INTRODUCTION

Parkinson’s disease (PD) was first identified in 1817 by James Parkinson who described the signs including tremor, rigidity and postural instability in his older patients in his publication ‘An assay on the Shaking Palsy’. It is characterized as a progressive neurodegenerative movement disorder in the elderly. Parkinson’s disease (PD), remains unclear. PD is a chronic neurodegenerative disorder that affects motor and cognitive functions. Although the precise cause of PD is unknown, studies in both mice and human suggest that alterations in the innate immunity may play a critical role in modulating PD progression. Here, we review recent advancements in our understanding of inflammation and the innate immune mechanisms in PD pathology.

INFLAMM-AGEING: AGING AND INNATE IMMUNE SYSTEM

One of the major achievements of our century is the increasing human longevity. However, this has also brought new challenges to maintain the quality of life in the elderly.
Ageing is the most important risk factor for major chronic age-related diseases including PD. While the cause of ageing is not fully understood, low-grade sterile chronic inflammation, referred to as inflamm-aging, has been recognized as one of the hallmarks associated with the ageing process. However, it is unclear whether inflammatory pathways drive ageing themselves and contribute directly to PD progression or if they fulfil reparative and regenerative functions. Through evolution, the maintenance of homeostasis is a key function of the innate immune system. The innate immune response is the most phylogenetically conserved protection mechanism that allows the organism to recognize and rapidly defend against danger. This is achieved by the sensing and responsiveness to markers of infection or endogenous stress by germ-line encoded pattern recognition receptors (PRRs). Activation of PRRs by pathogen-associated molecular patterns (PAMPs) or danger-associated molecular patterns (DAMPs) triggers downstream signalling cascades leading to cytokine production and activation of adaptive immunity. PD is a chronic neurodegenerative disease of the elderly, not traditionally associated with inflammation, has recently been associated with DAMPs-associated sterile inflammation, neuroinflammation. Neuroinflammation is now recognized as a PD pathological hallmark and common disease escalating factor. Over the years, the central nervous system (CNS) has been considered an immune privileged site. However, knowledge on how our immune system influences the brain function and how the brain regulates peripheral immune functions is still scarce. There is an increasing appreciation that immune cells that are responsible for tissue homeostasis, such as brain-resident macrophages, microglia, and circulating myeloid cells, play an important role in brain ageing and PD progression.

3 | MICROGLIA ORIGIN AND FUNCTIONS

Microglia are resident myeloid cells of the CNS in brain parenchyma. They play important roles in neurologic development and life-long brain maintenance. The term microglia was first introduced by Pio del Rio-Hortega, a Spanish scientist from Santiago Ramon y Cajal’s school, who distinguished them from neurons and other glial cells and highlighted their potential to differentiate from ramified to amoeboid cells. His finding indicated the existence of a small population of phagocytic, migratory cells within the CNS, which he proposed were of mesodermal origin. There was a long-lasting debate on the ontological origin of microglia until the recent discovery that microglia are derived from erythromyeloid progenitors originating from the yolk sack, colonizing the neuroepithelium during early embryogenesis. The development of microglia and primitive yolk sac macrophages is completely dependent on colony-stimulating factor 1 receptor (Csf1r). Microglia represent the only tissue-resident macrophages that are exclusively derived from yolk sac-derived progenitors. Subsequent differentiation into macrophages is indicated by expression of the fractalkine receptor C-X3-C Motif Chemokine Receptor 1 (CX3CR1), whereas mature tissue-resident macrophages additionally express F4/80 antigen (also known as Emr1, Ly71). Thus, these markers allow genetic labelling and visualization of macrophage progenitors early during embryonic development. However, it remains unclear whether PD-associated neuroinflammatory conditions may differently affect macrophage populations of distinct ontogenies. To understand the imprinting of the disease-associated states on microglia and monocyte-derived macrophage identity, it is important to first consider the effects of specialized tissue environments on tissue-resident macrophages. In post-natal development, under homeostatic conditions, microglia contribute to steady-state tissue homeostasis by a constant immune surveillance of the brain parenchyma by removing apoptotic debris, misfolded proteins and eliminating dysfunctional synapses to provide support to the neurons. In contrast, during infection or brain injury, microglia initiate a defence programme to protect against danger. This defence programme includes enhanced phagocytosis and an increase production of inflammatory cytokines, chemokines and/or interferons. Once dysregulated, they can cause collateral damage to the surrounding tissue and promote disease.

4 | MICROGLIA AND PARKINSON’S DISEASE

Chronic microglial activation is evident early in the nigrosstriatal system in living PD patients and remains a prominent feature in post-mortem PD brains. Additionally, reactive microglia have been described in different preclinical models of PD, including those using 1-methyl-4-phenyl-1,2,3,6 tetrahydropyridine (MPTP), 6-hydroxydopamine or rotenone. Although the exact role of microglial activation in PD is still not clear, neuroinflammation is now considered an additional pathological hallmark of PD. Microglia express a wide variety of PRRs associated with the clearance of fibrillar α-synuclein that can trigger inflammation, such as different Toll like receptors (TLRs) and Nucleotide oligomerization domain (NOD)-like receptors (NLRs), for example (NOD-1, Leucine rich repeat (LRR)- and pyrin domain-containing protein 3 (NLRP3) or NOD-, LRR- and card domain containing 4 (NLRC4). Triggering these receptors leads to release of inflammatory cytokines including interleukin-1-beta (IL-1β), interleukin-6 (IL-6) and Tumour necrosis factor alpha (TNFα), which mediate neuroinflammation and neurotoxicity that can lead to sustained...
low-grade chronic inflammation. Recombinant α-synuclein has been shown to directly activate microglia, with increased release of the pro-inflammatory cytokine TNFα and expression of IL-1β, as well as increased expression of PRRs such as TLR2 and TLR3. Importantly, in addition to direct activation by protein aggregates such as α-synuclein, microglia can also be activated by dying neurons. During physiological conditions, neurons keep microglia quiescent, when neurons are dying, they release molecules such as metalloproteinase-3 and lysophosphatidylcholines (LPCs), which can activate microglia to produce inflammatory cytokines and contribute to neurodegeneration. Therefore, both protein aggregates present during the early phase of PD as well as the dying neurons can contribute to microglial activation. These data raise the question whether immune responses seen in PD patients are part of the disease development or just a bystander reaction to brain damage.

Furthermore, although microglial activation is evident in almost all neurodegenerative disorders, both protective and detrimental functions have been attributed to their activation. For instance, TLR2 and TLR4 has been shown to play a role in α-synuclein microglial responses. While deletion of TLR4 mediates protection of mice against MPTP-induced murine model of PD, TLR2 is known to mediate microglia activation by sensing neuron-released α-synuclein, leading to release of reactive oxygen species and IL-1β synthesis. These findings indicate that microglia contribute to neurodegeneration and PD progression. Interestingly, microglial activation has also been shown important for hindering neurodegeneration in Alzheimer's diseases (AD). Deficiency in TLR2 is known to accelerate the cognitive impairments in AD by demonstrating TLR2 being important for the clearance of Aβ-plaques. Furthermore, inhibition of TLR4 accessory protein, CD14, reduces the microglial activation and is associated with neurotoxicity in an animal mode of AD and Amyotrophic lateral sclerosis (ALS). In PD, TLR4 deficiency has been shown to promote motor symptoms and dopaminergic neuron loss and lead to increased α-synuclein levels in a transgenic PD mouse model. Further, activation of a receptor in another class of PRRs known as Triggering receptor expressed on myeloid cells 2 (TREM2) is known to suppress inflammation and to promote tissue repair following activation. Mutations in this protein are risk factors for both AD, frontotemporal dementia and PD. Microglial activation seems to play a dual role, where it can be both beneficial and detrimental in neurodegenerative disease. Therefore, better understanding of the molecular mechanism underlying the pathology of PD is required. Moreover, it is important to note that most studies of microglia function has been done in preclinical mouse models of PD that has some limitations compared to humans, especially with regards to gene regulation during microglial ageing. The emerging tools available, such as isolated pluripotent stem cells from patients with neurodegenerative disorders could aid us in the translation from data in mice to human.

5 | PERIPHERAL INFLAMMATION AND PARKINSON’S DISEASE

Inflammation is not restricted to the brain during neurodegenerative diseases. There is a substantial evidence that PD patients exhibit increased levels of pro-inflammatory cytokines and enhanced activation of the circulating peripheral blood mononuclear cells. These data indicate a correlation of the peripheral immune system and CNS in the PD pathology. A relationship between the neuronal degeneration and systemic inflammation is further supported by in vivo animal studies of LPS-mediated systemic inflammation or infection. These reports indicate that peripheral induced inflammation leads to the loss of dopamine neurons within the brain. Moreover, clinical data support the notion that inflammation might be a causative factor contributing to PD pathology. PD patients with viral or bacterial infections showed marked motor and cognitive dysfunctions. Additionally, many PD patients display gastrointestinal symptoms such as constipation, which precedes the occurrence of motor symptoms as well as an altered microbiome compared to healthy individuals. Interestingly, gut microbiota has been indicated to affect α-synuclein aggregation and motor deficits in mice.

Notably, the Braak hypothesis proposes a model in which PD is initiated via immune dysregulation at the mucosal sites, nasal or intestinal. This hypothesis implies that PD is a multi-factorial systemic disease in which the immune system could play an important role (Figure 1). Peripheral inflammation can also induce permeability of blood-brain barrier allowing infiltration of inflammatory factors and peripheral immune cells into the CNS, which has been identified as one of the major contributing factors for PD development. However, to date, it remains controversial whether the conditions that induce a profound recruitment of myeloid cells from the periphery are beneficial or detrimental for the disease.

6 | PD RISK GENES: INFLAMMATION AND VESICULAR TRAFFICKING

Further support for an inflammatory role in PD has come from the emerging role of PD-associated risk genes in regulation of immune responses and molecular pathways of immune signalling. Until two decades ago, PD was believed to be a non-genetic disease. However, within the last decade, a number of genetic susceptibility factors have been identified for PD, all of which now can be broadly characterized as genes associated with vesicular trafficking and immune
regulation. Those genes include LRRK2, SNCA, VPS35, Parkin, PINK1, GBA1, and DJ1. All of these genes have been indicated to in some way regulate pathways associated with immune signalling (Figure 2). Here, we will shortly summarize the role of one of these genes, Leucine rich repeat kinase 2, LRRK2, in innate immune signalling.

Genetic variants in LRRK2 account for the majority of all known heritable PD. Recently, missense mutations in
LRRK2 gene have been identified as the most common genetic cause of both familial and sporadic PD.\(^1\) Of these, the most prevalent is the G2019S mutation in the kinase domain that causes elevated kinase activity and is responsible for 4% of familial and 1% of sporadic PD worldwide. Hence, LRRK2 kinase inhibition may be a promising therapeutic target for PD. LRRK2 is a large protein consisting of multiple functional domains, including a kinase and a GTPase domain.\(^2\) Interestingly, LRRK2 has higher expression in kidneys and lungs compared to brain. It is also highly expressed in different immune cells including monocytes, dendritic cells, B cells and macrophages indicating a potential role of LRRK2 in the innate immune system.\(^2\) In addition to PD, GWAS has revealed LRRK2 as a risk factor for other inflammatory diseases such as inflammatory bowel disease, Crohn’s disease and leprosy.\(^3\),\(^4\) Although the observations of LRRK2 association with pathology phenotype are consistent, the molecular mechanisms underlying the physiological and pathological functions of LRRK2 is not fully understood. LRRK2 has been described to play an important role in diverse biological functions ranging from protein translation, mitochondrial function to vesicular trafficking.\(^2\) LRRK2 has been consistently associated with membrane structures including mitochondria, endoplasmic reticulum, Golgi apparatus and endosome-lysosomal system. Interestingly, Rab small GTPases, the master regulators of vesicular trafficking, have been shown to be the physiological substrates for LRRK2.\(^4\) Rab GTPases regulate the process of phagosome maturation that play key roles in the phagocytosis and destruction of dying cells and microbes, making the Rab GTPases crucial players in innate immunity.\(^6\)

Several studies demonstrated the role of LRRK2 in control of intracellular bacterial infections including Salmonella Typhimurium,\(^4\) Listeria monocytogenes\(^4\) and Mycobacterium tuberculosis.\(^8\) Mice deficient in Lrrk2 show susceptibility to enteric bacterium, Salmonella Typhimurium, due to reduced LRRK2-mediated NLRC4 inflammasome activation while macrophages with PD-associated G2019S mutation were protected against S. Typhimurium.\(^4\) Similarly, ablation of Lrrk2 increases susceptibility to the oral infection to a different enteric pathogen, L. monocytogenes.\(^4\) In contrast, mice deficient in Lrrk2 were protected against M. tuberculosis. Mechanistically, LRRK2 knock-out macrophages promoted phagosome maturation via the recruitment of the class III phosphatidylinositol-3 kinase complex and Rubicon to the phagosome.\(^6\) Additionally, a recent study identified dysregulation of cGAS-mediated type I IFN signalling via mitochondrial damage in Lrrk2 null mice upon M. tuberculosis infection.\(^5\) These data show that LRRK2 is involved in the modulation of cytokine response to intracellular pathogens via modulation of PRRs signalling associated with membrane trafficking transport.

CONCLUDING REMARKS

There is substantial evidence that links inflammation to the progression of PD. Recent advances in the field had transformed our view on PD, being now considered as a multi-factorial chronic inflammatory disease. Several studies demonstrate that the pathways of α-synuclein deposition and inflammation may converge and synergize PD progression. However, despite the recent progress, molecular and cellular mechanisms underlying PD progression remain incompletely understood. Elucidating these mechanisms will help to provide better understanding of PD pathology and to identify new possibilities for therapy.

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AUTHORS CONTRIBUTION

MÖ, IF, DF, NZ, AH wrote the manuscript and designed the figures. All authors approved the manuscript and agreed to be accountable for the content of the work.

DATA AVAILABILITY STATEMENT

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