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INVITED REVIEW

# Coagulation and wound repair during COVID-19

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While COVID-19 is best known as a respiratory infection, SARS-CoV-2 causes systemic disease manifestations including coagulopathies. Both dysregulated extracellular matrix remodeling pathways and circulating coagulation proteins are hallmarks of severe COVID-19 and often continue after the resolution of acute infection. Coagulation proteins have proven effective as biomarkers for severe disease and anticoagulants are a mainstay of COVID-19 therapeutics in hospitalized patients. While much knowledge has been gained about the role of clotting pathway activation in COVID-19, much remains to be elucidated in this complex network of signaling pathways.
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Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) was first detected in late 2019 in a cluster of pneumonia patients in Wuhan, China.[1] While some patients have had asymptomatic infections, most present with a range of symptoms from mild to lethal disease.[2] COVID-19, the disease caused by SARS-CoV-2 infection, most commonly causes respiratory symptoms with patients experiencing fever, shortness of breath, hypoxia, cough and in severe cases respiratory failure, coagulopathies and multiple organ failure leading to death.[3-6] While the overall case fatality rate of COVID-19 is relatively low (~1%), the extraordinarily rapid spread of this new disease has resulted in overwhelmed medical facilities and exhausted medical providers.[7] Of increasingly recognized importance, COVID-19 patients do not all return to their previous baseline health status with 'long COVID' patients continuing to experience muscle weakness, shortness of breath, mental fogginess, and other symptoms 9+ months after their initial infection.[8] While novel SARS-CoV-2 vaccines and other therapeutics are expected to end the pandemic, the impact of COVID-19 will extend beyond this primary period of infection.

## Infection

SARS-CoV-2 utilizes the ACE2 receptor found on human epithelial cells in the airways as well as type II pneumocytes in the lung.[9] SARS-CoV-2 also has a broad affinity for ACE2 of other animal species and has been linked to progenitor CoV strains found in bats.[10] Although virus tropism is predominantly limited to ACE2 expressing respiratory epithelial cells, there has been evidence of virus replication outside of the respiratory tract including shedding of viral RNA in the feces, and occasional positive virus detection in the brain, heart, kidney and other organs.[11-13] Both in vitro and ex vivo infection of non-epithelial cells has been demonstrated, although most in vivo data has been for viral RNA and true in vivo replication data has been limited to date. While infection of other tissues has been reported, airway and lung ciliated epithelial cells represent the primary site of SARS-CoV-2 replication (Figure 1A). SARS-CoV-2, like SARS-CoV and influenza, preferentially infects type II pneumocytes versus type I C While type I pneumocytes make up most of the alveolar

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surface and are responsible for gas exchange, type II cells have a thick cuboidal shape and produce pulmonary surfactants necessary for lubricating the lung, thus reducing surface tension to allow for respiration.[14] Importantly, surfactant expression dramatically decreases following SARS-CoV-2 infection.[15,16] In addition, type II cells are the progenitor cells of the alveoli and differentiate into type I cells. Therefore, the loss of type II cells due to SARS-CoV-2 infection has a lasting impact and leaves the lung without a direct means to restore the alveoli. While type I pneumocytes can revert to type II cells, in vitro experimental systems suggest that the process can take weeks to occur.[17] This fact may contribute to the long recovery time required for COVID-19 patients.

## Cytokine storm and inflammation

Following SARS-CoV-2 infection, the host immune response produces a robust and large cytokine storm characterized by inflammatory mediators (Figure 1B). Responding to damage at the infection site, local alveolar macrophages and infiltrating neutrophils produce a cascade of inflammatory cytokines including IL-1, IL-6, and TNFa.[17] Type I interferons, drivers of the classical antiviral response, are produced at lower levels and later timepoints than observed in influenza infection.[18,19] Interferon autoantibodies have also been detected in patients with severe COVID-19, but not those with milder disease.[20] Mutations in interferon signaling pathways appear to be enriched in severe COVID-19.[21] High levels of C-reactive protein, complement activation, and lactate dehydrogenase all predict severe disease and contribute to tissue damage.[22] However, absent a strong and productive type I interferon response, these cytokines and inflammatory mediators have limited impact on SARS-CoV-2 replication and cause diffuse alveolar damage (DAD).[23-25] While many coronavirus proteins have interferon antagonist abilities,[26] the CoV E protein has been showed to exacerbate the inflammatory cascade via NFkB[27] in mouse models. Notably, other host conditions including age, obesity, and diabetes have been associated with increased inflammation and subsequent disease.[28] Lacking antiviral effect, the inflammatory cascade plays a detrimental role during COVID-19 infection, exacerbating lung damage and disease. Several COVID9 treatment approaches have focused on disrupting this inflammatory cascade including drugs like dexamethasone, IL-1 and IL-6 antagonists with modest effect.[29]

## Wound healing

The lung epithelium is part of the larger epithelial barrier that protects our tissues from the external environment, and it can be damaged chemical injury or infectious agents such as SARS-CoV-2. Wound healing or tissue repair is the complex processes by which injured cells are identified, removed, and eventually replaced with new, healthy tissue. While healthy lung cells have little cell turnover, the lung epithelium is capable of impressive regeneration after injury.[30] Following injury, epithelial cells can de-differentiate to replicate and replace specialized cells such as type I

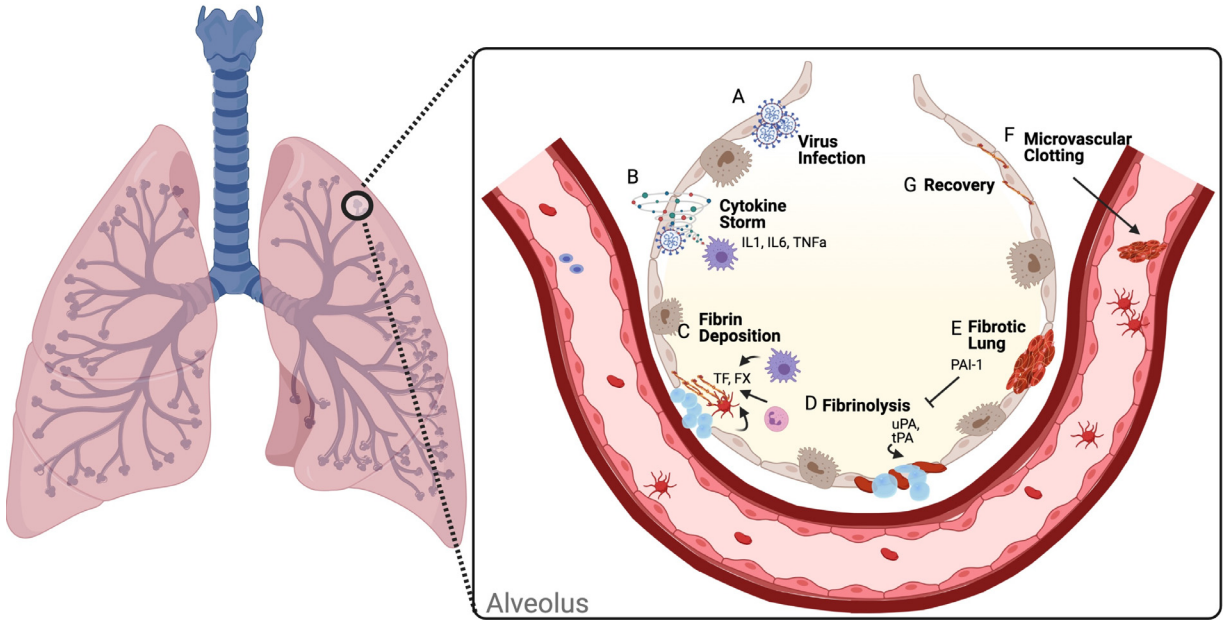


**Figure 1** Activation and modulation of coagulation pathways following SARS-CoV-2 infection. Schematic of the lung and an alveolus following SARS-CoV-2 infection. A) Virus infection of type I and type II pneumocytes. B) Cytokine storm including IL1, IL6, and TNFa induced in response to viral replication. C) Inflammation induced damage activates release of FX, tissue factor (TF) and other coagulation factors to activate fibrin deposition to limit fluid accumulation in alveolar spaces. D) Release of uPA and tPA initiate breakdown of fibrinous structures. E) PAI-1 blocks activity of uPA and tPA and leaves fibrinous structures intact and the lung more rigid. F) Release of pro-clotting factors into the circulatory systems that may impact other target organs. G) Return to baseline lung function with evidence of scarring and damage still in place. Figure generated using Biorender software.

and type II pneumocytes and secretory cells. Recent COVID-19 autopsy reports have noted a high percentage of proliferating AT2 cells,[31] indicating that epithelial cell regeneration occurs after SARS-CoV-2 induced lung injury. Crosstalk between epithelial cells and immune cells is critical for this process with activated neutrophils and macrophages producing TGF-b and other chemokines that promote epithelial cell migration to the site of tissue injury. Immune cells also clear apoptotic debris from the site of injury and release growth factors like EGF, VEGF and IGF that are important for the tissue regeneration process. Little human data on growth factor expression in COVID-19 patients is available[32,33]; however, previous work using a mouse model of SARS-CoV infection demonstrated that overactive EGFR signaling leads to enhanced lung disease pulmonary fibrosis,[34] indicating that an appropriate wound healing response is important for resolution of coronavirus-induced lung disease.

## Coagulation and extracellular matrix remodeling pathways

In response to infection and inflammation-induced damage, the host must take actions to maintain respiratory function through activation of extracellular matrix remodeling and coagulation pathways.[35] Loss of pneumocytes and diffuse alveolar damage caused by inflammation raises the risk of vascular leakage, fluid accumulation (edema), and hemorrhage in the alveolar spaces, thus preventing oxygen exchange[36] (Figure 1C). This tissue damage leads to cytokine production, stimulating increased expression of tissue factor on endothelial cells and exposure of TF to activate the coagulation pathway, leading to the cleavage of prothrombin to thrombin.[37,38] Interestingly, while tissue factor protein levels are increased in COVID-19 patients, the transcripts are not elevated,[39,40] indicating that regulation of SARS-CoV-2 induced thrombotic events is complex. Thrombin subsequently cleaves fibrinogen into fibrin,[41] a major component of clots. Fibrin is incorporated with collagen into hyaline membranes to seal the alveoli from fluid accumulation.[42] However, these sealing processes thicken the alveolar walls, limit oxygen exchange, and may lead to pulmonary fibrosis, endangering respiratory function.[43]

Additionally, epithelial damage, production of profibrotic cytokines, and chemokines such as TGFb and MCP-1 stimulate collagen and fibronectin production leading to a pro-fibrotic state.[44,45] This fibrotic lung stage also stimulates the fibrinolytic pathway, a process that breaks down fibrinous deposits through release of uPa and tPA[46] (Figure 1D). UPa and tPA activate plasminogen into plasmin which targets fibrin for breakdown.[47] The activity of tPA and uPa is regulated by plasminogen activator inhibitor-1 (PAI-1),[46] and alpha 2-antiplasmin. Plasmin itself is regulated by several serine protease inhibitors including a2-antiplasmin and there are extensive interactions between the complement and coagulation proteolytic pathways[35,48] (Figure 1E). Together, the fibrinolytic and coagulation pathways govern a delicate balance between hemorrhage/edema and fibrosis in order to maintain lung respiratory function. Once this axis is disrupted by coronavirus-induced acute respiratory distress (ARDS), patients are at high risk of respiratory failure from either pulmonary fibrosis or edema and DAD.

During SARS-CoV-2 infection, the balance of the coagulation signaling, including the fibrinolytic pathway can be disrupted in either direction leading to adverse outcomes. COVID-19 patients have been reported to have high levels of PAI-1 and D-dimers in their blood,[49,50] consistent with the microthrombi observed in COVID-19 patient autopsies. Confoundingly, intra-alveolar hemorrhage has also been observed in COVID-19 lungs and elevated levels of pro-fibrinolytic uPA and tPA have been associated with reduced respiratory function and more severe disease.[37]) Excessive levels of uPA and tPA can lead to breakdown of fibrin before damaged areas have been sufficiently repaired (Figure 1D). The results can be fluid accumulation in the alveolar spaces that disrupts oxygen exchange. However, during SARS-CoV-2 infection, coagulation has more often been identified as a persistent issue and a major factor contributing to mortality.[3] An increase in PAI-1 prevents the breakdown of fibrin by uPa and tPA, leaving a thickening of the alveolar walls that reduces respiratory function and makes it more difficult to breath[49] (Figure 1E). The pro-coagulation cascade also has an impact beyond the lung with the formation of microvascular clots in other organs and in the circulatory system[43] (Figure 1F). In addition, PAI-1 levels are increased in patients who are elderly or have hypertension, obesity, diabetes, and cardiovascular disease, consistent with increased susceptibility to COVID in these populations.[51] Even after resolution of infection, the lung can maintain fibrin and other scarring from the induced damage[52] (Figure 1G). Overall, both sides of the fibrinolytic/ coagulation pathway are critical to the SARS-CoV-2 response.

While experimental data is limited for SARS-CoV-2, disruption of uPa signaling had significant impact on susceptibility to the original SARS-CoV *in vivo*.[53] Mice deficient in PAI-1 had increased weight loss and mortality following challenge with SARS-CoV.[54] The absence of PAI-1 resulted in an increase in ARDS related gene signatures and extensive hemorrhage in the lung. Notably, the loss of PAI-1 had no significant impact on viral load. Conversely, mice deficient in tPA (PLAT) were also more susceptible to lethal SARS-CoV challenge.[54] $tPA^{-/-}$ mice had increased mortality compared to control animals following SARS-CoV challenge. While the tPA KO mice trended to less overall hemorrhage, the presence of exudates and increased lethality indicate the delicate balance required to recover from infection. It is anticipated that the fibrinolytic signaling pathway governs similar processes following SARS-CoV-2 infection.

## Monitoring and targeting COVID induced coagulation

Given the link to severe disease and mortality,[55] activated pathways associated with fibrinolysis and coagulation have

been used as a biomarkers for determining COVID-19 intervention strategies. Retrospective studies have determined that lethal SARS-CoV-2 cases had higher D-dimer and fibrin degradation products in their blood.[55,56] These patients also had longer prothrombin time and met criteria consistent with disseminated intravascular coagulopathy.[37] Similarly, low platelet counts and prolonged activated partial thromboplastin time were associated with more severe disease.[57]

Finally, lupus anticoagulant antibodies have also been identified in a subset of patients.[58] Together, the results suggest that monitoring coagulation metrics can predict disease severity and dictate intervention strategies.[29] Similarly, improvement in these coagulation metrics may signal appropriate waning of aggressive treatment approaches.

Prophylactic targeting of the coagulation pathways is now the routine treatment approach for hospitalized COVID-19 patients.[59] While not employed early during the outbreak, the combination of excess thrombin production, fibrinolysis shutdown, and evidence of micro thrombotic occlusions demonstrated the need to control coagulation pathways.[60] The standard treatment utilizes low-molecular weight heparin (LMWH) which inhibits heparinase activity, neutralizes cytokine storm, and interferes with leukocyte trafficking.[61,62] An alternative approach utilized inhalation of plasminogen to improve lung lesion and hypoxemia.[63] To counteract fibrin accumulation, tPA treatment and drugs that target PAI-1 have been attempted to improve outcomes.[49, 63] Together, these approaches to disrupt an exuberant coagulation response has produced improved outcome in hospitalized patients.

Despite being the standard of care, targeting the coagulation pathways offers a mitigation rather than preventive response. The disruption of the coagulation factors does not resolve the underlying inflammation and lung damage that initiated the response. Instead, treatments that disrupt the damage cascade may have the most significant impact on coagulation pathways activation. For example, antiviral drugs like remdesivir and EIDD-2801 and monoclonal antibodies target viral replication with best effect at early times points post infection[64, 65]; remdesivir has also been shown to reduce inflammatory responses and may reduce overall disease by diminishing damage.[66] Similarly, treatments that disrupt the inflammatory cascade may also change downstream coagulation activation. Anakinra and tocilizumab, drugs that target IL1 and IL6 respectively, have been utilized to treat COVID-19 patients.[67] These inflammation pathways have also been shown to activate coagulation pathways and treatments that target these inflammation cascades may reduce damage stimulating coagulation responses. Broad immune suppression drugs like dexamethosome may also produce the same results.[29] Further research into coagulation triggers and cascade activation in COVID-19 patients will help highlight areas for targeted therapeutics. Overall, efforts to prevent inflammation related damage potentially have more utility than targeting coagulation pathways in treating COVID-19.

## Conclusion

As SARS-CoV-2 has spread around the world, the connections between viral infection, inflammation, and the coagulation cascade have been further illuminated. While the emergent SARS-CoV-2 causes significant disease and death, damage from viral replication appears secondary to exuberant host responses. In an effort to maintain respiratory function, the delicate balance between hemorrhage and fibrosis in the lung is at the nexus of COVID-19 disease. Focusing on the coagulation and fibrinolytic pathways provides a means to evaluate the severity of disease in patients and potentially mitigate its damage with therapeutic treatments. However, preventing the inflammatory cascade that initiates and necessitates the coagulation response may be the only means prevent severe COVID-19 disease. Importantly, these observations of the coagulation pathways may have implications for other infections like influenza or Ebola. Overall, we need a better understanding of the coagulation host response to effectively treat and overcome SARS-CoV-2 and future emergent pathogens.

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