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Can COVID-19 Induce an Autoimmune Disease Associated with Long-Lasting Symptoms and Delayed Complications?

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Abstract

A subset of patients with Covid-19 develops late clinical symptoms or severe complications, with thromboinflammation affecting microcirculation and many organs, in addition to the acute severe respiratory syndrome. Complications occur when neutralizing antibodies are already present and the viral load is low or undetectable. We hypothesized that the SARS-CoV-2 high affinity binding to ACE2 through its spike protein RBD can induce a spreading of the immune response to the self-components involved in this cell entry complex, and especially to ACE2. The long-lasting complications and life-threatening critical illness arising as a rebound effect could be the consequences of autoimmune disease induced by the immune response to SARS-CoV-2. Arguments for supporting that hypothesis are presented, and include characteristics of the disease course, mechanisms of disease critical evolution, and benefits of some treatments.

Introduction

The recent outbreak of the SARS-CoV-2 infection, producing COVID-19, shows unexpected disease kinetics and clinical evolution in some affected patients, with long-lasting symptoms, although the viral load is undetectable. If the disease is often asymptomatic or mild, or only associated with cough, fever and sometimes intestinal complications, it can evolve to severe and critical illness with dyspnea, acute respiratory syndrome, thrombosis, especially in microcirculation and with endothelial damage, trhomboinflammation and DIC, multiorgan failure, and it is lethal in a significant number of patients [1-3]. Disease complications 'rate increases highly with age, especially after 65 years old, and they are associated with comorbidities, mainly respiratory or cardiovascular diseases, obesity, hypertension, and diabetes [4-6]. The surprising presentations concern the rebound effect, observed from one to various weeks, even various months, after the onset of symptoms with remaining clinical complications reported by many patients. In addition to the fast evolution to critical states in some people, delayed complications can develop subsequently to an exacerbated immune and inflammatory response at a time where neutralizing antibodies are present and at a high concentration, when the viral load is often undetected [7]. The clinical context can be associated with: Presence of the highest IgG, IgA or IgM antibody levels in the critically ill patients [8]; development of vasculitis and endothelial damages, even in children who develop a Kawasaki-like disease [6,9]. These observations led us recently to hypothesize that these unexpected complications could be the result of an autoimmune complication, following the immune response to SARS-CoV-2, which becomes alloimmune with generation of auto antibodies to some self-proteins, especially those involved in the virus cell entry complex [10]. Our first suspicion concerns autoantibodies to ACE2, or to its complexes with viral proteins, especially the spike protein or its subunits [11]. The viral infection greatly impacts the Renin-Angiotensin-Aldosterone System (RAAS), and this is probably among major causes for developing critical illness states and mortality [12]. Based on our present understanding of virus infection mechanisms [11,13-16], this report develops the major arguments which support this hypothesis and it proposes some research axis for investigating this possibility.

The Renin Angiotensin Aldosterone System and its Balance

A RAAS act as antibody's defense system, which role is to increase blood volume and pressure on the long-term when kidney cells detect a low vascular tone [17-19]. As all physiological systems, it is intimately regulated and balanced between activation and inhibition through 2 major enzymes, Angiotensin Converting Enzyme (ACE) and ACE2 [18,19]. Therefore, 2 axis with opposed actions control RAAS: First the Angiotensin II (AII)-ACE-AII receptor type 1 (AT1R)-Aldosterone axis, which increases vascular tone and blood volume, Na+ entry into cells, and is responsible for the

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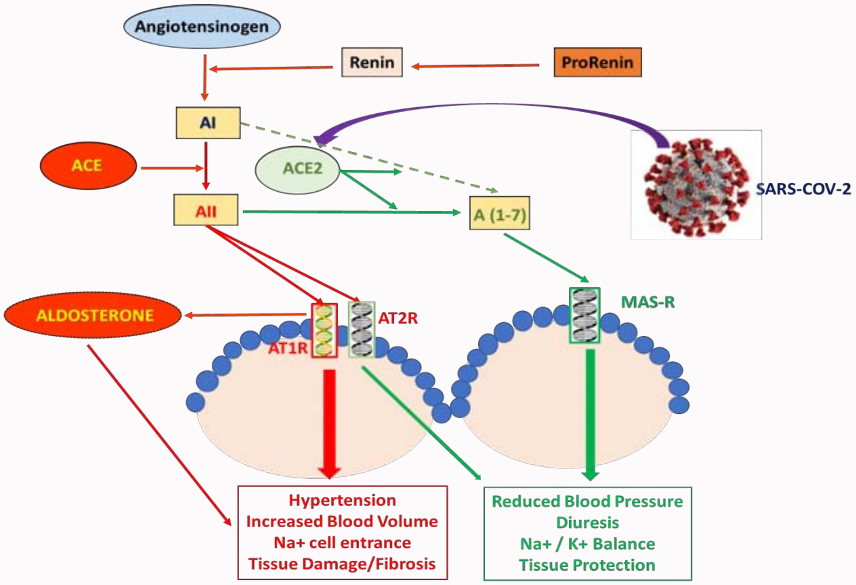

Figure 1: Factors which regulate the Renin-Angiotensin-Aldosterone System through the 2 axis with opposite actions: Angiotensin II (AII)-ACE-Angiotensin II Receptor 1 (AT1R)-Aldosterone axis, and A (1-7)-ACE2-Mas-Receptor axis; SARS-Cov-2 has 2 hits on this system by enhancing its activity, and shedding ACE2, down regulating its control.

hypertensive pathological manifestations when hyper-activated; and second the ACE2-Angiotensin 1-7 (A 1-7) - MAS Receptor (MAS-R)axis, with opposite actions (vasorelaxation, diuresis, tissue protectio). Noteworthy, a second AII receptor is present (AT2R), which develops in some circumstances the inverse actions of AT1R. The cell membrane receptors, AT1R, AT2R and MAS-R are all 7-domain transmembrane receptors. RAAS activation is initiated when renin releases Angiotensin I (AI) from angiotensinogen, and ACE cleaves the decapeptide AI and generates AII, an octapeptide, which mainly activates AT1R, and induces release of aldosterone among other activities [18,20]. When activated in excess, this ACE axis can produce pathological complications, such as microvascular lesions and fibrosis [17,19,21,22]. Conversely, ACE2 converts AII to Angiotensin 1-7 [A-(1-7)] and induces beneficial and tissue protective effects through the activation of MAS-R. ACE2 plays then a major role for preventing from hypertension and regulating the intracellular Na+/K+ balance; it reduces blood volume, favors diuresis, and protects from fibrosis [17]. ACE and ACE2 are both transmembrane receptors, and they show some sequence identity and similarity between them, but they have opposite biological effects [19,23]. This regulated RAAS activation mechanism is shown on Figure 1. ACE and ACE2 are not only cell surface receptors, but their extracellular domains can be cleaved and are then present in blood circulation, with remaining activity [23]. However, there is no evidence that these soluble forms in plasma reflect their cell density, as elevated plasma ACE2 can be measured in pathologies associated with an excess of RAAS activity [23], which produces various pathologies and can favor the development of diabetes. ACE2 has a beneficial effect in many pathological conditions: It is involved in regulating the pathogenesis of respiratory distress syndrome; it opposes liver and lung fibrosis and protects tissues from damages; it controls hypertension, as well as type II diabetes and obesity [18,19,21,22]. This cell surface receptor is a major component of RAAS, and it balances the effects of ACE responsible for blood volume increase, hypertension, and fibrosis [17-19,21]. A right balance between ACE and ACE2 activities is necessary for maintaining RAAS under control. Dysfunction of the RAAS system favors development of hypertension, obesity and diabetes [20,24]. Interestingly, the here above pathologies are the major comorbidities reported as at-risk clinical situations for COVID-19 patients who develop the most critical complications [1,3]. SARS-CoV-2 interferes in RAAS by binding to ACE2, which induces shedding of this cell surface receptor, and impacts its protective functions [25,26]. Interestingly, recombinant ACE2 becomes a pharmacological promising drug, and it is evaluated as a candidate treatment for patients with acute respiratory distress syndrome, and now for severe COVID-19 [16,27]. Therefore, the viral interference of viral infection in RAAS could be a major mechanism for disease pathogenicity, especially by enhancing its activation and lowering its down-regulation capacity [12]. This effect could explain the increased incidence of critical complications in patients with diabetes, obesity, hypertension, and cardiovascular or respiratory diseases, who already have a disturbed RAAS regulation [2,5]. Whether the ACE2 cell surface density or its distribution among tissues and organs is a key factor for infection is still debated. However, we can consider that only few ACE2 receptors are required for virus entry into cells, and only few copies are necessary for viral replication, although if presence of a high ACE2 cell surface density can favor infection kinetics. Tissue expression of ACE2 is especially relevant in lungs and the small intestine. But ACE2 is also present in many tissues and organs, which are then potential targets for viral infection, although there is no evidence that all are directly and effectively attacked by virus. However, they are concerned by the exacerbated immune and inflammatory reaction with the cytokine storm and macrophage activation [28,29]. Multiorgan failure can occur in severely ill patients. Delayed clinical complications, which concern various organs, such as heart, liver, kidney, and endothelium/vasculitis, neurological disorders, or gastrointestinal symptoms are frequently reported in addition to dyspnea and to the acute respiratory syndrome. The frequent presence of blood activation and thrombosis can be the consequence of viral cell destruction, which releases procoagulant and pro-inflammatory products into blood circulation, but also of the strong inflammatory response, with hyperfibrinogenemia,

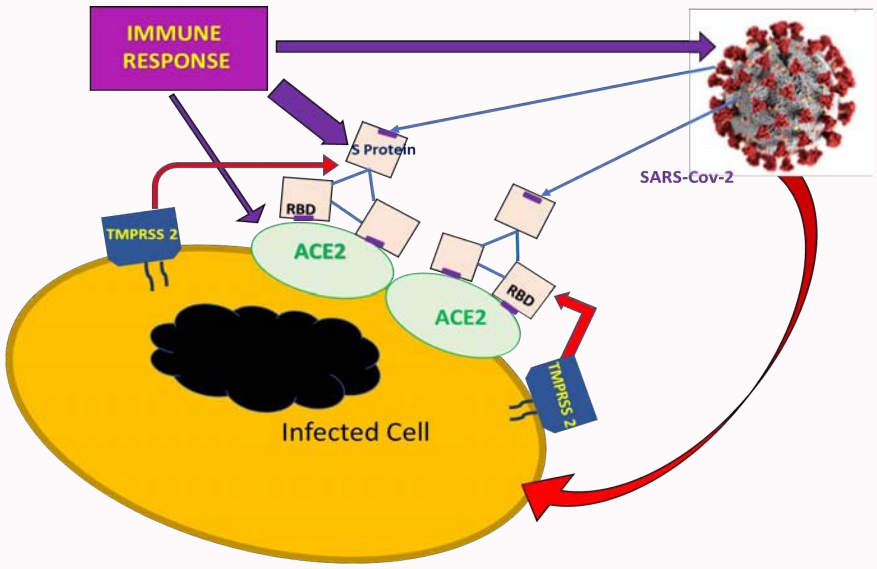

Figure 2: Two S protein trimers bind to an ACE2 dimer, through 2 of their Receptor Binding Domains (RBD) on the cell surface protein, followed by the S protein cleavage by TMPRSS2; this favors virus entry into cell and RNA replication. The immune response is expected to be targeted to the virus and its components; however, the strong binding of the S protein with ACE2 can deviates the immune response to generate autoantibodies to ACE2, or to the self-components of the virus entry complex.

vasoconstriction, decreased fibrinolysis, and organs' dysfunction [4,9,30,31].

SARS-CoV-2 Cell Infection through ACE2 and Body's Defenses

The viral attack mechanisms operate through the ACE2 cell-surface receptor for SARS CoV-2 cell entry [13,14,20]. When SARS-CoV-2 infects cells, it induces shedding of ACE2, as it was demonstrated for the 2002 SARS-CoV, with whom the same cell entry receptor is shared [13,14,25]. In addition, SARS-CoV-2 has a much higher affinity for ACE2 than the 2002 coronavirus [26]. The SARS-CoV-2 external spike protein (composed of 2 subunits: S1 and S2), contains a Receptor Binding Domain (RBD) sequence, which interacts strongly with ACE2 [32,33]. Subsequently, the S2 subunit is cleaved by the cell surface enzyme TMPRSS2 (a membrane serine esterase encoded by TMPRSS2 gene), which favors cell virus infection (Figure 2). Binding to ACE2 and viral protein cleavage allows the virus entry into cells and ACE2 internalization, which reduces the cell surface density of this receptor. Its tissue protective activity is then impaired and cannot counterbalance the harmful action of ACE. RAAS then becomes hyperactive and induces deleterious effects [13,15,32]. Therefore, in addition to cell destruction, many pathological consequences of SARS-CoV-2 infection, which induces COVID-19, can be related to its interference in RAAS, especially by altering the ACE2 protective function. Recently, it has been reported that SARS-CoV-2 morbidity and mortality is favored by 2 hits on the RAAS: Infection, hypercoagulability and inflammation which activates the ACE-AII-AT1R axis and ACE2 shedding which inactivates the ACE2-A (1-7)-MAS-R axis. As the authors outpoint, this could be a major mechanism for pathogenicity, for the severe disease evolution, and for mortality [12]. The strong complex formed between ACE2 and SARS-CoV-2 can be present on many body's organs and vasculature [15], where this cell receptor is expressed. The adaptive immune response, which should normally only be targeted to virus components, can be deviated as the consequence of epitope spreading, and it is then extended to the self-component ACE2 itself, when it is intimately complexed with the viral spike protein RBD. This process could lead to generation of autoantibodies to ACE2 in addition to those produced against viral proteins. Nevertheless, the autoimmune response could be targeted to any other self-component involved in the viral attack complex formed by spike protein and other viral proteins with ACE2 and other cell self-components. We recently hypothesized this possible disease development, which can induce an acute or chronic autoimmune pathology [10]. The acute phase is consistent with the exacerbated inflammatory and prothrombotic secondary clinical evolution. Figure 2 represents the cell entry complex, and the possible immune-stimulation mechanism, which could lead to generation of autoantibodies to ACE2/self-proteins in addition to antibodies to viral proteins. This mechanism could then generate a third RAAS hit for this disease. It can be responsible for the lasting symptoms, or those developing in delayed manner in a subset of infected patients, including many with a mild initial disease.

Evolution and Detection of the Immune Response

Specific antibodies are present 2 to 3 weeks after the onset of disease symptoms and become rapidly neutralizing [8,34-36]. These antibodies can last at least for several months [34]. Immunoassays for detecting the presence of antibodies generated in COVID-19 infection are currently designed with the spike protein S1 subunit, or better the RBD peptide, and with the nucleocapsid protein as capture antigens [34,36]. The highest antibody concentrations, including IgM, IgG and IgA isotypes, have been reported in critically ill patients and not in those with mild symptoms, although antibodies are neutralizing [8]. The unusual clinical course and duration of this disease, with the exaggerated and delayed strong inflammatory response, suggests that a pathological trigger can still be present, even when the viral load is low or undetectable, while the antibody response is high and expected to efficiently fight infection. This led us to formulate our hypothesis on the involvement of an autoimmune response, which can be deviated and targeted to some self-components such as ACE2, or to proteins involved in the virus entry mechanisms. The

unusual clinical presentation and evolution of this disease supports our hypothesis. Interestingly, some recent reports also suggest a possible autoimmune complication developing in some patients with COVID-19 [37,38]. In addition, presence of Lupus Anticoagulant (LA), Antiphospholipid Antibodies (APA) or Antinuclear Antibodies (ANA) have been observed in patients infected with SARS-CoV-2 [39,40]. Such immune reactivity can be observed in presence of different types of autoantibodies, especially those targeted to lipid-binding or transmembrane proteins, which is the case for proteins like ACE2.

Contribution of SARS-CoV-2 Induced Autoantibodies to Disease Evolution

How autoantibodies can contribute to disease evolution is deduced from our hypothesis concerning the immune response induced by the viral infection, which can turn to an alloimmune and be targeted to ACE2 itself. In presence of a persistent immune stimulation, the immune system is deceived and progressively targets all components of the viral pathological molecular complex containing non-self and self-components. The immune response could extend the illness damages to all organs exposing ACE2, even though no more viral antigens are present or not infected yet. This immune response could become autoimmune in some survivor patients when the viral material is eliminated, which can produce various long-lasting clinical symptoms. This mechanism has already been reported in some pathological complications [41]. As an example which illustrates this possible mechanism, we can cite the development of autoantibodies to human thrombin, when bovine thrombin was used for fibrin glue. Some patients developed first antibodies to bovine thrombin, rapidly extending to human thrombin [42]. The immune response was discriminant and first targeted to only epitopes present on bovine thrombin, but this specificity was rapidly lost and antibodies targeted the whole bovine thrombin molecule, which cross-reacted with human thrombin, and this provoked an acute disseminated thrombotic complication, often fatal [42]. The proposed mechanism also resembles the development of immune Heparin Induced Thrombocytopenia (HIT): When stoichiometric Heparin (H) and Platelet Factor 4 (PF4) concentrations are present, multimolecular HPF4 complexes are formed, and they can induce generation of antibodies responsible for platelet activation, destruction, and thrombosis [43]. Many other examples could be cited. Some studies reported that allo- or auto-antibodies can be generated during viral infections and can provoke severe clinical complications. During the viral varicella disease, some rare cases of autoantibodies to coagulation protein S have been reported, with occurrence of thrombosis in the macro- or micro-circulation [44]. Another example concerns Idiopathic Thrombocytopenic Purpura (ITP), which can be the consequence of the platelet viral infection by Epstein Bar or Cytomegalovirus (CMV). The immune response can be extended to the generation of autoantibodies to platelet surface glycoprotein's, such as GP Ib-IX, or GP IIb-IIIa. In some patients, this autoimmune disease, developing during viral infection, can become chronic with the persistence of platelet autoantibodies [45,46]. Many other examples have been reported in literature. Risk factors for development of the autoimmune response are not fully understood, but they can include genetic predisposition, or the occurrence of some specific antigen presentations or length of immune stimulation.

Laboratory Tools for Exploring RAAS Disturbance and Auto-Antibodies

We propose that complementary laboratory investigations to those currently practiced for COVID-19 study could be very informative and could possibly contribute to a better control of the disease course and of its harmful consequences. These testing's should focus on the viral infection impact on RAAS, which has a key function in body's defense regulation and control. Its imbalance resulting from an excessive activation produces hypertension, tissue damage and fibrosis, and can favor inflammation and hypercoagulability. SARS-CoV-2 impairs the ACE/ACE2 balance, reducing the beneficial and protective role of ACE2, and enhancing the harmful uncontrolled effect of the AII-ACE-AT1R-Aldosterone axis. This balance is however difficult to evaluate, as most of ACE and ACE2 activities occur at the cell surface, although soluble forms of ACE and ACE2 are present in plasma at several µg/ml concentrations [18]. There is no evidence that these plasma ACE or ACE2 activities reflect the corresponding cell surface activities. These soluble forms are cleaved from the cell surface exposed ACE or ACE2 receptors, and they could be only markers of an abnormal RAAS activity. Studies reporting elevated soluble plasma ACE2 concentration in some diseases support this statement [23].

Laboratory exploration of the various markers and activities involved in the RAAS could provide useful information on the pathological state and clinical risk of COVID-19 patients. Therefore, measurement of AII, A-(1-7), ACE and ACE2 activities in plasma should be considered in this disease. In addition, measuring the ACE2/ACE activity or antigen ratio could be highly informative. In our hypothesis, the possible presence of antibodies to ACE2, or to its complexes with the S1 viral protein, or to any other complex involving a self-component combined with viral material, should be explored. For testing for those antibodies, the Elisa technique could be envisageable. Recombinant human ACE2 and viral proteins (Spike protein, S1, RBD, S2) are now currently available from various suppliers, although at a very high cost. Conventional capture immunoassay principles, designed for autoantibodies testing through their binding to surface immobilized proteins or complexes, could be used. In practice, the ACE2 recombinant protein, alone or in combination with S1 or RBD, could be coated onto an Elisa plate and used for catching antibodies, when present, and then detected with a labeled conjugate specific for IgM, IgG, or IgA isotypes. Monitoring the antibody kinetics during the disease course could contribute to a better knowledge and management of this infectious pathology.

Discussion and Conclusions

The present understanding on SARS-CoV-2 infection mechanisms suggest that virus binding to ACE2 is essential for cells 'infection and disease development. Our hypothesis on the possible development of an allo-immunization, associated with an acute autoimmune response and a log-lasting chronic evolution, matches with the disease course observed in some patients, and the development of delayed symptoms [10]. Autoantibodies to ACE2 could be generated directly when ACE2 is complexed with viral proteins, especially when the viral infectious complex is present for a long time. Autoantibodies could be also induced by the exposure of ACE2 cryptic epitopes or denatured structures. They could then target an autoimmune response. This hypothesis needs to be demonstrated by developing the appropriate laboratory assays and testing patients, especially those with a delayed disease rebound occurring several weeks or months after the onset of the first symptoms, when the viral load is undetectable. Some delayed but acute clinical complications, such as the strong inflammatory and cytokine response [7,9], the chemoattraction of monocytes and macrophages to multiple pathological sites [29], the disease targeting

various organs and microcirculation, the disseminated pathogenic effects, the development of vasculitis in some patients [6], are clinical observations consistent with an autoimmune (maybe better allo-immune) disease evolution, which can slowly reverse when patients recover, but which could be fatal in some of them.

Among the SARS-CoV-2 deleterious effects, its impact on the RAAS could be of high relevance, especially because comorbidities are those associated with a dysfunction of that system, and because the virus targets ACE2, the protective side of this RAAS, which prevents from hypertension, fibrosis and tissue damage.

Obviously, the pathogenic mechanisms proposed in this review need to be investigated before any confirmation. However, as demonstrated in this article, this possible autoimmune reaction deserves to be investigated. Binding of 2002 SARS-CoV to ACE2 for cell entry was already identified in ARDS [13,25]. However, the binding of SARS-CoV-2 to ACE2 has a much higher affinity, and this could favor the immune system extended reactivity to the whole pathogenic complex, involving viral and self-components [33]. This affinity is of essence for supporting our autoimmune hypothesis [10]. This strong interaction could participate to the alteration or the ternary structure of ACE2, favoring the exposition of cryptic or hindered epitopes, and contribute to autoantibody generation.

Interestingly, in few children a possible association of Kawasaki-like disease induced by COVID-19 has been reported, with endothelial complications, especially in microcirculation. This Kawasaki disease has been strongly suspected to result from an autoimmune process [47]. Autoantibodies to ACE2 have already been described 10 years ago by Takahashi et al. [48] in connective tissue disease, associated with pathologies induced by a low ACE2 activity favoring the harmful effects of AII [48]. Our hypothesis is also in line with this study, which indirectly supports it.

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