Annals of Hematology (2020) 99:1701–1707
https://doi.org/10.1007/s00277-020-04138-8

REVIEW ARTICLE

COVID-19-driven endothelial damage: complement, HIF-1, and ABL2 are potential pathways of damage and targets for cure

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Received: 1 June 2020 / Accepted: 9 June 2020 / Published online: 24 June 2020

Abstract

COVID-19 pandemia is a major health emergency causing hundreds of deaths worldwide. The high reported morbidity has been related to hypoxia and inflammation leading to endothelial dysfunction and aberrant coagulation in small and large vessels. This review addresses some of the pathways leading to endothelial derangement, such as complement, HIF-1α, and ABL tyrosine kinases. This review also highlights potential targets for prevention and therapy of COVID-19-related organ damage and discusses the role of marketed drugs, such as eculizumab and imatinib, as suitable candidates for clinical trials.

Keywords COVID-19 · SARS-CoV · Complement · Thrombosis · Eculizumab · Imatinib · Endothelium · HIF-1-alpha

Introduction

The new coronavirus (SARS-COV-2) pandemic has rapidly spread to many countries [1] and caused several thousand deaths. Endothelial derangement and increased permeability are reported to be early hallmarks of organ damage in patients with COVID-10, such as lungs, kidney, and myocardium. Moreover, thrombotic complications are a relevant cause of death in patients with COVID-19. Finally, the interaction of SARS-CoV-2 with ACE2 possibly implies alterations of angiotensin II plasma levels. Therefore, the vascular system is increasingly being addressed as a major therapeutic target for defeating COVID-19 [2, 3].

The present paper in particular reviews some of the pathways leading to endothelial disruption in the course of COVID-19 infection, namely complement activation, hypoxia, platelets, and thyroxin kinases. Furthermore, the paper explores potential therapeutic strategies, particularly commercially available drugs, such as imatinib.

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Complement-mediated pathogenesis

Complement system and inflammation

Complement system is a 30 protein network belonging to both the innate and the adoptive immune system: it has opsonization properties, but it also enhances the activity of antibodies and macrophages in eliminating pathogens and damaged cells. C5a anaphylatoxin, a central complement protein, is involved in sepsis and acute lung injury mediated by CC-chemokine receptor 5 [4, 5]. C5a leads to exaggerated early proinflammatory responses and activation of neutrophils and macrophages (by the activation of PI3K/Akt and MAPK signaling pathways), with subsequent release of histones and reactive oxygen species that ultimately lead to endothelial damage, inflammation, and thrombosis; a functional decline of the innate immune system and multiorgan dysfunction follows [6, 7]. Moreover, C5a is involved in pyroptosis, which is a form of programmed cell death by a lytic modality catalyzed by caspase and aimed at eliminating immune cells infected by pathogens. Due to cell membrane break, pyroptosis induces an inflammatory damage and release of caspase, which activates interleukin-1. C5a itself also causes substantial cardiomyocyte dysfunction, which is reversed by complement blockade [8].

Complement and lung injury

Also, C3a complement fraction plays a relevant role in the pathogenesis of infection-related lung injury: high serum C3a predicts evolution to ARDS [9, 10], while both C3a and C5a increase endothelial permeability and activate endothelial cells, thereby increasing the expression of adhesion molecules and cytokines [11, 12], and the distal complement activation product C5 b-9 triggers intracellular fluxes of calcium in epithelial and endothelial cells. The vicious cycle might be sustained by hypoxia, which reduces the expression of CD55, a complement regulator, by HIF-1alpha, IL-2, and TNFα. This downregulation enhances C3a release and caspase 3 deposition onto endothelial cells [13]. The complement damage may also be triggered by some specific infective agents, such as staphylococcus, that provoke shedding of anti-complement surface proteins CD55 and CD59 from endothelial cells thus favoring cell lysis [14].

Complement and vascular damage

Complement also proved to be relevant for survival in patients with heart failure and sepsis-related miocardiopathy [15, 16]. Moreover, tocilizumab proved to reduce C5A receptor in myocardial infarction patients; therefore, its anti-cytokine efficacy in COVID-19 may be partly mediated by attenuation of complement hyperactivation [17]. In fact, SARS-CoV can directly activate complement system by lectin way and particularly acts onto T-lymphocytes in hypertensive patients, since an increased expression of C5a receptor has been reported in Treg Foxp3+ lymphocytes from these individuals [18]. Tissue damage by complement activation seems to be a common way to many pathogen viruses, including H1N1 influenza, SARS, CoV-2, and MERS-CoV [19–24]. Preliminary data show that C5a mediates MERS-CoV and SARS-CoV-2-induced pyroptosis in infected macrophage, dendritic cells, and CD4+ lymphocytes [24, 25]. C3 knockout mice proved to be resistant to organ damage induced by SARS-CoV, while the high serum and pulmonary concentrations of C5a and C5b-9 reported in mice infected with MERS-CoV and SARS-CoV could not cause lung damage if a C5a receptor inhibitor was administered [23, 25]. Inhibition of C5a or C3a receptor reduced lung damage and prolonged survival also in mice infected with H1N1 influenza virus [26]. Moreover, a reduced MERS-CoV viral replication was observed after inhibition of C5a receptor [23].

Anti-complement drugs

Specific inhibition of C5a biological activity could gain therapeutic benefit without affecting the protective immune response. In the last few years, several peptide and non-peptide antagonists of C5a have been discovered and tested in relevant pharmacological models.

Treatment with eculizumab, the first-in-class terminal complement inhibitor, reported a rate of meningococcal infection of 0.25/100 patient years and no deaths in patients temporarily treated with the drugs, i.e., patients with atypical hemolytic uremic syndrome, while the risk of meningococcus-related death was 3/10,000 patient years in chronically treated individuals [27]. Eculizumab was successfully used to treat virus-related hemolytic uremic syndrome (cytomegalovirus, human immunodeficiency virus, herpes zoster virus, influenza B virus) with no reported immunosuppressive effects [28–30]. The SOLID-C19 (NCT04288713) expanded access study is currently testing 900 mg administration of eculizumab weekly in patients with COVID-19 ARDS, and the PANAMO phase II study in The Netherlands (NCT04333420) is currently testing IFX-1, an anti-complement (C5a) monoclonal antibody.

Endothelial damage

Endothelial cells represent one-third of overall lung cells. Baseline endothelial damage may be chronically caused by increased adiponectins in diabetic and obese patients: this effect is related to the activation of inflammosome NLRP3 and autocrine production of IL-1β [31]. Additional damage to pulmonary endothelial dysfunctional cells is acutely provoked by infections and in turn causes excess thrombin generation and reduced fibrinolysis [32–34]. In fact, most dangerous infective agents, such as Dengue 2, adopt an adiponectin-like mechanism of endothelial damage [35].

Thrombin causes further endothelial damage, which can be prevented in vitro by CXCR4 agonists, such as ubiquitin [36]. Moreover, hypoxia may lead to increased hypoxia inducible factor-1α (HIF-1α) expression and hypercoagulability [37]. Therefore, a higher rate of thrombotic episodes is reported in patients with COVID-19 pneumonia, while increased vascular permeability seems to be strongly related to increased thrombosis. In particular, in patients with lymphopenic pneumonia and organ failure increased vascular permeability was strongly correlated with severe lymphopenia [30].

Lung computed tomography of patients infected with SARS-CoV-2 shows an earlier interstitial edema followed by a subsequent alveolar edema, which questioned the similarity of COVID-19 lung damage and ARDS. In pathology samples from COVID-19 patients, diffuse microcirculatory and macrovascular thrombosis have been detected in lung tissue, which is not typical for ARDS, and when a few endothelial cells were directly infected by SARS, several macrophages were instead [38]. However, no evidence of vasculitis has been reported by pathologists and no laboratory signs of diffuse intravascular coagulopathy were found in most of the patients, since antithrombin-III, fibrinogen, and platelet count rarely decline in the first phases of the disease, while D-dimer

usually shows a progressive increase during hospital stay and predicts a higher mortality [39]. Angiopoietin 2, thrombomodulin, ICAM 1, endothelin, and E-selectin are usually increased in cases of endothelial damage; however, quantitative data from COVID-19 patients are still awaited. Rather, severe early hypoalbuminemia and subsequent increased CPK, myoglobin, creatinine, and uric acid are observed in the majority of patients with COVID-19, resembling systemic capillary leak syndrome and explaining some cases of renal failure. Hypoalbuminemia is also a relevant prognostic factor of the lung injury prediction score in sepsis [40].

Apoptosis of human pulmonary microvascular endothelial cell may be chronically triggered by inflammation, such as in COPD, or acutely induced by ARDS; the latter is mediated by Bruton kinase (BTK), IL-17, and macrophage stimulating-1, while IL-35 seems protective [41–44]. LDH is typically released into the serum by apoptotic endothelial cells [42]. A different kind of damage to lung microvascular endothelial cells, namely autophagy, may be induced by NADPH oxidase 2 during viral infections, but prevented by NADPH oxidase 4 as a protecting way against oxidative stress [45, 46]. Furthermore, endothelial cells of lymph vessels in the lungs are particularly sensible to oxidative stress and might be the most damaged cell population in SARS-CoV-2 infection [47].

Drugs and endothelium

Several drugs can damage the endothelium. Endothelial damage secondary to ponatinib is mediated by NOTCH1 hyperactivation, but also propranolol and sirolimus inhibit endothelial proliferation and carteolol induces apoptosis in corneal endothelial cells by caspase- and mitochondria-dependent pathways [48–50]. Also, ACE2, a SARS-Cov-2 target, inhibits proliferation of endothelial cells; however, it also reduces endothelial inflammation [51]. Finally, steroids induce apoptosis in bone endothelial cells causing osteonecrosis, but such an effect has not been proven in pulmonary capillary cells.

A shorter list of drugs prevent endothelial apoptosis, namely recombinant adenosine deaminase, registered for SCID ADA deficient patients, casin, and plerixafor, which markedly expand endothelial proliferation in vitro, inducing also tubing and sprouting [51, 52]. However, cyclin-dependent kinases are upregulated by plerixafor, and endothelial permeability is therefore reduced [36].

Adrecizumab is a first-in-class monoclonal antibody targeting ad stabilizing plasma bioactive adrenomedullin (bio-ADM ®), a key hormone secreted by endothelial cells showing vasoprotective activity, preserving endothelial barrier function (i.e., keeping tight junctions) and preventing vascular leakage (ref shock 2018)[53]. Conversely, in the interstitium ADM has dangerous vasodilatory properties at high concentrations. The ongoing AdrenOSS-2 trial (NTC03085758) has enrolled 301 patients with early septic shock and high serum levels of bio-ADM: patients were randomized to receive adrecizumab or placebo in addition to standard care. Preliminary data confirmed the treatment safety (BJCP phase I) and showed a trend to a reduced 28-day mortality as compared with 28% in the placebo group (www.adrenomed.com).

Platelets

The role of platelets in inducing or amplifying the endothelial damage in COVID-19 patients is unknown. A low platelet count, possibly due to consumption, bone marrow infection, or autoimmune phenomena, was reported to increase COVID-19 mortality rate by five-fold, even though the rates were very heterogeneous among the analyzed studies [54–56]. Moreover, the opposite is more common in COVID-19 patients, being its platelet counts quite high or higher than in patients with sepsis or ARDS; increased serum levels of thrombopoietin caused by pulmonary inflammation have been supposed to explain this phenomenon [57].

Anti-thrombotic drugs

Organ damage to skin, CNS, heart, and kidney appears to be related to transient thrombotic or ischemic phases (hypoperfusion, hypoxemia). Heparin proved to protect tight junctions in alveolar endothelial cells from IL-6 induced hyperpermeability and thus may possibly improve the outcome of COVID-19 patients [39, 58]. It also antagonizes histones released from damaged cells by histone methylation and interaction with MAPK and NF-kB pathways [59, 60]. Furthermore, heparin has well-documented anti-inflammatory properties that include binding to inflammatory cytokines, inhibiting neutrophil chemotaxis and migration, neutralizing the positively charged C5a, and sequestering acute phase proteins [61]. Heparin polyanionic nature also seems to interact with SARS-CoV-2 spike S1 protein receptor binding domain (https://www.biorxiv.org/content/10.1101/2020.02.29.971093v1.full). Several COVID-19 cases reported atypical thromboses (renal veins, uterine veins, mesenteric vessels) and myocardial micro-thrombotic vessels; however, a large portion of thromboembolic events occurred in patients receiving prophylactic heparin doses. Furthermore, some centers reported the need for high heparin doses to achieve a target aPTT ratio in these patients and no standard level of anticoagulation has yet been established. Early, i.e., domiciliary, antithrombotic prophylaxis, and subsequent dose titration according to ARDS severity still need to be validated, especially in selected patients, such as older patients, those receiving antiplatelet therapies, and those with renal failure.

Defibrotide and rTPA have also been proposed to rescue patients with severe thrombotic events. Full (UFH 15,000 U/day or enoxaparin 60 mg/day) or intermediate (UFH 10,000/day or enoxaparin 40 mg/day) heparin dose was reported to

benefit COVID-19 patients with higher platelet counts and higher D-dimer levels [57]. An English trial is currently assigning patients to either aspirin 75 mg, clopidogrel 75 mg, rivaroxaban 2.5 mg, or omeprazole versus standard of care, in order to prevent cardiac complications of COVID-19 8 (NCT04333407). Other antiplatelet agents, such as prasugrel, a P2Y12 inhibitor, proved to reduce prost-myocardial infarction inflammation and might be a potential drug to be tested in the context of COVID-19-induced endothelial inflammation [62].

Hypoxia-mediated endothelial damage

Also, hypoxia is expected to play a central role in leading inflammation and endothelial activation: cells adapt to hypoxia by activating hypoxia-inducible factors HIF-1 and HIF-2 which in turn induce the expression of a number of genes promoting energy metabolism and cell survival and specifically endothelial cell adaptation (migration, growth, differentiation) (Whyte–hypoxia). A transition from HIF-1 to HIF-2 governs adaptation from acute to prolonged hypoxia, despite most genes may be regulated by both [63]. HIF-2α upon activation increases the expression of vascular-endothelial protein thyrosine phosphatase, which in turn decreases VE-caderin phosphorylation, supporting the integrity of adherens junctions and preventing loss of endothelial barrier function [64]. Contrarily, expression of HIF-1α in alveolar epithelial cells enhances lung inflammation in a NF-kB mediated way [65] and favors a cell-mediated inflammation (CD4+ CD8+) and proinflammatory cytokines (IL-2 and TNFα), which proportionately downregulate CD55 and augment complement-mediated endothelial damage [8]. Moreover, myeloid cell HIF-1α is a key driver of myeloid cell response in hypoxic and inflammatory microenvironments by modulating cellular energetics, upregulating glycolytic enzymes and glucose transporters to permit ATP generation under conditions of hypoxia, and preventing apoptosis of innate immunity cells. In chronic infections, however, HIF-1α was reported to prevent excessive lymphocyte recruitment into lung interstitium and avert immunopathological consequences to the host [66]. Despite there are no currently marketed drugs achieving a selective control of HIF-1α, imatinib proved to reduce HIF-1α levels and pulmonary hypertension caused by chronic hypoxia [67, 68].

The activation and damage of pulmonary endothelium is a hallmark of ARDS, and ACE+ circulating endothelial microparticles are markers of pulmonary endothelial injury predicting development of ARDS in septic patients [69]. Endothelial damage has been shown to induce the recruitment of circulating endothelial cells: circulating mature endothelial cells increased in patients with moderate or severe ARDS as compared with mild ARDS or non-ARDS septic patients [70]. Increased circulating endothelial progenitor cells (EPC) proved to positively correlate with survival [71]. However, also overall CD34+ CD45+ circulating cell count is associated with improved survival in sepsis-related ARDS. Inhaled nitric oxide was reported to induce mobilization of endothelial cell progenitors from bone marrow into circulation, contributing to repair lung vascular injury in vivo, while autotransplanted endothelial progenitor cells protected mice from LPS-induced lung injury [72, 73]. No data are yet available regarding phase-related mobilization of mature or progenitor endothelial cells during COVID-19 infection. Beta-blockers favor migration of endothelial progenitor cells mediated by SDF-1 thanks to the inhibition of beta2adrenergic receptors onto circulating mononuclear cells and bone marrow stem cells [74].

Finally, an increased synthesis of hyaluronic acid seems to explain the huge shift of liquids into the interstitium of patients with SARS-CoV-2-related endothelial damage and respiratory failure. This phenomenon, however, might be counteracted by marketed hymecromone or intranasal hyaluronidase [75–77].

Imatinib

The permeabilizing action of VEGF on the endothelium of the pulmonary capillaries, typical of ARDS, can be counteracted by inhibiting ABL2 (Arg). Imatinib is an ABL1 and ABL2 tyrosine kinase inhibitor with EMA designation of orphan drug for the treatment of ARDS (January 12, 2015) by virtue of its demonstrated in vitro and in vivo ability to attenuate the expression of VCAM-1 in endothelial cells, restoring VE junctions-caderine and thus reducing the ARDS secondary to sepsis, mechanical ventilation, and ischemia and mediated by VEGF, thrombin, and histamine [78–81]. Also, the anti-cytokine action of imatinib, mediated by the inhibition of the NF-kB pathway in myeloid-derived cells, has been widely demonstrated with efficacy in asthma, rheumatoid arthritis, systemic sclerosis, and pulmonary hypertension [82, 83]. Several cases of acute lung inflammation induced by toxic agents (bleomycin, gemcitabine) or sepsis got rapid clinical improvement after treatment with low doses of imatinb [84, 85]. Furthermore, the immunomodulatory action of imatinib is proven: the inhibition exerted on c-Kit in bone marrow stem cells favors the mobilization of myeloid cells already at low doses [86]. In primates with concomitant HIV infection and *Mycobacterium tuberculosis*, imatinib has demonstrated an effective action directly to the host [87]. A phase II clinical trial (IMPACT-TB, NCT03891901) is enrolling patients with mycobacteriosis TB (± HIV) to concomitant imatinib therapy.

Finally, a direct anti-viral action of imatinib has also been documented: it appears to inhibit the fusion of SARS-CoV2 with the late endosome membrane at micromolar doses (EC 50 9.8 μM/L), a phase necessary for subsequent viral replication [88–90]. Based on the above rational, the COUNTER-COVID-randomized, placebo-controlled, clinical trial is currently enrolling in Amsterdam (*EudraCT* number, 2020-001236-10).

Discussion

Several pathways have been identified as possible drivers in the pathogenesis of SARS-CoV-2: some pathways, such as the complement, may be targeted by available drugs, while some others are orphan of specific therapies, such as HIF-1α and HIF-2α. Several drugs currently marketed for blood diseases, such as imatinib, ruxolitinib, heparins, tocilizumab, and eculizumab, are currently being tested for patients with COVID-19 symptoms. Hematologists, who are expert on such drugs, are therefore called into multidisciplinary teams for managing patient selection and therapy monitoring. While awaiting vaccines and effective antiviral therapies, their expertise needs to be combined with the updated evidence on the pathogenesis of COVID-19, as they have the chance to contribute to amelioration of patient outcomes. Appropriate trial designs still need to be developed in order to address some fundamental issues, such as COVID-19 patient stratification and testing of multiple drugs. Furthermore, trials are challenged by heterogeneous support therapies for COVID-19 and partial non-comparability of patients belonging to different clinical centers. Nevertheless, most of the above cited candidate drugs have a favorable safety profile, especially in the short term, and are promising tools for defeating COVID-19.

Compliance with ethical standards

Conflict of interest MM has received speaker honorarium from Novartis and consultant fees from Gilead.

Ethical approval This article does not contain any studies with human participants performed by any of the authors.

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