Review of: "Regulation of the acetylcholine/α7nAChR anti-inflammatory pathway in COVID-19 patients"

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

First of all, I would like to appreciate the authors for their pioneering attempt to relate cholinergic system with hypercytokinemia in COVID-19 patients focusing on alpha7 nAChR.

The authors found COVID-19 patients without CHRFAM7A expression showed increased TNF pathway expression in whole blood. However, in healthy volunteers, although statistically significant, the contribution of reduced FAM7A mRNA expression to the increase of TNF mRNA and protein expression is considered to be marginal due to low coefficient of determination (r x r = 0.28).

Moreover, because the pattern and intensity of the mRNA expression for nAChR subtypes in immune cells alter during immunological activation (Qian et al; doi: 10.1038/gene.2010.72), the mRNA expression for nAChR subtypes should vary among individuals depending on their immunological status (Sato et al; doi: 10.1016/S0304-3940(99)00259-1). Therefore, longitudinal analysis in each patient is definitely required for investigation of the relation of hypercytokinemia with the expression of CHRNA7 and CHRFAM7A, as admitted by the authors in the Discussion. Because CHRNA7 is almost ubiquitously expressed in human immune cells (Sato et al; doi: 10.1016/S0304-3940(99)00259-1), it would be better to try with the other primers. Furthermore, α7 nAChRs in T cells and antigen presenting cells play divergent roles in regulation of TNF-α synthesis (Mashimo et al; doi: 10.3389/fimmu.2019.01102; doi: 10.1016/j.intimp.2020.106306). Therefore, in order to make it possible to explain that α7 nAChRs expressed in specific cell type are responsible for the changes in cytokine synthesis, it is strongly recommended to use samples after cell-sorting in future studies.