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Biochemical Pharmacology 197 (2022) 114909

Contents lists available at ScienceDirect

Biochemical Pharmacology

journal homepage: www.elsevier.com/locate/biochempharm

Review

Vascular endotheliitis associated with infections: Its pathogenetic role and therapeutic implication

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ARTICLE INFO

Keywords:
COVID-19
Endothelial cells
Endotheliitis
Organ dysfunction
Sepsis

ABSTRACT

Vascular endothelial cells are major participants in and regulators of immune responses and inflammation. Vascular endotheliitis is regarded as a host immune-inflammatory response of the endothelium forming the inner surface of blood vessels in association with a direct consequence of infectious pathogen invasion. Vascular endotheliitis and consequent endothelial dysfunction can be a principle determinant of microvascular failure, which would favor impaired perfusion, tissue hypoxia, and subsequent organ failure. Emerging evidence suggests the role of vascular endotheliitis in the pathogenesis of coronavirus disease 2019 (COVID-19) and its related complications. Thus, once initiated, vascular endotheliitis and resultant cytokine storm cause systemic hyper-inflammation and a thrombotic phenomenon in COVID-19, leading to acute respiratory distress syndrome and widespread organ damage. Vascular endotheliitis also appears to be a contributory factor to vasculopathy and coagulopathy in sepsis that is defined as life-threatening organ dysfunction due to a dysregulated response of the host to infection. Therefore, protecting endothelial cells and reversing vascular endotheliitis may be a leading therapeutic goal for these diseases associated with vascular endotheliitis. In this review, we outline the etiological and pathogenic importance of vascular endotheliitis in infection-related inflammatory diseases, including COVID-19, and possible mechanisms leading to vascular endotheliitis. We also discuss pharmacological agents which may be now considered as potential endotheliitis-based treatment modalities for those diseases.

1. Introduction

The endothelium, a single layer of squamous endothelial cells that lines the interior surface of blood vessels and lymphatics, not only serves as a physical barrier that restricts the flow of substances and fluid into and out of tissues, but also emerges as a key player in regulating the homeostasis of vascular tone by releasing vasodilatory factors, such as nitric oxide (NO) and prostacyclin, and vasoconstrictive factors, such as endothelin-1 and thromboxane A_2 (TXA_2) [1,2]. The endothelium is also a source of a wide variety of factors that locally regulate permeability, cell growth and migration, platelet function, and inflammation [3–5]. Since inflammation crucially involves adhesion, vascular leak, and infiltration of immune cells as well as activation of these infiltrated immune cells [6], it becomes clear that endothelial cell activation can contribute to vascular and ultimately tissue inflammation, although the role of vascular adventitia and vasa vasorum in vascular inflammation has been described based on studies on atherosclerosis [7,8].

Endotheliitis (or endothelialitis) is recognized as inflammation of the endothelium lining the lumen of blood vessels in association with a direct consequence of infectious pathogen invasion and the host immune

Abbreviations: NO, nitric oxide; TXA_2, thromboxane A_2; HSV, herpes simplex virus; CMV, cytomegalovirus; COVID-19, coronavirus disease 2019; TLR, Toll-like receptor; NF-κB, nuclear factor-κB; VCAM-1, vascular cell adhesion molecule-1; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; ARDS, acute respiratory distress syndrome; ACE2, angiotensin-converting enzyme-2; CNS, central nervous system; MIS, multisystem inflammatory syndrome; ICAM-1, intracellular adhesion molecule-1; vWF, von Willebrand factor; TF, tissue factor; TNF-α, tumor necrosis factor-α; AP-1, activating protein-1; ROS, reactive oxygen species; IL, interleukin; eNOS, endothelial nitric oxide synthase; GR, glucocorticoid receptor; GRE, glucocorticoid response elements; IR-6R, interleukin-6 receptor; ASA, acetylsalicylic acid.

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https://doi.org/10.1016/j.bcp.2022.114909
Received 28 November 2021; Received in revised form 3 January 2022; Accepted 4 January 2022
Available online 10 January 2022

response. The term "endotheliitis" was initially employed when the corneal endothelium was inflamed by virus causes, including herpes simplex virus (HSV), cytomegalovirus (CMV), and mumps virus [9–11].

Intriguingly, the existence of vasculitis and vasculopathy has been highlighted as a defining feature of numerous systemic complications of coronavirus disease 2019 (COVID-19) that is an ongoing global concern [12,13]. Especially, emerging evidence suggests that vascular endotheliitis may be the underlying pathological process that can lead to multiple organ failure and even death in COVID-19 [14–16]. It thus appears that endotheliitis in blood vessels may play a pathogenic role in the development and progression of diseases that manifest systemic inflammation and end-organ damage. However, a greater understanding has not been so far promoted as to the entity of endotheliitis from the perspective of basic and clinical medicine.

In this review article, we cover the topic of vascular endotheliitis associated with infections, addressing mainly COVID-19. We thus provide an overview about the historical context of endotheliitis, the etiology of endotheliitis, the contributory role of endotheliitis in different diseases, and possible mechanisms underlying the endotheliitis development. We also discuss the potential endotheliitis-based treatment modalities for infection-related inflammatory diseases.

2. Corneal endotheliitis

The cornea is the clear outermost surface of the eye that covers the iris, pupil, and anterior chamber, and allows light to enter the eye. The corneal endothelium is a monocellular layer lining the posterior cornea and plays an integral role in regulating corneal hydration and clarity. Corneal endotheliitis is a spectrum of disorders in which the corneal endothelium is the primary site of inflammation. It is characterized by corneal edema, keratic precipitates, and mild anterior chamber reaction, and its most common symptoms include eye pain, photophobia, and visual disturbances [9,11].

Corneal endotheliitis was first reported as two cases that occurred secondary to autoimmune corneal graft rejection and were improved with corticosteroid administration by Khodadoust and Attarzadeh in 1982 [17]. Subsequently, accumulating evidence has shown that the disease etiology consists of various viral infections, including HSV, varicella zoster virus, mumps virus, and CMV [9–11]. In addition, Epstein-Barr virus, coxsackie virus, and rhabdovirus have been implicated as a case of corneal endotheliitis [11]. Several bacteria, such as *Staphylococcus aureus*, *Pseudomonas aeruginosa*, coagulate-negative *Streptococci*, and *Streptococcus pneumoniae*, may cause inflammation of both the corneal epithelium and endothelium, but there are no reports in the literature of isolated endotheliitis of bacterial origin [9]. Fungal origin, which is a well-documented cause of stromal and interstitial keratitis, may be considered in case of infectious endotheliitis refractory to antiviral treatment, although it appears to be extremely rare [11].

The pathogenesis of corneal endotheliitis is not fully understood. When the role of Toll-like receptors (TLRs), pattern-recognition receptors that initiate innate immune responses to microbial infections [18], in viral corneal endotheliitis has been examined using immortalized human corneal endothelial cells, it has been observed that TLR9, which recognizes bacterial or viral DNA and RNA containing unmethylated CpG motifs [19], is highly expressed within the cell and that HSV-1 infection can stimulate nuclear factor-κB (NF-κB) activity and induce NF-κB-related pro-inflammatory cytokines and chemokines in human corneal endothelial cells [10,20]. The up-regulation of pro-inflammatory cytokines and chemokines in corneal endothelial cells infected with HSV-1 could be reduced by treatment with a TLR9 inhibitory oligonucleotide [10,20]. These results suggest that TLR9 signaling may play a major role in inflamedeness in viral corneal endotheliitis.

A choice of treatment regimen for corneal endotheliitis is dependent on the underlying etiology of the disease process. Topical administration of steroids is generally used to suppress inflammation, and, if viral infection is suspected, concomitant antivirus agents can be applicable [9,11]. Intravitreous injection of foscarnet, an antiviral prescription medicine classified as a pyrophosphate analog DNA polymerase inhibitor, may be considered in resistant cases of CMV or HSV endotheliitis [11]. However, no guidelines are currently established for dosage of treatment of viral endotheliitis [11]. Further understanding of molecular pathogenesis of corneal endotheliitis may be helpful to find out more effective treatment of this disorder.

3. Endoteliitis in hepatitis

In the liver, endotheliitis has been considered to be an important histologic feature of acute liver transplant rejection and graft-versus-host disease [21]. However, endotheliitis can occur in a variety of liver diseases with a varying incidence and activity, such as acute hepatitis and liver cirrhosis [22]. In liver biopsies of patients with chronic hepatitis due to hepatitis C viral infection, endotheliitis-like changes have been demonstrated to predominate in small portal veins[23]. Portal endotheliitis appear to be more common with higher grade hepatitis C [24]. No significant difference has been reported in the scores of endotheliitis between hepatitis C and hepatitis B [25]. Portal vein endotheliitis can be defined as lymphocyte attachment to endothelial cells [22]. It is thus considered to be an intimate lymphocyte-endothelial cell interaction universally associated with active hepatic inflammation [22]. Although the pathogenesis of endotheliitis-like changes in chronic hepatitis C is not known so far, endotheliitis-like changes may represent a reaction related to the inflammatory response to hepatitis virus and be attributed to immune-mediated mechanisms taking place in close vicinity, and endothelial cells in small portal veins may be the site of direct immune-mediated damage [26].

Histochemical examination of a liver biopsy of patients with autoimmune hepatitis, a form of hepatitis that is characterized by autoantibodies and hypergrammaglobulinemia, also show central vein and hepatic sinusoidal endotheliitis [26]. In this study, it has been suggested that central vein and sinusoidal endothelial cells promote the activation of dendritic cells in autoimmune hepatitis [26]. This endotheliitis is likely to stem from the subendothelial infiltration of dendritic cells and their activation of cytotoxic T cells [27]. Vascular cell adhesion molecule-1 (VCAM-1) expression was evident in hepatic sinusoids and the central vein in autoimmune hepatitis [26]. VCAM-1 plays a major role in inducing changes to the shape and structure of endothelial cells during transendothelial migration of leukocytes [28]. In this regard, the integrins lymphocyte function adhesion molecule-1 (LFA-1) and very late antigen-1 (VLA-1, CD49a/CD29) on dendritic cells may also play an important role in their firm adhesion to endothelial cells and their transmigration to sites of immune action [29]. However, it is still unsettled whether a similar molecular process of cell adhesion is responsible for the genesis of endotheliitis in infectious hepatitis.

4. Endotheliitis in COVID-19

Since the outbreak of a contagious disease by the novel coronavirus, now called severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), in Wuhan, Hubein province, China in December 2019, COVID-19 has spread to many countries in a blink and the World Health Organization (WHO) classified COVID-19 as a worldwide pandemic in March 2020. Clinically, the symptoms that are quite usual with COVID-19 include fever, cough, shortness of breath, and loss of sense of taste and smell. Furthermore, COVID-19 patients suffer from a broad spectrum of clinical respiratory symptoms, ranging from mild upper airway symptoms to progressive pneumonia that can occasionally develop into an atypical form of acute respiratory distress syndrome (ARDS) [14,30,31,32,33]. The most severe stage of COVID-19 is characterized by systemic hyperinflammation and hypercoagulopathies, thereby resulting in multiple organ failure and eventually death [34].

SARS-CoV-2 binds to the integral membrane protein angiotensin-

converting enzyme-2 (ACE2) receptor [35,36]. The ACE2 receptor is abundantly expressed in the lungs, the respiratory epithelium, and alveolar monocytes [37], which may explain the many cases of rapidly occurring lung failure. The ACE2 receptor is also expressed widely by endothelial cells in the macrovascular system, lung, heart, kidney, intestine, liver, and central nervous system (CNS) [38–41]. Therefore, endothelial cells can directly be infected by SARS-CoV-2. In addition, further receptors which can mediate the entry of SARS-CoV-2 are present on the surface of human cells. These receptors include sialic acid receptors [42], transmembrane serine protease (TMPRSS) 2 [43], and extracellular matrix metalloproteinase inducer (CD147) [44]. It should be noted that these receptors are also expressed by endothelial cells [45–47].

Ackermann *et al.* [14] have examined the morphological and molecular features of lungs obtained during autopsy from patients who died from COVID-19, and have discovered significantly greater number of ACE2 receptor-positive cells in capillaries from lungs of patients with COVID-19 than in those from healthy controls. Furthermore, transmission electron microscopy of the COVID-19 endothelium has shown the presence of SARS-CoV-2 virus within the endothelial cells [14]. Significant changes in endothelial morphology, including cell swelling, disruption of intracellular junction, and basal membrane contact loss, have been detected in the specimens from patients who died of COVID-19-associated respiratory failure [14]. All lung specimens from patients with COVID-19 have diffuse alveolar damage, which may be attributed to pulmonary vascular endotheliitis along with direct viral invasion. Moreover, Varga *et al.* [16] have provided evidence for SARS-CoV-2 infection to endothelial cells in several organs and widespread endothelial inflammation and injury involving apoptosis, and have asserted this state as endotheliitis with viral elements within endothelial cells and recruitment of inflammatory immune cells. Additionally, Smadja *et al.* [48] have revealed that angiopoietin-2, which is a maker of endothelial damage, is significantly elevated in critical COVID-19 patients. These findings strongly indicate that systemic endotheliitis, which can cause endothelial injury and dysfunction in blood vessels in principle organs, including lung, heart, kidney, and brain, plays a key role in the pathobiology of COVID-19, and thus protecting endothelial cells and reversing endotheliitis may be an essential therapeutic goal [49].

Endotheliitis may be associated with thrombus formation in COVID-19. The levels of coagulation markers such as D-dimers have been shown to be elevated in blood from patients with severe COVID-19 [50]. Autopsy reports have revealed widespread microvascular thrombi in the lungs of deceased patients [14,51]. Another study has also shown that the pattern of COVID-19 pneumonitis is predominantly a pauci-inflammatory septal capillary injury accompanied by significant deposits of membrane attack complex and complement lectin pathway activators in the microvasculature [52], which is in accordance with the idea that severe COVID-19 may cause a catastrophic microvascular injury syndrome that includes activation of complement pathways, endotheliitis, and an associated procoagulant state. In severe COVID-19, furthermore, an atypical form of ARDS, which was named microvascular COVID-19 lung vessels obstructive thromboinflammatory syndrome (MicroCLOTS), has been documented [53]. MicroCLOTS presents as a progressive, diffuse endothelial thromboinflammatory syndrome that is characterized by the development of microvascular pulmonary thrombosis [53]. The formation of platelet microthrombi has also been reported in liver biopsy samples from COVID-19 patients in the postmortem study [54]. While unperturbed endothelial cells display potent anti-coagulant and profibrinolytic properties, endothelial cell injury can lead to procoagulant behavior [55]. Considering that the endothelium loses its physiological roles in regulating homeostasis, fibrinolysis, and antiaggregation by endothelial injury and dysfunction, immunothrombosis could be triggered, resulting in coagulopathy far and wide in patients with COVID-19 [56]. Consequently, a narrowing of organ-supplying arteries as well as abnormal microcirculatory disorders in major organs occurs in severe COVID-19 [57]. Diffuse intravascular coagulation and large-vessel thrombosis can be linked to multiple organ failure in COVID-19 patients [58–60]. Taken together, systemic endotheliitis likely plays a central role in the development of COVID-19-related procoagulant state resulting in thrombosis and manifesting clinically as respiratory failure and multi-organ dysfunction, and could explain fatal outcomes in patients with COVID-19.

Most children and adolescents with SARS-CoV-2 infection have mild COVID-19 leading no medical intervention, but Kawasaki-like disease has been reported in pediatric patients with multisystem inflammatory syndrome (MIS) associated with SARS-CoV-2 infection [61,62]. Kawasaki-like disease and MIS reported in children with COVID-19 share similarities with Kawasaki's disease: coronary artery aneurysms and Kawasaki's disease-like features have been documented [62]. Unlike Kawasaki's disease, however, early reports have suggested that Kawasaki-like disease and MIS can affect adolescents and children older than 5 years of age and are associated with more frequent cardiovascular involvement [62]. Histopathological examination has shown evidence for cardiac endotheliitis as pathologic characteristics of MIS after COVID-19 [63]. Kawasaki-like disease can typically occur in children and adolescents without discernible COVID-19 pneumonia or active infection, implying that direct viral infection is unlikely to be a factor [64].

Clinically manifesting CNS symptoms have been documented in patients with COVID-19. In a review of 214 patients hospitalized in three dedicated COVID-19 hospitals in Wuhan, China, 36% of COVID-19 patients had neurological symptoms, including dizziness, headache, disturbed consciousness, and paresthesia [65]. Patients with severe SARS-CoV-2 infection may represent ischemic stroke [66] and even fetal intracerebral hemorrhage [67]. Autopsy reports have shown brain tissue edema and partial neuronal degeneration in deceased patients [68]. Furthermore, the postmortem exam has found evidence for cerebral petechial hemorrhages and microthrombi in brain autopsies from SARS-CoV-2-infected patients [69]. This study has also reported intravascular lymphocytic and monocytic inflammation with occasional apoptosis in the brain vasculature, consistent with the presence of intracerebral endotheliitis, in the patients diagnosed with SARS-CoV-2 infection [69]. Thus, cerebral endotheliitis may be responsible for the cerebrovascular pathology in COVID-19 and contribute to an increased risk of ischemic stroke and hemorrhagic encephalopathy. It is notable that higher ACE2 receptor expression in brain vasculature of COVID-19 patients with cerebral endotheliitis can be detected than in COVID-19 patients without cerebral endotheliitis or than in control patients [69].

Hypertension, diabetes, heart failure, coronary heart disease, smoking, and advanced age are known to be risk factors for severe COVID-19. Interestingly, they have a certain thing in common: their vascular endothelial function is significantly impaired [70]. If the patients with pre-existing endothelial dysfunction become infected with SARS-CoV-2, aggregation of endothelial dysfunction by COVID-19 endotheliitis may impair organ perfusion and cause a procoagulant state leading to macro- and microvascular thrombotic events. Recent reports have also revealed a robust and independent association of obesity with COVID-19 severity [71,72]. In obesity, there exists low-grade chronic inflammation, and this status is conditioned by dysregulated endocrine and paracrine actions of adipocyte-derived factor, which could in turn disrupt vascular homeostasis and lead to endothelial dysfunction [73]. Although the exact mechanisms by which COVID-19 can be exacerbated in obesity are not fully understood, it seems plausible that obese subjects with pre-existing endothelial dysfunction are vulnerable to a more severe disease course given the critical role of the endothelium in vascular homeostasis and tissue perfusion.

In summary, COVID-19 is not limited to a disease affecting the respiratory tract but is a multisystem syndrome in which systemic endotheliitis may play a pathogenic role. Thus, an accumulating body of evidence points toward a crucial role of endotheliitis in the pathogenesis of COVID-19 (Fig. 1). Endotheliitis as well as direct viral effects on vasculature would bring about endothelial injury and dysfunction,

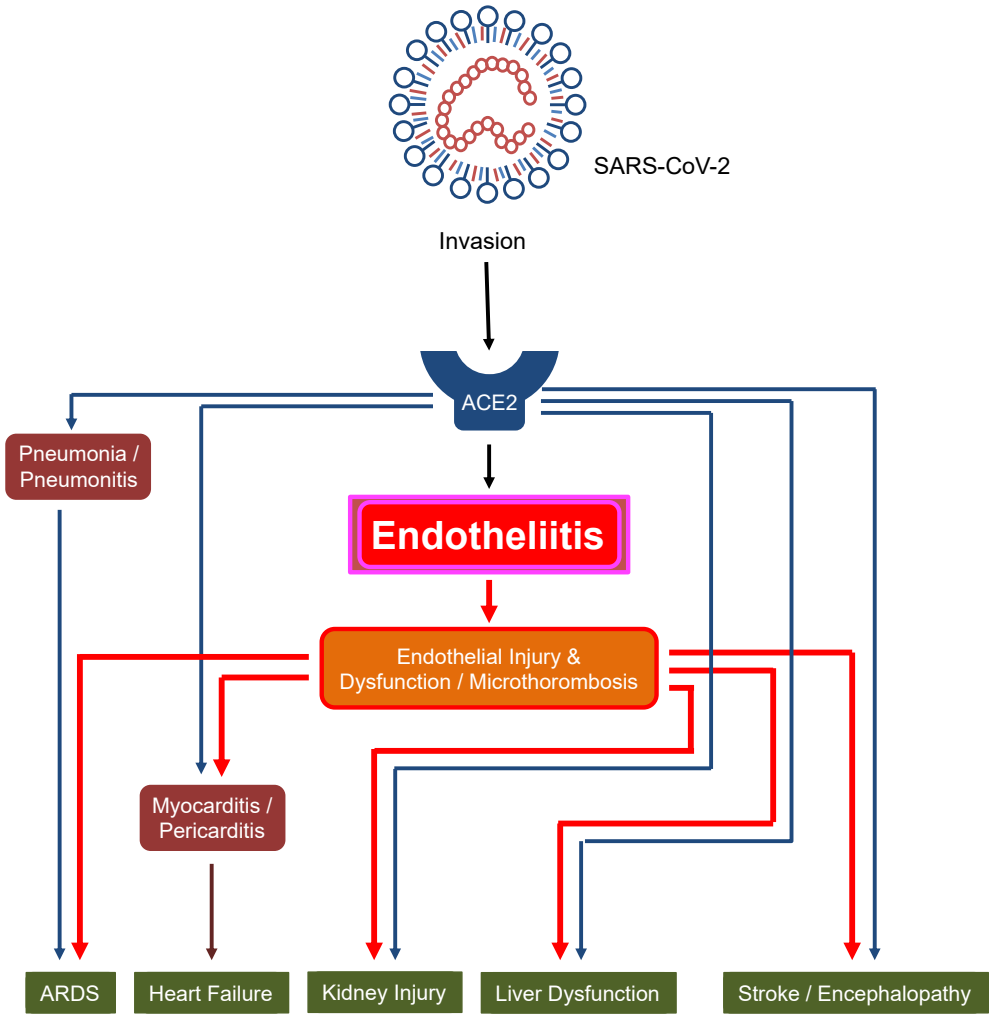

Fig. 1. Schematic diagram depicting endotheliitis to contribute to systemic complications in COVID-19. The ACE2 receptor is abundantly expressed in human tissues. It is also widely expressed on vascular endothelial cells in major organs, such as the lung, heart, kidney, and liver, allowing endothelial cells to be infected by SARS-CoV2 and leading to vascular endotheliitis. Vascular endotheliitis may be situated as the sequence of cellular events leading to endothelial injury and dysfunction. SARS-CoV2 infection can cause lung complications such as interstitial pneumonia ranging from mild to severe clinical conditions. While the subsequent immune reaction may lead to progressive interstitial and alveolar edema, impairing gas exchange and eventually resulting in ARDS, vascular endotheliitis likely plays a pivotal role in the development of ARDS. Widespread endotheliitis can also adversely affect other organs beyond the lung, importantly the heart, kidney, and liver.

which could contribute to functional derangements of different internal organs in COVID-19 in consequence of vasculopathy and coagulopathy. Future studies may focus on the multifaced role and therapeutic targeting of endotheliitis, endothelial injury, and endothelial dysfunction in COVID-19 and its complications.

5. Possible presence of endotheliitis in sepsis

Sepsis and its sequalae are the leading cause of mortality in the critically ill patient population. It is fully accepted that sepsis represents a continuum of a syndrome encompassing multiple pathological processes, including systemic inflammation, coagulopathy, and systemic vascular collapse, and sepsis is now defined as life-threatening organ dysfunction due to a dysregulated response of the host to infection [74]. Indeed, sepsis can affect major organs in the body, such as lung, liver, kidney, and heart, ultimately leading to their failure. The development of the failure of one or more organs poses a major threat to the survival of patients, and sepsis mortality is most often attributable to multiple organ dysfunction [75].

The pathological process in the development of multiple organ dysfunction in sepsis is incompletely understood. Vascular endothelial activation and dysfunction are critical hallmarks of sepsis, which likely play a key role in the sepsis phenotype [76–79]. Endothelial activation *per se* is not harmful because it represents a physiological adaptation to different stimuli and can be considered a response to injury [80]. However, endothelial activation is an early step in fueling endothelial damage. In sepsis, vascular endothelial cells become activated and dysfunctional, causing hemostatic disturbance, increased leukocyte trafficking, amplified inflammation, altered vasomotor tone, and loss of barrier function [79,81,82,83]. Consequently, disturbed endothelial function could play an integral role in microvascular dysfunction which is characterized by heterogeneous perfusion of tissues due to the lack, or intermittent perfusion, of capillaries adjacent to those with normal perfusion [84]. The heterogeneity of microcirculation in sepsis can be considered to break down tissue oxygenation, leading to hypoxic areas even in the presence of preserved total blood flow to organs [85]. Microvascular failure would favor impaired perfusion, tissue hypoxia, and subsequent organ failure. Accordingly, vascular endothelial activation and dysfunction may be a primary cause of organ damage in sepsis [79].

The interaction of endothelial cells with neutrophils or monocytes plays a crucial role in the pathogenesis of sepsis [78]. This interaction is transmitted by adhesion molecules to which leukocytes anchor themselves, allowing them to eventually stray into extravascular tissues. The surface expression of adhesion molecules, such as P-selectin, E-selectin, VCAM-1, and intracellular adhesion molecule-1 (ICAM-1), are strikingly up-regulated in endothelial cells when activated by bacterial products or pro-inflammatory cytokines [86–89]. Selectins serve as a medium for sticking and rolling, while VCAM-1 and ICAM-1 are the key in mediating firm adhesion and act as a gatekeeper of leukocyte transendothelial migration. In such moments, leukocytes can release inflammatory mediators and reactive molecules to destroy pathogens, but at the same time their release would lead to endothelial damage. Alternatively, exposure to bacterial products or pro-inflammatory cytokines would

result in the inflamed endothelium which may be referred to as endotheliitis.

Vascular endothelial cells express and synthesize the molecules that are vital in regulating hemostasis, including von Willebrand factor (vWF), tissue factor (TF), and plasminogen activator inhibitor type 1 (PAI-1) [78]. When the inflammatory host response to infection become exaggerated in association with the severity of sepsis, excessive inflammation drives hemestasis toward a prothrombotic and anti-fibrolytic state, leading to disseminated microvascular thrombosis, organ ischemia, and ultimately multiple organ dysfunction syndrome [78,90]. The blood clotting protein vWF can be considered as a marker of inflammation and endothelial activation, and accelerates platelet adhesion to the damaged vessel wall and thrombus formation on a collagen surface under flow condition [91,92]. In sepsis, the procoagulant glycoprotein TF can be highly released not only by mononuclear phagocytes such as monocytes and macrophages but also by endothelial cells [93]. Meanwhile, TF pathway inhibitor, which is predominantly expressed by endothelial cells, is both consumed and degraded in sepsis, abetting a procoagulant state [94]. Although activated protein C is a potent anticoagulant that also displays profibrinolytic and anti-inflammatory properties, the protein C system is significantly impaired in sepsis possibly due to accentuated consumption and limited activation of protein C resulting from the down-regulation of endothelial expression of thrombomodulin and endothelial protein C receptors [95]. In severe sepsis, furthermore, the synthesis of the serine protease antithrombin, a natural antagonist to thrombin that is activated several fold by circulating heparin-like substances, is down-regulated and its consumption is markedly increased due to ongoing thrombin formation [96], which would accelerate a procoagulant state. In addition, the fibrinolytic pathway in sepsis is suppressed by the increase in the release of PAI-1 from activated endothelial cells and platelets. Such a series of imbalances can ultimately lead to the dissemination of fibrin-rich microvascular thrombi which is observed as the development of overt disseminated intravascular coagulation (DIC) in septic patients [78].

Vascular endothelial cell apoptosis may play a contributory role in the development of endothelial dysfunction in sepsis, producing multi-organ failure. Apoptosis has been considered to be a second prominent feature of sepsis [97–99]. Over the last a few decades, abundant *in vitro* studies have shown that endothelial cell apoptosis can occur in response to bacterial products or pro-inflammatory cytokines [99–101]. Endothelial apoptosis has been also revealed in *in vivo* rodent models of sepsis [102–104]. Furthermore, an increase in circulating endothelial cells has been identified in septic patients [105], suggesting that vascular endothelial cell apoptosis may occur in human sepsis. Indeed, evidence for vascular endothelial cell apoptosis has been reported in postmortem biopsies obtained from patients who had died of sepsis-related ARDS [106]. Interestingly, it has been demonstrated that the prevention of vascular endothelial apoptosis by in vivo systemic delivery of siRNAs targeting caspase-8/caspase-3 or Fas-associated death domain (FADD) can confer a survival advantage in mice with microbial sepsis [107,108]. However, we need to take into account that the survival benefit of caspase-8/caspase-3 or FADD siRNAs may arise from the preventive effect on apoptotic death of not only vascular endothelial cells but also of other cell types, such as lymphocytes and parenchymal cells.

Evidence is emerging to suggest that vascular endotheliitis appears to be a contributory factor to vasculopathy and coagulopathy in sepsis. On a background of endothelial dysfunction, systemic endotheliitis likely plays a pivotal role in the pathogenesis of sepsis leading to multiorgan failure syndrome. Further understanding of the pathogenic role of endotheliitis in sepsis would be imperative to delineating clinical implications for adverse outcome prevention and potential therapeutic interventions.

6. Pathogenetic mechanism of infection-associated vascular endotheliitis

Vascular endotheliitis could be attributed to adhesion molecules, pro-inflammatory cytokines, and pro-inflammatory chemokines, which would be released by activated endothelial cells or leukocytes (Fig. 2). Endothelial cells may be activated by bacterial products, pro-inflammatory cytokines, or direct viral infection of endothelial cells. In activated endothelial cells, expression on endothelial surfaces of adhesion molecules, such as P-selectin, E-selectin, VCAM-1, and ICAM-1, is promoted [86–89]. The signal transduction pathways for these adhesion molecules in vascular endothelial cells appear to include the transcription of NF-κB [86,109]. This can be supported by the finding that the inhibition of NF-κB by the use of a truncated IκBα protein is refractory to the up-regulation of E-selectin and ICAM-1 expression in human endothelial cells stimulated with tumor necrosis factor (TNF)-α [110], although it has also been reported that TNF-α induces expression of c-Fos and c-Jun, which together bind to an activating protein-1 (AP-1) consensus element to enhance the transcription of VCAM-1 [111]. Furthermore, activated endothelial cells characteristically produce reactive oxygen species (ROS) at an accelerated rate, which can contribute to transcription-dependent adhesion molecule expression and synthesis by activating NF-κB and AP-1 [112–114]. The up-regulation of endothelial cell adhesion molecule expression induced by pro-inflammatory cytokines and oxidative stress would allow for a sustained increase in leukocyte rolling, firm adherence, and trans-migration. Whereas, some naturally occurring biological substances in endothelial cells, such as NO and prostacyclin, appear to serve as endogenous anti-adhesion molecules by which leukocyte-endothelial cell adhesion is largely absent in the normal healthy microcirculation. The endothelial activated state would tip the balance between NO production and ROS generation in favor of the latter and thereby forward the adhesion of leukocytes to vascular endothelium.

Different subsets of leukocytes, such as neutrophils and monocytes, can also produce ROS [115]. Since ROS are components of innate immunity [116], these leukocyte subsets play a role as innate immune cells and serve as key players against infections. Indeed, most immune cells possess high levels of functional NADPH oxidases and may be capable of generating ROS at much higher levels than vascular endothelial cells [117,118]. ROS from adhered immune cells would further promote an oxidative environment and lead to facilitating endothelial cell activation and priming the endothelium for the adhesion of additional circulating immune cells from the bloodstream, which could contribute to endothelial injury and eventually dysfunction [116,119]. Furthermore, these immune cells express a broad range of pro-inflammatory cytokines, such as TNF-α and interleukin (IL)-6, that are responsible for the inflammatory process and endothelial damage. When pro-inflammatory cytokines are driven from the inflamed organs and are accumulated in the bloodstream, they could also make a contribution to the development of vascular endotheliitis.

7. Potential pharmacotherapy targeting vascular endotheliitis

A number of medicinal drugs with endotheliitis-targeted therapeutic properties may be an ideal potential therapeutic candidate for prevention and treatment of the development of multiorgan dysfunction in infection-associated inflammatory diseases. Numerous clinical trials have been conducted and are underway to assess the therapeutic potential of these drugs. Here we offer potential therapeutic interventions that could target vascular endotheliitis with a central focus on treatment of COVID-19 (Table 1).

7.1. Statins

Statins, which are widely prescribed for treatment of lipid disorders, may be a promising agent for treating vascular endotheliitis. They can

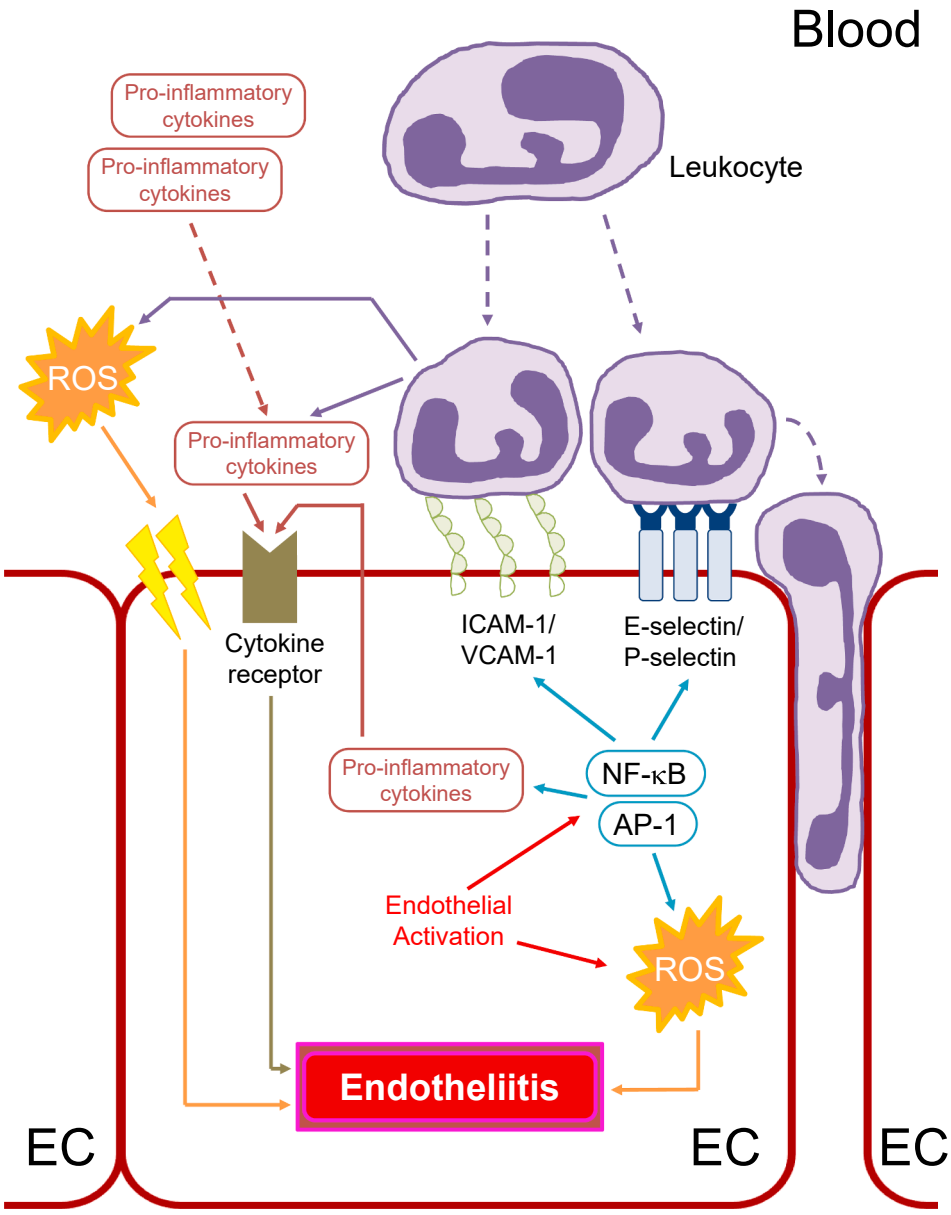

Fig. 2. Scheme illustrating initiations of vascular endotheliitis. When endothelial cells are activated, expression on endothelial surfaces of adhesion molecules, such as ICAM-1, VCAM-1, E-selectin, and P-selectin, is promoted by activating NF-κB and AP-1, thereby facilitating leukocyte rolling, adherence, and transmigration. Endothelial firm adhesion of circulating leukocytes from the blood stream contributes to the development of endotheliitis through the release of pro-inflammatory cytokines and the generation of extracellular ROS. Endothelial ROS are formed and pro-inflammatory cytokines are produced by activated endothelial cells. They are also responsible for developing endotheliitis. Pro-inflammatory cytokines, which are induced by inflammation due to tissue damage or infection and are carried in the blood, also play a role in the endotheliitis development. EC = endothelial cells.

Table 1
Therapeutic interventions that could potentially target vascular endotheliitis.

Drugs	Pharmacological actions potentially contributing to endotheliitis treatment	Reference number for COVID-19 clinical studies
Statins	Endothelial protection, Antioxidant Immunomodulation, Anti-inflammation	131, 132
Chloroquine/ Hydroxychloroquine	Anti-inflammation	141, 142, 143, 144
Glucocorticoids	Anti-inflammation Immunosuppression	154
Defibrotide	Antithrombotic Anticoagulant, Anti-ischemia Anti-inflammation	163, 164
Tocilizumab/Sarilumab	IL-6R inhibition	172, 173, 174, 175, 176, 177, 178, 179, 180, 181
Aspirin	Anticoagulant, Anti-platelet	183

improve endothelial functions through different mechanisms, including an increase in expression of endothelial NO synthase (eNOS), an increase in eNOS activity, an improvement of eNOS uncoupling, a decrease in caveolin-1 activity, a suppression of pro-oxidant enzymes such as NADPH oxidase in a Rac-1-dependent manner, and an inhibition of NF-κB and other pro-inflammatory transcriptional and signal transduction pathways [120–123]. A lot of evidence shows that statins exhibit immunomodulatory and anti-inflammatory activities [124,125]. In this regard, statins are known to possess multiple beneficial effects termed as statin pleiotropy that is independent of their low-density lipoprotein cholesterol-lowering function [126]. The beneficial pleiotropic effects of statins may be based on the induction of the Nrf2-heme oxygenase-1 system [127,128], but the improvement of the function of endothelial progenitor cells could play a role in their protective profile [129]. We have shown that fluvastatin improves impaired endothelial function in endotoxemic rabbits [130], suggesting that statins may be helpful in inflammatory conditions characterized by endothelial injury and dysfunction. Interestingly, in a retrospective cohort study, statin use has been found to be associated with lower mortality when compared with non-use in COVID-19 [131]. A small observation study in elderly nursing

home subjects has also revealed a higher chance of a symptom-free COVID-19 in statin-users *vs*. non-users [132]. These reports may imply that statins are recommended to continue in patients with COVID-19 unless contraindications are present. However, whether the clinical benefit of statins for COVID-19 is largely attributed to their ability to prevent and manage COVID-19 endotheliitis awaits further study. Several intervention studies with statins are currently underway to explore this concept [70].

7.2. Chloroquine and hydroxychloroquine

The anti-malaria drugs chloroquine and hydroxychloroquine have been used as an anti-inflammatory agent to treat rheumatoid arthritis and systemic lupus erythematosus [133,134]. Past studies have shown that chloroquine can stimulate NO synthesis in human endothelial cells [135,136]. Furthermore, the cardioprotective effects of chloroquine and hydroxychloroquine have been documented to be attributable to the improvement of endothelial function as well as the reduction in inflammation and oxidative stress [137]. As far as it is based on the above reports, these anti-malaria drugs might be effective to prevent the development of endotheliitis. In animal experiments, it has been shown that chloroquine can decrease serum levels of pro-inflammatory cytokines in mice with cecal ligation and puncture-induced sepsis and protect mice from sepsis-induced acute kidney injury [138]. Additionally, the protective effect of chloroquine on sepsis lethality has been documented to be mediated by the inhibition of release of high mobility group box-1 (HMGB1) from macrophages, monocytes, and endothelial cells [139]. Since chloroquine and hydroxychloroquine have also antiviral activity *in vitro* [140], early optimistic reports from uncontrolled trials and the wide availability of these anti-malaria drugs transformed into the standard for COVID-19 therapy in many countries [141,142]. However, data from clinical trials have not confirmed the benefit of chloroquine and hydroxychloroquine in either prophylaxis or therapy [143,144]. Most recently, it has been demonstrated that chloroquine induces endothelial injury through lysosomal dysfunction and oxidative stress [145], suggesting that endothelial cell injury may account for the failure of chloroquine and hydroxychloroquine as a medication for treating COVID-19.

7.3. Glucocorticoids

Glucocorticoids are widely used for anti-inflammatory therapy in chronic inflammatory diseases, including asthma, rheumatoid arthritis, inflammatory bowel disease, and autoimmune diseases, all of which are associated with increased expression of inflammatory genes. Glucocorticoids are known to suppress inflammation through several molecular mechanisms [146–148]. Glucocorticoids bind to cytosolic glucocorticoid receptors (GRs) which then dimerize and translocate to the nucleus, where they bind to glucocorticoid response elements (GRE) on glucocorticoid-responsive genes, resulting in increased transcription. Glucocorticoids can increase the transcription of genes coding for anti-inflammatory proteins, including lipocortin-1, IL-10, IL-1 receptor antagonist, and neutral endopeptidase, but this is unlikely to account for all of the broad-spectrum anti-inflammatory actions of glucocorticoids. The most striking effect of glucocorticoids is to repress the expression of multiple inflammatory genes, such as pro-inflammatory cytokines, enzymes, receptors, and adhesion molecules. This cannot be due to a direct interaction between GRs and GRE, as these binding sites are absent from the promoter regions of most inflammatory genes. It is more likely to be due to a direct inhibitory interaction between activated GRs and activated transcription factors, such as AP-1 and NF-κB, which regulate the inflammatory gene expression.

In the vascular system, GRs are expressed not only by vascular smooth muscle cells but also by endothelial cells [149]. The effects of glucocorticoids on endothelial cells under physiological condition may lead to impaired endothelial function [150,151]. However, the role of glucocorticoids in endothelial function under inflammatory conditions appears to be different from that under physiological conditions. Compelling evidence supports a beneficial effect of glucocorticoids on high-grade inflammation associated with septic shock, an effect which is mediated by activation of endothelial GRs [152,153]. Possible mechanisms involved in the beneficial effects of glucocorticoids on endothelial cells under inflammatory conditions are likely due to decreased endothelial expression of pro-inflammatory cytokines, chemokines, and inflammatory mediators. The RECOVERY trial, a large multi-center, randomized, open-label study, has provided epidemiological evidence for good therapeutic efficacy of dexamethasone in severe COVID-19 with reducing mortality among patients who are receiving invasive mechanical ventilation or oxygen but not among those receiving no respiratory support [154]. Given that COVID-19 can damage the endothelial system, causing disturbance of microcirculation and consequently leading to dysfunction of internal organs, the beneficial effect of glucocorticoids on endothelial inflammation and damage may be the main explanation for their efficacy in patients with severe COVID-19 [155].

7.4. Defibrotide

Defibrotide is a sodium salt complex mixture of single-stranded phosphodiester oligodeoxyribonucleotides derived from porcine intestinal mucosal DNA by controlled depolymerisation [156–158]. Defibrotide is approved for treatment of hepatic veno-occlusive disease, also called sinusoidal obstruction syndrome, which mainly occurs following high-dose chemotherapy in the setting of allogeneic hematopoietic stem cell transplantation [157,159]. The mode of action of defibrotide remains largely unknown but it has been reported to have multiple antithrombotic, anti-ischemic, anti-inflammatory, anti-adhesive and pro-fibrinolytic, and anticoagulant properties [156–158]. *In vitro* studies using endothelial cell lines have revealed that defibrotide can suppress the up-regulation of VCAM-1, ICAM-1, VE-cadherin, and vWF in response to acute graft-*vs*.-host disease sera [160]. Furthermore, defibrotide has been found to inhibit leukocyte-endothelial interactions by down-regulating expression of endothelial adhesion molecules in a fully major histocompatibility complex-mismatched murine model of allogeneic hematopoietic stem cell transplantation [161]. Moreover, it is suggested that defibrotide may restore thrombotic-fibrinolytic balance at the endothelial level and protect endothelial cells [158]. The multitarget and endothelial-based pleiotropic properties of defibrotide make it an attractive candidate for the treatment of the advanced stage of COVID-19 and the systemic endothelial complications underpinning both its pathobiology and ensuing mortality [49,162]. In this regard, there is a recent report showing complete resolution and no attributable toxicity in two critically ill pediatric patients who received defibrotide for a SARS-CoV-2-associated multisystem inflammatory syndrome [163]. In the ongoing Spanish DEFACOVID phase IIb randomized clinical trial, as well as other international studies either planned or already under way in Italy, Ireland, the United Kingdom, and the United States, preliminary results support both safety and promising potential efficacy of defibrotide in COVID-19 patients to date [162,164].

7.5. Tocilizumab and sarilumab

IL-6 is produced in response to infections and tissue injuries and contributes to host defense through the regulation of the immune reaction, the acute-phase response, hematopoiesis, and inflammation [165]. IL-6 exerts its biological activities *via* two molecules: IL-6 receptors (IL-6Rs) and gp130 [166]. Tocilizumab and sarilumab are monoclonal antibodies directed against IL-6Rs and are used to treat inflammatory conditions, such as rheumatoid arthritis. Sarilumab is a fully human monoclonal antibody that binds specifically to both soluble and membrane-bound IL-6Rs, and inhibits IL-6-mediated signaling through these receptors, while tocilizumab is a recombinant humanized

monoclonal antibody also directed against IL-6Rs.

In addition to immune-mediated cells, endothelial cells are also involved in the production of IL-6 in response to various stimuli [165]. IL-6Rs are expressed on the surface of human vascular endothelial cells [167]. Then, IL-6 directly affects vascular endothelial cells and could be the cause of endothelial cell dysregulation, characterized by hyper-inflammation, abnormal coagulation, and vascular leakage. Since IL-6 promotes endothelial dysfunction, it has been suggested that this cytokine may play a role in the vascular endothelial dysfunction associated with COVID-19 [168]. In a recent work, moreover, the crucial role of IL-6 signaling in endothelial dysregulation during bacterial infection, sepsis, and COVID-19 has been noted [169]. The signal transduction of IL-6 involves activation of Janus kinase (JAK), then leading to activation of the transcription factor signal transducer and activator of transcription 3 (STAT3) [170]. Systemic delivery of STAT3 decoy oligodeoxynucleotides has been found to minimize major end-organ injury and improve mortality in mice with cecal ligation and puncture-induced sepsis [171]. The clinical usefulness of tocilizumab and sarilumab for COVID-19 has been sequentially reported [172–174]. In addition, when tocilizumab and sarilumab in an ongoing international, multifactorial, adaptive platform trial have been evaluated, it has been demonstrated that their treatment can improve outcomes, including survival, in critically ill patients with COVID-19 receiving organ support in intensive care units [175], although it should be kept in mind that a number of randomized, controlled trials to date have largely negative [176–181].

7.6. Asprin

Endotheliitis can lead to the formation of microthrombi, which may be responsible for the development of multiorgan damage. Aspirin, also called acetylsalicylic acid (ASA), which irreversibly inhibits cyclooxygenase-1 and results in preventing platelet aggregation by blocking the formation and release of TXA_2, is well-established medication for the secondary prevention of cardiovascular and cerebrovascular events [182]. In patients with mild to moderate COVID-19, Frorêncio *et al.* [183] have reported that ASA treatment could offer relief of symptoms without hemorrhagic complications or other adverse effects. Although this is only a case series, with no control group and a low number of patients, they assume that ASA may useful as a secondary prophylaxis of thrombotic events in COVID-19 patients with multisystemic endotheliitis. The possible benefit of the prophylactic anticoagulation has been indicated by the use of heparin in moderate to severe COVID-19 [184]. Furthermore, the anticoagulation agent dipyridamole has been found to markedly improve clinical outcomes in severely ill patients with COVID-19 [185]. Despite the plausible theoretical rationale, however, the role of empiric therapeutic anticoagulation in COVID-19 remains elusive with an urging call for further clinical study.

8. Conclusions

The vascular endothelium, which is a dynamic endocrine, paracrine, and autocrine organ, plays a vital role in regulating vascular tone and homeostasis. Endotheliitis, hyperinflammation of the blood vessel endothelium, is actually associated with vascular endothelial dysfunction, thrombus formation, and hyperpermeability, and is the important step in the pathogenesis that underlies the development of diffuse inflammatory diseases leading to organ damage. In severe COVID-19, emerging data indicate a crucial role of widespread endotheliitis as a key player in provoking scattered microvascular disruption and eventually dysfunction of different organ systems. Further studies are warranted to uncover further precise role of endotheliitis in the pathobiology of a variety of diffuse or systemic inflammatory diseases associated with infections and to discover promising therapeutic interventions that target this disorder.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

This work was supported by Grant-in-Aid for Scientific Research (17K08586, 19H03757) and for Young Scientists (20K17776) from Japan Society for Promotion of Science.

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