Reversing the Pathogenesis of Parkinson's Disease

Involvement of the kynurenine pathway in the pathogenesis of Parkinson's disease

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"The kynurenine pathway (KP) of tryptophan catabolism is one of the major regulators of the immune response and is also likely to be implicated in the inflammatory and neurotoxic events in Parkinsonism. Several neuroactive compounds are produced through the KP that can be either a neurotoxic, neuroprotective or immunomodulator. Among these metabolites, kynurenic acid (KYNA), produced by astrocytes, is considered as neuroprotective whereas quinolinic acid (QUIN), released by activated microglia, can activate the N-methyl-d-aspartate (NMDA) receptor-signaling pathway, leading to excitotoxicity and amplify the inflammatory response." [1]

Kynurenine pathway in Parkinson's disease—An update

"It was stated that the compounds associated with the kynurenine pathway (KP) could cross the blood-brain barrier easily and enter into cerebral spinal fluid (CSF). It is suspected that there is a direct or indirect connection between Parkinson's disease (PD) and KP metabolites along with variations in blood. In ageing, up-regulated levels of indoleamine-2,3-dioxygenases (IDO) in the blood can be observed in PD. Moreover, the ratio of KYN/KYNA in αSyn expressing fruit flies and urine of PD patients were found to be increased ."

"KP metabolites are associated with neurotransmission of dopamine (DA), glutamatergic and cholinergic regulation, thus targeting KP might relieve motor and non-motor symptoms in PD"

"Various researches in KP has led to the speculation that metabolites in the downstream pathway lead to the development of disorders like PD, hence these metabolites serve as a potential therapeutic target. Besides, the major component of KP is tryptophan (TRP), targeting TRP enzyme can reduce the toxicity in neurons and provide neuroprotection in PD. The possibility of targeting KP to reduce QUIN and further increase the level of KYNA in the brain offers a new approach to decrease excitotoxicity and enhance neuroprotection." [2]

Interferon-γ signaling synergizes with LRRK2 in neurons and microglia derived from human induced pluripotent stem cells

"Supporting a possible role of IFN-γ in pathological processes, increased IFN-γ levels in the serum, and increased IFN-γ production by peripheral CD4+ T cells relative to healthy controls have been detected in PD patients. Moreover, higher levels of IFN-γ, with a significant co-expression of α-synuclein, have been found in the substantia nigra of PD patients. Experimental models also corroborate this connection: IFN-γ has been linked to progressive DA neurodegeneration in rodents. More recent studies further support the interaction between PD-related genes and IFN-γ induced DA neuronal loss" [3]

Plasma from young donors (yFFP®) drops the levels of the levels of the interferon gamma and Kyn/Tryp ratio as well as the levels of indoleamine-2,3-dioxygenases (IDO) - hence dropping neuroinflammation and enabling the brain to heal. [4]

Young Plasma Induces Antidepressant-Like Efects in Aged Rats Subjected to Chronic Mild Stress by Suppressing Indoleamine 2,3-Dioxygenase Enzyme and Kynurenine Pathway in the Prefrontal Cortex

Furthermore, young plasma markedly reduced the levels of interferon-gamma (IFN-γ), IDO, Kyn, and Kyn to tryptophan (Kyn/ Trp) ratio in PFC tissue. Expression levels of the serotonin transporter and growth-associated protein (GAP)-43 were also significantly increased after chronic administration of young plasma. [5]

Study shows how blocking cellular housekeeping system leads to buildup and spread of abnormal protein aggregates in the brain

The p62 protein normally assists in autophagy, a waste-management system that helps cells get rid of potentially harmful protein aggregates. The researchers found evidence that in cell and animal models of Parkinson's, p62 is S-nitrosylated at abnormally high levels in affected neurons. This alteration of p62 inhibits autophagy, causing a buildup of alpha-synuclein aggregates. The buildup of aggregates, in turn, leads to the secretion of the aggregates by affected neurons, and some of these aggregates are taken up by nearby neurons. [6]

Young plasma reverses age-dependent alterations in hepatic function through the restoration of autophagy

Aging also markedly elevated p62 protein expression in the liver, while young plasma markedly attenuated p62 protein expression in the old rats (Figure 4a, b). This observation was confirmed by the transmission electron microscopy (TEM) analysis of autophagosome. In young rats, the number of autophagosomes was statistically higher in livers than those in the old rats. Moreover, young plasma partially restored the aging-induced loss of autophagosomes (Figure 4c, d). Furthermore, young plasma restored the aging-impaired autophagic flux, as shown by marked increase in LC3B-II and p62 expression in aged livers by chloroquine. [7]

[1] https://www.sciencedirect.com/science/article/pii/S0301008215300551?via%3Dihub

[2] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7585940

[3] https://www.nature.com/articles/s41467-020-18755-4

[4] https://pubmed.ncbi.nlm.nih.gov/34626305

[5] https://link.springer.com/article/10.1007%2Fs11064-021-03440-9

[6]https://www.sciencedaily.com/releases/2022/02/220223094316.htm?utm_source=feedburner&utm_medium=email&fbclid=IwAR0kwod4uO2wHscRx7WOD8dznjwETb0WEpPPhYOmE96h1_BpwZVEYLsbXb0

[7] https://onlinelibrary.wiley.com/doi/full/10.1111/acel.12708