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The roles and potential therapeutic implications of C5a in the pathogenesis of COVID-19-associated coagulopathy

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\textbf{ABSTRACT}

Emerging evidence has documented that multisystem organ failure in coronavirus disease 2019 (COVID-19) patients is strongly associated with various coagulopathies. Treatments for COVID-19-associated coagulopathy are still a clinical challenge. An advancement in the knowledge of mechanisms of the excessive or inappropriate activation of the complement cascade involved in the genesis of COVID-19-associated coagulopathy might be a fundamental approach for developing novel classes of anticoagulant drugs. In this context, there is emerging evidence indicating that C5a, a component of the complement system, and its receptors (C5aRs) play a critical role in the genesis of the COVID-19-associated hypercoagulable state. Thus, this review describes the mechanisms by which C5a/C5aR signaling participates in the cascade of events involved in the pathophysiology of COVID-19-associated coagulopathy. Furthermore, it highlights the current possibilities for the development of a novel therapeutic approach for COVID-19 patients that targets C5a/C5aRs signaling.

1. Introduction

The global pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) \cite{1} has afflicted more than 17 million individuals worldwide. As of today (October 5, 2020), SARS-CoV-2 has infected 35,027,546 people and killed over 1,034,837 worldwide (data from regularly released WHO reports) \cite{2}. Clinically, patients with coronavirus disease 2019 (COVID-19) have labored breathing, progressive hypoxemia, elevated D-dimer levels and fibrin/fibrinogen degradation products \cite{3}. The distinctive features of COVID-19 pulmonary autopsy specimens include diffuse intravascular coagulation and large vessel thrombosis \cite{4}, which are linked to multisystem organ failure, including acute respiratory distress syndrome (ARDS), heart failure and kidney failure. Although additional research is needed to elucidate the relationship of these findings with the clinical course of COVID-19, emerging evidence documents that multisystem organ failure in COVID-19 patients is strongly associated with various coagulopathies. The latest data suggest that the incidence of thrombotic complications is between 16% and 49% in patients with COVID-19 admitted to intensive care units \cite{5}. However, a central question that could inform the management of COVID-19-associated coagulopathy remains under debate: are the hemostatic changes a consequence of severe inflammation, or are they a specific effect mediated by the virus \cite{5}?

The pathogenesis of COVID-19-associated coagulopathy has not been fully elucidated. However, recent studies have indicated that thrombotic coagulopathy in COVID-19 patients is mediated through C5a and its receptors (C5aRs) \cite{9}. In this article, we summarize recent developments in our understanding of the role of C5a in mediating COVID-19-associated coagulopathy.

2. Complement cascade activation

The complement system plays an important role in host defense...
against microbial infection. However, the complement cascade can be excessively or inappropriately activated through three major pathways (namely, the classical, alternative and lectin pathways) in different courses of COVID-19 [6]. The classical pathway is activated by the C1q/r/s complex assembled on antigen-bound antibodies or in an antibody-independent manner, resulting in generation of the cofactor C4b, which accelerates enzymatic generation of C3a, C3b and the mild anaphylatoxin C4a [7]. The lectin pathway is initiated by mannose binding lectin (MBL)/MBL-associated serine proteases (MASPs) attached to carbohydrates on the surface of microorganisms. Both pathways converge to release C3 convertase (C4b2b). The alternative pathway is constitutively active at a low level due to the spontaneous breakdown of C3 into anaphylatoxin C3a and the active C3b fragment. C3b also serves to generate the next generation of C5 convertases. C5 convertases cleave the C5 molecule into the C5a anaphylatoxin and the C5b fragment, which initiates the terminal MAC and target cell lysis.

Fig. 1. Complement cascade activation pathway. The classical pathway is activated by the C1q/r/s complex, and the lectin pathway is activated by MBL/MASPs attached to carbohydrates on the surface of microorganisms. Both pathways converge to release C3 convertase (C4b2b). The alternative pathway is constitutively active at a low level due to the spontaneous breakdown of C3 into anaphylatoxin C3a and the active C3b fragment. C3b also serves to generate the next generation of C5 convertases. C5 convertases cleave the C5 molecule into the C5a anaphylatoxin and the C5b fragment, which initiates the terminal MAC and target cell lysis.

resulting in cell death [9]. A schematic representation of the complement cascade activation pathway is shown in Fig. 1. As a potent inflammatory mediator and chemoattractant, the complement anaphylatoxin C5a contributes to endothelial barrier loss and organ injury and potentially enhances the pathogenesis of COVID-19-associated coagulopathy [10].

3. Clinical presentations of COVID-19-associated coagulopathy

Coagulation disorders are emerging as an important issue in patients with COVID-19 [11]. COVID-19 is associated with thrombogenic coagulopathy with a range of presentations [12]. Preliminary reports on initial coagulopathy of COVID-19 have shown that infected patients may have elevated D-dimer (46.4 %) and commonly develop thrombocytopenia (36.2 %) [13], and these rates are even higher in patients with severe COVID-19 (59.6 % and 57.7 %, respectively) [13]. Emerging data support that prominent elevation of D-dimer and fibrin/fibrinogen degradation product levels and abnormalities in platelet counts, prothrombin time, and partial thromboplastin time are associated with poor prognosis in patients affected by the novel
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ischemic injury. Altering the hemostatic balance with subsequent coagulation-induced lysis pathways contributes to COVID-19 severity, possibly through inhibitor; activation of protein C, which promotes fibrin generation and limits minogen activator inhibitor-1 (PAI-1) and tissue factor pathway inhib

4. COVID-19-associated coagulopathy and disease severity

Findings from the SARS-CoV-2 pandemic indicate that the presence of coagulopathy is consistently associated with disease severity and mortality in patients with COVID-19. Coagulopathy has been reported in up to 50% of patients with severe COVID-19 manifestations [17]. Autopsy studies of patients who died of COVID-19 identified small vessel occlusion and endotheliitis in the lungs, kidneys, liver, heart, and intestine [18]. Additionally, a recent study indicated that multiple processes may contribute to COVID-19-associated microvascular and macrovascular thrombosis. These processes include cytokine storm with activation of leukocytes, endothelium and platelets, resulting in upregulation of tissue factor, activation of coagulation, thrombin generation and fibrin formation; disrupted coagulation with imbalances in plasminogen activator inhibitor-1 (PAI-1) and tissue factor pathway inhibitor; activation of protein C, which promotes fibrin generation and limits fibrinolysis; and direct viral effects resulting in cell activation [17]. These findings highlight that dysregulation of coagulation and fibrinolysis pathways contributes to COVID-19 severity, possibly through altering the hemostatic balance with subsequent coagulation-induced ischemic injury.

The complete spectrum of presentations of COVID-19-associated coagulopathy has not been fully elucidated. Both α-dimer elevation and thrombocytopenia can be explained by the excessive activation of the coagulation cascade and platelets [[11]]. Multiple pathogenic mediators are involved in the imbalance between procoagulant and anticoagulant homeostatic mechanisms in COVID-19, including endothelial Dysfunction [19], neutrophil activation and neutrophil extracellular trap (NET) release [20,21], and complement system activation [22]. Emerging data suggest that C5a activation provides rapid protection from infectious challenge and can also transition to the ‘dark side’, becoming a driver or exacerbator of pathology in COVID-19-associated coagulopathy [10,23].

5. C5a and C5aRs in COVID-19

Human C5a is a 74-amino acid protein composed of four α-helices in an antiparallel configuration with bridging disulfide bonds. It is formed by cleavage of the amino terminus of C5 by the C5a convertase in the plasma. C5a exerts its functions via two distinct receptors, C5aR1 and C5aR2 [24], both of which harbor seven transmembrane (7 T M) helix architectures. C5aR1, also referred to as CD88, is a prototypical G-protein-coupled receptor (GPCR) [24] that is expressed on all cells of myeloid origin (such as neutrophils, subpopulations of monocytes, and macrophages), some lymphocytes, and many nonmyeloid cells, including epithelial cells [25]. The C5a-C5aR1 interaction is generally acknowledged to have proinflammatory roles in promoting adhesion molecule expression, chemotaxis, degranulation, phagocytosis, and oxidative bursts. From a signaling perspective, C5a-C5aR1 activation alters cAMP/PKA, ERK1/2, p38 MAPK, calcium mobilization, and β-arrestin (jarrr)–mediated signaling responses to modulate cytokine production and secretion [26]. However, uncontrolled activation of the C5a-C5aR1 axis has been associated with a myriad of acute and chronic inflammatory diseases [25].

Interestingly, Skendros and colleagues demonstrated that C5aR1 blockade attenuates platelet-mediated, NET-driven, COVID-19-associated thrombogenicity [27]. These data presented in a recent study support the role of the C5a-C5aR1 axis in inflammatory mechanisms underlying coagulopathy development in patients at early or late stages of SARS–COV-2 infection [28].

C5aR2, also referred to as C5L2 or GPR77, is abundantly expressed in human tissues, such as the bone marrow, spleen and lungs [25]. It displays predominant intracellular expression in most myeloid cells and selected T cell subsets, such as neutrophils, monocytes, monocyte-derived macrophages, and NK cells [29]. Although a detailed mechanism of C5aR2 signaling and its functional consequences remains to be elucidated, recent progress has shown that C5aR2 binds C5a and desarginated C5a (C5a-desArg) and internalizes them for intracellular degradation, thereby providing a negative regulatory mechanism to remove excess C5a from the circulation [25]. C5aR2 serves as a negative regulator and balancer of C5aR1 surface expression and helps to prevent overactivation of C5aR1 [28]. Additionally, C5aR2 induces robust high mobility group box 1 (HMGB1) production upon C5a stimulation associated with MEK1/2, JNK1/2, and PI3K/Akt activation [30]. C5aR2 also exerts significant immunomodulatory effects on other pattern recognition receptors and innate immune systems, such as NOD-like receptor protein 3 (NLRP3) inflammasomes [31].

Fatal COVID-19 has been associated with a systemic inflammatory response accompanied by a coagulopathy state and organ damage, particularly microvascular thrombi in the lungs and kidneys. As the strongest inflammatory peptide in the complement cascade that induces proinflammatory cytokine release [32], C5a and C5aRs involved in the pathogenesis of SARS-CoV-2 infection were examined in a recent study [33]. We review recent developments in the role of C5a in mediating COVID-19-associated coagulopathy through the prism of Virchow’s triad.

6. C5a and vessel wall abnormalities in COVID-19

Emerging studies have shown that extensive endotheliitis in the lung, heart, kidneys, liver, and small bowel is associated with an accumulation of inflammatory cells in patients with severe COVID-19 [34]. Endothelial cell swelling with foam-like changes, subendothelial expansion, and endothelial proliferation were observed in COVID-19-associated endotheliitis [35]. Deposition of the complement-derived fragment C5 in lung autopsies [36] and elevated circulatory levels of C5a were observed in severe cases of COVID-19 [33]. Together with evidence that treatment of COVID-19 patients with an anti-C5a antibody led to immediate clinical improvement, as measured by increased lung oxygenation and decreased systemic inflammation [33], we support the hypothesis that C5a, as a potent anaphylatoxin, plays a critical role in the pathogenesis of COVID-19-associated endotheliitis. The proposed central role of endothelial cells in contributing to the initiation and propagation of severe COVID-19 prompts the question of whether vascular normalization strategies could be useful in the management of COVID-19-associated coagulopathy [37]. Three clinical trials have been registered for off-label compassionate use of eculizumab to verify the use of a complement C5 inhibitor for the treatment of patients with COVID-19 (ClinicalTrials.gov Identifiers: NCT04288713, NCT04346797, and NCT04355494) [34]. Normalization of the vascular wall through a C5a inhibitor could be considered a potential route of intervention in COVID-19-associated coagulopathy.

7. C5a and altered blood flow in COVID-19

The vascular endothelium is a dynamic endocrine, paracrine, and autocrine organ with a vital role in regulating vascular tone and homeostasis. Secretion by the endothelium includes fibrinolytic agents, antiplatelet agents and venodilators, which in turn are related to the rheological properties of the blood. Through control of the degree of vascular relaxation and constriction, the endothelium regulates regional
blood flow [38]. Endothelial dysfunction leads to abnormalities in the anticoagulant and fibrinolytic mechanisms, abnormalities of blood coagulation factors (such as increases in plasma D-dimer, circulating thrombin and activated protein C) and detrimental shifts in the vascular equilibrium towards vasoconstriction, inflammation, and a procoagulant state resulting in thrombosis [39, 40]. Recently, emerging studies have shown that thrombotic events in COVID-19-associated coagulopathy are associated with endothelial cell dysfunction [19]. Moreover, Henry et al. proposed that complement activation and direct viral invasion of the endothelium could be responsible for endothelial dysfunction [41]. Several underlying mechanisms associated with COVID-19-associated coagulopathy have not been clearly defined, but the association of endothelial dysfunction with COVID-19 and enhancement of the activated complement components C5a and C3a has been verified in severe COVID-19 patients [42].

The glycocalyx is a thick coat of proteins and carbohydrates on the outer surface of the vascular endothelium [43]. It is formed by glycoproteins and proteoglycans (PG) and has a multilayer structure that reduces endothelial contact with cellular and macromolecular blood components. The glycocalyx plays an important role in vascular homeostasis, regulating vascular permeability and cell adhesion [44]. It can also act as a mechanotransducer, enabling the detection of mechanical stress through its intracellular protein domain [44]. The link between the glycocalyx and vascular endothelial cell dysfunction in COVID-19 is not clearly defined [45]; however, evidence increasingly suggests that COVID-19 induces multiple injuries, including damage to the endothelial glycocalyx and endothelial dysfunction, which has been attributed to endothelial activation and dysfunction [46]. Interestingly, Bongoni et al. demonstrated that complement protein C5a plays a key role in endothelial dysfunction through damage to the vasculoprotective endothelial glycocalyx [47]. The combination of endothelial dysfunction and complement C5a may contribute to the overall procoagulative state described in COVID-19.

8. C5a and hypercoagulability of blood in COVID-19

Recent prospective studies of autopsy findings from consecutive deaths from COVID-19 found that thromboembolic events were a common cause of mortality in patients infected with COVID-19 [48]. Initial cohort studies showed that the incidence of thromboembolic complications in patients with COVID-19 is 35–45 % [49]. As the pandemic is spreading and the complete details are yet unknown, these emerging studies provide important insight into the hypercoagulable state and thromboembolic events associated with COVID-19 [50].

The underlying pathophysiology contributing to the hypercoagulable state may be related to the cytokine storm, which is characterized by high concentrations of proinflammatory cytokines and chemokines.
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9. Experimental and clinical therapeutic applications of C5a

Inhibitors of complement C5a have long been of interest as potential drugs for the treatment of diseases such as sepsis, ischemia-reperfusion injuries, atypical hemolytic-uremic syndrome (aHUS), antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, rheumatoid arthritis, and inflammatory bowel disease [66-68]. More recently, a role of C5a inhibitors in viral infectious diseases, such as COVID-19, has been identified. In general, these small molecule C5a inhibitors can be divided into three types: anti-C5a antibodies (mAbs) [69], C5a antagonists [66], and chimeric C5a compounds (C-terminal- or N-terminal-modified C5a) [70].

BDB-001 is a mouse-human chimeric antibody against human C5a [33]. Experimental results demonstrated that BDB-001 can significantly alleviate N protein-induced C5a activation and lung injury in vitro and in vivo [33]. Moreover, clinical outcomes in eculizumab (an anti-C5a complement mAb)-treated COVID-19 patients showed significant improvements in respiratory symptoms and radiographic pulmonary lesions and a decrease in circulating D-dimer levels [65]. Currently, clinical trial outcomes also suggest that C5a antagonists, as anticoagulants, could be employed to minimize lung damage and prevent systemic involvement in COVID-19 patients [71]. Zilucoplan is a small compound composed of a 15-amino acid macrocyclic peptide that binds to C5 with high affinity and specificity [72]. In the field of C5 complement therapeutics for COVID-19 (shown in Table 1), a recent registered clinical trial (EudraCT 2020–001736-95, registered April 28, 2020) has been undertaken to evaluate the safety and efficacy of zilucoplan in COVID-19 patients [12,73].

10. Conclusion

Collectively, the present review strongly indicates that activation of the complement anaphylatoxin C5a plays a significant role in the extensive endothelitis, endothelial dysfunction, and hypercoagulable state in COVID-19 patients; contributes to the generation of endothelial barrier loss and organ injury and potentially enhances the pathogenesis of COVID-19-associated coagulopathy. Moreover, the increasing body of data demonstrates that targeting C5a and C5aR signaling will lead novel therapeutic options for the prevention or attenuation of the hypercoagulable state that is currently observed in patients with COVID-19.

Declaration of Competing Interest

The authors report no declarations of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jcytogr.2020.12.001.

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