Role of neuroinflammation and latent transcription factors in pathogenesis of Parkinson's disease

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Parkinson's disease (PD) the second most common age-associated progressive neurodegenerative disorder is characterized by loss of dopaminergic neurons, cytoplasmic inclusions of aggregated proteins (Lewy bodies), and neuroinflammation. The inflammation of neurons causes release of various inflammatory mediators (IFNs, EGF, IL5, IL6, HGF, LIF and BMP2). The hallmarks of neuroinflammation are the presence of activated microglia and reactive astrocytes in the parenchyma of the CNS and increased production of cytokines, chemokines, prostaglandins, complement cascade proteins, and reactive oxygen and nitrogen species (ROS/RNS) which in some cases can result in disruption of the blood brain barrier and direct participation of the adaptive immune system. Latent transcription factors such as NF-κB, STAT 3, AP1, and SMAD 7, Toll like receptors and FAF 1 are constitutively upregulated in activated microglia. Toll-like receptors when activated promote NF-κB signaling thus promoting a vicious cycle of neuroinflammation. These transcription factors take dopaminergic neurons to apoptotic pathway via p53 and other death domain receptors. Neuroprotective signaling pathways such as mTOR, SOCS, and TGF-β down regulated during development of PD. YY1 signaling, which has protective effect against α-Synuclein toxicity, is significantly decreased in PD patients. In summary we can say that transcription factors promoting inflammation such as NF-κB, STAT 3, AP 1, and Toll-like receptors are constitutively upregulated in PD, while neuroprotective pathways such as mTOR, TGF-β, and YY1 are substantially downregulated in microglia of PD patients.

Keywords: Neuroinflammation, Neuro-degenerative disorder, Signaling pathways, Transcription factor, Apoptosis

Introduction

Parkinson's disease (PD) is second most common neurodegenerative disorder after Alzheimer's and is characterized by progressive loss of dopaminergic neurons from basal ganglia, which results in abnormalities in control of the movement. Bradykinesia, muscular rigidity, resting tremor, and postural hypotension are primary symptoms of PD while loss of dopaminergic neurons from the basal ganglia and Lewy bodies are the pathological characteristics of the PD (Fig. 1).[1]

PD is characterized by the loss of dopaminergic (DA) neurons from the substantia nigra pars compacta (SNpc) (Fig. 2).[2,6] Approximately 1% of the population is affected at 65–70 years of age, which increases to 4–5% in 85-year-olds.[3] Various epidemiological studies and pathological analyses have demonstrated that mean age of onset in sporadic PD, which accounts for about 95% of cases of Parkinsonism is 70 years.[4,7] Familial form of PD linked to genetic mutations and has prevalence rate of 4%. Familial PD patients develop early-onset disease before the age of 50.[8,9] Researchers have been able to link mutations in specific genes to heritable forms of PD.[4] Recessively inherited parkinsonism has been linked with mutations in Parkin, DJ-1, and PINK1,[10,11] whereas dominantly inherited parkinsonism is linked with mutations in α-synuclein and LRRK2.[12–14] Various studies have linked PD with impaired mitochondrial function.[15–20]

Astrocytes have primarily neuroprotective effect, linked to release of glutathione and removal of excess extracellular excitotoxic agents such as glutamate and calcium. Some recent studies have been able to link astrocytosis with development of PD.[21]

Oligodendrocytes, which are involved in process of myelination, are the only glial cell, which have not been implicated in PD.[22]

PD is also attributed to microglial activation by latent transcription factors as a result of marked neuroinflammation. Inflamed dopaminergic neurons release inflammatory mediators (IFNs, EGF, IL5, IL6, HGF, LIF and BMP2). Inflammatory mediators such as TNFα, IL-1β, IL-6 are elevated in PD.[24–26] These cytokines then cause activation of nicotinamide adenine dinucleotide phosphate oxidase and inducible nitric oxide synthase (iNOS). As a result

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