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Impairment of the cholinergic anti-inflammatory pathway in older subjects with severe COVID-19

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Introduction

Elderly subjects are at increased risk for severe COVID-19 and mortality [1]. Immunosenescence, a dysfunctional state of innate and adaptive immunity in older age, is associated with low-grade inflammation (inflammaging) and is considered a negative prognostic factor for COVID-19 survival [2]. Elderly subjects affected by COVID-19 infection show higher levels of proinflammatory cytokines than younger patients [3]. High plasma cytokines levels have been associated with severe lung alveolar pathology and increased mortality. Increased plasma IL-6 levels are associated with greater viral load and may thus represent a response to the persistence of the virus in the older subjects due immunosenescence [4]. However, several observations suggest that the greater risk for the development of a cytokine storm in older COVID-19 subjects may also arise from factors unrelated to decreased viral elimination which, to our knowledge, have not yet been considered. More specifically, we are proposing that senescence and/or COVID-19-related disruption of the cholinergic anti-inflammatory pathway (CAP), which is known to modulate the innate immune response [5], should also be considered as an additional mechanism for the marked elevations in proinflammatory cytokines and the increased mortality in older COVID-19 subjects. CAP activation is believed to begin with the detection of inflammation in the periphery. This information is relayed by vagal afferent neurons to the nucleus tractus solitarius (NTS) resulting in increased vagal efferent outflow to sympathetic ganglia that innervate the spleen and release norepinephrine (NE). This NE activates β2-adrenergic receptor (β2AR) on choline acetyltransferase ($ChAT^+$) T cells that function as signaling intermediaries causing acetylcholine (ACh) to be synthesized and released. Adjacent macrophages express the nicotinic α7-receptor (α7R), which when activated by T cell-derived ACh reduces NF-κB signaling and prevents tumor necrosis factor (TNF)-α production. Importantly increases in brain cholinergic activity using acetylcholinesterase (AChE), or butyrylcholinesterase (BChE) inhibitors or M1-muscarinic agonists increase vagal efferent activity, reduce pro-inflammatory cytokines production, and decrease lethality in response to acute endotoxemia and other immune challenges [5].

Aging and various types of dementias, especially Alzheimer's disease, which may be overrepresented among nursing home populations which reportedly have the highest COVID-19-related mortality, are known to be associated with atrophy of basal forebrain neurons and reductions in cholinergic function in other brain areas which may be involved in the regulation of vagal outflow and innate immune response. A recent study also found the *APOE4* genotype, which is accompanied with extensive brain cholinergic deficits, was associated with severe disease in hospitalized older individuals with COVID-19 [6]. In preclinical experiments, mice lacking T lymphocytes or recipients of transferred T cells with short hairpin RNA mediated knockdown of ChAT, were not protected from endotoxemia by vagal neural stimulation [7]. Importantly, patients with COVID-19 have significant reductions in circulating and spleen CD^+ T cells. A greater percentage of elderly with COVID-19 than young have been reported to show significant reductions in circulating CD^+ T cells. This raises the possibility that splenic $ChAT^+$ CD T cells which are critically involved in the activation of the CAP, may also be reduced. Increasing age and disorders which are more prevalent among the elderly including hypertension, obesity, type 2 diabetes mellitus and AD have been associated with increased tissue or circulating BChE or AChE levels [8,9]. These increases could reduce ACh concentrations and its binding to alpha7 nAChRs on macrophages, neutrophils and other inflammatory cells and thus also contribute to an attenuation of CAP and an increase proinflammatory cytokine response to COVID-19 in the elderly.

Thus, a reduction in brain cholinergic function and/or in splenic $ChAT^+$ T cells as well as increased tissue and/or circulating BChE and/or AChE levels might contribute to an attenuation of the cholinergic anti-inflammatory innate response in older subjects with COVID-19. If so, interventions that will increase vagal efferent activity and CAP including BChE and AChE inhibitors and/or splenic $ChAT^+$ T cells, may have a role in the prevention and treatment of cytokine storm and its complications associated with COVID-19 in older adults.

Conflict of interest statement

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the

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manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties. No writing assistance was utilized in the production of this manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mehy.2020.110274.

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