Pathology

The proteolytic enzyme plasmin is formed by the activation of its precursor plasminogen by tPA and urokinase-type plasminogen activator (uPA). tPA is involved in the regulation of breakdown of fibrin and in neurologic functions, whereas uPA participates in many physiological and pathological processes including acute inflammation, wound healing, and tissue repair, as well as tumor growth and metastasis. uPA and plasmin are both activators of latent metalloproteinases in extracellular matrix remodeling,[31] along with their respective regulatory protein networks.[32,33] Both uPA and tPA are inhibited by PAI-1. During the acute injury in severe pneumonia, the virus attaches to the alveolar cells (as discussed above) and causes acute inflammatory response with exudation of fibrinogen into the alveola with fibrin and hyaline membrane formation. These changes are shown in both SARS[31,34] and COVID-19.[35–37] As the disease progresses to ARDS, more fibrin and fluid fill the alveolar spaces with perialveolar capillaries blocked by microthrombi.[38] The increased presence of uPA was also demonstrated in vitro in human lung-derived epithelial cells (A549).[31] uPA is bound to its receptor (uPAR) on the cell surface, forming a uPA/uPAR complex, which effectively enhances the ability to activate plasminogen to plasmin (►**Fig. 2**). In the lungs of experimental animals and in human bronchial lavage, there is also increased PAI-1. This inhibitor keeps in check the excessive activity of uPA and prevents its further deterioration into intra-alveolar hemorrhage. On the other hand, overexpression of PAI-1 and other inhibitors of plasmin, such as antiplasmin, will result in a poor resolution of alveolar lesions and increase the risk of fibrosis. PAI-1 is well known to promote tissue fibrosis in pathological healing in many disorders.[39,40] There is thus a delicate balance between excessive fibrinolysis, which increases the risk of intra-alveolar hemorrhage, and excessive PAI-1, which ultimately fosters fibrosis. As antifibrinolytic agents such as tranexamic acid are available, the lung lesions can thus be a suitable therapeutic target. On the other hand, the lung has a high content of tissue factor; thus, conditions with lung injury are prothrombotic. Fibrinolytic therapy with uPA, streptokinase, and tPA had been used in the past for ARDS.[41,42] It has also been proposed that therapeutic tPA may be used in selected patients with COVID-19 with severe ARDS.[43] Ongoing clinical trials are going to verify this concept.

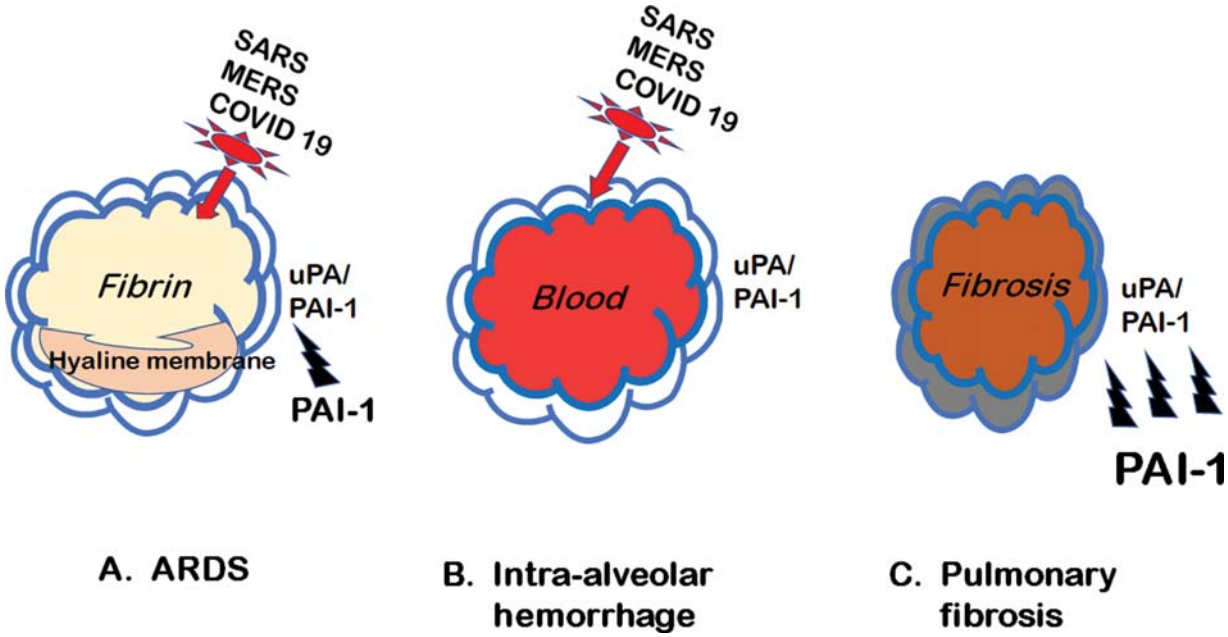

Fig. 2 Different scenarios in the pulmonary alveoli in the pulmonary lesions seen in the acute respiratory syndromes of SARS, MERS, and COVID-19. (**A**) ARDS occurs with exudation of fluid with fibrin and hyaline membrane formation as fibrinolysis by uPA/uPAR is inhibited by PAI-1 and fails to clear the fibrin. (**B**) Excessive fibrinolysis with a low PAI-1 response results in intra-alveolar hemorrhage. (**C**) Excessive PAI-1 increases the risk of resolution by fibrosis. ARDS, Acute respiratory distress syndrome; COVID-19, coronavirus disease 2019; MERS, Middle East respiratory syndrome; PAI-1, plasminogen activator inhibitor-1; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; uPA, urokinase-type plasminogen activator; uPAR, urokinase plasminogen activator receptor.

In conclusion, the large number of patients infected by the SAR-CoV-2 virus during the current epidemic brings a challenge to many. Many aspects of the pathology of COVID-19 are similar to those seen in SARS and MERS, including the involvement of several components of the fibrinolytic system. This provides an opportunity to target specific sites of the fibrinolytic system by either enhancing fibrinolysis or inhibiting PAI-1.

Conflict of Interest

The author has no conflict of interest to report.

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