From Biology to Diagnosis and Therapeutic Targets, the Immune System in Parkinson's Disease

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Introduction

Parkinson's Disease (PD) is a complex and heterogeneous progressive neurodegenerative condition characterized by characteristic motor features caused by dopaminergic neuron loss in the substantia nigra. However, the wide range of clinical manifestations shows that Parkinson's disease is more than just a movement disorder affecting peripheral organs like the heart and gut. At the neuropathological level, Parkinson's Disease (PD) is distinguished by an accumulation of Alpha-Synuclein (aSyn) positive inclusions known as Lewy bodies and Lewy neurites. However, the causal role of Lewy pathology in Parkinson's disease and other synucleinopathies has not been definitively established, necessitating urgent efforts to understand the molecular underpinnings of PD. Original research using post-mortem human brain tissue revealed neuroinflammatory responses in the Parkinson's brain. Inflammatory processes can then be detected in peripheral blood and Cerebrospinal Fluid (CSF). Notably, several genetic changes in immune response modulators have been linked to familial forms of Parkinson's disease or an increased risk of developing the disease. As a result, it is clear that the interaction between the immune system and Parkinson's disease is a hot topic.

Weiss et al. begin by providing a general overview of immune responses in the Parkinson's disease brain [1]. They explore the evidence for different astrocytic responses and describe the occurrence of infiltration of peripheral immune cells in the PD brain, as observed in post-mortem studies, and how these responses play a role in neuronal cell death. discuss recent evidence confirming immune system alterations and that this can be detected by monitoring peripheral biological fluids, where chronic pro-inflammatory signals can be measured. The precise origin of this chronic inflammation is still unclear. Still, it may arise due to alterations in the gut microbiome, which could enhance immune cell responses, thereby fuelling inflammation. They propose that studies using large patient cohorts and control groups will be important to further validate existing findings and aid the discovery of novel biomarkers

Amin et al. investigate the role of inflammation in Dementia with Lewy Bodies (DLB), the second most common type of neurodegeneration-related dementia after Alzheimer's disease [2]. This is an excellent review, as our knowledge of the role of inflammation in DLB is still limited. The authors discuss evidence derived from various methodologies in a variety of biological fluids, as well as PET imaging and neuropathological examination of postmortem brain tissue. Overall, the authors argue that aSyn directly promotes inflammation, but they also emphasise that AD co-pathology is a significant factor contributing to neuro-inflammation in DLB.

Stoll and Sortwell then investigate how pre-clinical studies using the aSyn Preformed Fibril (PFF) model are allowing studies to dissect the contribution of aSyn pathology or nigrostriatal degeneration to immune system activation and neuroinflammation [3]. On the one hand, existing evidence suggests that aSyn pathology is immunogenic in and of itself. Longitudinal studies will be required to determine the source of inflammatory stimuli that trigger the various types of responses. The PFF model emerges as a useful model in this context for investigating these issues in laboratory models *in vivo*.

Domingues et al. investigate the effects of extracellular aSyn species, which exist as a corollary of the prion-like spreading hypothesis [4]. They specifically discuss how cells may sense such aSyn species, which proteins appear to act as receptors, what signaling responses may be elicited, and their biological effects.

They emphasize the effects on the glial-neuronal interface, which may be particularly important in the spread of aSyn pathology. Abdi et al. discuss evidence that immune-related changes may be useful as biomarkers for Parkinson's disease [5]. Because the immune system appears to play a role in the pathology of Parkinson's disease, supporting the idea of an interaction between the periphery and the central nervous system, it is likely that markers of immune system activation in the periphery will report on disease-specific alterations that can be used as markers of diagnosis as well as disease progression.

Gopinath et al. provide an important overview of the role of inflammation and gliotransmitters in Parkinson's disease [6]. They begin by emphasising our limited understanding of the role of innate and adaptive immune cell function in brain health, and then argue that identifying immune and inflammatory pathways that impact neuronal function, health, and survival will be critical for developing strategies to limit their effects in order to modify or prevent brain diseases like Parkinson's disease.

Russo et al. focus on the *LRRK2* protein, which has been linked to both familial and sporadic forms of Parkinson's disease. They specifically discuss how *LRRK2* can be used as a target for modulating immune system responses, as LRRK2 mutations have been found in a broader group of patients with immune-related disorders [7]. They discuss how *LRRK2* inhibitors and anti-inflammatory drugs may help reduce disease risk and progression in PD patients and mutation carriers.

Mamais et al. investigate the evidence for the convergence of signalling pathways in innate immune responses and genetic forms of Parkinson's disease [8]. They discuss how signalling pathways associated with genetic forms of Parkinson's disease, such as MAPK, NF-kB, Wnt, and inflammasome signalling, are also relevant to inflammatory signalling, as demonstrated by post-mortem analyses of brain tissue and studies using PD patients' Cerebrospinal Fluid (CSF).

Tsafaras and Baekelandt also discuss the link between Parkinson's disease and inflammatory diseases, focusing on the role of *LRRK2* in the periphery [9]. They specifically discuss the possible role of *LRRK2* in the spread of aSyn pathology as well as its role in peripheral inflammation. This understanding should contribute to a better understanding of the mechanisms involved in Parkinson's disease and the relationship between Parkinson's disease and other inflammatory diseases.

Finally, Karampetsou et al. investigate the TGF-superfamily as a therapeutic target, citing its regulatory role in the central nervous system [10]. TGF-signaling pathways are involved in the differentiation and maintenance of

synaptic function in dopaminergic neurons, which are particularly affected in Parkinson's disease, as well as in the activation of astrocytes and microglia, putting the TGF-superfamily at the interface between inflammation and Parkinson's disease. The authors discuss how animal model studies have been critical in determining the value of targeting this family of proteins as therapeutic targets.

Taken together, immune response-associated alterations hold promise as biomarkers and therapeutic targets. This is the theme of this special issue, and we are confident that it will spark additional research on this important topic.

There is no known cure for Parkinson's disease. Medications, surgery, and physical therapy may provide relief, improve a person's quality of life, and are far more effective than treatments for other neurological disorders such as Alzheimer's disease, motor neuron disease, and Parkinson-plus syndromes. Levodopa, which is always combined with a dopamine decarboxylase inhibitor and sometimes also with a COMT inhibitor, dopamine agonists, and MAO-B inhibitors are the main drug families used to treat motor symptoms. Which group is most useful is determined by the stage of the disease and the age at disease onset [11-13].

Break staging of Parkinson's disease employs six stages that distinguish between early, middle, and late stages. The first stage, in which some disability has already developed and pharmacological treatment is required, is followed by later stages associated with the development of complications related to levodopa use, and a third stage, in which symptoms unrelated to dopamine deficiency or levodopa treatment may predominate [14-16].

The first stage of treatment seeks an optimal trade-off between symptom control and treatment side effects. Levodopa treatment can be delayed by first using other medications, such as MAO-B inhibitors and dopamine agonists, in the hope of delaying the onset of complications caused by levodopa use [17].

In later stages, the goal is to reduce PD symptoms while controlling medication effect fluctuations. Medication withdrawal symptoms or overuse must be managed. When oral medications fail to control symptoms, surgery (such as deep brain stimulation or, more recently, high-intensity focused ultrasound, subcutaneous waking-day apomorphine infusion, and enteral dopa pumps) may be used. Late-stage Parkinson's disease presents numerous challenges that necessitate a variety of treatments, including those for psychiatric symptoms such as depression, orthostatic hypotension, bladder dysfunction, and erectile dysfunction. Palliative care is provided in the final stages of a disease to improve a person's quality of life [18].

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