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The involvement of JAK/STAT signaling pathway in the treatment of Parkinson's disease

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Abstract

Parkinson's disease (PD) is a neurodegenerative disorder in which inflammation and oxidative stress play key etiopathological role. The pathology of PD brain is characterized by inclusions of aggregated α-synuclein (α-SYN) in the cytoplasmic region of neurons. Clinical evidence suggests that stimulation of pro-inflammatory cytokines leads to neuroinflammation in the affected brain regions. Upon neuroinflammation, the Janus Kinase/Signal Transducers and Activators of Transcription (JAK/STAT) signaling pathway, and other transcription factors such as nuclear factor κB (NF-κB), NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3), mammalian target of rapamycin (mTOR), and toll-like receptors (TLRs) are upregulated and induce the microglial activation, contributing to PD via dopaminergic neuron autophagy. Aberrant activation or phosphorylation of the components of JAK/STAT signaling pathway has been implicated in increased transcription of the inflammation-associated genes and many neurodegenerative disorders such as PD. Interferon gamma (IFN-γ), and interleukine (IL)-6 are two of the most potent activators of the JAK/STAT pathway, and it was shown to be elevated in PD. Stimulation of microglial cell with aggregated α-SYN results in production of nitric oxide (NO), tumor necrosis factor (TNF)-α, and IL-1β in PD. Dysregulation of the JAK/STAT in PD and its involvement in various inflammatory pathways make it a promising PD therapy approach. So far, a variety of synthetic or natural small-molecule JAK inhibitors (Jakinibs) have been found promising in managing a spectrum of ailments, many of which are in preclinical research or clinical trials. Herein, we provided a perspective on the function of the JAK/STAT signaling pathway in PD progression and gathered data that describe the rationale evidence on the potential application of Jakinibs to improve neuroinflammation in PD.

Keywords: JAK/STAT; Jakinibs; Neuroinflammation; Parkinson's disease.

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