Involvement of Reactive Oxygen Species (ROS) and Coagulation in Coronaviral Infection

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Abstract
Coronaviral infection induces various molecular network pathways. Coronavirus pathogenesis pathway is involved in molecules in production of reactive oxygen species (ROS), oxidative stress responses and coagulation system. Several literatures have revealed the association of ROS and coagulation in infection of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In this Editorial, the involvement of ROS and coagulation in coronavirus infectious disease (COVID)-19 pathogenesis is summarized.

Reactive Oxygen Species (ROS) in Coagulation System
ROS are oxygen-derived molecules that oxidize molecules or are converted into oxygen radicals [1]. ROS have dual-effects which are cell damaging or beneficial roles [1-3]. ROS generated by NOX2, a NADPH oxidase, in macrophage play an important role in killing of phagocytosed microorganisms [3]. The ROS accumulation cause mitochondrial dysfunction which leads to coagulopathy associated with inflammatory signaling pathways [4]. Polymorphonuclear leucocytes, commonly referred to as
neutrophils, generate large amounts of ROS via the NADPH oxidase complex [5]. The ROS released from the polymorphonuclear leucocytes following trauma and haemorrhagic shock led to lung injury and coagulopathy [5]. Serpin family A member 1 (SERPINA1/alpha-1-antitrypsin), a serine protease inhibitor, inhibits coagulation factor 2a (thrombin) [6]. SERPINA1 is a member of low-density lipoprotein (LDL) and involved in ROS network [7]. ROS are required for release of granzyme B (GzmB), a cytotoxic lymphocyte protease, into the cytosol [8]. SERPINA1 is converted into a ROS-sensitive granzyme B (GzmB) inhibitor by replacing the P4-P3’ reactive center loop residues [8]. Thrombin activates NADPH oxidase and produce ROS, which leads to fibroblast proliferation [9]. Endothelial exposure of thrombin induces NOX-dependent superoxide anion and hydrogen peroxide [10, 11].

**How is reactive oxygen species (ROS) involved in coronavirus infection?**

ROS is generated upon the infection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in coronavirus disease 2019 (COVID-19), and induces oxidative stress [12]. SARS-CoV-2 infection induces cytokine storm [13,14]. Cytokine storm includes ROS-induced oxidative stress and immune cell dysregulation. Glutathione S-transferase genes, which have functions in the elimination of ROS, involves the morbidity and mortality from COVID-19 [14]. The heme oxygenase-1 (HO-1) induction may be involved in the inflammation-induced coagulation in COVID-19 [14]. ROS quenching by vitamin C, E, b-carotene and polyphenols has been suggested in COVID-19 in the point of view of the nutrient, since oxidative stress causes inflammation [15]. Potential roles of omega-3 fatty acids accompanied by antioxidants have been suggested in the cytokine storm due to SARS-CoV-2 infection [16].

**Coagulation and Coronavirus**

SARS-CoV-2 enters the blood stream and promotes coagulation cascade and induces blood clots [12]. SARS-CoV-2 upregulates complement and coagulation cascade in macaques [17]. Coagulation abnormalities and thrombosis are observed in SARS-CoV-2 infection [18]. COVID-19 patients have an increased risk of arterial and venous thrombosis, and elevated D-dimer levels are associated with the increased thrombosis and mortality [18]. The elevated D-dimer and fibrin degradation product levels are associated with poor prognosis in patients with SARS-CoV-2 pneumonia [19]. Cytokine storm and inflammation leads to the increases in D-dimer and poor prognosis of COVID-19 [20]. During early phase of SARS-CoV-2 infection, whereas coagulation test abnormalities are seen, they do not result in clinical bleeding [21]. Excess coagulation progresses disseminated intravascular coagulation (DIC) in COVID-19 patients at the later phase of the diseases [21]. Severe infections cause activation of coagulation, where coagulation itself is not clinically relevant, however robust coagulation leads to consumption of clotting factors and platelets and coagulation proteins, and DIC that is characterized by the thrombotic deposition in the microvasculature and increased bleeding tendency [22]. The activation of the coagulation system and the following DIC is observed in patients with severe leptospirosis as well [23]. Various physical properties of blood cells, such as lymphocyte stiffness, monocyte size, neutrophil size and deformability, and heterogeneity of erythrocyte deformation and size are altered in COVID-19 [24]. Oxygen delivery of erythrocyte might be affected by the changes in the physical properties of blood cells in COVID-19 [24]. COVID-19 pathogenesis involves renin-angiotensin system and bradykinin system, of which dysregulation causes hypokalemia, hyper-permeability, inflammation, hypotension, vasodilation,
and pulmonary edema, as well [25]. The careful consideration in coagulopathies is needed to understand the coronavirus pathogenesis.

**Conclusion**
The involvement of ROS and coagulation system in coronavirus pathogenesis has been investigated in this article. Coagulation abnormalities and thrombosis are associated with severe condition in COVID-19, where ROS seem to have a role in coagulation cascade and cytokine storm. The mechanism in which ROS play a role on coronavirus infectious disease need to be carefully focused.

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