Neuroinflammation in Parkinson's Disease

Subjects: Neurosciences

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Parkinson's disease (PD) is a common neurodegenerative disease characterized by the loss of dopaminergic (DAergic) neurons in the substantia nigra pars compacta (SNpc). Its main symptoms include resting tremors, rigidity, shuffling gait, and bradykinesia. Genome-wide association studies have identified many genetic variants associated with PD. Studies of animal models, neuroimages, and postmortem pathology have also provided substantial insights into the involvement of neuroinflammation in PD pathogenesis, and indicate that cytokine-induced inflammatory responses may play a vital role.

Keywords: Parkinson's disease ; inflammation ; PD-causative genes

1. Genetic Mutations Involved in Neuroinflammation in PD

1.1. Leucine-Rich Repeat Kinase 2

Mutations in leucine-rich repeat kinase 2 (LRRK2) are the most common monogenic genetic causes of both familial and sporadic PD [1][2], and they are also present in other inflammatory diseases such as Crohn's disease and leprosy [3][4]. LRRK2 expression and kinase activity are upregulated in lipopolysaccharide (LPS)-activated rat microglia, whereas the inhibition of LRRK2 kinase reduces the secretion of TNF-α [5]. Increased secretion of IL-1β and IL-6 is also noted in LPS-activated microglia derived from *LRRK* (p.R1441G) transgenic mice [6]. These findings support the role of LRRK2 in neuroinflammation in PD [6]. *LRRK2* (p.G2019S) transgenic rats demonstrate increased microglial activation in the SN and pronounced DAergic neurodegeneration in response to the overexpression of α-synuclein [7]. Neuroinflammation associated with the *LRRK2* (p.G2019S) mutation could be diminished by LRRK2 kinase inhibition [7]. A study showed that microglia from *LRRK2* (p.G2019S) transgenic mice demonstrate increased expression of IL-6 and TNFα, following injection with recombinant α-synuclein fibrils [8]. Chronic dextran sodium sulfate-induced colitis aggravates microglial activation, loss of DAergic neurons, and locomotor deficits in *LRRK2* (p.G2019S) transgenic mice, whereas treatment with anti-TNF-α antibody attenuates neuroinflammation and neurodegeneration [9]. In *LRRK2* (p.G2019S) knockin mice treated with LPS, depletion of microglia by PLX-3397 diminishes weight loss and increases home-cage activity [10], supporting the interaction between neuroinflammation and LRRK2-mediated neurodegeneration.

1.2. PTEN-Induced Putative Kinase 1

Mutations in PTEN-induced putative kinase 1 (*PINK1)* are linked to familial PD with autosomal recessive inheritance [11][12][13]. PINK1 senses mitochondrial dysfunction and phosphorylates parkin to degrade damaged mitochondria through mitophagy [14][15]. PINK1 is also involved in the regulation of proinflammatory cytokines. *PINK1* knockout mice demonstrate increased striatal IL-1β levels, IL-12, and IL-10 after treatment with LPS [16]. In the cortical slices of *PINK1* knockout mice, LPS also augments the upregulation of TNF-α, IL-1β, and IL-6 levels [17]. Moreover, mitochondrial stress leads to the release of DAMPs to activate inflammation, whereas mitophagy mitigates inflammation by removing the damaged mitochondria [18][19][20][21][22]. These results support the role of PINK1-mediated and parkin-mediated mitophagy in inhibiting neuroinflammation.

1.3. Parkin (PRKN)

Mutations in *PRKN* are commonly seen in patients with autosomal recessive early-onset PD [23][24][25]. *PRKN* encodes an E3 ubiquitin ligase (parkin), which plays a neuroprotective role against α-synuclein toxicity and oxidative stress [26][27]. Together with PINK1, parkin participates in mitophagy to degrade damaged mitochondria. The nigral DAergic neurons in *PRKN* knockout mice are vulnerable to LPS-induced inflammation [28]. LPS and TNF-α also downregulate parkin expression in BV2 mouse microglial cells [29], suggesting that chronic inflammation modulates *PRKN* expression.

1.4. DJ-1

Mutations in *DJ-1* are found in the familial recessive form of PD [30]. These mutations disturb the function of the protein in the regulation of membrane receptor tracking and signal transduction [31], TLR3/4 mediated endocytosis [31], and production of IL-6 and IL-1β [31][32]. In BV2 mouse microglial cells, DJ-1 binds to the p65 subunit of NFκB, and DJ-1 knockdown promotes p65 nuclear translocation [33]. *DJ-1* knockout mice exhibit profound microglial activation compared with wild-type littermate controls, especially in response to LPS treatment [33]. *DJ-1* knockdown in N9 mouse microglial cells also reduces the expression of triggering receptors on myeloid cells 2 (TREM2), which is a pivotal regulator of proinflammatory cytokines such as IL-1β and IL-6 [34].

2. Anti-Inflammation Strategies for PDs

Molecular and neuroimaging studies have indicated the role of neuroinflammation in PD pathogenesis. Therefore, anti-inflammatory therapies may be a strategy against neurodegeneration in PD. Different anti-inflammatory strategies, including nonsteroid anti-inflammatory drugs (NSAIDs), inhibitors of TNF-α and NLR family pyrin domain containing 3 (NLRP3), agonists of nuclear factor erythroid 2-related factor 2 (NRF2), and peroxisome proliferator-activated receptor (PPAR)-γ, have been studied for treating PD.

2.1. NSAIDs

In addition to inhibiting cyclooxygenase, NSAIDs downregulate the expression of the deactivate nonsteroidal anti-inflammatory drug-activated gene-1 to suppress microglial activation [35]. In MPTP-treated mice, sodium salicylate decreases microglial activity and lymphocyte infiltrations, and reduces the death of DAergic neurons in SN [36][37][38]. Ibuprofen and piroxicam protect DAergic neurons in SN against rotenone-induced toxicity in rats [39]. Aspirin, acetaminophen, and ibuprofen protect DAergic neurons against glutamate-mediated excitotoxicity in a rat embryonic mesencephalon neuronal model [40]. These animal studies have indicated that NSAIDs may preserve neuronal integrity and survival [40]. However, epidemiological studies have shown no association between ibuprofen or acetaminophen and PD [41]. Neither meta-analysis nor observational studies have provided solid evidence that NSAIDs decrease the risk of PD or modify disease progression [42][43]. Further studies are required to verify the protective role of NSAIDs in patients with PD.

2.2. TNF-α Inhibitor

MPTP administration upregulates TNF-α expression in mouse striatum preceding the loss of DAergic neurons [36], suggesting the role of TNF-α in preclinical or early-stage PD. MPTP-induced loss of DAergic neurons is abolished in transgenic mice carrying homozygous mutant alleles for *TNFRs* [36]. Thalidomide, an inhibitor of TNF-α synthesis, and *TNF-α* knockout attenuate MPTP-induced neuronal damage in the mouse striatum [44]. A cohort study reported that early exposure to anti-TNF therapy is associated with reduced PD incidence [45]. In this study, patients with inflammatory bowel disease (IBD) were 28% more likely to develop PD than matched individuals without IBD. Patients who are exposed to anti-TNF therapy show a 78% reduction in PD incidence compared with unexposed patients [45]. Although the study has positive results, anti-TNF compounds may have limited CNS effects due to their poor penetration across the blood–brain barrier [46].

2.3. NLRP3 Inhibitor

α-Synuclein binds to TLR2 to activate the NLRP3 inflammasome and its downstream IL-1β pathway [47]. A pathological study showed the upregulation of NLRP3 colocalized with microglia in the SN of patients with PD [48]. The small-molecule NLRP3 inhibitor MCC950 decreases inflammasome activation and effectively mitigates motor deficits, nigrostriatal DAergic degeneration, and accumulation of α-synuclein aggregates in 6-hydroxydopa- and α-synuclein fibrils-treated mice [48]. These observations suggest that NLRP3 persistently promotes neuroinflammation, driving progressive DAergic neuropathology, highlighting its potential as a target for PD treatment [48].

2.4. NRF2 Enhancer

NRF2 is a transcription factor that regulates endogenous antioxidative and anti-inflammatory pathways [49]. Neuroinflammation is a prominent cause of oxidative stress in PD [50]. Therefore, the reduction of oxidative stress and neuroinflammation by NRF2 enhancers could be a therapeutic strategy for PD. Dimethyl fumarate, a well-known medication in multiple sclerosis, is a potent NRF2 enhancer that reduces the production of reactive oxygen species in the neurons of *SNCA* (p.A53T) transgenic mice [51]. Dimethyl fumarate also prevents nigral DAergic neuron damage and

decreases microgliosis in MPTP- and α-synuclein-treated mice [52][53]. These findings suggest that NRF2 is a viable target for therapeutic interventions in PD.

2.5. PPAR-γ Agonist

PPAR-γ is a member of the nuclear receptor superfamily that regulates mitochondrial function and modulates lipid and glucose metabolism [54]. PPAR-γ agonists, such as pioglitazone, reduce inflammation by inhibiting the expression of IL-6 and TNF-α [55]. Pioglitazone attenuates inflammatory responses and preserves DAergic nigrostriatal function in the brain of MPTP-treated monkeys [56]. Furthermore, administration of pioglitazone attenuates MPTP-induced glial activation and prevents the loss of dopaminergic neurons in SN of MPTP-treated mice [57][58]. Another PPAR-γ agonist, rosiglitazone, also prevents the loss of DAergic neurons in the SN of MPTP-treated mice [59]. These results support the application of PPAR-γ agonists as putative anti-inflammatory therapies for halting PD progression.

2.6. Steroid Drugs

Dexamethasone, a well-known anti-inflammation agent, protects nigral DAergic neurons against LPS-induced toxicity [60]. Steroid precursors such as dehydroepiandrosterone (DHEA) and pregnenolone provide another treatment option for PD [61]. Pregnenolone alleviates synaptic defects and hyperdopaminergic activity in rats [62]. In MPTP-treated monkeys, DHEA improves parkinsonian phenotypes and potentiates the effect of L-dopa [63]. A recent cohort study indicated that dexamethasone was associated with decreased odds of PD, suggesting that corticosteroids are a potential disease-modifying drug in PD [64].

The aforementioned findings indicate the potential of anti-inflammatory therapies for treating PD. These results should be validated by large randomized controlled trials in patients with PD.

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