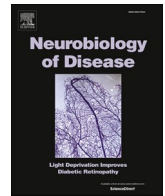




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## Neurobiology of Disease

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## Editorial

## The immune system in Parkinson's disease: From biology to diagnosis and therapeutic targets

Parkinson's disease (PD) is a complex and heterogeneous progressive neurodegenerative condition known for characteristic motor features resulting from the loss of dopaminergic neurons from the substantia nigra. However, the broad range of clinical manifestations demonstrates that PD is more than just a movement disorder affecting peripheral organs such as the heart and gut. At the neuropathological level, PD is characterized by the accumulation of alpha-synuclein (aSyn) positive inclusions known as Lewy bodies and Lewy neurites. However, the causal role of Lewy pathology in PD, as well as in other synucleinopathies, has not been definitively established, demanding urgent efforts towards our understanding of the molecular underpinnings of PD. Original studies employing post-mortem human brain tissue showed neuroinflammatory responses in the PD brain. Subsequently, inflammatory processes can also be detected in peripheral blood and the cerebrospinal fluid (CSF). Notably, several genetic alterations in modulators of immune responses have been associated with either familial forms of PD or increased risk for developing PD. Thus, it is evident that the interplay between the immune system and PD is a topic of great interest.

Weiss et al. start by providing a general overview of the immune responses in the PD brain (Weiss et al., 2022). 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.

Bartl et al. 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 (Bartl et al., 2022). 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. focus on the role of inflammation in dementia with Lewy bodies (DLB), the second most common type of neurodegeneration-associated dementia, after Alzheimer's disease (Amin et al., 2022). This is an insightful review, as our understanding of the role of inflammation in DLB is still limited. The authors cover evidence derived from the use of different methodologies in a variety of biological fluids and also from PET imaging and neuropathological examination of post-mortem brain tissue. Overall, the authors argue that aSyn directly promotes inflammation but significantly, raise the point that AD co-pathology is also an important factor contributing to neuroinflammation in DLB.

Stoll and Sortwell then explore how pre-clinical studies using the preformed fibril (PFF) model of aSyn are enabling studies aimed at dissecting the contribution of aSyn pathology or nigrostriatal degeneration to immune system activation and neuroinflammation (Stoll and Sortwell, 2022). On one hand, existing findings suggest that aSyn pathology is immunogenic itself. Still, longitudinal studies will be necessary to establish further the source of inflammatory stimuli that trigger the different types of responses. In this context, the PFF model emerges as a useful model to investigate these issues in laboratory models in vivo.

Domingues et al. focus on the effects that extracellular aSyn species, which exist as a corollary of the prion-like spreading hypothesis, may have (Domingues et al., 2022). In particular, they discuss how such aSyn species may be sensed by cells, which proteins appear to act as receptors, what signaling responses may be elicited, and their biological effects. They highlight effects on the glial-neuronal interface, as this may be particularly relevant for spreading aSyn pathology.

Abdi et al. discuss evidence suggesting that immune-related alterations may be useful as biomarkers for PD (Abdi et al., 2022). Since the immune system appears to play a role in the pathology of PD, 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 may report on disease-specific alterations that can be used as markers of diagnosis as well as of disease progression.

Gopinath et al. present a critical overview of the role of inflammation and gliotransmitters in PD (Gopinath et al., 2022). They start by highlighting 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 the design of strategies that limit their effects to modify or prevent brain diseases such as PD.

Russo et al. focus on a key player in PD due to its association with familial and sporadic disease forms - the LRRK2 protein. In particular, they discuss how LRRK2 can be used as a target for modulating immune system responses, as mutations in LRRK2 have been found in a wider group of patients with immune-related disorders (Russo et al., 2022). They discuss how LRRK2 inhibitors and anti-inflammatory drugs may be beneficial for reducing disease risk and progression in mutation carriers and PD patients.

Mamais et al. explore the evidence supporting the convergence of signaling pathways in innate immune responses and genetic forms of PD (Mamais et al., 2022). They discuss how signaling pathways associated with genetic forms of PD are also relevant to inflammatory signaling pathways, such as the MAPK, NF- $\kappa$ B, Wnt, and inflammasome signaling, as demonstrated by post-mortem analyses of brain tissue and by studies using cerebrospinal fluid (CSF) from PD patients.

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Tsafaras and Baekelandt also provide their views on the connection between PD and inflammatory diseases by focusing on the role of LRRK2 in the periphery (Tsafaras and Baekelandt, 2022). In particular, they discuss the possible role of LRRK2 in spreading aSyn pathology and its role in peripheral inflammation. This understanding should inform on the mechanisms involved in PD and the connection between PD and other inflammatory diseases.

Finally, Karampetsou et al. explore the TGF- $\beta$  superfamily as a target for therapeutic intervention, given its regulatory role in the central nervous system (Karampetsou et al., 2022). Since, TGF- $\beta$  signaling pathways are involved in the differentiation and maintenance of synaptic function in dopaminergic neurons, which are particularly affected in PD, and also in the activation of astrocytes and microglia, the TGF- $\beta$  superfamily is positioned at the interface between inflammation and PD. The authors discuss how studies in animal models have been important for assessing the value of targeting this family of proteins as targets for therapeutic intervention.

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

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