

Current Therapeutic Options for Parkinson's Disease and the Role of Proinflammatory Cytokines

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Abstract

In Parkinson's disease, dopaminergic neurons in the substantia nigra region of the brain gradually degenerate, resulting in a progressive loss of function. Because the origin of this disease is unclear, treatment is symptomatic and ineffective in terms of slowing the progression of the condition. Recent research, on the other hand, has established a clear link between neuroinflammation and proinflammatory cytokines and the pathophysiology of several diseases. A discussion of the relationship between proinflammatory cytokines and the pathophysiology of Parkinson's disease is presented in this paper, which also considers current therapy options that target these pathways.

Keywords: *Parkinson's disease; Neurodegenerative disease; Neuroinflammation; Current approaches; Proinflammatory cytokines*

INTRODUCTION

Parkinson's disease is a degenerative neurological system ailment that mainly affects people in their middle and later ages. It begins at an average age of 50-60 years and progresses gradually over a period of roughly 10-20 years, depending on the individual. Parkinson's disease has

been claimed to affect more than one in every 1000 people, with 2 percent to 3 percent of patients over the age of 65 being diagnosed with the disease. A number of studies have demonstrated that neuroinflammation is a significant factor in the aetiology of Parkinson's disease. Proinflammatory cytokines, such as

interleukin-1 beta (IL1 beta), interleukin-6 (IL-6), interleukin-2 (IL-2), and tumour necrosis factor alpha (TNF-alpha), have been postulated to be involved in the immune response to tissue damage in particular. Preclinical and therapeutic research in Parkinson's disease and other neurodegenerative illnesses, as well as clinical and preclinical studies in these diseases, all suggest the presence of a neuroinflammatory cascade. The presence of activated microglia cells, as well as enhanced expression of proinflammatory mediators, was discovered in the substantia nigra regions of patients suffering from Parkinson's disease. Patients with Parkinson's disease had significantly greater amounts of interleukin-1 β (IL-1 β) in their blood, according to research. Several studies have found that inflammation may have a role in the development of both motor and non-motor symptoms. A variety of pathogenic mechanisms, including abnormal protein processing by the ubiquitin-protease and autophagy-lysosome systems, oxidative stress, mitochondrial dysfunction, inflammation, and other factors, have been reported to cause the death of dopaminergic and nondopaminergic cells in the brains of Parkinson's patients.

One of the most challenging aspects of Parkinson's disease is the development of motor symptoms following the loss of more than half of nigrostriatal dopaminergic neurons. This makes treatment more difficult because the condition is not detected early enough, and as a result, treatment is not initiated in a timely manner. Another issue is that treatment options are insufficient because the pathology of the disease has not been determined. In Parkinson's disease, drug therapy is symptomatic, with the goal of alleviating the symptoms. In the later stages of the disease, when neuronal loss has progressed further, the addition of new pharmaceuticals to the treatment regimen or the increase in the dose of currently available drugs has been shown to considerably increase the incidence of drug-related side effects. With inadequate therapy, high costs, and dangerous side effects associated with Parkinson's disease, new treatment options are required. It is critical to have a good understanding of the aetiology of the disease in order to develop successful novel therapeutics. It is the purpose of this review to analyse the association between proinflammatory cytokines and Parkinson's disease, as well as to describe current therapeutic options. The importance of neuroinflammation in the pathogenesis of disease is underlined.

New pathways and targets associated with cytokines in Parkinson's disease

Parkinson's disease is characterised by neuroinflammation caused by microglial activation, and microRNAs (miRs) are important players in this process. In particular, overexpression of miR-195 decreases the production of pro-inflammatory cytokines such as IL-6 and TNF- while simultaneously increasing the secretion of anti-inflammatory cytokines such as IL-4 and IL-10. The Rho-associated kinase 1 (ROCK1) pathway plays a crucial role in this mechanism and has been identified as a potential therapeutic target for Parkinson's disease. The downregulation of miR-21, which inhibits 1-Methyl-4-phenylpyridinium-mediated toxicity by decreasing pro-inflammatory cytokines [IL -6, IL-1, and TNF-] and reactive oxygen species (ROS) generation, may represent a novel therapeutic target in Parkinson's disease.

According to another study, downregulation of the protein kinase-1 and -3 / mixed lineage kinase domain-like protein (RIP1 / RIP3 / MLKL) pathway was shown to ameliorate 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced Parkinson's disease via inflammation cytokines and dopaminergic

neurons, and these genes were reported to be effective in disease pathology.

The immunological response found in Parkinson's disease is not only a result of microglial activation in the brain, but also a result of changes in the immune system in the peripheral blood. According to one study, blood monocytic cells from patients with Parkinson's disease were found to be unresponsive to certain stimulations and to have a shorter viability.

Researchers have discovered that the RAGE receptor, which is involved in the modulation of inflammation, can be effective in neuroinflammation and dopaminergic neuron loss in Parkinson's disease. This receptor is regarded to be a potential therapy target for the condition. It is hypothesised that the G protein-coupled oestrogen receptor (GPER), which is known to induce neurotoxic effects, can be exploited to slow the course of parkinsonism by exerting an anti-inflammatory impact. According to some researchers, cerebral hypoperfusion contributes to cognitive impairment in Parkinson's disease through promoting neuroinflammation.

A number of research focusing on cannabinoid receptors have also been

carried out recently. Δ^9 -caryophyllene (BCP), a naturally occurring cannabinoid type two receptors (CB2) receptor agonist, is a potential therapeutic agent with antioxidant and anti-inflammatory properties that are mediated by cannabinoid type two receptors (CB2) activation. BCP has been shown to have antioxidant and anti-inflammatory properties.

It has been discovered that a newly identified proinflammatory cytokine, interleukin (IL)-32, worsens MPTP neurotoxicity by causing neuroinflammation and that it is responsible for this finding. Additional cytokines, including IL-4 and IL-13, have been proposed to have an influence on cognitive skills via stimulating astrocytes, and attention has been given to the link between these cytokines and dementia caused by Parkinson's disease. According to the findings of a study investigating the association between air pollution and genetic variables in the development of parkinson's disease, traffic-related air pollution and genetic variation in the proinflammatory cytokine gene IL1B may both be associated with disease development.

According to the Parkinson's Disease Association, around 20% of persons with Parkinson's disease will develop depressive problems at some point in their lives. When you take into consideration the fact that proinflammatory cytokines play a role in the pathophysiology of both depression and Parkinson's disease, you can see why we believe that approaches that target this pathway will play an important role in both the treatment and understanding the cause of the disease.

Current treatment approaches associated with cytokines

Aggregated forms of the synaptic protein - synuclein (S) have a role in the progression of Parkinson's disease by inducing an inflammatory response in microglia and causing neurodegeneration. The pretreatment effect of rifampicin and rifampicin quinone on microglial cell culture generated by recombinant human S was investigated in a research of microglial cell culture caused by recombinant human S. Rifampicin and rifampicin quinone inhibited both the PI3K and non-PI3K signalling pathways, which resulted in a reduction in microglial activation and inflammation. Researchers discovered that rifampicin quinone had a stronger neuroprotective effect than rifampicin, and that PI3K inhibition was

particularly important in the control of oxidative stress. It was suggested that Rifampicin quinone might be a promising anti-parkinsonian drug, and that rifampicin quinone might be a promising anti-parkinsonian drug.

The hypoxia-inducible factor-1 alpha (HIF-1 alpha) and nuclear receptor related-1 (Nurr1) genes are crucial for the survival of dopaminergic neurons, and mutations in these genes may have a role in the development of Parkinson's disease. Albendazole, an anthelmintic benzimidazole known to promote Nurr1 activation, was found to have a neuroprotective impact in the rotenone-induced Parkinson model by raising the expression of the genes involved in this process. In addition to enhancing strial dopamine levels and motor capabilities in the substantia nigra, albendazole is thought to be efficient in reducing the development of neurotoxic proinflammatory cytokines, which is thought to be a result of its neuroprotective impact.

FARREOL reduced the synthesis of lipopolysaccharide (LPS)-induced inflammatory mediators such as interleukin-6, interleukin-1 beta, TNF-a, and cyclooxygenase 2 (COX-2) in BV-2 cells in vitro and increased the production

of nitric oxide synthase in BV-2 cells (iNOS). This method is hypothesised to be triggered by suppressing NF-B p65 and AKT phosphorylation, which are both important transcription factors. Aside from that, farrerol displayed neuroprotective effects by lowering microglial activation and dopaminergic cell death in the LPS-induced rat Parkinson's disease model, and it was considered to be a promising treatment for the condition.

It has been demonstrated that raloxifene, a selective oestrogen receptor modulator, is a promising medication for the treatment of early Parkinson's disease because it prevents systemic inflammation and peripheral neuronal dysfunction.

Conventional medications can provide symptomatic relief in Parkinson's disease, but the disease's slow progression has prompted the concept of developing a natural substance-based treatment. In order to accomplish this, Phloretin was tested on mice models of MPTP-induced Parkinson's disease. When MPTP was used to cause lower dopamine (DA) levels, motor impairments, reduced tyrosine hydroxylase (TH) enzyme protein production, and inflammation, phloretin was found to be significantly effective in alleviating these symptoms. Phloretin has

been shown to have neuroprotective effects by decreasing levels of specific inflammatory markers such as glial fibrillary acidic protein (GFAP) and proinflammatory cytokines such as IL-6 and TNF- α . Phloretin has also been shown to have neuroprotective effects by decreasing levels of proinflammatory cytokines such as IL-6 and TNF- α .

The antioxidant thymoquinone was found to boost antioxidant enzyme levels, prevent lipid peroxidation, and ameliorate pro-inflammatory cytokines in a study on the MPTP-induced Parkinson's disease in mice model. Thymoquinone also caused an increase in the levels of inflammatory markers such as COX-2 and iNOS, and it also inhibited cell death caused by aggregation of α -synuclein and the formation of fibrils. Thymol, a dietary monoterpene phenol, was found to have a neuroprotective effect in the rotenone (ROT) -induced Parkinson model, by maintaining the endogenous antioxidant defence mechanism and decreasing inflammatory mediators such as cytokines and enzymes.

Because of its antioxidant and anti-inflammatory qualities, nerolidol, a sesquiterpene alcohol, had neuroprotective

effects in a rotenone-induced animal model of Parkinson's disease.

On the other hand, it has been demonstrated to have a therapeutic impact against neurodegenerative disorders in rat models, and it is assumed to play a role in the regulation of the proinflammatory system.

Baicalein, a significant bioactive flavone, demonstrated antiparkinsonian activity in animal models by decreasing the generation of proinflammatory cytokines, modulating astrocyte and microglial activation, and inhibiting the nuclear factor- κ B (NF- κ B) pathway.

Curcumin, which has antioxidant and anti-inflammatory effects, has been proposed as a potential treatment option for Parkinson's disease. It is hypothesised to work by preventing α -synuclein aggregation in dopaminergic neurons in the brain.

When researchers looked into the effect of probiotics on patients with Parkinson's disease, it was discovered that the strains *Lactobacillus salivarius* LS01 and *L. acidophilus*, in particular, decreased the level of pro-inflammatory cytokines and increased the level of anti-inflammatory cytokines, and that treatment with

probiotics was considered to be promising for the disease. In this investigation, it is interesting that the strains that were found to be successful did not include the *tdc* gene, which has been shown to decrease levodopa bioavailability in patients with Parkinson's disease.

Intriguingly, it has been discovered that the pathway of proinflammatory cytokines is involved in the action of both acupuncture and electroacupuncture, both of which are used as alternative treatments for Parkinson's disease.

CONCLUSION

The research have demonstrated the role of neuroinflammation in the mechanisms of dopaminergic neuron loss, which is the primary cause of Parkinson's disease. For the treatment of Parkinson's disease, it is obvious that targeting proinflammatory cytokines and neuroinflammation pathways will play a critical role in the development of new medicines. Further research is required to fully understand these pathways.

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