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Potential Benefit of Soluble Thrombomodulin in Coping with COVID-19/SARS-CoV-2-Induced Coagulopathy

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Perspective

Researchers should investigate the coagulopathy that accompanies Coronavirus Disease 2019 (COVID-19), as the incidence, as well as the mortality associated with coagulopathy, is higher than expected in COVID-19 patients. We read with interest the article published by Tang N et al. suggesting that elevated plasma levels of the fibrin degradation product D-dimer might be a predictive marker for mortality of patients with COVID-19 [1]. The same authors also reported that the use of heparin improved the prognosis of COVID-19 patients with severe coagulopathy and D-dimer levels >6-fold of the normal upper limit [2]. The high plasma levels of D-dimer suggest that the fibrinolytic system is not inhibited; nonetheless, thrombotic events are frequently noted in COVID-19 patients transferred to intensive care units [3]. Curiously, severe cases of COVID-19 are complicated by cytokine release syndrome in conjunction with Hemophagocytic Lymphohistiocytosis (HLH) [4], suggesting that extremely exaggerated hypercoagulability is induced in COVID-19. The pathophysiology of COVID-19-induced coagulopathy has not been fully elucidated. However, recently, postmortem examination of patients with COVID-19 who died of respiratory failure found thrombi in parallel with the deposition of the C5b-9 complex in the microvasculature, indicating terminal complement activation [5]. These pathological findings are reminiscent of the pathogenesis of Transplant-Associated Thrombotic Microangiopathy (TA-TMA) and atypical Hemolytic Uremic Syndrome (aHUS), in which activation of the complement system plays a role. Other possible factors involved in the pathogenesis of COVID-19-induced coagulopathy may be related to the tropism of Severe Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), the pathogen that causes COVID-19, to vascular endothelial cells [6]. SARS-CoV-2 infects vascular endothelial cells *via* the Angiotensin-Converting Enzyme 2 (ACE2) receptor, leading to vascular derangement, so-called endotheliitis, which may result in coagulopathy and TMA.

Thrombomodulin (TM) is a cell-surface expressed glycoprotein comprising six distinct domains, including an NH2-terminal lectin-like region, six tandem Epidermal Growth Factor (EGF)-like structures, an O-glycosylation site-rich domain, a transmembrane domain, and a cytoplasmic tail domain [7]. TM binds to thrombin via its EGF-like region and Converts Protein C (PC) to Activated PC (APC), which inhibits coagulant factors FVIIIa and FVa in the presence of protein S, thereby inhibiting further thrombin generation. Interestingly, TM has an anti-inflammatory effect; the lectin-like domain of TM binds and degrades High Mobility Group Box-1 (HMGB1) and attenuates inflammation. Additionally, after interacting with thrombin, TM converts carboxypeptidase Thrombin-Activatable Fibrinolysis Inhibitor (TAFI) to activated TAFI (TAFIa), which inactivates C3 and C5. Furthermore, the fifth domain of EGF-like region of TM (TME5) interacts with the cell-surface chemokine receptor G protein-coupled receptor protein 15 (GPR15) and then exerts cytoprotective effects on vascular endothelial cells in association with upregulation of antiapoptotic MCl-1 proteins, which is mediated by the activation of extracellular signal-regulated kinase [7]. Recombinant human soluble TM (rhTM) comprises extracellular domains of TM. A clinical trial comparing the efficacy and safety of rhTM with Unfractionated Heparin (UFH) in patients with Intravascular Coagulation (DIC) caused by hematological malignancies or infection found that a greater number of patients treated with rhTM recovered from DIC with acceptable toxicity profiles than those who received UFH. Based on these results, the use of rhTM has been approved for the treatment of DIC in Japan since 2008. The use of rhTM effectively treated many patients with DIC with various types of underlying diseases, including transplant-associated complications such as TA-TMA, hepatic sinusoidal obstruction syndrome/veno-occlusive disease and engraftment syndrome [8]. Importantly, endothliitis plays a role in the development of all of these conditions, suggesting the possible cytoprotective roles of rhTM in vascular endothelial cells. Moreover, prompt improvement of DIC caused by HLH developed in association with immune reconstitution syndrome after initiation of highly active antiretroviral therapy for acquired immunodeficiency syndrome was noted in the individual who received rhTM [9].

Thus, the use of anticoagulant rhTM with additional activities for immune systems and vascular endothelial cells could counteract severe COVID-19 with coagulopathy, although a systematic review and meta-analysis of rhTM therapy for sepsis-induced coagulopathy failed to prove the significant improvement of clinical outcomes of patients with sepsis-induced coagulopathy [10].

Authorship Details

T. Ikezoe contributed to the concept, design of this study, and wrote the manuscript. H. Mori provided the intellectual content.

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