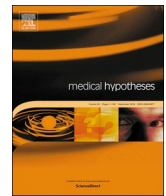




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The triggering of post-COVID-19 autoimmunity phenomena could be associated with both transient immunosuppression and an inappropriate form of immune reconstitution in susceptible individuals



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ABSTRACT

With the progression of the COVID-19 pandemic, there have been different reports about the development of autoimmune diseases once the infection is controlled. After entering the respiratory epithelial cells, SARS-CoV-2—the virus that causes the disease—triggers a severe inflammatory state in some patients known as “cytokine storm” and the development of thrombotic phenomena—both conditions being associated with high mortality. Patients additionally present severe lymphopenia and, in some cases, complement consumption and autoantibody development. There is a normalization of lymphocytes once the infection is controlled. After this, autoimmune conditions of unknown etiology may occur. A hypothesis for the development of post-COVID-19 autoimmunity is proposed based on the consequences of both a transient immunosuppression (both of innate and acquired immunity) in which self-tolerance is lost and an inappropriate form of immune reconstitution that amplifies the process.

Background to hypothesis

In December 2019, there was a new highly contagious infectious disease outbreak in Wuhan, China [1]. Some infected patients developed severe acute respiratory syndrome (SARS) and a systemic inflammatory response syndrome (SIRS) associated with a high mortality rate [2]. This disease then rapidly spread throughout the world and a pandemic was declared in March 2020 [3]. The causative agent of the novel disease known as Covid-19 (Coronavirus Disease 2019) was isolated and identified as a new coronavirus, known as SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2) [4]. Studies report that S protein from the virion surface binds to the angiotensin-converting enzyme 2 (ACE-2) expressed in respiratory epithelial cells, thus triggering mechanisms that cause the virus enter the cell where it manages to generate its replicants [5]. At least two types of biological response have been identified and are related to the pathogenesis of the disease: the induction of an inflammatory response and the generation of a procoagulant state.

The immune/inflammatory response can be mild and rapidly self-limiting, thus ensuring individual asymptomatic or causing mild symptoms. Patients with less severe disease symptoms achieve, as far as is known, both cellular and humoral immunity for protection against future virus exposures [6,7]. This immune response may be poorly regulated in other infected individuals, progressing to SARS and SIRS,

both of which are associated with high mortality rates [8].

On the other hand, after SARS-CoV-2 infection, some patients developed autoimmune conditions such as systemic lupus erythematosus [9], autoimmune hemolytic anemia [10], autoimmune thrombocytopenia [11], Guillain-Barré syndrome [12–14], vasculitis [15–18] or multiple sclerosis [19,20], as well as some autoinflammatory conditions in children [21], including Kawasaki disease [22]. Several symptoms associated with systemic autoimmune diseases may appear during infection and persist after its control, such as fatigue, joint pain, dry syndrome, and myalgias, among others [23,24]. Some thrombotic phenomena have been associated with the development of antiphospholipid antibodies, with antiphospholipid syndrome most likely occurring [25]. Complement consumption [26–28], deposition of immune complexes [29], as well as most probably the development of anti-nuclear antibodies and anti-DNA antibodies [9,30] in some cases, also may be associated to autoimmunity phenomena.

This type of outcome is well-known in other viral infections such as those caused by hepatitis C virus [31] or by alpha viruses, such as chikungunya or O'nyong-nyong [32]. An increase in the amount of cases of rheumatoid arthritis (RA) has been reported after various viral epidemics [33].

Several hypotheses associated with SARS-CoV-2 infection may be proposed in this regard. The chain of events that takes place in some patients, which leads to a process of hyper-inflammation, has been well

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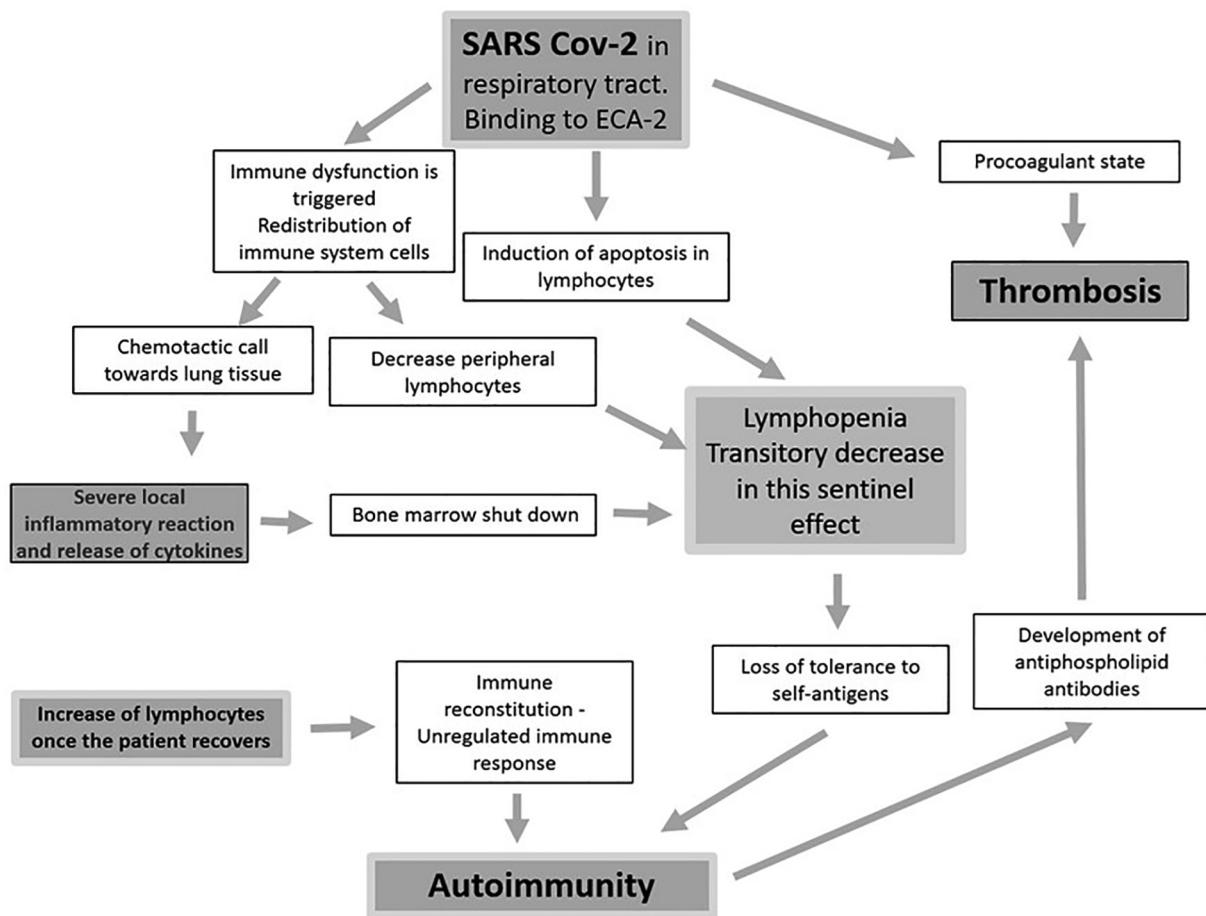


Fig. 1. SARS-CoV-2 may trigger autoimmunity phenomena associated with a state of transient immunodeficiency of components of both innate and acquired immunity in which the immune system fails to properly recognize of autoantigens. This is associated a form of immune reconstitution that would magnify this anomaly in the convalescence of the disease. Other components of the pathogenesis of COVID-19 as thrombosis is exposed.

documented. Here, lymphoplasmocyte cell infiltrates are involved (mainly at the lung level), as well as the expression of pro-inflammatory cytokines such as interleukin (IL) IL-1, IL-6, IL-17, and TNF- α , and markers of systemic inflammation such as C-reactive protein or ferritin [34]. A parallelism of events was found with RA, where there are similar infiltrates at the synovial level, with expression of the same group of proinflammatory cytokines and elevation of acute-phase reactants [35]. However, this route is unlikely, given that there has been no increase in exacerbations of RA patients concomitantly suffering from COVID-19 and no increase in new cases during the pandemic so far. Based on a four-phase model of the disease (Phase 1: “viral phase” in which the virus enters the body, 2- Phase 2: hyperresponsiveness of the immune system, Phase 3: state of hypercoagulability and Phase 4: organ injury and failure occur), Rodríguez et al. [36] propose the development of a “crossroad” of autoimmunity/autoinflammation related to the pathogenesis of Covid-19.

Statement of hypothesis

Loss of immune tolerance that leads to autoimmunity in SARS-CoV-2 infection could be associated with loss of tolerance to certain self-antigens due to transient immunosuppression, which occurs during disease, as well as a form of immune reconstitution in convalescence. In COVID-19, there is a marked decrease in lymphocytes from various lineages, including T lymphocytes (TL) CD4 +, CD8 +, and regulatory TL. The cause of this transient lymphopenia is unclear, but we can assume that it is multifactorial and includes the induction of apoptosis [37], the effect of cytokines such as type I interferon [38,39], bone

marrow shut down [40], or redistribution caused by the chemotactic call towards lung tissue [41]. The redistribution of immune system cells also includes components of innate immunity such as monocytes/macrophages and dendritic cells [41]. Lymphocyte levels increase again once the patient recovers [42]; at this time, a form of immune reconstitution may be occurring where an unregulated response may arise.

Some of the cellular components of innate immunity, such as monocytes/macrophages and dendritic cells, perform the function of permanently checking on all tissues in order to identify self-cells against which they would not react, and non-self cells against which an immune/inflammatory response would be triggered [43]. The immunosuppression that occurs during a SARS-CoV-2 infection, as well as the redistribution of immune system cells, could be associated with a transitory decrease in this sentinel effect, with the possibility of losing self-tolerance towards some self-antigens. It has also been reported that regulatory T cells are also transiently suppressed, the effect of which could contribute to the activation of lymphocytes with lineages of reactivity [44,45]. Similar phenomena are observed in clinical practice, where a form of transient immunosuppression or immunodeficiency occurs before a sudden reactivation of the immune components, which is associated with the triggering of autoimmunity or autoinflammation phenomena. This is the case with postpartum [46], withdrawal of chemotherapy for cancer [47], withdrawal of glucocorticoids [48], withdrawal of anti-TNF medication in patients with tuberculosis [49], or initiation of treatment for HIV infection [50], among others.

It has been proposed that SARS-CoV-2 may trigger autoimmunity phenomena associated with a state of transient immunodeficiency of components of both innate and acquired immunity in which the fails to

properly recognize of autoantigens. This is associated with a form of immune reconstitution that would magnify this anomaly (See Fig. 1).

Testing the hypothesis

The probability of developing autoimmunity phenomena is based on genetic predisposition, which involves human leukocyte antigens (HLA) polymorphisms [51] and some non-HLA genes [52]; the effect of gender, being more common in the female gender [53]; age, being more common in reproductive age due to the effect of estrogens [54]; a family history of autoimmune diseases [55]; an individual history of autoimmune diseases (which makes an individual more susceptible to developing another autoimmune condition) [56]; and the presence of autoantibodies such as anti-nuclear antibodies [57]. Each of these predisposing components are additive when evaluating individual susceptibility for developing autoimmunity [58], which is a condition where a tendency to lose immune self-tolerance is observed [59]. A cohort of patients with transient lymphopenia who develop COVID-19 can be screened for their personal (gender, age, previous autoimmune disease, among others) and family background regarding autoimmunity and HLA typing, and the development of *de novo* autoantibodies, an increase in their previously positive titers, or the development of *de novo* autoimmune pathologies can be monitored during the post-COVID-19 period.

Furthermore, studies with laboratory animals that combine the expression of genes associated with predisposition to autoimmunity [60] and human ACE-2 in lung tissues (COVID-19 model) [61] could be proposed, where they would be subjected to SARS-CoV-2 infection in order to assess the development of autoimmunity and its mechanisms, including transient immunosuppression and immune reconstitution.

Conclusion

The development of autoimmune conditions subsequent to COVID-19 infection could be related to both factors: transient immunosuppression of innate and acquired immunity leading to a loss of self-tolerance to self-antigens, and a form of inappropriate immune reconstitution in individuals with predisposing conditions of autoimmunity.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.mehy.2020.110345>.

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