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COMMENTARY

Molecular insights into onset of autoimmunity in SARS-CoV-2 infected patients

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Abstract

Some of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infected patients are facing long-term devastating effects like induction of autoimmune diseases. Here, I discuss molecular mechanisms and risk factors involved in the induction of autoimmune diseases after SARS-CoV-2 infections. Transcript editing genes were upregulated during SARS-CoV-2 infections, which might have edited host gene transcripts and paved the way for autoantigens generation and presented as nonself to generate autoantibodies followed by auto immunogenicity after SARS-CoV-2 infections. Therefore, some SARS-CoV-2 patients acquire autoimmunity. The transient and/or innocuous autoimmune response in some SARS-CoV-2 infected patients may be due to a lack of repeated production of autoantibodies to host autoantigens and/or viral antigens, which are needed to boost autoimmune response. In the future, SARS-CoV-2 mediated autoimmune disease onset will be a challenging task. Therefore, possible preventive measures and strategies to minimize and/or preclude such SARS-CoV-2 mediated autoimmune diseases have been presented in this commentary.

KEYWORDS

autoimmunity, cytokine storm, mutations, RNA editing, SARS-CoV-2 pathogenesis, type I interferons

Highlights

- Host immune-mediated upregulation of RNA editing APOBEC3G/F and ADAR1 genes leads to the viral genome and host transcriptome editing during SARS-CoV-2 infections and paves the way for the generation of autoantigens.
- Such autoantigens will be presented as foreign by the host immune system to generate autoantibodies followed by induction of auto immunogenicity and the onset of transient or sustained autoimmune diseases as an aftermath of SARS-CoV-2 infections.
- The preventive measures and strategies are postulated to combat future SARS-CoV-2 infections and their aftermaths and to minimize and/or preclude SARS-CoV-2 mediated ill effects like autoimmune diseases.

Newly emerged severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is highly transmissible and has rapidly spread globally, resulting in a devastating pandemic. The initial aftermath of this pandemic is the expression of autoimmune symptoms in some SARS-CoV-2 patients.[1] Recent studies demonstrated the occurrence of autoantibodies against cytokines, chemokines, complement components, cell surface proteins, and other tissue-associated antigens in SARS-CoV-2 patients, those individuals exhibiting autoimmune symptoms.[2–4] In this Commentary, I attempted to decipher the molecular mechanism(s) involved in the process of origination of autoantigens (auAgs), which leads to the generation of autoantibodies (auAbs)

followed by auto immunogenicity after SARS-CoV-2 infection.

Based on available information in the literature, I wish to postulate the possible cause(s) for the emergence of autoimmunity in post-SARS-CoV-2 infections. The onset of some autoimmune diseases is associated with prior repeated viral infections.[5] During the early stage, SARS-CoV-2 patients undergo immunosuppression induced by viral proteins such as ORF6 and ORF9b.[6,7] In the late stage, patients show a hyperinflammatory immune state demonstrated by the extreme production of pro-inflammatory cytokines.[8] However, the interferon (IFN) signaling is still attenuated. This may be due to the adaptation of multiple immunosuppression strategies by the SARS-CoV-2 during different phases of infection. Moreover, delayed and constitutive IFN expression and insufficient host IFN responses are probably due to the inhibition of IFN signaling by viral ORF6 and ORF9b proteins since SARS-CoV-2 patients undergo immunosuppression by viral evasion by distinct mechanisms as they interfere with host innate antiviral immunity in multiple ways such as innate sensing, IFN production, IFN signaling, and interferon-stimulated gene effector functions.[9–12]

An activated immune response emerges to a certain extent in the late stage of the disease and causes cytokine storms in patients in severe and critical stages of SARS-CoV-2 patients.[8] Molecular mimicry, bystander activation, and viral persistence initiate unnecessary immunoreactivity, resulting in the onset of autoimmunity.[13] Autoantibodies induced by molecular mimicry led to tissue destruction. Virus infections lead to significant activation of antigen presenting cells (APCs) followed by activation of autoreactive $CD8^+$ T cells. Those $CD8^+$ T cells recognize infected cells and kill them by releasing cytotoxic granules. The inflammatory cytokines such as tumor necrosis factor (TNF), lymphotoxin (LT), and nitric oxide (NO), released in this process, will lead to bystander killing of normal neighboring cells and cause tissue damage.[13,14] Persistent viral infections can lead to immune-mediated injury, as described above, due to the constant presence of viral antigens driving the immune response.[14] After infection, covid patients who recovered from the acute disease phase may develop a persistent infection by harboring viral particles in host cells without apparent symptoms. T-cell responses against virus-infected cells lead to inflammation. Therefore, all these three events result in the cytokine storm in the later stages of SARS-CoV-2 infections.[8] Such a combined effect will result in constitutive activation of type I IFNs and type I IFNs inducible genes. Induction of such a vicious cycle will promote the survival and activation of naive T cells, which leads to the production of auAbs via B-cell stimulation followed by the onset of autoimmunity.[15]

What are the risk factors involved, and how are they causing autoimmunity in post-SARS-CoV-2 infections? As described earlier, in addition to cytokine storm, SARS-CoV-2 patients exhibit autoimmune symptoms.[2] The hallmark of autoimmunity is the presence of antibodies against self-molecules such as DNA, RNA, and protein. The process of autoimmunity is not an uncommon occurrence because the immune system mounts immunity when it recognizes altered own molecules since the presence of auAbs in healthy individuals has been well documented.[16,17] Structural changes in DNA, RNA, and protein molecules initiate autoimmune responses and induce auAbs production.[18] Studies demonstrated that the immune system recognizes altered DNA, RNA, and protein molecules as foreign and generates auAbs.[18] Such an autoimmune response is strengthened by helper T-cell activation.[19] Constitutive expressions of type I IFN during repeated viral infections and cancer patients treated with type I IFN for prolonged periods acerbated the onset of some autoimmune diseases, which reveals a vital role of type I IFNs in initiating autoimmunity.[20] IFNs upregulate several genes, including RNA editing enzymes such as Apolipoprotein B editing catalytic polypeptide 3G and F (APOBEC3G/F) and Adenosine Deaminase that act on RNA1 (ADAR1).[21,22] These enzymes play an important role in the innate immune response against viral infections by editing and mutating viral genomes. The SARS-CoV-2 genomes isolated from patients exhibited a plethora of mutations induced in the host environment.[23–25] The APOBEC and ADAR enzymes not only edit viral genomes but also host gene transcripts. The overexpression of ADAR1 and APOBEC3G in response to type I IFNs and other unknown mechanisms described above might be responsible for the induction of mutations in SARS-CoV-2 patients' transcriptomes.[26–28] About 100 million A to I editing sites were identified in the human transcriptome.[29] Therefore, there is a lot of chance for such structurally altered host DNA, RNA, and protein molecules generated during SARS-CoV-2 infections can be presented as nonself (auAgs) and generate auAbs and auto immunogenicity. Therefore, it is surmised that structurally altered DNA, RNA, and protein molecules by the process of editing and/or acquiring mutations pave the way for auAb generation.[11,30] The mechanisms involved in this process have been well explored and summarized as follows; (a) occurrence of editing and induction of mutations in DNA, RNA, and protein molecules followed by host cell death by apoptosis, pyroptosis, and necrosis, initiates the formation of immune complexes (ICs) containing auAgs; (b) the plasmacytoid dendritic cell (pDC) are activated by ICs resulting in the production of endogenous interferon alpha; (c) upregulation of Type I IFNs and/or IFN-inducible genes, will promote the survival and activation of naive T cells, which pave the way for production of auAbs via B-cell stimulation; (d) this results in the repetition of ICs formation and endogenous type I IFNs production by natural interferon alpha–producing cells (NIPCs)/pDCs to repeat the vicious cycle as described above and initiate autoimmune response followed by the onset of autoimmunity[30]; (e) type I IFN regulated superantigens (SAgs) induce massive T cell activation, cytokine release and aid in sustaining autoimmunity.[31]

The destruction of the target antigens (Ag) by the auAbs depends on their binding potential since the auAbs damage their target Ag by complement-mediated lysis or by causing hydrogen peroxide production.[32,33] Therefore, depending on the quality and quantity of auAbs, and the specificity of the corresponding Ags

located on cellular components, tissue, and organs, the auAbs may become immunopathogenic or remain dormant. The viral infection initiates and propagates autoimmune pathogenesis.[5] Therefore, some SARS-CoV-2 patients acquire autoimmunity, and others experience transient autoimmune symptoms. In contrast, some other SARS-CoV-2 patients exhibit no such symptoms in the postinfection period, based on the quality and/or quantity of auAbs they generate. The transient and/or innocuous autoimmune response in some post-SARS-CoV-2 infections is also due to the lack of repeated production of auAbs to host auAgs and/or viral antigens, which is needed to boost autoimmune response.[15] Acquisition of autoimmunity by some cancer patients treated with type I IFNs strengthens this concept.[20]

Regulatory T (Treg) cells suppress antiviral T cell responses and enhance pro-inflammatory effects during the severe phase of the disease.[34] Treg-cell depletion helps in the maturation of antigen-presenting DCs exacerbating antigen-specific humoral and cellular immunity against emerging SARS-CoV-2 antigens. Therefore, transient depletion of Treg cells induces protective adaptive immunity to SARS-CoV-2 by activating antigen-presenting DCs during the severe phase of the disease.[35] Restoring Treg cell function in the post-SARS-CoV-2 infection period will help in avoiding the onset of autoimmunity.

In the future, SARS-CoV-2 mediated autoimmune disease onset will be a challenging task and can be minimized by (a) controlling the cytokine storm, with cytokine-specific antibody therapy based on individual patient needs (precision therapy) during SARS-CoV-2 infections. This strategy will decrease the chance of attaining autoimmunity and also help substantially in reducing the morbidity rate; (b) inhibiting IC mediated IFN production by NIPCs to control excessive endogenous IFN production during post-SARS-CoV-2 infections to minimize auAg production, such a feat can be achieved by precision therapy using medications such as immunosuppressant and steroids; (c) inhibiting inflammation and ADAR1 and APOBEC gene upregulations to diminish auAg formation by using appropriate anti-inflammatory agents; (d) inhibiting apoptosis, necroptosis, and pyroptosis to prevent cell death and mutated and/or edited molecules to be presented as auAgs. Controlled specific signaling pathways involved in those cellular events help to achieve the goal; (e) upregulating nucleases and proteases to clear the presence of viral as well as host altered and/or mutated DNA, RNA, and protein molecules to attenuate auto immunogenicity. Novel therapies formulated by using specific nucleases and proteases will curb these unwanted impacts; (f) controlling constant T-cell activation by using T-cell receptor antagonists and drugs like cell cycle inhibitors and immunosuppressants during autoimmunity-susceptible post infections stages to dampen the constitutive unnecessary immune response. Since the above described events are involved in the initiation and/or propagation of post-SARS-CoV-2 induction of autoimmune pathogenesis. Therefore, the above postulated preventive measures and strategies will help to minimize and/or preclude such SARS-CoV-2 mediated autoimmune diseases.

AUTHOR CONTRIBUTION

The author conceived the concept, analyzed the data, wrote the manuscript, and made critical revisions. The author reviewed and approved the final manuscript.

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CONFLICT OF INTEREST

The author declares no conflict of interest.

DATA AVAILABILITY STATEMENT

Data Availability Statement is not available.

ETHICS STATEMENT

No human and animal subjects are involved.

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Graphical Abstract

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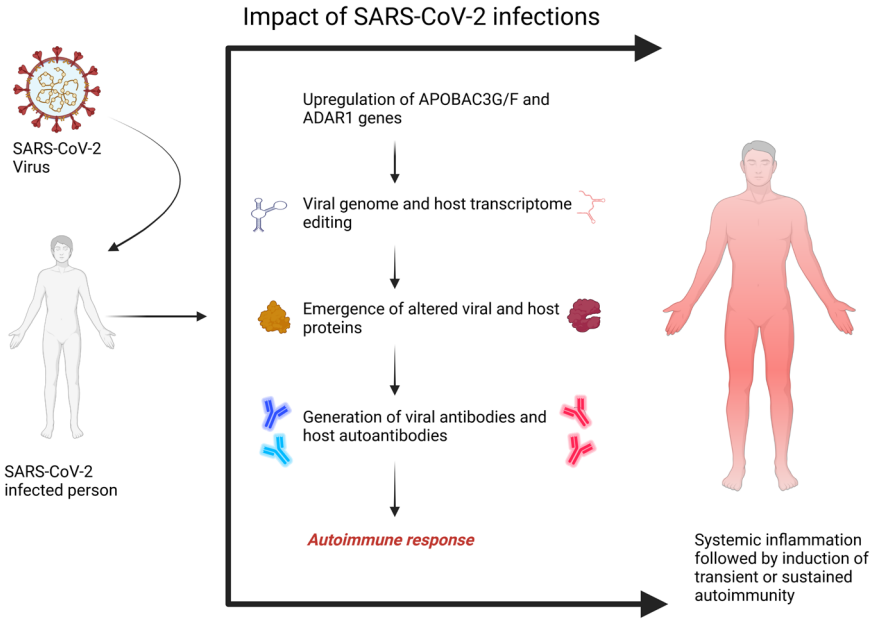

Molecular mechanisms involved in the induction of transient or sustained autoimmunity after SARS-CoV-2 infection.