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BITS AND BYTES

Is the mechanism of COVID-19 coagulopathy still a rabbit's hole?

Ashna Rajan[1] · Ganesh Keshav Thirunavukkarasu[2] · Richard F. Lockey[3] · Narasaiah Kolliputi[3]

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Abstract
The pathophysiology of COVID-19 is an enigma with its severity often determined by the extent of coagulopathy. Several regulatory pathways targeted by the SARS-CoV-2 include the renin-angiotensin system, von Willebrand Factor, and most importantly, the complement pathway. This article discusses these pathways to help design potential future therapies.

Keywords COVID-19 · Coagulopathy · ACE2 · SARS-CoV2 · Complement · Thromboinflammation

COVID-19 (Coronavirus Disease 2019) related coagulopathy increases the risk of death (Tang et al. 2020). Zhou et al. (2020) reported elevated d-dimer protein fragment in 36% of the first 99 subjects studied with COVID-19. The severity of the infection correlated with the degree of thromboinflammation (Levi et al. 2020). The affinity of SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) to affect multiple organs and to trigger an immunologic storm is what makes the disease so difficult to treat. Is the complement pathway to blame and therefore an ideal target for treatment?

SARS-CoV-2 enters via the ACE-2 (angiotensin converting enzyme -2) receptor on epithelial cells of the lungs, intestine, blood vessels, heart, kidney and testis (Crackower et al. 2002). This progress seems to be accentuated via the presence of co-receptors which include neuropilin, heparan sulfate, and sialic acids (Zamorano Cuervo and Grandvaux 2020). ACE 2 converts angiotensin (Ang) I and II to Ang derivatives responsible for vasodilation and anti-inflammation, -apoptotic and -oxidative effects. It counter-balances the effects of Ang II which via the Ang T2 receptor causes vasoconstriction, inflammation, apoptosis and oxidative stress (Abassi et al. 2020). When SARS-CoV-2 enters via the ACE 2 receptor, it causes internalization and shedding of the ACE-2 into the blood causing activation of the pro-coagulant and pro-inflammatory arm of the renin-angiotensin system (RAS) (Abassi et al. 2020). As a result of increased vascular permeability due to Ang II, neutrophil infiltration causes destruction of alveolar epithelial cells leading to an 'atypical' acute respiratory distress syndrome (ARDS) (Diamond 2020).

The pathophysiology of COVID-19 DIC (disseminated intravascular coagulation) is different from that seen in critically ill subjects from other diseases (Helms et al. 2020). Coagulation parameters, specifically PT (prothrombin time), antithrombin, fibrinogen and platelet levels, are significantly elevated in SARS-CoV-2-infected subjects, not in DIC from other causes (Helms et al. 2020). Helms et al (2020) hypothesised that the elevated levels of vWF (Von Willebrand Factor):antigen complex and factor VIII detected in their study implicated endothelial inflammation as the core mechanism for thrombosis. Hypoxia contributed to the DIC cascade secondary to vasodilation and activation of HIFs (hypoxia-inducible factors) (Helms et al. 2020). The occurrence of this procoagulant activity in lung tissue causes excessive accumulation of fibrin within the alveolar spaces affecting gas exchange and inducing more hypoxia (Hoste et al. 2005). This accumulation of fibrinous material is thought to be due to decreased fibrinolytic activity within the alveolar space secondary to the presence of elevated plasminogen activator(PA) inhibitor-1 (PAI-1) (Idell et al. 1989). Increased levels of this inhibitor were found in the blood samples of subjects infected with the SARS-CoV-1 in 2003 (Wu et al. 2006). Helms et al (Helms et al. 2020) did

✉ Narasaiah Kolliputi
nkollipu@usf.edu

[1] Division of Geriatrics Medicine, Brown University Alpert School of Medicine, Providence, RI 02903, USA

[2] Division of Cardiovascular Medicine, Department of Internal Medicine, State University of New York-Downstate Medical Center, Brooklyn, NY 11203, USA

[3] Division of Allergy and Immunology, Department of Internal Medicine, Morsani College of Medicine, University of South Florida, 2901 Bruce B. Downs Blvd, Tampa, FL 33612, USA

not measure PAI-1 levels. However, these authors believed that since they were able to show elevated levels of vWF and since PAI-1 is shed by endothelial cells, as is vWF, the PAI-1 levels also would be elevated with SARS-CoV-2 infection.

The possible role of vWF is enhanced by studies that indicate that vWF-mediated activation of platelets in dengue and malaria leads to increased recruitment of p-selectin on platelet surfaces that binds to P-selectin glycoprotein ligand (PSGL) on leukocytes, thus causing vascular endothelial damage (Guo and Rondina 2019). The expression of p-selectin on alveolar epithelial cells has been demonstrated in a subject infected with SARS-CoV-1 (Yen et al. 2006). It is postulated that this mechanism occurs with SARS-CoV-2 as well.

The complement pathway is postulated to be involved in microvascular thrombosis. Magro et al (2020) suggest that the terminal complement complex and C4d deposition causes thrombosis in the cutaneous and lung capillaries. This assumption is based on case reports of 5 subjects with severe COVID-19 infection. They noticed that a pauci-inflammatory mechanism caused microvascular thrombotic injury in the cutaneous tissue resulting in retiform and purpuric lesions and septal capillary injury in the alveolar capillaries (Magro et al. 2020). They thought these changes correlated with elevated d-dimers in 3 of 5 of their subjects. However, Helms et al. described lower d-dimer levels in COVID-19 versus non-COVID-19 ARDS subjects in an observational study (Helms et al. 2020).

Previous mouse models of SARS CoV-1 infection demonstrate that C3−/− versus wild mice have less neutrophilia and respiratory dysfunction (Gralinski et al. 2018). These findings enhanced the speculation that C5a-mediated expression of cytokines by neutrophils causes downstream procoagulant activity via a "cytokine storm" (Wang et al. 2015). As a consequence, neutrophilia has become a reliable prognostic marker for the severity of COVID-19 infection.

Another possible pathway of COVID-19 coagulopathy appears to be via MASP-2 (mannan-binding lectin-associated serine protease 2), as described by Magro et al (2020) in 2 of their COVID-19 subjects. They postulate that the nucleoprotein secreted by MERS, SARS-CoV-1 and SARS CoV-2 induces activation of MASP-2, a lectin pathway initiator, which in turn generates C3 convertase and the MAC (membrane attack complex) (Gao et al. 2020). In short, this indicates that both lectin and the alternative complement pathways may be involved in the pathogenesis of severe COVID-19.

While the complement pathway appears to be involved in severe life-threatening SARS-CoV-2 infected subjects, it also could be a first line barrier against infection. Anti-A and anti-B antibodies found in O type blood groups are thought to result in rapid clearance of the virus via the timely activation of the complement pathway (Wu et al. 2020). The attachment of the SARS-CoV spike protein to ACE-2 also is impaired in vitro due to the presence of anti-A antibody (Guillon et al. 2008). This concept is supported by the vulnerability of older patients to the SARS-CoV-2 (CDC 2019), hypothesized to be due to the lack of diversity of IgM antibodies (Martin et al. 2015). This could lead to poor control of the viral load during the asymptomatic phase.

With the emergence of vaccines against COVID-19, research towards identification of therapeutic targets for COVID-19 continues to be essential due to the lack of evidence regarding the trajectory of this pandemic. While therapeutic agents like recombinant human ACE-2, anti-C3 as well as anti-C5 (Mahmudpour et al. 2020) appear to be options with good potential, more studies are needed to determine their efficacy and role in the near future.

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Declarations

Conflict of interest No conflicts of interest, financial or otherwise, are declared by the authors.

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