Review of: "Is SARS-CoV-2 Spike glycoprotein impairing macrophage polarization via α7-nicotinic acetylcholine receptors?"

Rostyslav Bubnov[1]

1 National Academy of Sciences of Ukraine

Potential competing interests: The author(s) declared that no potential competing interests exist.

The manuscript `Is SARS-CoV-2 Spike glycoprotein impairing macrophage polarization via α7-nicotinic acetylcholine receptors?` is a very interesting short communication suggesting a novel hypothesis stressing largely important and underestimated aspect of the mechanism of COVID-19 development.

I do agree with criticism of above reviews, however, manuscript is hypothetical and presented ideas are potentially valuable in the pandemia period.

Therefore, modification, style improvement needed before manuscript can be supposed for acceptance.

Although few hypothetical reviews in the field, like [Andersson, U. The cholinergic anti-inflammatory pathway alleviates acute lung injury. *Mol Med* **26,** 64 (2020). https://doi.org/10.1186/s10020-020-00184-0], and *in vitro* studies [https://doi.org/10.1186/s10020-020-00224-9] have been published, the added value of current contribution should be explained.

Number of points need to be clarified, justified with existing studies, own unpublished research (if any?).

What exactly is a role/part of SARS-CoV-2 spike glycoprotein via a cryptic epitope with the α7-nicotinic acetylcholine receptors in Type-1 macrophages polarization in overall immune response in COVID-19?

Authors noticed that `In silico studies predict a direct SARS-CoV-2 spike glycoprotein interaction with nicotinic acetylcholine receptors`, that lies at the background of the hypothesis. More references to rigorous preclinical evidence needed in this regard, and also to clinical finding (if any, even pilot) that can at least theoretically support the hypothesis.

No relevant citation to the studies by authors provided.

More explanations needed for the overall importance of α7-nicotinic acetylcholine receptors in COVID-19 and overall imbalance of adrenergic / cholinergic pathways, links to immunity, between the infection site and the peripheral and central nervous systems.

An illustration of overall mechanism suggested with clear plan, designs for further studies could be added to visualize complexity of pro/anti inflammatory activities involved in the disease progression

as a short communication paper can be suggested

Clear formulate highlights of hypothesis, potential benefits and needs for further research.

What groups of patients could benefit from the potential findings? Potential relation to smokers?

How the personalized treatment can be updated from developing the hypothesis, diagnostic tests to be potentially

designed for patients diagnosis, stratification, perspectives for adding further studies` results to the protocols.