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Review Article

From Immune Activation to Neurodegeneration: Understanding the Inflammatory Landscape of Parkinson's Disease

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Abstract

Parkinson's Disease (PD) is a complex neurodegenerative disorder characterized by the progressive loss of dopaminergic neurons in the nigrostriatal pathway, leading to both motor and non-motor symptoms. Recent insights have expanded our understanding of PD beyond its classical motor presentations, highlighting the significant role of neuroinflammation in its pathogenesis and progression. This review explores the multifaceted relationship between neuroinflammatory processes, the immune response, and the onset of PD. It discusses the involvement of both innate and adaptive immunity specifically the activation of microglia and the role of T and B cells in the degeneration of dopaminergic neurons. Additionally, we examine how genetic predispositions, environmental factors, and viral infections may contribute to inflammation and ultimately neurodegeneration. We delve into the implications of chronic inflammation, emphasizing its potential as a therapeutic target and a source of biomarkers for early diagnosis and progression monitoring. Recent therapeutic approaches, including immunotherapies targeting α-synuclein, present promising avenues for intervention. Overall, this review underscores the intricate interplay between neuroinflammation and the pathophysiology of Parkinson's disease, advocating for a deeper exploration of inflammatory pathways as both contributors to and markers of disease progression.

Keywords: Parkinson's disease; B cells; Disease progression; Pathophysiology

Introduction

PD is a prevalent neurodegenerative condition primarily marked by a decline in motor functions, stemming from damage to the dopaminergic nigrostriatal pathway. This damage involves the death of dopamine-producing neurons that extend from the substantia nigra pars compacta to the striatum's caudate-putamen, leading to a decrease in dopamine neurotransmission. The main motor symptoms include rest tremors, slowed movements (bradykinesia), stiffness (rigidity), and balance issues (postural instability) [1-3]. Initially, PD was identified solely as a movement disorder without any cognitive decline, but it is now recognized that PD's progression also impacts other brain pathways, leading to non-motor symptoms such as loss of smell (anosmia), sleep disturbances, constipation, and cognitive and emotional issues, including dementia and depression [4,5].

The disease begins years before the first symptoms manifest, but the exact cause of the neuronal death is still not fully understood. Genetic factors account for 5%-10% of PD cases, with mutations in specific genes (such as *PARK* genes, alpha-Synuclein, *DJ-1, PINK, LRRK2*) leading to an early onset of the disease. However, the majority of PD cases are idiopathic, with a link to aging [6-10]. Environmental risk factors, including exposure to toxins, pesticides, heavy metals, injuries, and infections, have been associated with PD, particularly through their role in promoting inflammation. The connection between inflammation and Parkinsonian symptoms has been explored since the observation of Parkinson-like symptoms in individuals with influenza virus infections (encephalitis lethargica) [11-13]. Subsequent research has linked PD onset to various viral pathogens, including influenza A, Herpes Simplex Virus-1 (HSV-1), Ebola virus, and others, suggesting that these pathogens may reach the brain through the nasal or intestinal pathways, triggering neuroinflammatory and neurodegenerative processes in the nigrostriatal pathway [14-16].

Interestingly, some viral proteins, such as those from HSV-

1 and EBV, can mimic alpha-Synuclein (α-Syn), leading to its aggregation and the formation of Lewy bodies, which are characteristic of PD. Additionally, α-Syn plays a role in attracting immune cells like neutrophils and monocytes in response to viral infections, indicating its involvement in both systemic and brain inflammatory responses in PD's development [17-21].

Inflammation serves as a critical defense mechanism against harmful pathogens or injury, designed to shield the body from harmful agents and aid in tissue healing. Traditionally, the Central Nervous System (CNS) was viewed as immune-privileged due to the Blood-Brain Barrier (BBB) isolating it from the body's general immune system. However, this view has evolved.

The CNS can indeed mount a strong innate immune response to Pathogen-Associated Molecular Patterns (PAMPs) and Damage-Associated Molecular Patterns (DAMPs) [22-24]. Normally, microglia and astroglia patrol the brain's environment to keep the CNS in balance by releasing growth factors, clearing away excess glutamate, and modifying synapses, among other tasks. Yet, these glial cells can become activated by PAMPs and DAMPs, like those from injured neurons or protein clumps, leading to ongoing neuroinflammation. While not always the initial cause, chronic neuroinflammation is increasingly seen as a contributing factor in the progression of PD [25-29].

Further discussions and a wealth of data from human studies and animal research highlight inflammation's role in PD's onset. The precise catalyst for this inflammatory response is still uncertain. It's possible that inflammation results from the continuous death of neuronal cells in PD, but the misfolding of α-Synuclein could also have a direct impact [30-33].

Beyond the significant microgliosis and astrogliosis observed in PD-affected brains, peripheral inflammation and genes linked to PD risk underscore the significant role of chronic inflammation in the disease's advancement. This article will offer a comprehensive review of the cellular and molecular players in neuroinflammation and their potential effects on the progression of PD [34-38].

Inflammation in PD: Pathogenesis and progression

Age stands as the most significant risk factor for numerous neurodegenerative diseases, yet the aging immune system's role is often overlooked and insufficiently researched in the context of neurodegeneration. Immunosenescence, the aging of the immune system, is marked by two main aspects: An age-related decline in immune function and inflammaging. Inflammaging refers to the chronic, low-grade increase in circulating inflammatory mediators or cytokines, particularly C-Reactive Protein (CRP), IL-6, and Tumor Necrosis Factor (TNF), produced by persistently activated immune cells. Both the innate and adaptive branches of the immune system deteriorate with age and exhibit notable changes in PD [39-42].

Innate immunity

Microglia are found in high numbers in the substantia nigra pars compacta and striatum within the brain, both of which are impacted by PD. An early indication of the connection between neuroinflammation and PD's development was presented in 1988, when researchers discovered HLA-DR+ reactive microglia in the post-mortem brain tissue of PD patients. The presence of HLA-DR+ microglia escalates alongside neuronal degeneration in the nigrostriatal pathway. These activated microglia contribute to increased levels of TNF, IL-1β, TGFβ, IL-6, Reactive Oxygen Species (ROS), nitric oxide species, and pro-apoptotic proteins in the substantia nigra pars compacta, striatum, and Cerebrospinal Fluid (CSF) of PD patients [43-45]. The activity of microglia in living patients has been studied using Positron Emission Tomography (PET) with specific ligands to trace neuroinflammation in PD brains. Ligands like 11C-PK11195, targeting the Translocator Protein (TSPO), have indicated heightened microglial activity in PD brains, although this activity does not directly correlate with the clinical severity. This method has led researchers to believe that microglia activation occurs early in PD, contributing to neuroinflammation in areas prone to PD [46-50]. However, the reliability and interpretation of TSPO radioligand binding face challenges like TSPO polymorphisms with second-generation ligands, low TSPO density in healthy brains, and expression in multiple cell types, including peripheral cells. Therefore, new targets are needed for better specificity and understanding of microglia function [51-53].

Traditionally, microglia in neurodegenerative regions were labeled as 'activated' due to their ameboid shape, suggesting a harmful inflammatory state. Yet, current evidence shows that microglia exhibit a range of behaviors and play various roles in PD's pathology. For instance, microglia can cause neuronal death by producing inflammatory factors, interact with α-synuclein to promote its aggregation, or alternatively, offer protection through the production of neurotrophic factors [54-58]. Dysfunctional phagocytosis in glial cells, resulting from PD-related genetic mutations, may contribute to microgliosis and neuroinflammation. Extracellular α-synuclein can activate microglia in a manner dependent on its conformation and specific mutations, with fibrils and mutations linked to early-onset PD eliciting strong immune responses in BV2 microglial-like cells [59,60]. The NLRP3 inflammasome signaling in microglia, a complex involved in promoting an inflammatory state, is activated by α-synuclein in PD models. Different α-synuclein variants trigger specific NLRP3 inflammasome responses in microglia, including α-synuclein breakdown, highlighting its potential significance in PD [61-64].

Beyond microglia, monocytes also play a role in the development of diseases. Specifically, within the monocyte group, the proportion of classical CD14+CD16- monocytes is higher in individuals with PD, and these cells exhibit changes in their gene expression. One notable change is the

increased expression of CC-chemokine Ligand 2 (CCL2), indicating a rise in monocyte recruitment and inflammation in PD patients [65-69]. Additionally, levels of Leucine-Rich Repeat Kinase 2 (LRRK2) are higher in monocytes from PD patients, which is linked to abnormalities in monocyte function. Early stages of the disease show unique monocyte gene expression profiles, including genes related to immune response such as *HLA-DQB1, MYD88, REL*, and *TNF*. More recent studies, including a transcriptome-wide association study, have identified connections between genes related to lysosomal functions and innate immune responses in the dorsolateral prefrontal cortex and peripheral monocytes, highlighting them as risk factors for PD [70-72].

Adaptive immunity

Substantial evidence points to the involvement of adaptive immunity in the development of diseases. In an initial study that discovered HLA-DR+ microglia in the brains of PD patients, researchers found that CD3+ T cells were present in the brains of these patients, a finding that has been confirmed by further research and in animal studies. Later research has delved into the specific types of T cells in the brain and their peripheral counterparts to better understand their contribution to the inflammatory processes linked to PD. In the brains of PD patients, higher levels of CD4+ and CD8+ T cells were observed in the substantia nigra pars compacta compared to controls [73-76]. In the bloodstream, numerous studies, including a meta-analysis involving 943 PD cases, have noted a decrease in circulating CD4+ T cells among patients. More precisely, increases in HLA-DR+ T cells and CD45RO+ memory T cells have been observed in PD patients compared to healthy individuals, whereas naive CD4+ T cells were found to be lower, and the frequency of CD25+ regulatory T (Treg) cells has shown inconsistent results. In PD patients, CD4+FOXP3+ Treg cells exhibit heightened suppressive capabilities. This is in line with the discovery that dopamine, which PD patients lack, reduces Treg cell functionality [77-80]. However, functional studies have not shown a difference in T cell activity between patients receiving dopamine-replacement therapy and those who are not, indicating that dopaminergic medications might not influence T cell behavior. Interestingly, the severity of PD in patients has been linked to the expression of specific dopamine receptors on T cell subsets, suggesting a possible role for immune cell dopamine receptors in the disease's development or progression. The dysregulation of T cells in PD is indicated by their increased expression of TNF receptors and the elevated production of IFNγ and TNF by effector T cells, despite the presence of Treg cells [81-84]. During a comprehensive study it was proposed that in PD patients, certain T cell subsets, particularly CD4+ T cells, recognize specific α-synuclein peptides, further underscoring the significance of adaptive immunity in PD pathology. More recent research has linked α-synuclein T cell reactivity in peripheral blood mononuclear cells with preclinical and early motor stages of PD, suggesting that tracking this could allow for earlier disease detection in susceptible individuals [85-89]. Although there are inconsistencies in the findings regarding T cell dysregulation and their roles in PD pathology, some of this variation might be attributed to the diverse nature of the studied patient groups. Nonetheless, it is evident that disruptions in immune cell movement can foster an inflammatory setting conducive to the neuronal death seen in PD [90-93].

The understanding of B cells' involvement in PD is still developing, with ongoing research into their role. Studies indicate a decrease in B cell numbers in the blood of PD patients compared to healthy individuals, although these results vary between studies. There have been discoveries of IgG deposits on the brain's dopaminergic neurons and the presence of the IgG receptor FcγRI on activated microglia, hinting at the involvement of humoral immunity in neuroinflammation and neurodegeneration [94-97]. Furthermore, autoantibodies targeting α-synuclein, dopamine, and melanin have been identified in the serum and CSF of PD patients. The concentration of α-synuclein autoantibodies in the CSF and plasma of patients with mild or moderate PD has been linked to the severity of the disease, suggesting these autoantibodies might be useful as biomarkers for PD. Previous infections could trigger the production of these autoantibodies through a process known as molecular mimicry, as proposed for infections like HSV1 and Helicobacter pylori [98,99].

Microglia activation

Microglia are the brain's immune cells, playing roles in both protecting and potentially harming the nervous system. In a healthy state, these cells patrol the CNS, looking for signs of danger while maintaining balance and releasing growth-supporting factors like NGF and basic Fibroblast Growth Factor (bFGF). They can be activated by a variety of antigens, including infectious agents, foreign bodies, prions, abnormal CNS proteins, aggregates, and dying cells. Common triggers for microglia activation include Interferon (IFN)-γ, β-Amyloid (Aβ), lipopolysaccharide (LPS), and α-synuclein, both in laboratory settings and in living organisms [100-102].

Activated microglia have been implicated in the neuroinflammation observed in PD, as evidenced by studies in both tissue cultures and animal models. Autopsies of PD patients have shown significant microglial activation, particularly through the increased expression of HLA-DR, a specific immune system receptor, in brain regions most affected by the disease, such as the Substantia Nigra pars compacta (SNpc). These HLA molecules, presented by Dopamine (DA) neurons, display processed antigenic peptides to CD4+ T lymphocytes [103-105]. While neurons typically do not express MHC molecules, those in the substantia nigra and Locus Coeruleus (LC) have been found to do so following IFNγ exposure. This, combined with the BBB becoming permeable to CD4+ and CD8+ T cells, might explain the pathological observations in PD brains. Additionally, activated microglia release various inflammatory mediators like TNFα, IL-6, NOS2, COX2,

and ROS, which facilitate the presentation of new antigens to CD4+ T cells through the MHC-II pathway, leading to cell proliferation, gradual degeneration, and ultimately the death of DA neurons [106,107]. This phenomenon has been observed in rat models of PD and confirmed through PET imaging in living PD patients. Thus, chronic activation of microglia in PD may worsen the disease by producing excessive pro-inflammatory and cytotoxic factors, which could serve as potential biomarkers for early diagnosis and monitoring of PD progression. Conversely, a recent study in mice highlighted the protective role of microglia in clearing α-synuclein released by neurons, underscoring their complex role in the brain's immune response [108-110].

Specific cytokine signaling in PD

The involvement of cytokines such as IL-1α, IL2, IL-1β, TNF-α, IL-6, TGF-β, and IFNγ in the deterioration of DA neurons within the SNpc has been linked to microglia activation. This activation leads to an increase in pro-inflammatory cytokines, signaling an immune response to DA neuron damage. Research analyzing CSF and blood from patients with PD predominantly reveals higher levels of IL-1β and IL-6 in serum and an increase in TGF-β in CSF [111,112]. Additionally, a significant rise in IL-6 mRNA expression in the hippocampus of PD patients also experiencing dementia was observed. In terms of TNF-α, blocking soluble TNF signaling through the administration of the recombinant dominant-negative TNF inhibitor XENP345 resulted in the preservation of about 50% of DA neurons in various animal studies [113,114].

IL9, another cytokine implicated in PD's development, serves both pro-inflammatory and regulatory roles, varying by the context of induction and the cell type producing it. It affects various cell types within the immune system and the CNS, with Th9 cells/IL9 signaling linked to neurodegeneration and autoimmune diseases of the CNS. Unlike other cytokines, IL9 is noted for its neuroprotective functions and support in repair mechanisms. Recent findings of reduced IL9 levels in PD patients suggest a disruption in IL9 signaling, potentially affecting the neuroprotective capabilities in PD [115-117].

Thus, a specific inflammatory profile is evident in PD patients, characterized by reduced IL9 levels and increased CRP, MIP-1β, and TNF-α concentrations. This profile, along with its correlation with the disease's clinical stage, underscores the role of peripheral inflammation in the progression of PD.

Viral infections

The potential link between PD and viral infections has been under investigation since the early 20th century, following the encephalitic lethargica outbreak. This condition, along with postencephalitic parkinsonism, emerged years after the influenza A virus pandemic. Initially, these diseases were not directly connected to PD, but similarities in brain pathology, such as neurofibrillary tangles and the loss of DA neurons in the substantia nigra, hinted at a possible causative relationship, despite the absence of Lewy body inclusions [118-120].

Animal studies, particularly with the H5N1 influenza virus, have shown similar pathological outcomes. The spread of H5N1 from the peripheral to the CNS triggers specific immune responses leading to the degeneration of DA neurons. Although this dopaminergic loss was temporary, the resulting inflammation lasted much longer [121,122].

In studies involving the H1N1 virus, which does not typically affect the nervous system in mice, an inflammatory response begins in the body and then moves to the CNS, leading to neurodegeneration and protein aggregation. Further research using mice infected with H1N1 and treated with MPTP, a neurotoxin, showed increased microglia activation and subsequent degeneration. Importantly, this study demonstrated that administering an H1N1 vaccine or antiviral treatment could limit inflammation to the areas affected by the MPTP, significantly reducing the impact of H1N1 [123-127].

Research over the last ten years has explored how immune responses to HSV-1 affect individuals with PD, particularly looking at how prior infections influence PD progression. Studies have shown that antigens from HSV-1 can activate T-cells and B-cells that also respond to antigens from a-synuclein. This suggests a potential molecular mimicry between HSV-1 and a-synuclein in the dopamine-producing neurons of the SNpc. Research into the immune response has found that people with PD have higher levels of antibodies against HSV-1 and against a-synuclein peptides that resemble viral epitopes, compared to those without PD [128-130].

Similarly, the relationship between Epstein-Barr Virus (EBV) infection and PD has been examined. Epidemiological data indicate that people with PD are more likely to have been infected with EBV than the general population. Studies suggest a molecular mimicry mechanism here as well, with antibodies against EBV's Latent Membrane Protein 1 (LMP1) in genetically susceptible individuals also reacting with a similar epitope on a-synuclein, leading to its oligomerization. Neurohistological examinations have found immunoglobulins close to dopamine-producing neurons in the brains of PD patients, hinting at interactions between microglia and B lymphocytes [131-135].

Autoimmunity and the role of A-Synuclein

Alpha-synuclein aggregates primarily accumulate in the SNpc in PD, but they are also present in neurons across the CNS, the Peripheral Nervous System (PNS), sympathetic ganglia, and the intestinal myenteric plexus. Furthermore, mutations in the *SNCA* gene, which encodes for α-synuclein, are linked to hereditary forms of PD. Lewy bodies, which are highly structured α-synuclein aggregates that also contain ubiquitin and various cellular proteins, are

a hallmark of the disease [136-138].

The phosphorylation, improper folding, and excessive buildup of α-synuclein are key factors in PD's pathogenesis. Activated microglia engulf α-synuclein aggregates, triggering an immune response that leads to neurodegeneration. Numerous studies in animals and cell cultures have demonstrated that α-synuclein strongly activates microglia, causing inflammation. Specifically, injecting short α-synuclein fibrils leads to the production of chemokines, the activation of the Major Histocompatibility Complex II (MHCII) in microglia, and the attraction of peripheral macrophages and monocytes [139-141]. This activation of MHCII continues over time and can even spread to other brain areas, such as the striatum, six months post-injection. The activation of microglia and the ensuing immune response, which spreads throughout the brain alongside the α-synuclein inclusions, results in the loss of dopaminergic neurons. This underscores the role of the innate immune system in the progression of PD, particularly highlighting the early involvement of α-synuclein fibrils, making them potential biomarkers for detecting PD before clinical symptoms appear [142-144].

Additionally, a recent case-control study has identified α-synuclein-specific T cell responses as a promising indicator in the preclinical and initial stages of PD. These T cells were found before the clinical diagnosis of motor symptoms in PD and decreased in number afterwards. The presence of T cells reacting to α-synuclein-derived epitopes suggests an autoimmune aspect to PD. This specific T cell response not only correlates with the timing of diagnosis but also with the patient's age and a lower dose of levodopa (less than 1000 mg/day) [145-147].

A different study assessed CSF alpha-synuclein levels using ELISA and discovered that average alpha-synuclein concentrations were notably lower in patients with PD, Multiple System Atrophy (MSA), and Lewy Body Dementia compared to patients with other neurological conditions. However, this approach lacked specificity, though it offered a high positive predictive value useful for patient stratification in upcoming clinical studies [148,149].

An innovative technique for identifying abnormal alpha-synuclein is the Real-Time quaking-Induced Conversion (RT-QuIC) method. This process involves using aggregated alpha-synuclein to trigger further aggregation of soluble alpha-synuclein in a repetitive manner. Abnormal CSF alpha-synuclein levels were detected using RT-QuIC, achieving a sensitivity of 95% and a specificity of 100% [150-153].

The involvement of the adaptive immune system in the development of neurodegeneration in PD has been suggested as well. Studies in both humans and animals have demonstrated the infiltration of CD8+ and CD4+ T cells into the substantia nigra in individuals with PD. Specifically, research using a mouse model indicated a shift towards a Tc1/Th1-type immune response in PD, highlighted by an increased ratio of CD8+ Tc to CD4+ Th cells and a higher proportion of IFN-γ producing T cells compared to IL-4 producing T cells. This shift towards pro-inflammatory Th1 cells over anti-inflammatory Th2 and Treg cells likely contributes to ongoing neuroinflammation and subsequent neuronal loss [154,155]. A case-control study was thus designed to explore the association between PD and T cell recognition of alpha-synuclein epitopes presented by specific MHC alleles. Sultzer et al. observed a T cell response primarily driven by IL-4 or IFNγ-producing CD4+ T cells, with a possible role for CD8+/IFNγ producing T cells, responding to alpha-synuclein epitopes in both its native extracellular and fibrillized forms [156].

Regarding B cell involvement, the evidence remains mixed. Some studies have reported a reduction in B lymphocyte populations, while others have found no changes in the peripheral blood of PD patients. Recent research focused on naturally occurring antibodies targeting Parkinson's disease pathology. This study isolated memory B cells producing anti-alpha-synuclein antibodies and found that three of these antibodies were capable of inhibiting the seeding of intracellular alpha-synuclein aggregation, suggesting a protective role of IgGs in the pathogenesis of PD [157-159].

Gut-brain axis in PD

Discoveries of Lewy body formations in the intestines have prompted scientists to delve deeper into the potential gut-brain link in PD patients. It is believed that environmental elements, such as the composition of the gut microbiome, may act as catalysts for the clumping of alpha-synuclein. This hypothesis gained support from experiments on genetically modified mice, which demonstrated that inducing high levels of human alpha-synuclein in these animals resulted in Parkinson's-like symptoms and the accumulation of alpha-synuclein in both the gut and brain. Interestingly, when these mice were raised in sterile environments or treated with antibiotics that target a wide range of bacteria, they did not develop signs of Parkinson's or show typical brain pathology [160-163].

The interaction between gut bacteria and brain microglia suggests that the makeup of gut bacteria could influence the progression of the disease and might correlate with specific symptoms. A notable study found a direct link between the increased presence of Enterobacteriaceae bacteria in the gut and more severe issues with balance and walking [164-168].

Research comparing PD patients with healthy individuals has consistently shown ongoing inflammation in the intestines of those with PD. Initially, it was understood that this inflammation could activate the CNS through the vagus nerve. This connection led to research on patients who had undergone a vagotomy, a surgical procedure to remove part of the vagus nerve, to see if it impacted the likelihood of developing PD. Results from these studies

suggest that those who had a complete vagotomy showed a potentially lower risk of developing Parkinson's compared to those who had a more selective form of the surgery and the broader population [169-172].

The breach in the BBB appeared to facilitate the entry of peripheral proinflammatory factors and activated immune cells into the brain's tissue. In more detail, researchers examined the mRNA expression levels of pro-inflammatory agents, including cytokines and glial markers, in colon biopsy samples from both PD patients and healthy controls. They observed a notable increase in the levels of TNF-α, IFN-γ, IL-6, and IL-1β in individuals with Parkinson's compared to those without the disease. It appears that these activated immune cells play a role in disrupting the BBB and causing neuroinflammation. Similar observations were made in stool samples from PD patients, where there was an increase in proteins associated with angiogenesis and elevated levels of cytokines such as IL-1α, IL-1β, and IL-8 [173-175].

In another study involving mice, the duodenal intestinal lining was injected with alpha-synuclein Preformed Fibrils (PFFs). The results showed that PFFs directly interfered with the connectivity of the Enteric Nervous System (ENS) and facilitated the progression of alpha-synuclein pathology to the brainstem. Notably, this process was more pronounced in older mice, which exhibited lower levels of striatal dopamine, indicating that age plays a crucial role in this mechanism [176-178].

Molecular biomarkers, therapeutic approaches, and neuroinflammation

Over the last ten years, the quest to identify biomarkers for early detection and risk assessment in PD has been a significant challenge for researchers. PD is characterized by its complexity, encompassing various clinical manifestations and a broad spectrum of disease progression, necessitating a range of biomarkers including clinical, genetic, biochemical, and imaging markers. The exploration into neuroinflammation's role in PD has yielded several potential biomarkers. Genetic variations in genes like *LRRK2, S100B*, and *NURR1*, which are linked to inflammation, have been shown to elevate PD risk. These findings suggest the potential of using the expression levels of inflammatory proteins in CSF as biomarkers for PD diagnosis or prognosis [179-181].

Ubiquitin C-terminal hydrolase-L1 (UCH-L1), a deubiquitinating enzyme, plays a crucial role in brain protein metabolism by eliminating excess, oxidized, or improperly folded proteins in neurons, thereby preventing the accumulation of Lewy bodies within cells. Dysfunctional UCH-L1 activity leads to decreased breakdown of a-synuclein. A specific polymorphism (S18Y) in the *UCH-L1* gene has been linked to a reduced risk of sporadic PD, providing an antioxidant protective effect [182-185]. Furthermore, research has shown a significant reduction in UCH-L1 levels in the CSF of PD patients compared to healthy individuals and those with other parkinsonian disorders. PD patients exhibited the lowest UCH-L1 concentrations in the CSF, suggesting its potential as a diagnostic marker for PD. Enhancing the biomarker's specificity could involve measuring CSF levels of a-synuclein, given the strong positive correlation between the two proteins [186-188].

β-Glucocerebrosidase (GCase), a lysosomal enzyme encoded by the *GBA1* gene, is crucial for the breakdown of α-synuclein. Mutations that reduce GCase's function lead to Gaucher disease (GD), a rare, inherited lysosomal storage disorder. This connection between GD and parkinsonism emerged when it was observed that a number of individuals with Gaucher disease exhibited symptoms of PD, and PD was found to be more common in the relatives of those with GD. The pathway to synucleinopathies, diseases characterized by the accumulation of α-synuclein, is linked to these mutations in the *GCase* gene and changes in the metabolism of sphingolipids [189-193]. The reduction in GCase activity impairs the breakdown of proteins in lysosomes, elevates α-synuclein levels in neurons, and leads to neurotoxicity through the aggregation of these proteins. Both the malfunction of lysosomes and the accumulation of α-synuclein are believed to play roles in the development of PD. Research has shown that measuring both the ratio of oligomeric to total α-synuclein and the activity of β-Glucocerebrosidase could enhance the precision of PD diagnoses, underscoring the importance of utilizing a variety of biomarkers for early detection of the disease [194-196].

CCL28, also known as Mucosae-associated Epithelial Chemokine (MEC), is another biomarker significant for its role in detecting neuroinflammation and its diagnostic value for Parkinson's disease. CCL28 is naturally produced in mucosal tissues and is found at moderate levels in the small intestine, kidneys, and brain, specifically within neurons rather than glial cells. It plays a dual role in the immune system: its C-terminus possesses antimicrobial properties, while its N-terminus is involved in the migration of lymphocytes [197-200]. In recent studies, CCL28 was identified as the sole biomarker elevated in PD patients compared to healthy controls. The increase in CCL28 levels in the CSF may suggest that viral and microbial infections, along with changes in the gut microbiota, could elevate the risk of developing PD or even act as early triggers for the disease. Additionally, the rise in CCL28 levels could be due to its release from deteriorating neurons [201-203].

Plasminogen Activators (PAs), a group of enzymes known for their role in preventing blood clots, have recently been explored as potential markers for inflammation in Parkinson's disease. This group includes tissue Plasminogen Activator (tPA), urokinase Plasminogen Activator (uPA), and their natural inhibitor, PA Inhibitor-1 (PAI-1). PAs are crucial for axonal repair, remodeling of the extracellular matrix, breaking down fibrin, and supporting the migration and adaptability of neuronal cells. Notably, neurons

release PAs to activate the production of pro-inflammatory cytokines by microglia, which in turn can release PAs as well. Thus, the expression of plasminogen activators could be a promising and accurate marker for inflammation in the central nervous system, as suggested by recent research [204-206].

Mitochondrial dysfunction is known to both cause and result from neuroinflammation and neurodegeneration. Fibroblast Growth Factor 21 (FGF21), which is involved in various metabolic processes, has also been linked to mitochondrial issues within neurons. When mitochondrial function is compromised, neurons initiate a comprehensive stress response that leads to the release of FGF21. This response has been observed in the brains of mice with tauopathy and prion disease, suggesting FGF21's role as a mitokine and its potential as an indicator of mitochondrial dysfunction in the brain [207-209].

The undeniable influence of neuroinflammation on the development and progression of PD highlights the urgent need for therapeutic interventions derived from this in-depth research. Initially, research on animals and experimental studies indicated that Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) like ibuprofen and piroxicam could potentially lower the risk of PD. However, further investigations through epidemiological studies and meta-analyses did not support the notion that NSAIDs could decrease PD risk or alter its progression [210,211].

Another area of interest has been anti-TNF therapies, based on their in vitro effects. TNF is known to significantly harm dopaminergic neurons in laboratory settings, and the application of general TNF inhibitors, such as thalidomide, has shown promise in certain animal models, including MPTP-treated mice and LPS-treated rats. An observational study also noted a reduced PD incidence among inflammatory bowel disease patients who were receiving anti-TNF treatments compared to those who were not [212-214].

Research into Isobavachalcone, a key compound in the Chinese herbal medicine Psoralea corylifolia, has demonstrated its potential as both a neuroprotective and immunomodulatory agent in mouse models. It appears to work by inhibiting NF-κB signaling, which in turn helps improve motor function, reduce neuronal death, and lower levels of inflammatory markers like IL-6 and IL-1 [215-217].

In recent developments within immunomodulatory treatments, various immunotherapies targeting alpha-synuclein have been explored as a means to extract this protein from the extracellular space, aiming to diminish its accumulation in the brain. This approach mirrors similar strategies in Alzheimer's disease research, where immunotherapies focus on amyloid beta and, more recently, the tau protein. The strategies against alpha-synuclein include both active and passive immunotherapies. Active immunization involves generating antibodies against alpha-synuclein in an animal's immune system, with the first vaccine developed producing high antibody titers against aggregated alpha-synuclein, successfully reducing its buildup and associated neural degeneration. Passive immunization involves administering antibodies that target various parts of alpha-synuclein, with the goal of promoting microglial activation, facilitating the removal of extracellular alpha-synuclein, and blocking its propagation from cell to cell [218-221].

Conclusion

In summary, the evolving understanding of Parkinson's disease emphasizes the critical role of neuroinflammation in its pathogenesis and progression. The intricate interplay between the immune system and neurodegeneration reveals how both innate and adaptive immune responses contribute to neuronal damage through chronic inflammation, altered immune cell function, and the pathological effects of α-synuclein. This review highlights the importance of recognizing inflammation not only as a consequence of neuronal loss but as a pivotal player in the disease's development.

The potential for early detection through inflammatory biomarkers underscores the need for further research into the specific molecular pathways involved. Understanding these pathways could pave the way for novel therapeutic strategies aimed at modulating the immune response, thus slowing or even reversing disease progression. The exploration of immunotherapeutic approaches targeting α-synuclein demonstrates an exciting frontier in PD management, yet ongoing studies are essential to fully elucidate their effectiveness and safety.

As we advance our knowledge of the neuroimmune interactions in Parkinson's disease, there is a critical opportunity to integrate this understanding into clinical practice. By targeting neuroinflammation, we can enhance diagnostic accuracy and develop more effective, personalized treatment options for patients, ultimately improving outcomes and quality of life. The journey towards unraveling the complexities of PD continues, with hope for innovative solutions that honor the dynamic relationship between the brain and the immune system.

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