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Opinion

Long Haul COVID 19 is the Result of B Lymphocyte Anergy Reversal

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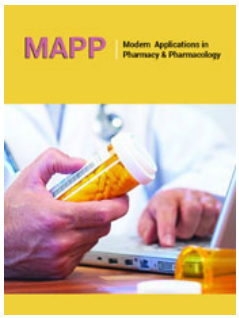

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Abstract

SARS-CoV-2 elevates angiotensin 2 which then activates Angiotensin 2 Type 1 Receptor (AT1R) in anergic B cells which reverses anergy (immune tolerance), thereby producing autoimmunity.

Keywords: COVID 19; Autoimmune; SARS-CoV-2; Long-haul; Intervention

Introduction

Autoimmunity has been suggested as a contributor long haul COVID [1-4] and new-onset IgG autoantibodies have been shown to appear in hospitalized COVID-19 patients [5]. Autoantibodies to diverse autoantigen targets [6] suggests diverse clinical outcomes are possible. A general reversal of anergy might explain the wide swath of symptoms, including the earlier "cytokine storms" seen in the acute infections.

About 40% of human B lymphocytes (B cells) are autoreactive, but anergic (inactivated) [7]. Reversal of the anergy in these B cells would lead to autoimmunity. The clinical outcome would depend on the specific antibody target in the cells that were reversed (lost tolerance). One way to reverse anergy is to activate phosphatidylinositol 3 kinase [8].

Angiotensin 2 (ANG 2) receptors are present on B cells [9] and the Angiotensin 2 Type 1 Receptor (AT1R) subtype is present in human B-lymphocytes [10]. Angiotensin 2 stimulation, at least in T cells, leads phosphatidylinositol 3-kinase (p-PI3K) activity increase, enhanced proliferation of the lymphocytes, and that effect was attenuated by Losartan, an antagonist of AT1R [11].

SARS-CoV-2 spike proteins bind Angiotensin 2 Converting Enzyme (ACE2) and downregulate ACE2 levels, leading to increased levels of angiotensin 2 [12]. It has been suggested that SARS- CoV-2 more directly causes elevation of angiotensin 2 and that inflammatory pathway effects may be related to COVID 19 symptoms [13]. I found no direct evidence that ACE2 activity is directly altered by SARS-CoV-2 spike protein binding, but it seems plausible that it might inhibit its ability to break down angiotensin 2 and further result in even higher angiotensin 2 concentrations.

So, the hypothesis is that SARS-CoV-2 elevates angiotensin 2 which then activates Angiotensin 2 Type 1 Receptor (AT1R) in anergic B lymphocytes and reverses anergy, thereby producing autoimmunity. The outcomes would vary widely in symptoms and severity.

This suggests a therapy to prevent the COVID 19 long haul outcome, and possibly the initial severe cases ("cytokine storm"). Administration of an approved ACE inhibitor (such as Lisinopril) during the early infectious phase of COVID19, before anergy reversal, might prevent the more severe consequences of SARS-CoV-2 infections. This has some support from a meta- analysis that found that hypertensive patients with COVID-19 who were on

angiotensin-converting enzyme inhibitors or angiotensin receptor blockers were less likely to have critical outcomes and also had lower risk of death [14]. After that point of anergy reversal, ACE inhibition would be unlikely to help.

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