The Possible Protective Role of α-Synuclein Against Severe Acute Respiratory Syndrome Coronavirus 2 Infections in Patients With Parkinson's Disease

Parkinson's disease (PD) is a multisystem disease in which both the central nervous system (CNS) and peripheral nervous system (PNS) are affected. It is characterized by the loss of dopaminergic neurons in the substantia nigra pars compacta as the result of abnormal accumulation and aggregation of α-synuclein (α-syn) in the form of Lewy bodies and Lewy neurites.[1] α-Syn plays an important role in the pathogenesis of neurodegenerative diseases and is considered to be the pathological hallmark of PD and Lewy body dementia.[2]

α-Syn is expressed in neurons (both the CNS and PNS) as well as in erythrocytes and most immune cells. Indeed, several studies have shown that α-syn is upregulated after immune stimulation.[3-5] Recent reports have shown significant deficiency in T cell development in α-syn knock-out mice, which implicates α-syn in both the development of B-lymphocytes[6] and in regulation of T cell phenotypes and function. It has multiple immunomodulatory functions, which can promote disease pathogenicity and also offer protection against proinflammatory responses.[7] In addition, it has been shown that α-syn can also facilitate immune reactions against infections.[8] Moreover, yet little is known about the innate neuron-specific inhibitors of viral infections in the CNS.

Neuronal expression of α-syn restricts the replication of RNA viruses and protects mice from virus-induced neuronal injury. By contrast, in the absence of α-syn, endoplasmic reticulum stress signaling was significantly altered in mice contaminated by neurotrophic RNA viruses, such as West Nile virus and Venezuelan equine encephalitis.[3] This supports the hypothesis that α-syn may play an important role in immune defense responses.[4] In addition, it has been hypothesized that the α-syn inhibits viral neuroinvasion from the PNS to the CNS.[9]

Microglia are the resident immune cells of the brain; they play a major role in the neuroinfilammatory process with a high phagocytic capacity.[10] It has been shown that a reduction of the α-syn expression level in microglia highly increases their response to lipopolysaccharides, whereas it decreases their phagocytic ability.[11] This is a consequence of overactivation of phospholipase D2 and cyclooxygenase-2, which suggests that α-syn is implicated in lipid-mediated signaling by microglia.[12] Moreover, α-syn may be an activating extracellular ligand for microglia.[12] This supports the findings mentioned previously in relation to its neuroprotective effect.[3]

Coronavirus 2019 (COVID-19) can infect neurons and cause disease.[13] It has been shown that it induces neurological diseases such as polyneuropathy, encephalitis, aortic ischemic stroke, and other neurological diseases.[14,15] Neurological manifestations of COVID-19 infection have been classified into 2 categories: CNS and PNS manifestations. CNS symptoms include dizziness, headache, impaired consciousness, acute cerebrovascular disease, ataxia, and epilepsy. However, PNS symptoms are less severe and include hyposmia, hypoplasia, neuralgia, and hypogeusia.[16]

Taken together, the evidence noted previously suggests that the overexpression of α-syn in patients suffering from PD might prevent neuroinvasion by the coronavirus, possibly by inhibiting the spread of the virus from the PNS to the CNS. Consistent with this hypothesis, a retrospective cohort study conducted in Japan showed that patients with parkinsonism hospitalized for pneumonia had a lower rate of in-hospital mortality.[17] This hypothesis can be confirmed by using a large cohort of patients with PD experiencing a severe acute respiratory syndrome attributed to COVID-19 infection.

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