In June, 2021 I wrote the following:

“Long Haul COVID 19 is the result of B lymphocyte anergy reversal” was rejected by Medical Hypotheses (Elsevier) so I put it in the public domain in case anybody is interested.

Editor and Reviewer comments:

Although your manuscript falls within the aim and scope of this journal, it is being declined due to LACK OF SUFFICIENT NOVELTY. We receive a much larger number of papers than we are able to accept.

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Long Haul COVID 19 is the result of B lymphocyte anergy reversal.

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.
Key words: COVID 19, SARS-CoV-2, long-haul, treatment

Autoimmunity has been suggested as a contributor long haul COVID (1, 2) and autoantibodies to diverse autoantigen targets (3) 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) (4). 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 (5).

Angiotensin 2 (ANG 2) receptors are present on B cells (6) and the angiotensin 2 type 1 receptor (AT1R) subtype is present in human B-lymphocytes (7). 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. (8).

SARS-CoV-2 spike proteins bind angiotensin 2 converting enzyme (ACE2) and downregulate ACE2 levels, leading to increased levels of angiotensin 2 (9). 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. (10). 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 (11).

After that point of anergy reversal, ACE inhibition would be unlikely to help.

I have no conflict of interest
Consent statement/Ethical approval: Not required

(1) Ehrenfeld M, Tincani A, Andreoli L, et al. Covid-19 and autoimmunity. Autoimmun Rev. 2020 Aug;19(8):102597. doi: 10.1016/j.autrev.2020.102597. Epub 2020 Jun 11. PMID: 32535093; PMCID: PMC7289100.

(2) Al-Aly Z, Xie Y, Bowe B. High dimensional characterization of post-acute sequalae of COVID-19. Nature. April 22, 2021. DOI: 10.1038/s41586-021-03553-9.

(3) Wang EY, Mao T, Klein J, et al. Diverse Functional Autoantibodies in Patients with COVID-19. Nature. 2021 May 19. doi: 10.1038/s41586-021-03631-y. Epub ahead of print. PMID: 34010947.

(4) Smith MJ, Ford BR, Rihanek M, et al. Elevated PTEN expression maintains anergy in human B cells and reveals unexpectedly high repertoire autoreactivity. JCI Insight. 2019;4(3). https ://doi.org/10.1172/jci.insight.123384

(5) Franks SE, Cambier JC. Putting on the brakes: regulatory kinases and phosphatases maintaining B cell anergy. Front. Immunol. 2018;9:665. https://doi.org/10.3389/ fimmu.2018.00665. eCollection 2018.

(6) Chan CT, Sobey CG, Lieu M, et al. Obligatory Role for B Cells in the Development of Angiotensin II-Dependent Hypertension. Hypertension. 2015 Nov;66(5):1023-33. doi: 10.1161/HYPERTENSIONAHA.115.05779. Epub 2015 Sep 8. PMID: 26351030.

(7) Rasini E, Cosentino M, Marino F, et al. Angiotensin II type 1 receptor expression on human leukocyte subsets: a flow cytometric and RT-PCR study. Regul Pept. 2006 May 15;134(2-3):69-74. doi: 10.1016/j.regpep.2006.01.007. Epub 2006 Mar 13. PMID: 16530863.

(8) Zhang GH, Miao FA, Xu JG, Zhang Y. Angiotensin II enhances the proliferation of Natural Killer/T-cell lymphoma cells via activating PI3K/Akt signaling pathway. Biosci Rep. 2020 Oct 30;40(10):BSR20202388. doi: 10.1042/BSR20202388. PMID: 32969473; PMCID: PMC7560539.

(9) Banu N, Panikar SS, Leal LR, Leal AR. Protective role of ACE2 and its downregulation in SARS-CoV-2 infection leading to Macrophage Activation Syndrome: Therapeutic implications. Life Sciences. 2020 Sep;256:117905. DOI: 10.1016/j.lfs.2020.117905.

(10) Xavier LL, Neves PFR, Paz LV, et al. Does Angiotensin II Peak in Response to SARS-CoV-2? Front. Immunol. (2021) 11:577875. doi: 10.3389/fimmu.2020.577875

(11) Baral R, White M, Vassiliou VS. Effect of Renin-Angiotensin-Aldosterone System Inhibitors in Patients with COVID-19: a Systematic Review and Meta-analysis of 28,872 Patients. Curr Atheroscler Rep. 2020 Aug 24;22(10):61. doi: 10.1007/s11883-020-00880-6. PMID: 32830286; PMCID: PMC7443394.