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Review Article

Role of S protein in thromboembolic complications during COVID19 and activated protein C as a serious therapeutic avenue in severe forms of patients

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Abstract
COVID-19 (Coronavirus disease 2019) is a public health emergency of international concern. There is a pressing urgency to find treatments based upon currently available scientific knowledge and epidemiological data. In this article, we provide a novel hypothesis describing how the severity of the pathology is mainly resulting from the Antibody responses to SARS-CoV-2 (virus causing COVID-19) and not due to the direct action of the virus. SARS-CoV-2 appears to alter the endothelial cell. The pathophysiological mechanism is not yet elucidated. The damage caused resembles a systemic, multi-organ vasculitis predominantly in the lungs. An increase in thromboembolic complications has been observed in COVID-19 patients. These are manifested by pulmonary embolisms or systemic microembolism manifested by microangiopathy affecting the lungs, brain, liver, kidneys and intestines. Therefore, we hypothesize that an auto-immune acquired Protein S (PS) deficiency may be involved in the pathogenesis of thrombotic events in Covid-19. Auto-antibodies to Protein S may form immune complexes, inducing increased clearance of PS or interfering with the protein C-protein S system. COVID-19 early thromboprophylaxis in infected patients, or even effective anticoagulation, could prevent the progression to severe forms, thus reducing mortality in patients with COVID-19. Activated Protein C (APC), a physiological coagulation inhibitor with cytoprotective properties, could be an interesting avenue for the treatment of severe forms of the disease in intensive care; its administration in hypoxic patients could improve tissue oxygenation. Randomized resuscitation studies in patients with COVID19 are also needed to confirm our hypothesis.

Keywords: Activated protein C, Anticoagulation, COVID19, Protein S deficiency, Thromboembolic

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INTRODUCTION

SARS COV is a single-stranded RNA virus, belonging to the coronavirus family, of positive polarity, of approximately 30 kilobases, which replicates in the cytoplasm of host cells; the 5' end of the genome has a cap-like structure and the 3' end of the genome has a 3' end, has a polyA tail. This virus is enveloped and has on its surface peplomeric structures called spicules.

An epidemic of atypical pneumonia, known as Severe Acute Respiratory Syndrome (SARS), spread to various countries (Vietnam, Hong Kong, Singapore, Thailand and Canada) during the first quarter of 2003, following an initial outbreak in China in the last quarter of 2002. The severity of the disease is such that the mortality rate is approximately 3 to 6%.

The determination of the causative agent of this disease has been undertaken by many laboratories around the world. In March 2003, a new coronavirus (SARS-CoV, SARS virus or SARS virus, in French) was isolated, in association with cases of the severe acute respiratory syndrome. (Ksiazek *et al.*, 2003; Drosten *et al.*, 2003; Peiris *et al.*, 2003; Sean Wei Xiang Lee *et al.*, 2020). No treatment or vaccine has been developed against this virus so far.

A second strain emerged in December 2019 in WUHUN (SARS-COV 2) and spread in pandemic mode. COVID 19 is currently a global health problem with health, safety, security, economic and social implications.

SARS-COV 2 as a serious and deadly virus: The virus has a very high contagion potential, and it can spread rapidly in an exponential pattern contaminating thousands of people in the absence of barrier measures and strict means of containment. The disease is highly contagious. No country is spared.

The virus causes cellular lesions in the lungs causing acute respiratory distress with a rapid evolution requiring recourse to mechanical ventilation and a mortality rate that varies between 1 and 10 percent.

A vascular tropism: COVID 19 is a vasculitis: The virus appears to alter the endothelial cell: The pathophysiological mechanism is not yet elucidated, however, the SARS-COV 2 S protein (a major antigenic determinant of the virus) has a high affinity for cellular angiotensin-2 receptors using the angiotensin-2 converting enzyme (ACE2) to enter host cells (Hofmann *et al*., 2020). These ACE2 receptors are highly expressed at the endothelial level in the lungs, brain, gastrointestinal tract, liver and kidney. This suggests that the damage caused resembles a systemic, multi-organ vasculitis predominantly in the lungs.

Role of S protein in frequent and serious thromboembolic complications: The Spike protein is the major antigenic protein of coronaviruses: the S1 domain contains most of the epitopes recognized by neutralizing antibodies during infection (Godet *et al*., 1994; Hofmann *et al*., 2004; Sayaka *et al*., 1991; Walls *et al*., 2020), although sites have been described in other regions of the S protein (YangYang *et al*., 2014).

S Protein plays a major role in viral entry (Belouzard *et al*.,2012). It is a strongly N-glycosylated type I transmembrane protein of 180 to 200 kDa that assembles into homotrimers on the surface of the viral particle (Delmas et Laude, 1990). It has a long N-terminal domain and a short C-terminal domain. It plays a double function in the viral entry by allowing on the one hand the binding of the cell receptor and on the other hand the fusion of the viral envelope with the membranes of the target cells. It has a decisive role in cellular tropism and pathogenicity (Hulswit *et al*., 2016).

It appears that patients who have been infected with CoV-SARS retain antibodies to the receptor-binding domain (RBD) of S protein for at least 3 years after infection of Spike protein (Cao *et al*., 2010).

The attachment of the virion to the host cell is initiated by interactions between the RBD of S protein and its receptor, which determines the host spectrum, but also the tissue tropism of the coronavirus. CoV-SARS uses the enzyme conversion of angiotensin 2 (ACE2) to enter host cells (Hofmann *et al*., 2005).

The neutralization of infection by antibodies is a mechanism of protection against viruses. Infection can be inhibited by blocking binding to cell receptors or by interfering with viral fusion. In addition, in the case of enveloped viruses, antibodies can recruit effector cells or complement, allowing the destruction of infected cells or lysis of viral particles (Corti et Lanzavecchia, 2013).

The seroconversion time of Antibodies, IgM and IgG antibodies appeared consequently with a median seroconversion day of 11, 12 and 14 respectively. There is a strong positive correlation between clinical severity and antibodies titer since 2-weeks after illness onset, for the first time in COVID-19 patients. The high Antibodies titer may be considered as a risk factor of critical illness, independently from older age, male gender and comorbidities (Zhao *et al.,* 2020).

An increase in thromboembolic complications has been observed in COVID 19. These are manifested by pulmonary embolisms or systemic microembolisms manifested by microangiopathy affecting the lungs, brain, liver, kidneys and intestines. The retina may be affected.The virus has the ability to make the endothelium pro clotting by activating it and causing lesions. These thromboembolic complications are usually observed during the second week of the disease period corresponding to the antibody seroconversion time.

Plasma protein S, discovered in Seattle, is a 69 KDa-dependent vitamin K glycoprotein synthesized by hepatocytes, endothelial cells, megakaryocytes and osteoblasts. Its synthesis requires the presence of vit K. Its half-life is 42 h and its plasma concentration is 25 mg /l. It plays a major role in the inhibition of coagulation factors. A constitutional or acquired deficiency causes thromboembolic diseases. Protein S also plays an important role in the immune response by promoting apoptosis.

A secondary deficiency of free protein S caused by COVID-19 is strongly implicated in the genesis of these thromboembolic complications. The inflammatory syndrome, by increasing the concentration of Human Complement C4b-binding protein (C4BP), leads to a decrease in the free fraction of protein S (Van de poel et al, 1999). Anti-S protein antibodies, synthesized during the immune response, can lead to a secondary deficiency as in the case of the varicella and Lupus (Rashid Khan et al, 2019).

The dosage of protein S in patients with COVID-19 is an interesting lead that could objectify a secondary deficit and confirm our hypothesis.

The severity of the pathology resulting from the host's immune response and not due to the direct action of the virus. The severity of symptoms is proportionally related to the increase in antibody levels. Indeed, these antibodies directed to neutralize the virus induce a secondary deficit or dysfunction in plasma protein S responsible for thromboembolic events. Activated protein C, a physiological inhibitor of coagulation, is an interesting therapeutic agent in severe forms of the disease.

Conclusion

In conclusion, we propose, a new concept linking the severity of the pathology to the Antibody re-

sponses to SARS-CoV-2. Specifically, COVID-19 infection stimulates the production of anti-Spike protein antibodies developed against this viral protein. Due to similarities between this protein and protein S, the antibodies attack protein S resulting in its reduction or dysfunction. This, in turn promote thrombosis. The hypothesis might be further challenged by additional clinical studies and by experimental observations measuring protein S and anti-protein S antibodies in patients with COVID-19 in the intensive care unit.

As a consequence, an immunosuppressive treatment such as hydroxychloroquine or an immunomodulatory drugs such as tocilizumab may be suggested in controlling the disease in early forms by reducing the host's immune response. Early thromboprophylaxis in infected patients, or even effective anticoagulation, could prevent the progression to severe forms and thromboembolic complications, thus reducing severe forms and mortality in patients with COVID19. Activated protein C, a physiological coagulation inhibitor with cytoprotective properties, could be an interesting avenue for the treatment of severe forms of the disease in intensive care; its administration in hypoxic patients could improve tissue oxygenation. It is hoped that this hypothesis will serve as a stimulus for further investigation into this issue, through randomized resuscitation studies in patients with COVID19.

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