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Review Article

Tissue factor in COVID-19-associated coagulopathy

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ABSTRACT

Evidence of micro- and macro-thrombi in the arteries and veins of critically ill COVID-19 patients and in autopsies highlight the occurrence of COVID-19-associated coagulopathy (CAC). Clinical findings of critically ill COVID-19 patients point to various mechanisms for CAC; however, the definitive underlying cause is unclear. Multiple factors may contribute to the prothrombotic state in patients with COVID-19. Aberrant expression of tissue factor (TF), an initiator of the extrinsic coagulation pathway, leads to thrombotic complications during injury, inflammation, and infections. Clinical evidence suggests that TF-dependent coagulation activation likely plays a role in CAC. Multiple factors could trigger abnormal TF expression and coagulation activation in patients with severe COVID-19 infection. Proinflammatory cytokines that are highly elevated in COVID-19 (IL-1β, IL-6 and TNF-α) are known induce TF expression on leukocytes (e.g. monocytes, macrophages) and non-immune cells (e.g. endothelium, epithelium) in other conditions. Antiphospholipid antibodies, TF-positive extracellular vesicles, pattern recognition receptor (PRR) pathways and complement activation are all candidate factors that could trigger TF-dependent procoagulant activity. In addition, coagulation factors, such as thrombin, may further potentiate the induction of TF via protease-activated receptors on cells. In this systematic review, with other viral infections, we discuss potential mechanisms and cell-type-specific expressions of TF during SARS-CoV-2 infection and its role in the development of CAC.

1. Introduction

Coronavirus disease-2019 (COVID-19), caused by SARS-CoV-2, presents with a wide spectrum of phenotypes ranging from asymptomatic to mild or severe complications. Multiple organ failure seems to be a hallmark of COVID-19 severity and is associated with increased morbidity and mortality [1–3]. A hypercoagulable state leading to the development of micro-/macro-vascular thrombus formation has been incriminated with a critical role [4,5]. Patients with severe COVID-19 are at higher risk of developing thrombotic events including pulmonary embolism, deep vein thrombosis and arterial thrombosis (incidence rates 4.4 %) [6]. The anatomical distribution of arterial thrombotic events was wide, occurring in limb arteries (39 %), cerebral arteries (24 %), great vessels (aorta, common iliac, common carotid, and brachiocephalic trunk; 19 %), coronary arteries (9 %), and superior mesenteric artery (8 %) [6,7]. Moreover, critically ill COVID-19 patients display other coagulation abnormalities which resemble disseminated intravascular coagulation (DIC) as seen in bacterial sepsis. However, clinical and laboratory findings suggest that COVID-19-associated coagulopathy (CAC) represents a unique entity which does not necessarily meet all the diagnostic criteria for DIC of the International Society on Thrombosis and Haemostasis (ISTH) [8,9]. In contrast to the typical picture of DIC from other causes, a prolonged prothrombin time (PT) and activated partial thromboplastin time (aPTT) are not frequently observed in severe COVID-19 patients [10]. CAC is characterized by elevated levels of fibrinogen [11–13]. Furthermore, thrombocytopenia is often relatively mild in COVID-19 patients [14,15]. A hypofibrinolytic state in the alveolar spaces was observed in SARS-CoV-1 and SARS-CoV-2-induced acute respiratory distress syndrome (ARDS) due to increased levels of fibrinolytic inhibitors such as plasminogen activator inhibitor-1 [16,17]. Furthermore, low antithrombin (AT)-III levels are linked to procoagulant and inflammatory responses [18], and mortality in COVID-19, especially among patients with obesity [19]. A case series of seven autopsies revealed an ~9-fold higher occurrence of alveolar capillary microthrombi in COVID-19 as compared to H1N1 patients [20]. The presence of thromboembolic and fibrin-rich thrombi in the pulmonary

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vasculature is suggestive of a distinct COVID-19 pathology [21–25]. Accordingly, the ISTH proposed to categorize CAC as a new form of intravascular coagulation syndrome with the need for defining its diagnostic criteria [14,26]. There are multiple mechanisms and factors that could potentially contribute to the prothrombotic milieu in COVID-19. In addition to the thrombotic complications, prolonged bleeding times and a risk for major hemorrhage is a relevant cause of morbidity in patients with COVID-19 [27–29].

Vaccine-induced immune thrombotic thrombocytopenia (VITT) is caused by antibodies that recognize platelet factor 4 (PF4, also called CXCL4) bound to platelets [30]. These antibodies are immunoglobulin G (IgG) molecules that activate platelets via low affinity platelet FcγIIa receptors (receptors on the platelet surface that bind the Fc region of IgG) [31]. Ultimately, platelet activation, and possibly activation of other cells such as neutrophils, results in marked stimulation of the coagulation system and clinically significant thromboembolic complications [32,33]. CAC has distinct pathophysiological mechanisms from VITT for the activation of coagulation system. In this review, we have focused on the role of tissue factor (TF) in CAC.

2. Tissue factor pathway

Tissue factor (TF) is a transmembrane glycoprotein and a well-known hemostatic regulator that essentially protects vital organs prone to mechanical injury [34]. The TF cDNA was cloned in 1987 by four independent research groups [35–39]. Deletion of the TF gene in mice leads to embryonic development, indicating the importance of TF for survival [40–42]. Parry and Mackman reported that mouse embryogenesis requires the TF extracellular domain but not the cytoplasmic domain [43]. TF is highly expressed in subendothelial tissues of vascularized organs, such as the brain, lungs, placenta, heart, and kidneys [44–46]. Other reviews discuss TF structure and functions, its expression in different cell types, antigen measurement by various methods, and so forth, in further detail [46,47].

TF serves as a high affinity cell surface receptor and cofactor for coagulation factors VII and VIIa [48,49]. This TF:FVIIa complex activates factor IX (FIX) and factor X (FX), triggering a cascade that generates thrombin, fibrin and activates platelets, resulting in a hemostatic plug at the site of injury [34,50,51]. Besides the role of surface full length TF (flTF) expression (decryptic form) in procoagulant activity [52,53], alternatively spliced TF (asTF; lacking exon 5) was identified as a soluble form of TF [54], which circulates in blood and also exhibits pro-coagulant activity [55,56]. However, we do not have any experimental data to support the contribution of soluble TF to COVID-19 pathogenesis.

3. Tissue factor and viral infections

Activation of TF pathway is the key triggering route in sepsis-induced activation of the coagulation cascade [5,57,58]. Patients with acute respiratory distress syndrome (ARDS) and/or pneumonia as well as ventilator-associated pneumonia showed elevated TF and FVIIa activity in bronchoalveolar lavage (BAL) fluids, together with enhanced release of plasminogen activator inhibitor-1 [59,60]. Interestingly, usage of mechanical ventilation in healthy human lungs showed activation of TF pathway and alveolar coagulation without causing lung injury [61].

TF-mediated extrinsic coagulation activation may be the underlying cause of arterial and venous thrombosis in severe COVID-19 patients [62–64]. Exposure to pathogens results in rapid and transient upregulation of TF expression in immune cells (monocytes, macrophages and dendritic cells) and non-immune cells (endothelial and epithelial cells) [45,65–68]. Expression of TF on endothelial cells and leukocytes combined with endothelial microinjuries (which expose subendothelial TF) results in increased fibrin generation and formation of microthrombi [69].

Influenza (IAV/H1N1) patients with ARDS have an activated coagulation system and increased risk of thrombosis. IAV hospitalized patients showed elevated levels of D-dimer, which was associated with a higher risk of disease progression [64]. A recent report showed that ARDS patients with H1N1 had high Venus thromboembolism incidence (49 %) compared to non-H1N1 patients (29 %) [70]. Mice infected with either IAV/1918 H1N1 [17] or infected with the mouse-adapted PR8/H1N1 variant displayed an increase in lung TF mRNA and TF activity [71]. Similarly, mice infected with SARS-CoV-1 (MA15) showed profoundly greater TF RNA expression at 2-days post infection (dpi) which remained elevated at 4 and 7-dpi [17] (Table 1).

Blockade of TF or TF-FVIIa binary complex attenuates coagulopathy and sepsis-associated mortality in animal models [45,72–74]. Similarly, in rhesus monkeys infected with the Ebola virus, treatment with a recombinant inhibitor of FVIIa/TF achieved a prolonged survival time and attenuation of the coagulation and proinflammatory responses [75]. Dengue virus, Respiratory Syncytial Virus, adenovirus, Measles, cytomegalovirus, Zika virus, Puumala Hantann virus, and Herpes simplex virus (HSV) infections induce TF expression in cultured endothelial cells [76–84]. Microvesicular TF activity correlated with plasma IL-8 and predicted mortality from severe influenza A (H1N1) infection in a multicenter study of 12 patients [85] (Table 1).

Autopsy lung tissues from COVID-19 patients showed higher expression of TF that correlated with areas of fibrin-enriched thrombi [86,87]. Transcriptomic profiling of inflammatory cells from BAL fluid revealed that COVID-19 patients had increased expression of procoagulant genes (e.g. TF, vWF, thrombin, FXIII, FVII, F12) and decreased levels of anticoagulant genes (e.g. PROCR, PROS1, THBD) and fibrinolytic genes (e.g. PLAU) [88]. One major limitation of this study was that the transcripts from the BAL fluid were not analyzed with respect to specific-cell types. In severe COVID-19, TF expression on activated monocytes was associated with elevated fibrinogen and D-dimer levels [89]. Moreover, higher quantities of monocyte TF were present in patients who required mechanical ventilation or had a lethal course of disease [90]. It was recently reported that SARS-CoV-2 infection induces the activation of TF-mediated coagulation via activation of acid sphingomyelinase [91].

A recent prospective study showed a positive correlation between increased circulating levels of TF, IL-6, IL-8, VCAM-1, complement anaphylatoxin C5a, growth arrest specific (GAS) gene 6, pentraxin-3, TNF-α and mortality in COVID-19 patients in the ICU [92]. SARS-CoV-2 infection of human lung epithelial cells, and pulmonary endothelial cells overexpressing hACE2, induced expression of TF and led to procoagulant and proinflammatory responses [93–95] (Table 2).

These findings support the concept that induced overexpression of TF on circulating monocytes, endothelial cells, and lung epithelium may act as a trigger for CAC.

Alternatively, virus surface–host cell communication via TF in the viral envelope and lipid bilayers (as demonstrated for HSV type-1) could also directly trigger the procoagulant response in COVID-19 [96–98] (Table 1). Further studies are needed to understand SARS-CoV-2 viral envelope and glycoproteins interactions with host cells and the subsequent thrombo-inflammatory responses.

4. Pattern recognition receptors and TF in COVID-19

Activation of inflammatory and coagulation pathways is an integral part of host defense responses against infections. These mechanisms have evolved to limit pathogen dissemination, and to orchestrate pathogen killing and tissue repair. On the other hand, dysregulation and excessive activation of these pathways can contribute to thrombosis and tissue damage [99–102].

Pattern recognition receptors (PRRs) sense conserved molecular structures known as pathogen-/damage-associated molecular patterns which are released from pathogens (PAMPs) or damaged host cells (DAMPs). Toll-like receptors (TLRs) belong to the family of PRRs.

Table 1
TF expression during other viral infections.

Virus	Species	Source	Experimental system	Findings	References
Dengue virus	Human	HUVECs	In vitro	↑ TF ↑ TM ↑ tPA	[259,260]
	Human	Monocytes	In vitro	↑ TF ↑ PAI-1	[261–263]
	Human	Plasma	Clinical	↑ TF ↑ PAI-1 ↑ tPA	[264,265]
	Human	Plasma	Clinical (children)	↑ TF ↑ vWF ↑ PAI-1	[266]
	Human	Monocytes (from patients)	Clinical	↑ TF	[267]
Ebola virus	Human	Monocytes/macrophages	In vitro	↑ TF ↓ Plasma protein C	[109]
	Macaques	1. Lymphoid macrophages 2. Peripheral blood cell	In vivo	1. ↑ TF 2. ↑ TF membrane microparticles	[75,109]
Puumala ortho-hanta virus	Human	Plasma	In vivo	1. Circulating EV-TF 2. ↑ PAI-1 3. ↑ tPA	[78]
	Human	HUVECs	In vitro	↑ TF, ↑ PAI-1	[79]
Zika virus	Human	HUVECs	In vitro	↑ TF ↑ IL-6 ↑ IL-8	[80]
Cytomegalovirus	Human	HUVECs	In vitro	↑ TF	[82]
	Human	HUVECs	In vitro	↑ PCA	[83]
	Human	Monocytes	In vitro	↑ TF	[81]
Measles virus	Human	HUVECs	In vitro	↑ TF ↑ IL-1beta	[84]
Herpes simplex virus	Human	HUVECs	In vitro	↑ TF ↓ TM ↓ PAI-1	[76,268]
	Mares	Peripheral monocytes	In vitro	↑ TF, ↑ FXa generation	[269]
	Virus	Virus envelope	In vitro	↑ TF ↑ PCA	[96,270]
	Mouse	Virus envelope	In vivo	↑ PCA	[97]
Adenovirus	Human	HUVECs	In vitro	↑ PCA	[83]
Influenza virus	Human	HUVECs	In vitro	↑ PCA	[83]
	Human	Monocytes	In vitro	↑ TF	[81]
	Mouse	1. Lung mRNA 2. BALF	In vivo	↑ TF ↑ BALF MV-TF	[17,71,271]
Human immuno-deficiency virus	Human	Peripheral monocytes	In vitro	↑ TF and PCA	[272]
	Human	Peripheral monocytes	Clinical	↑ TF ↑ D-dimer	[110]
	Human	Plasma	Clinical	↑ MP-TF	[273]
	Human	Platelets and platelet microparticle	Clinical	↑ platelet MP-TF	[274]
Respiratory syncytial virus	Human	HUVECs	In vitro	↑ PCA	[83]

TF, tissue factor; PCA, procoagulant activity; MP-TF, tissue factor positive microparticles; TM, thrombomodulin; vWF, von Willebrand factor; PAI-1, plasminogen activator inhibitor-1; tPA, tissue plasminogen activator.

Table 2
Evidence for a role of TF in SARS-CoV infections.

Virus	Species	Source	Experimental system	Findings	References
SARS-CoV-1 (SARS MA15-mouse-adapted)	Mouse	Lung mRNA	In vivo	↑ TF	[17]
SARS-CoV-2	Human	BALF cells (bulk-RNA seq)	Clinical	↑ TF	[275]
	Human	BALF cells (single-cell RNA seq)	Clinical	↑ TF in lung epithelial cell population	[276,277]
	Human	PBMCs (bulk-RNA seq)	Clinical	↑ TF	[275,277]
	Human	Whole blood (monocytes, granulocytes, and platelets)	Clinical	↑ TF	[90,278]
	Human	Serum	Clinical	↑ EV-TF and activity	[253]
	Human	Plasma	Clinical	↑ EV-TF ↑ D-dimer	[255,256,279–281]
	Human	PMECs (hACE2 overexpressed)	In vitro	↑ TF	[94]
	Human	Monocytes-derived macrophages	In vitro	↑ TF and PCA via sphingomyelinase	[91]
	Human	Lung epithelial cells (bulk-RNA seq)	In vitro	↑ TF	[282]
	Mouse (K18-hACE2)	Lung mRNA	In vivo	↑ TF	[283]

TF, tissue factor; PCA, procoagulant activity; MP-TF, tissue factor positive microparticles.

Substantial evidence indicates that TLR activation during viral infections induce TF gene expression with a subsequent imbalance of the pro- and anti-coagulant states [66,103,104]. The TLR3 agonist polyinosinic:polycytidylic acid [poly(I:C)], which mimics viral double stranded RNA, triggers TF expression in human endothelial cells and in mice [105–107]. Viruses, such as Dengue, Hantaan, Marburg, Lassa, and Ebola, induce expression of TF on infected endothelial cells and monocytes [77,79,108–110]. In line with these findings, studies have suggested that SARS-CoV-2 virions can be present in/on endothelial cells and might induce vascular damage [111,112]. However, the extent of direct and productive infection of endothelial cells by SARS-CoV-2 remains controversial [113]. An increased TF expression in endothelial cells and monocytes could contribute to the prothrombotic events in patients infected with COVID-19. Moreover, SARS-CoV-2 genomic RNA activates TLR7/TLR8 (ssRNA) and TLR3 (by dsRNA intermediates during viral replication) that mount an acute inflammatory response through the activation of nuclear factor kappa B (NF-κB) and the interferon regulatory factors (IRFs), leading to the synthesis and release of proinflammatory cytokines including IL-1, IL-6 and TNF-α [114]. In line with this notion, recent studies have suggested the involvement of TLR7/TLR8 and TLR3 in the inflammatory and interferon (IFN) responses induced by SARS-CoV-2 in plasmacytoid dendritic cells and epithelial cells [115–120]. Similarly, SARS-CoV-2 replication induces a delayed IFN response that begins after sensing of viral RNA by the cytosolic MDA5 and RIG-I sensors in lung epithelial cells [121,122]. Interestingly, SARS-CoV-2 spike protein, as well as mouse-adapted coronavirus MHV-A59, interact with TLR4 for subsequent initiation of IL-1β expression in THP-1 cells [123]. This response promotes inflammation, local influx of neutrophils and macrophages to the alveoli and activation of the adaptive immune response. IL-1β and other proinflammatory cytokines are likely to induce TF expression on endothelial and epithelial cells and alter vascular permeability [124–128].

Inflammasomes are key components of the innate immune system. Inflammasome activation is initiated by several cytosolic PPRs (e.g. NOD-like receptors) that respond to either microbe-derived PAMPs or DAMPs generated by injured host cells [129]. Canonical inflammasome activation of caspase-1 (CASP1) has been shown to induce the generation of highly procoagulant TF-bearing extracellular vesicles from macrophages [130]. Moreover, endogenous DAMPs, such as high mobility group box 1 (HMGB1), also activate the non-canonical caspase 11 (CASP11). CASP11 can increase the procoagulant activity of TF on innate immune cells through gasdermin D (GSDMD) and transmembrane protein 16F (TMEM16F)-mediated phosphatidylserine translocation [131]. Recent clinical findings demonstrated that NLRP3 inflammasome-derived products, such as Casp1p20, IL-1β, and IL-18, correlated with markers of disease severity in the sera of COVID-19 patients, including IL-6 and lactate dehydrogenase [132,133]. Similarly, Ferreira et al. reported that infection severity in COVID-19 may be associated with inflammasome activation in monocytes and downstream production of large amounts of IL-1β, IL-6 and TNF-α [134]. Monocyte TF expression and platelet activation are correlated with markers, such as fibrinogen and D-dimers, in patients with invasive mechanical ventilation or a lethal outcome [89]. While it is unclear whether inflammasome-mediated pyroptosis pathways contribute to coagulation activation in severe COVID-19 infection [135], a pyroptosis and Gasdermin D inhibitor (Disulfiram) was associated with a lower risk of COVID-19 in a retrospective cohort study [136], and is currently tested in clinical trials. Higher expression of caspase-1 in the endothelium of COVID-19 patients as compared with H1N1 and control groups revealed the occurrence of pyroptosis in capillary-alveolar endothelial cells [137].

High levels of TF, D-dimers and thrombin in BAL fluids of patients with ARDS coincided with a strong activation of coagulation [138]. Fibrin deposition in alveolar spaces is a key feature of acute lung injury. The mechanisms that contribute to disturbed bronchoalveolar fibrin turnover are localized TF-mediated thrombin generation and downregulation of fibrinolysis pathway due to increased activity of fibrinolytic inhibitors, in particular PAI-1 [139].

Overall, activation of PRRs contributes to the propagation of inflammation and initial coagulation activation in viral infection. Further investigations of PRR activation in COVID-19 and TF signaling are needed to advance our understanding of the pathogenesis of COVID-19 and CAC.

5. Cytokine storm and TF in COVID-19

The immunopathology of the SARS-CoV-2-induced cytokine release is complex, and the underlying molecular mechanisms are not completely characterized. IL-1β, IL-6, IL-18, IFN-γ, and TNF-α are key proinflammatory cytokines that are thought to play central immunopathologic roles in the development of the cytokine storm [140]. A recent report proposed that IL-6 signaling causes harmful changes to liver sinusoidal endothelial cells and may promote blood clotting and contribute to liver injury [141]. In line with this, targeted inhibition of IL-1β and IL-6 has been shown to reduce inflammatory and thrombosis biomarkers and moderately improve survival rates in COVID-19 patients [142–148]. Inflammation-induced coagulation is the net result of the overexpression/activation of coagulant factors (e.g. TF), decreased production of anti-coagulant factors (e.g. TF pathway inhibitor, thrombomodulin, protein C) and suppression of fibrinolytic proteins [149]. Activation of TLRs on alveolar epithelial cells, macrophages, and circulating blood monocytes plays an important role in innate immunity and inflammatory response during viral infections. A recent study revealed that SARS-CoV-2 is internalized by human monocytes and macrophages [150,151]. TLR activation by viral products (e.g. spike protein) [123] and single stranded RNA (ssRNA) [119] activates downstream signaling leading to the production of proinflammatory cytokines and chemokines. These cytokines and chemokines orchestrate in the recruitment of immune cells, such as neutrophils, monocytes and T cells, to the lungs resulting in widespread lung inflammation [152–154]. Accumulating clinical data also suggest that cytokine release is associated with COVID-19 severity and that cytokines are mediators of death from COVID-19 [155]. Pro-inflammatory cytokines, including IL-1α, IL-1β, IL-6, IL-8, MCP-1, IFN-γ, TNF-α, [156,157] may induce CAC via expression of TF on endothelial cells, monocytes, macrophages and T cells [124,158–164] and may promote blood clotting. In contrast, a recent study demonstrated that the baseline levels of IFN-γ were negatively associated with increased lung fibrosis in COVID-19 patients at discharge. However, this study was performed with a relatively small number of patients. The authors speculate that IFN-γ is anti-fibrotic because it mediates a more rapid clearance of SARS-CoV-2. Thus, low circulating IFN-γ and its risk associated with fibrosis in COVID-19 patients need further validation [165].

Activated coagulation factors, including FXa, thrombin and fibrin, promote the synthesis of pro-inflammatory cytokines (IL-6, IL-8, MCP-1) and cell adhesion molecules (E-selectin, ICAM-1, and VCAM-1) in endothelial and epithelial cells [166–169]. Moreover, the TF-thrombin-PAR1/2 signaling axis further potentiates TLR3-mediated expression of TF, IL-8, E-selectin, ICAM-1, and VCAM-1 in endothelial cells [106,107,170]. Thus, elevated levels of thrombin during SARS-CoV-2 infection may play a crucial role in propagation of cytokine release and TF-dependent activation of coagulation. In addition, SARS-CoV-2 infection of endothelial cells also causes cell death, which leads to vascular leakage and induces a cytopathic effect on airway epithelial cells and multiorgan failure [140,151,171–173].

Overall, the current data support the concept that an early and excessive release of cytokines as well as dysregulated coagulation activity (FXa, thrombin, and fibrin) may contribute to the thrombo-inflammatory responses in COVID-19. Further studies on cytokine-mediated expression of TF in COVID-19 could advance our understanding of the molecular mechanisms of CAC.

6. Antiphospholipid (aPL) antibodies and TF in COVID-19

Anti-phospholipid syndrome (APS) is an autoimmune prothrombotic disease characterized by persistent presence of aPL antibodies, leading to recurrent arterial and venous thromboembolic events [174]. Patients with APS produce high-avidity autoantibodies to phospholipids and phospholipid-binding proteins (aPL antibodies), including prothrombin, plasminogen, cardiolipin, and β2 glycoprotein I (β2GPI) [174]. The prevalence of APS varies with the presence of aPL antibodies in ~1–5 % of healthy young individuals to ~50 % in elderly populations with chronic diseases [175,176]. These aPL antibodies bind to cell surfaces and activate endothelial cells, platelets, monocytes, and neutrophils [177,178]. aPL antibodies induce expression of cell adhesion molecules in endothelial cells, and of TF in endothelial cells and monocytes. Additionally, aPL antibodies may also induce shedding of TF-positive microparticles, which contribute to thrombotic events [179–182]. Transient aPL antibodies occur in patients with viral infections, which include human immunodeficiency virus (HIV), varicella zoster virus, hepatitis C virus, cytomegalovirus (CMV), Epstein–Barr virus (EBV), adenovirus, and parvovirus B19 [183,184]. Notably, a recent case study found high levels of aPL antibodies (β2GPI IgA, β2GPI IgG; anti-cardiolipin IgA) in three patients with severe COVID-19 with coagulopathy and preexisting comorbidities [185]. However, the relevance of elevated aPL antibodies in COVID-19 is hard to evaluate because such antibodies can also arise transiently in patients with other critical illnesses and life-threatening infections [186–188].

β2GPI is a plasma protein that is crucial in maintaining hemostasis and the most common target of pathogenic aPL antibodies [189–191]. aPL antibodies can also activate platelets that express high levels of glycoprotein(Gp) IIb/IIIa [192] and thromboxane A2 [193]. Furthermore, aPL antibodies can induce complement activation via the classical pathway to generate complement fragments which propagate inflammatory cells to initiate thrombosis and tissue injury via the membrane attack complex (C5b-9) and anaphylatoxins (C3a, C5a) receptors-mediated responses [194–196]. Muller-Calleja et al. showed that monoclonal cofactor-independent aPL antibodies rapidly activate TF on myelomonocytic cells in mice [197]. Moreover, aPL antibodies from serum of hospitalized COVID-19 patients are potently thrombogenic [198]. In our ongoing proteomics studies, β2GPI, GpIIb/IIIa, and thromboxane A2 receptor were increased in platelets of SARS-CoV-2-infected K18-hACE2 mice [199]. Higher antigen levels of these proteins could further instigate the production of aPL antibodies in COVID-19, since platelets can bind to professional antigen presenting cells in blood followed by phagocytosis for antigen processing and presentation [200].

In recent years, studies on Neutrophil Extracellular Traps (NETs) have shown evidence that autoantibodies against β2GPI induce NETs and enhance thrombosis. NETosis is a unique form of cell death and the formation of NETs is characterized by the release of decondensed chromatin and granular contents to the extracellular space [201]. COVID-19 patients often have high amounts of NETs in their blood [202–204], which many contribute to the procoagulant response. Folco et al. reported that NETs induce VCAM-1, ICAM-1, and TF expression towards an increased procoagulant state of endothelial cells, which is further augmented by IL-1α and Cathepsin G [205].

On one hand, aPL antibodies can directly activate monocytes, which in turn interact with the endothelium via MCP-1, resulting in TF-dependent pro-thrombotic events [206–209]. On the other hand, aPL antibodies can directly activate β2GPI expressing monocytes, which subsequently upregulates NF-κB-mediated TF expression via activation of mitogen-activated protein kinases (MAPK) [210].

Additional studies confirmed an increased expression of TF and elevated procoagulant activity in circulating monocytes of patients with aPL antibodies [180,209]. aPL antibodies can also mediate inflammatory response of endothelial cells through the activation of innate immune receptors TLR2 and TLR4. These TLRs serve as binding sites for dimeric β2GPI, which results in endothelial dysfunction by increased expression of TF and adhesion molecules [211–214]. Treatment of endothelial cells with IgG-aPL antibodies from clinically active APS induced expression of TF, IL-6, and IL-8 via activation of p38 MAPK and NF-kB pathways [215]. Similar to this observation, human sera from n = 118 hospitalized COVID-19 patients contained anticardiolipin IgG/IgM and anti-phosphatidlyserine/prothrombin (anti-PS/PT) IgG/IgM. These aPL antibodies in the COVID-19 patients' sera upregulated the expression of surface adhesion markers (E-selectin, VCAM-1, and ICAM-1) in cultured endothelial cells [216]. In contrast, Borghi et al. reported a low prevalence of aPL antibodies in COVID-19 patients and no association with major thrombotic events [217].

In conclusion, the aPL antibodies may contribute to the development of arterial and venous thrombosis through various mechanisms in severe COVID-19 patients. However, more data is needed on the occurrence of aPL antibodies during SARS-CoV-2 infection. The mechanisms underlying aPL antibody-mediated coagulopathy are understudied. Further clinical and experimental studies will help to better assess the role of APS in the pathogenesis of COVID-19 and CAC.

7. Complement activation and TF in COVID-19

Complement activation products (e.g. C5b-9, C5a, C3a) can enhance neutrophil/monocyte activation and their recruitment to the infected lungs. Several complement effectors, acting in concert with platelets, can fuel thrombo-inflammation and endothelial dysfunction [218]. A complement-driven prothrombotic state is observed in diseases such as paroxysmal nocturnal hemoglobinuria, glomerulonephritis, and vasculitis [219–221]. Complement activation induces TF expression in various cell types, and skews mast cells and basophils towards a prothrombotic phenotype [222]. Activation of the complement and kallikrein/kinin system in critically ill COVID-19 patients is linked to thromboinflammation [223]. Spike protein of SARS-CoV-2 is recognized by Mannose-binding lectin, which results in both viral inhibition and complement activation [224]. The alternative pathway (down-regulation of cellular complement inhibitors [CD46, CD55, CD59] in infected cells) and the classical pathway (after anti-SARS-CoV-2 or auto-antibody production ensues) also contribute to complement activation [225–228].

The anaphylatoxins, C3a and C5a, play critical roles in immune modulation and regulation of cellular adaptation via their cell surface receptors (C3aR, C5aR1, C5aR2) [229]. Anaphylatoxins promote TF-dependent activation of coagulation pathways [230–234]. The plasma/serum concentrations of sC5b-9 and C5a are elevated in hospitalized COVID-19 patients [235–237]. In line with this, two cases of COVID-19 patients treated with an anti-C5a antibody showed a clinical improvement, as measured by increased lung oxygenation and decreased systemic inflammation [238]. An association of endothelial dysfunction with COVID-19 and enhancement by complement fragments, C5a and C3a, has been verified in patients with severe COVID-19. C5a-mediated activation of endothelial C5aR1 induces TF production [239]. Three clinical trials have been registered for eculizumab, a complement C5 inhibitor, as a treatment for patients with COVID-19 (ClinicalTrials.gov Identifiers: NCT04288713, NCT04346797, and NCT04355494) [240,241]. Recently, a combination of ruxolitinib (a JAK1/2 inhibitor) and eculizumab was administered to severely ill COVID-19 patients with a hypercoagulable state and ARDS. This resulted in significant improvements in respiratory symptoms, pulmonary lesions, and decreased D-dimer concentrations [236,242].

A dysregulation of the complement system could promote thrombotic events in patients with severe COVID-19 [21]. A deposition of membrane attack complex pores in vascular cell membranes is a key feature of several microthrombotic syndromes and has also been demonstrated in COVID-19 [243]. Initial genetic evidence suggests that TF as well as regulators of the complement and coagulation pathways are associated with the development of severe COVID-19 pathologies

[199,244]. Complement activation has also been shown to directly regulate TF activity on monocytes by activating thiol-isomerase pathways required for TF functions in thrombosis [197,245,246].

In summary, complement activation and anaphylatoxins may regulate TF-mediated thrombosis, which would support the approach of testing complement inhibitors for beneficial therapeutic effects on CAC.

8. Extracellular vesicles and TF in COVID-19

Extracellular vesicles (EV) are a heterogeneous group of cell-derived membranous structures containing exosomes and microvesicles, which originate from the endosomal system or which are shed from the plasma membrane, respectively [247]. EVs are released by various cells during lung inflammation and innate immune responses [248,249].

Several studies have shown that TF is often incorporated into microparticles and EVs, where it exerts critical pathophysiological activities and propagates inflammation, including during COVID-19 [250,251]. Zaid et al. showed increased levels of platelet-derived CD41^{+}-EVs in the plasma of COVID-19 patients [252]. Balbi et al. demonstrated elevated levels of 37 EV antigens involved in inflammation, platelet activation, coagulation processes, and endothelial dysfunction, including CD62P, CD142 (TF), and CD41, in serum samples from COVID-19 patients [253]. Another study demonstrated association of elevated levels of circulating EV-TF activity with disease severity and mortality in COVID-19 patients [254]. Longitudinal evaluation of MVs in COVID-19 patients plasma samples revealed that a significant

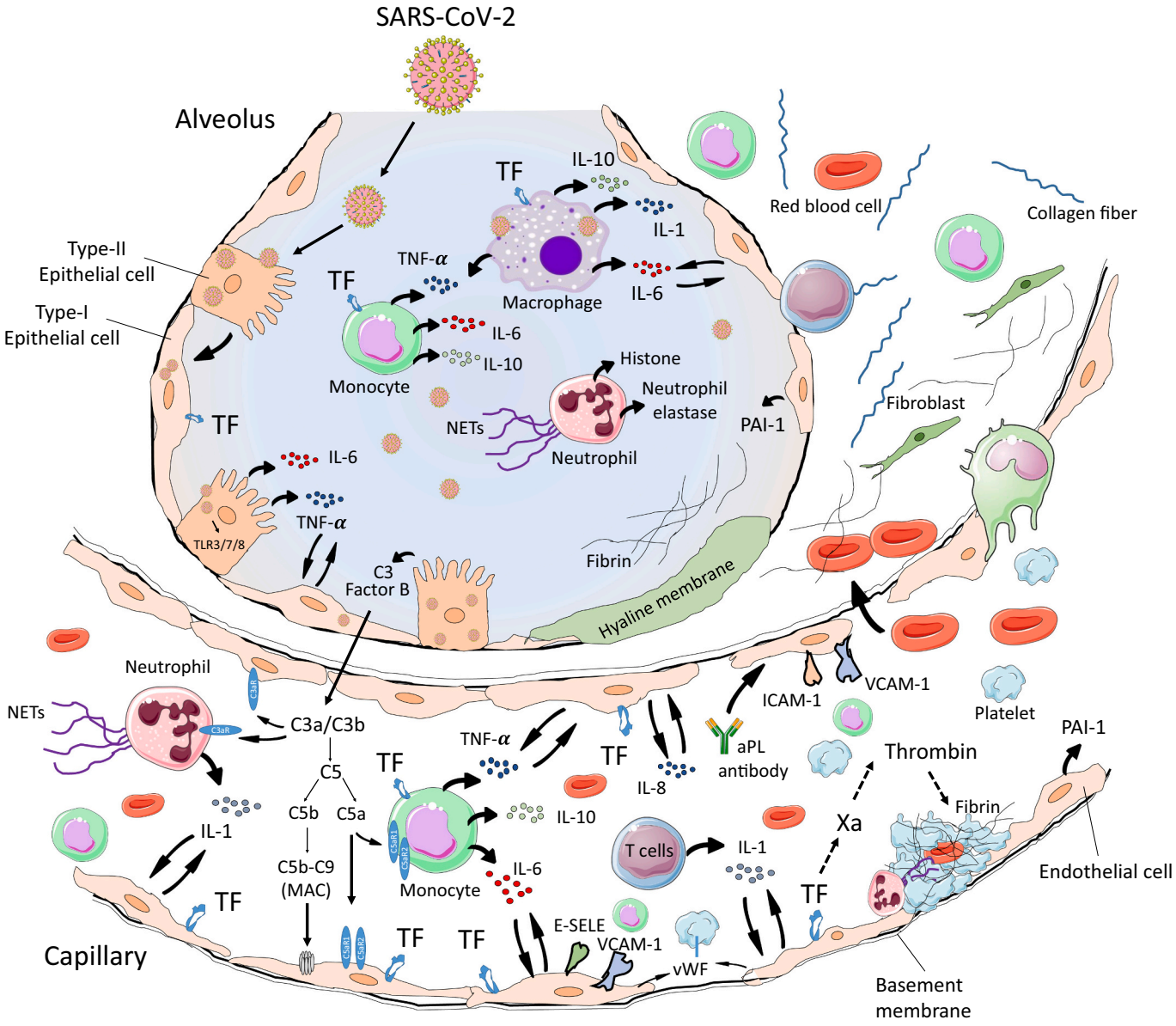

Fig. 1. Current concepts of TF in COVID-19-associated coagulopathy (CAC). Multiple mechanisms may contribute to TF expression, including direct infection of type I/II epithelial cells and monocytes, pattern-recognition receptors activation (TLR-3/-7/-8), complement-mediated MAC (C5b-C9) and anaphylatoxins (C5a, C3a), excessive cytokine release (IL-1, IL-6, IL-8, TNF-α) from immune and non-immune cells. These events subsequently lead to barrier dysfunction, increased vascular permeability, and activation of blood coagulation. Antiphospholipid antibodies may contribute to the activation of coagulation and endothelial cell-leukocyte interactions. TF-dependent activation of Xa/thrombin and excessive PAI-1 (which inhibits fibrinolysis) during SARS-CoV-2 infection results in the formation of fibrin-rich thrombi. IL, interleukin; NETs, neutrophil extracellular traps; vWF, von Willebrand factor; PAI-1, plasminogen activator inhibitor-1; TF, tissue factor; TNF-α, tumor necrosis factor-alpha; E-SELE, E-selectin; VCAM-1, vascular cell adhesion protein 1; ICAM-1, intercellular adhesion molecule-1; C3, complement 3; C5, complement 5; aPL antibody, antiphospholipid antibody.

decreased plasma concentrations of endothelium-derived EVs (E-Selectin+), endothelium-derived bearing TF (E-Selectin+TF+), endothelium-derived bearing ACE2 (E-Selectin+ACE2+) and leukocyte-EVs bearing TF (CD45+TF+) at 30-days post-discharge. Interestingly, platelet- and leukocyte-EVs further increased 30-days after post discharge, indicating that cellular activation persists long after the acute phase [255]. A comparative study of septic shock patients revealed that increased presence of distinct EVs with a higher EV-TF correlated with the thrombotic risk in severe COVID-19 patients [256].

These findings support the concept that circulating EV-associated TF may contribute to CAC and microthrombi formation. More prospective and retrospective clinical studies could enhance our understanding of the EV-TF-mediated hypercoagulatory state in COVID-19.

9. Perspectives

Arterial and venous thrombosis are frequently encountered in patients with severe COVID-19 and contribute to increased morbidity and mortality. In the absence of a monocausal explanation, it seems likely that the coagulopathy of COVID-19 is a cumulative result of several dysregulated pathways. Emerging evidence provides support for the concept that increased expression of TF is quite likely to contribute to thrombosis in severe COVID-19 (Fig. 1). High expression of TF on endothelial cells and monocytes may command increased fibrin formation and platelet activation during COVID-19 infection. Based on the existing evidence, we speculate that endothelial procoagulant and inflammatory responses could be due to the combination of aPL-, complement-, and cytokine-mediated expression of TF, rather than direct infection of the endothelium or blood cells. TF-coated EVs may specifically contribute to the development of CAC. Of note, the induction of TF expression is not necessarily restricted to PRR pathways with a direct role in viral immune recognition (TLR7, TLR8, RIG-I/MDA5), but may be related to DAMPs released during infection-associated tissue injury. In fact, it is a fluid scientific discussion to what extent endothelial cells, platelets and leukocytes are active replication site for SARS-CoV-2; or if an infrequent uptake of virions into these cells is better termed 'abortive infection'. The suggested correlation of aPL antibodies with an increased risk of CAC demands further preclinical investigations and controlled clinical studies. Systematic approaches will be most suitable to test the hypothesis if TF is essential or redundant for the pathogenesis of CAC.

Transgenic mice with tissue-specific TF deficiency in lung epithelial cells showed increased lung hemorrhage and mortality when infected with IAV/H1N1, highlighting the essential role of TF for hemostasis during lung infection [71]. On the other hand, excessive activation of TF may cause thrombotic complications [71,257]. This doubled edged sword response of TF could be further studied using existing TF-low or cell-type specific TF-deficient mouse models.

Further translational studies would especially benefit from tailored animal models that recapitulate the coagulation abnormalities and micro-/macro-vascular thrombosis of human COVID-19. While numerous animal species can be exploited to better understand COVID-19 pathology [258], a further refinement is needed for studying CAC. For example, humanized hACE2 mice do not seem to develop macrovascular thrombosis and pulmonary embolism from SARS-CoV-2 infection alone. Additional vascular insults (e.g. $FeCl_3$-induced vascular injury, subtotal V. cava ligation) may be needed to precipitate major thrombotic events and screen for the efficacy of TF blocking drug candidates in small animals. Targeting TF could be a therapeutic approach in selected COVID-19 patients, who show abnormal clinical markers associated with thrombotic coagulopathy (e.g. ↑D-dimers). In conclusion, a better understanding of TF-dependent prothrombotic mechanisms could greatly facilitate the development of novel therapies to reduce the occurrence and severe consequences of CAC.

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CRediT authorship contribution statement

Contribution: S.S. wrote and revised the manuscript. H.K., and M.B., provided critical feedback and contributed to writing the manuscript. All the authors are responsible for the content of this publication.

Declaration of competing interest

None of the authors declare any conflict of interest.

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