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Assessment of vessels endothelial dysfunction by protease-activated receptors (PARs) signaling in COVID-19 patients

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***Abstract*---**PAR-1-mediated the endothelial disruption that occurs in the context of thromboinflammation. In addition, PAR1 promotes a profibrotic phenotype in fibroblasts, alveolar inflammation, and apoptosis. This is an active area of research; more data are needed to clarify similarities and differences of the PARs and their modulators in Post and Critical cases of COVID-19. Such issues are especially relevant given the potential use PAR-1 as a marker of promote thrombosis and tissue injury through a proposed mechanism between inflammation and thrombosis that was reported previously. This paper would track the theoretical role of PAR-1 as a marker of promote thrombosis in COVID-19 cases by looking for the following questions: What is the Cross Talk Between Thromboinflammation and Protease-activated receptors during Post and Critical cases of COVID-19?

***Keywords*---**COVID-19, PAR-1, Thrombosis, Post COVID.

COVID-19 Pandemic

Since 2019, Chinese researchers found a new betacoronavirus strain known as the 2019-new coronavirus (2019-nCoV)[1]. It is identified as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and causes a highly contagious and infectious disease known as Coronavirus Disease 2019 (COVID-19)[2]. This disease has spread to 2,761 people in China, resulting in 80 deaths, and has infected 33 people in ten other countries as of January 26, 2020[3]. The World Health Organization (WHO) declared COVID-19 a global pandemic on March 11,

2020, because the disease has a global impact, affecting more than 200 countries and causing one million cases and 60 000 deaths[4].

The 2019-new coronavirus (2019-nCoV)

The virus envelope is made up of the spike –S-, envelope –E-, and membrane –M-proteins, as well as the nucleocapsid –N- inside the virion, which coats the nucleic material (RNA)[5]. Coronaviruses enter host cells by binding to a host receptor and then fusing viral and host membranes via an envelope-anchored spike protein (S protein), which is defined by the receptor-binding domain (RBD) of SARS-CoV spike, which recognizes the host receptor angiotensin-converting enzyme 2 (ACE2)[6-8]. The S protein is a glycoprotein that is made up of two subunits: S1 and S2. The S1 subunit is responsible for binding to the host cell receptor, while the S2 subunit aids in viral and host cell fusion[9]. ACE2 is highly expressed on the surface of alveolar type II epithelial cells in the human lung. In addition, other types of cells are infected , such as immune cells[10] .

COVID-19 Symptoms

COVID-19 causes a wide range of symptoms, ranging from complete asymptomatic infection to mild flu-like symptoms to the life-threatening acute respiratory distress syndrome (ARDS)[11]. According to estimates, up to 86 percent of cases in China are asymptomatic or mildly symptomatic, and thus they are unrecognized[12]. Fever, cough, myalgia, anosmia, and fatigue are the most common symptoms at the start of an illness[11]. Bilateral ground–glassopacity, interlobular septal thickening, and pleural thickening are all common chest radiological findings[13]. Patients with ARDS have severe hypoxemia, and respiratory failure, heart failure, fulminant myocarditis, and multi-organ failure(MOF) are the leading causes of death[11].

Coagulopathy in COVID-19

COVID-19 is compatible with the thromboinflammation or coagulopathy model[14]. This implies that inflammation and coagulation are inextricably linked in both directions. Inflammation can activate the coagulation system via pro-inflammatory cytokines such as IL-6, IL-1, IL-8, TNF-, and MCP-1, which play a role in the activation of coagulation by inflammation, while the coagulation system has an impact on inflammatory activity via thrombin, which is the most important player in the activation of PARs, which up-regulates inflammatory molecules such as cytokines, chemokines, growth factors Increased thrombin signaling via proteinase-activated receptors (PARs) on multiple cell types (e.g., platelets, endothelial and epithelial cells, and fibroblasts) leads to tissue injury[15] .

Platelet activation and the coagulation cascade are two main components of the coagulopathy or thromboinflammation[16]. Platelet activation is initiated by many stimulants, including collagen via glycoprotein (GP) VI receptors and thrombin via protease-activated receptors (PAR) 1 and 4[17] . Platelets change shape from discoid to stellate when activated, due to calcium mobilization and dephosphorylation of vasodilator-stimulated phosphoprotein (VASP)[17]. Platelets

aggregate as a result of this conformational change. Platelets also release extracellular substances such as thromboxane A2 (pro-aggregatory and vasoconstrictory factor), adenosine diphosphate ADP (stimulating and amplifying platelet activation), serotonin (aggregatory factor), P-selectin (proinflammatory and procoagulant factor), and phosphatidylserine, all of which have a 50- to 100-fold higher procoagulant activity than activated[18]. The coagulation cascade is divided into three pathways, the extrinsic pathway or called tissue factor (TF) pathway , the intrinsic pathway or called contact pathway , and common pathway that activates of factor X that acts with factor V and Ca+2 to convert prothrombin(FII) into thrombin . Thrombin breaks down soluble fibrinogen into insoluble fibrin, which then forms interweaving strands that are further stabilized by factor XIII[15].

Endothelial dysfunction in COVID-19

Endothelial cells are found primarily in the inner layer of blood vessels, and their functions and structures vary depending on the tissues and organs[19]. Controlling vascular permeability and regulating vascular tone are two well-known functions of endothelial cells in maintaining body physiology homeostasis[20] . Thrombin activates protease activated receptor-1 (PAR-1) on endothelial cells, allowing them to synthesize and release nitric oxide (NO), prostaglandin (PG), endothelin (ET), thromboxane A2 (TXA2), reactive oxygen species (ROS), and angiotensin II (Ang II), all of which act as proinfalmmatory, vasoconstrictive, vasodilatative, and/or procoagulatory[19]. They also play a role in platelet adhesion and aggregation, leukocyte activation, adhesion, and migration, and fibrin formation[21]. The loss of tight junctions, vessel permeability, and endothelial dysfunction occur as a result of endothelial hyperactivation during viral infection as a direct consequence, pulmonary hemorrhage and alveolar edema develop in the lungs [11] .

During coagulopathy and endothelial dysfunction, PAR-1 expression on endothelial cells increases[15]. The coagulation pathway can be activated by a dysfunctional endothelial response to viral infection, resulting in anticoagulation imbalance[20]. Patients who died from COVID-19 had dysfunctional epithelial cells swelling with foamy degeneration and a few areas of segmental fibrin thrombus in glomerular capillary loops[22]. Disruption of vascular integrity and epithelial cell apoptosis result in exposure of the thrombogenic basement membrane and activation of the coagulation cascade after endothelial activation and dysfunction[20] . In the plasma of COVID-19 patients with severe and critical cases, comprehensive coagulation analysis revealed elevated levels of D-dimer, increased fibrinogen, enhanced platelet activation, and increased viscoelastic variables[19]. Thus, heparin for VTE prevention, anticoagulant, and anti-platelet therapies can be suggested for the treatment of coagulopathy caused by endothelial activation and dysfunction[23].

Diagnosis of Coagulopathy and Endothelial dysfunction in COVID-19
D-dimer

Regarding thrombin's cleavage of fibrinogen into monomers, the monomers can align and cross-link via covalent bonds in responding to activated factor XIII,

calcium, and platelets. Plasmin degrades cross-linked fibrin to fibrin degradation products, including D-dimers[24]. The D-dimer can be used as a diagnostic test to rule out thromboembolic diseases or to track the progression of Coagulopathy[24]. D-dimer is a good marker of thrombin activity and fibrin turnover, and thus reflects both haemostasis and fibrinolysis, despite the fact that it is produced during fibrinolysis. It also has an 8-hour half-life and is detectable in blood 2 hours after index thrombus formation[24]. D-dimer above 0.5 mg/L was found in 46.4 percent of patients tested in China, with only 43 percent having raised D-dimer if the disease was mild, and about 60% having severe illness[25, 26] . On COVID-19 patients, measure D-dimer , as recommended by the International Society of Thrombosis and Haemostasis (ISTH) guidance.

Platelet counts

Platelet (PLT) count is a significant parameter in COVID-19 infection due to the sheer presence of thrombocytopenia shows the presence of an utilization coagulopathy[27] . A low platelet count is linked to a higher risk of death and critical cases[28]. Damaged lung tissues and pulmonary endothelial dysfunction can cause megakaryocyte rupture, which results a low Platelet count. The majority of patients with thrombocytopenia have high D-dimer concentrations, as well as changes in coagulation parameters[29]. Finally, COVID-19 patients had a significantly higher mean platelet volume (MPV) than critically ill non-COVID-19 patients when platelet counts were matched[27].

Knowledge gap

PAR expression on endothelial cells is increased during inflammation and endothelial dysfunction[15]. Nitric oxide exerts direct effects on leukocytes, preventing their activation into motile forms that are capable of entering tissues .Hence, it cannot be produced sufficient amounts in dysfunctional endothelial response to damage. Therefore, a decline in its amount always represents endothelial dysfunction[19]A dysfunctional endothelial response to viral infection can activate the coagulation pathway and lead to anticoagulation imbalance[20]. Comprehensive coagulation analyzes of patients with COVID-19 indicate elevated levels of D-dimer, increased fibrinogen, enhanced platelet activation, and increased variables of viscoelastic in the plasma of severe cases

The pathological manifestations leading to severe COVID-19 have been recently considered as vascular leakage inflammatory reactions, anticoagulation imbalance, and endothelial dysfunction which may play a central role in the aforementioned procedure[30] . Accordingly, most patients with critical COVID-19 die from ARDS, pulmonary edema, cytokine storm, sepsis and diffuse coagulopathy[31] . Among the aforementioned causes, ARDS has been considered a result of pulmonary endothelial damage and dysfunction[30]. In addition to venous thromboembolism, the association of microthrombus formation with multiple organ failure and acro-ischemic change has been proposed[23] .

Therefore, understanding the mechanisms of endothelial activation and dysfunction during the course of COVID-19 infection will help in the early

identification of individuals which are at risk of suffering from severe complications[19, 32, 33]

This review is a part of a master proposal suggesting the probability of using diagnostic value of Protease-activated receptors (PARs) level which may represent an essential link between coagulation and inflammation in the pathophysiology of COVID-19. A literature study was performed and considered a databases that published on a many considerable journals and it was focused on a broad extent of Protease-activated receptor in pre and post COVID cases. Therefore reviewing the previous studies could bring the light to a critical contribution for a crucial improvement in coagulation and inflammation markers that could be a part of the knowledge gap which significantly affect their medical applications.

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