Review of: "The α7 Nicotinic Acetylcholine Receptor: a Key Molecule in Post-COVID Syndrome?"

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Potential competing interests: No potential competing interests to declare.

A generally interesting article and I would be specific and structure it. Very interesting findings, needs some further editing.

I attach my comments and recommendations:

Abstract:

1. PASC should this be referred to after as effects of SARS-CoV-2 induced COVID-19.
2. Also, in the abstract I would find it useful to compare to other conditions that could be considered similar potentially as long COVID aetiology does remain unclear as you say. Mortality rate is most likely over 700,000 people globally or more Coronavirus Dashboard (ncov2019.live) or ourworld in data can be used in supplementary materials section for these.
3. Thereafter the article should be structured into Introduction, Complete Methods with sample size (n=x), Results, Discussion, Limitations and then Conclusion
4. A diagram of the range of nicotinic receptors would be helpful for the reader and state potential systemic multi-system organ disorder which may affect cells following initial SARS-CoV-2 infection. Also please mention microglial cells.
5. Long COVID estimates can be viewed here with a cohort size of around 200,000 surveyed Prevalence of ongoing symptoms following coronavirus (COVID-19) infection in the UK - Office for National Statistics (ons.gov.uk)
6. For the structure of the receptors, I would introduce that above with the date of characterisation and then a diagram underneath.

Below could be mentioned mostly in the discussion/conclusion sections.

7. The reference to monocytes. I would put that monocytes can reversibly differentiate into two other types of antigen presenting cell that include dendritic cells of at least 4 subtypes, as well as macrophages (M1/M2) that can be affected through α7-nAChRs that are also expressed by microglia. You could mention monocytic or MDMs i think.

doi: 10.1007/s00018-016-2175-4

Also this is recent and seems to indicate, at least *in vivo*, that in 2 cell types the monocytes/microglia this the nicotinic receptor, α7 nAChR, may regulate autophagy through TLR4 degradation where adenylyl cyclase-6 can co-localise in lipid rafts of macrophages and directly interact. The resultant activation of adenylyl cyclase-6 leads to increased degradation of

TLR4 and therefore although the a7 nAchR is anti-inflammatory, other conditions like smoking may affect this pathway. TLR4 is a known pattern sensing receptor on cell membranes.

https://doi.org/10.1111/bph.15412

This indicates that a7 regulates the MAPK pathway

doi: 10.1007/s00018-016-2175-4

Early in vivo studies indicate that these are the relevant cytokines that in humans regulate T cell phenotypes including helper type I/ type II, regulatory T cells, cytotoxic and Th17 cells: IL-2, IFN-γ, IL-4, IL-17, and IL-6 through the a7 nAChR when excessively stimulated with an agonist.

doi: 10.3389/fimmu.2019.01102

8. It would be nice to see this article rounded off with data in the discussion that the Bloom lab and also Bernasconi provide which further correborate your findings.

“Statistical Analysis of Immune Cell Epitopes affected by ACE2 mutation” indicating that the epitope 674-685 you have researched may indeed correlate with other B/T cell epitope immunogens.

9. This article is comprehensive on the cluster of differentiation markers with immune cell phenotypes.

Vaccines | Free Full-Text | Innate and Adaptive Immunity during SARS-CoV-2 Infection: Biomolecular Cellular Markers and Mechanisms (mdpi.com)

10. Finally it could be worth checking CCR5 relevance to this receptor.