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Commentary

Curb complement to cure COVID-19

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The disastrous consequences of severe acute respiratory syndrome following infection with coronavirus 2 (SARS-CoV-2) are responsible for the current pandemic resulting in an escalating number of cases and fatalities worldwide [1,2]. Before the current pandemic of the associated coronavirus disease 2019 (COVID-19), there had been two major coronavirus pandemics: The Middle Eastern respiratory syndrome (MERS) in 2012 and the 2002 SARS outbreak [3]. Therapeutic intervention for pandemics with coronaviruses will be an infinite challenge as the virus transmits from one species to another and mutates. Many predictions threaten that novel pandemic-causing strains will appear in the future unless an efficient vaccine or targeted therapy is produced. Preliminary evidence suggested the cause of adverse outcomes in infected individuals was associated with the excessive production of interleukin-6 (IL-6), a key inflammatory mediator of the so-called "cytokine storm" or "cytokine release syndrome" (CRS) [4,5]. Apart from the FDA approved a recombinant monoclonal antibody against human IL-6 receptors (tocilizumab), empirical treatment modalities for people with COVID-19 have included corticosteroids, cytokine inhibitors, intravenous immunoglobulin, and other novel anti-inflammatory molecules [6]. The lack of effective vaccines has encouraged efforts to advance the COVID-19 therapies exploiting several antiviral, anti-inflammatory and immune modulating treatments [7–10]. However, the exact mechanisms of excessive inflammation and hypercoagulation in COVID-19 patients remain perplexing and poorly understood. Complete understanding of the pathogenesis of COVID-19 will therefore be necessary to identify pharmacological targets for the development of effective therapies in anticipation of future pandemics.

The complement system is a major part of innate immunity and comprises a cascade of proteins that directly or indirectly destroy invading organisms and damaged cells, and interacts with the adaptive immune system extra- or intra-cellularly [11–14]. There is cumulative evidence for the existence of a cross-talk between the complement and coagulation pathways (Fig. 1) which allows prompt amplification of their otherwise targeted responses and contributes to devastating and prolonged systemic inflammation [11]. Preliminary evidence from current COVID-19 and past coronavirus epidemics suggests that patients suffer from thrombotic complications with poor outcome caused by imbalanced complement activation as well as disproportionate coagulation [15,16]. An obstinate task is to understand how the excessive activation of the complement cascade in people with COVID-19 is associated with thrombosis. Therapeutics based on targeting complement molecules has gained interest as potential drug candidates for treating the detrimental sequelae of infection with SARS-CoV-2 [17]. Whether C3 inhibition can deliver the same or superior therapeutic effects with terminal pathway inhibitors (i.e, C5 or C5aR1 inhibitors) remains to be determined. Early clinical reports have indicated that C3 inhibition can abrogate COVID-19 hyperinflammation promoting resolution of SARS-CoV-2-associated ARDS [26] and that administration of the anti-C5 humanized monoclonal antibody (mAb) eculizumab may lead to complete recovery [18].

In the accompanying manuscript Mastellos and colleagues [19] compared for the first time the clinical and biological efficacy of the compstatin-based C3-targeted drug AMY-101 (Amyndas) with that of C5-targeting monoclonal antibody eculizumab (Soliris) in small independent cohorts of patients with severe COVID-19 [19]. The early clinical results reported in this paper have revealed clinical characteristics that reflect the differential mechanistic basis of complement inhibition in the complex pathology of COVID-19. The preliminary findings indicated that C3 inhibition is associated with a broader therapeutic profile in COVID-19 patients, marked by faster lymphocyte recovery, decrease in neutrophil numbers and significant reduction of neutrophil extracellular traps (NET)-driven thromboinflammation. The findings by Mastellos and colleagues advocate the broader clinical potential of C3 inhibition in COVID-19 patients and support previously subtle aspects of complement's pathogenic contribution in COVID-19. Further research and larger prospective trials will be needed to validate the clinical efficacy of complement C3 inhibitor AMY-101 in severe COVID-19 patients and its superiority to other complement inhibitors.

In summary, the intricate immune dysregulation witnessed in patients with severe COVID-19 remains a therapeutic challenge. The pharmacological targeting of complement activation may mitigate the increased mortality observed in patients with adamant thromboinflammation, renal failure, cardiac arrest and terminal respiratory failure associated with SARS-CoV-2 pneumonia. As both complement and coagulation cascades activate complex inflammatory networks and show many analogous characteristics regarding the specialized

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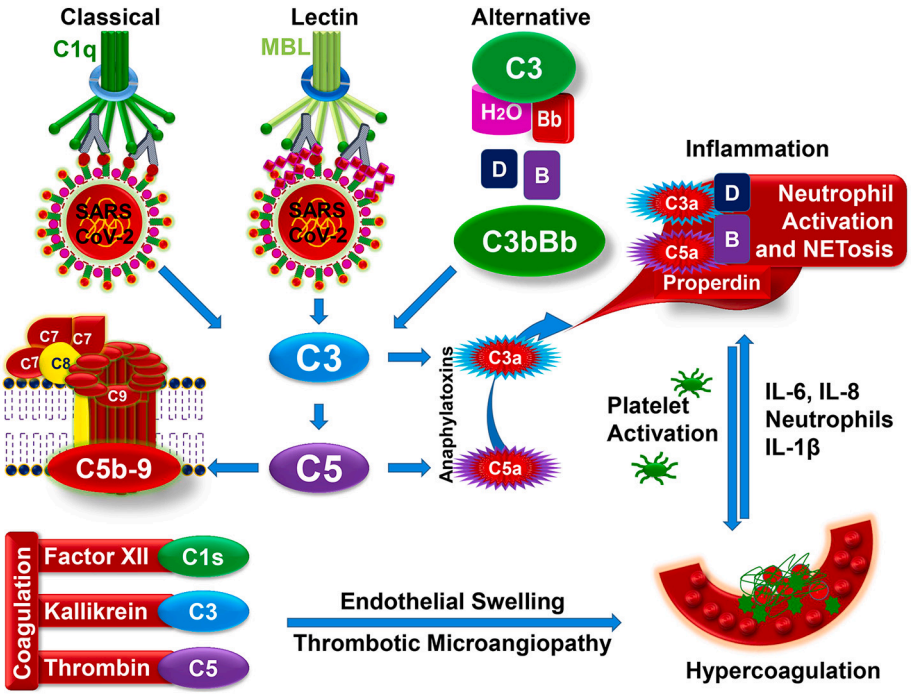

Fig. 1. Crosstalk between complement and coagulation cascade in COVID-19: There are 3 major self-regulating and overlapping pathways of complement activation system. The classical pathway triggered by binding of SARS-CoV antigens with immunoglobulins (IgG or IgM) to form immune complexes, which bind to the complement component (C) 1 complex. These antibodies are not necessarily the ones produced in to response to the virus as naturally occurring antibodies are known to bind injured cells and activate complement [21]. The lectin pathway is activated by the binding of mannose-binding lectin (MBL) with the viral spike protein. The classical and lectin pathways lead to the formation of the C3 convertase (C4bC2a) of the classical/lectin pathways. The alternative pathway is uninterruptedly activated in plasma by hydrolysis of C3 which forms C3(H2O) and promptly engages factors B (B) and D (D) to form a C3 convertase [C3(H2O)Bb] of the alternative pathway. The C3 convertases cleave C3 into C3a, an anaphylotoxin, and C3b, which deposits on cell surfaces. Additionally, C3b contributes to the formation of the C5 convertases that cleave C5, producing the anaphylatoxin C5a that attracts and activates inflammatory leukocytes, and C5b. C5b initiates the late events of complement activation, leading to the formation of the C5b-9 membrane-attack complex (MAC). C3a and C5a are potent chemoattractants for neutrophils and monocytes. Activated neutrophils generate web-like extracellular traps (NETs), in a process recognized as NETosis, that surround components such as C3, properdin, factor D (D) and factor B (B) that activate the alternative complement pathway and engage an inflammation. MAC also induces endothelial damage and tissue injury. MAC-induced endothelial injury results in thrombosis which stimulates the release of serine proteases, such as thrombin and kallikrein. It was shown that thrombin [22] and kallikrein [23] is capable of activating complement system. Complement activation product C5a can be cleaved by thrombin in the absence of C3a [24]. Factor XII cleaves C1s and thereby activates the classical complement pathway [25]. These alterations amplify a crosstalk between complement and coagulation pathways. Such interactions among endothelial injury, NETosis, inflammation, hypercoagulability, and complement activation cause tissue damage, such as acute kidney injury (AKI), acute respiratory distress syndrome (ARDS), stroke, and are frequently accompanying with a thrombotic microangiopathy.

functions of their activators and inhibitors, complement and coagulation modulating therapies ideally will gain a place in an evolving armamentarium of COVID-19 treatment approaches. Existing *in vitro* platforms [20] can also be utilized to study the biology of COVID-19 related cellular injury and drug toxicity. Patient friendly well-designed clinical investigations will be needed to determine the outcomes of complement inhibition in lager cohorts without creating any imbalance between viral clearance and prevention of secondary infections. Vigilant observation should be of paramount importance to observe beneficial and adverse effects associated with therapeutic complement inhibition.

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