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

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

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As the authors mention, the cholinergic anti-inflammatory pathway (CAP) has been proposed as a potential regulator of COVID-19-induced cytokine storm. The CAP is a concept that involves anti-inflammatory effect of vagus nerve by the release of acetylcholine (ACh). Activation of nicotinic acetylcholine receptor subtype alpha7 (α7nAChR) by ACh is involved for the inhibitory effect of macrophage-TNF release and hypercytokinemia.

The present case-control study examined whole-blood expression of cholinergic components and correlated them with COVID-19 severity and healthy aged-matched controls. The results are interesting and provide supporting information about the COVID-19-induced hypercytokinemia might associated with decreased expression of the pro-inflammatory dominant negative duplicate CHRFAM7A, a partial duplication of the CHRNA7 gene. However, comments are as follow;

- Number of sample in each COVID-19 severity and control group is quite low. Further study with a large number of patients is needed to concrete the finding of this initial data.
- Confounding factors that may interfere the analysis of data is present in this study. For example, the authors mentioned to use a healthy aged-matched control for comparison. It seem likely that the mean age of healthy control group is lower than COVID-19 patient groups especially critical COVID-19 group. Furthermore, other significant confounding factors that may associated with the modulation of the whole-blood cholinergic components such as chronic inflammation-associated diseases like hypertension, cardiovascular diseases, and diabetes, are also present in the COVID-19 patient group but not found in control-group.
- The authors mentioned that the severity of COVID-19 was classified based on the adaptation of the 6th revised trail version of the novel coronavirus pneumonia diagnosis and treatment guidance. Details of the adaptation and critical criteria should be provided in details.
- Since it has been demonstrated that the chimeric gene CHRFAM7A, a partial duplication of the CHRNA7 gene, is a dominant negative regulator of α7*nAChR function. A reduction of CHRFAM7A expression might be beneficial for treatment of inflammation. Further study on this hypothesis is needed. It has been shown that some mild to moderate COVID-19 patients can further develop to severe or critical

progression. The prospective study on the modulation of cholinergic components during disease progression should be carried out.