BRAIN
REVIEW ARTICLE

The immune system in Parkinson's disease: what we know so far

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Parkinson's disease is characterized neuropathologically by the degeneration of dopaminergic neurons in the ventral midbrain, the accumulation of α-synuclein (α-syn) aggregates in neurons and chronic neuroinflammation. In the past two decades, *in vitro*, *ex vivo* and *in vivo* studies have consistently shown the involvement of inflammatory responses mediated by microglia and astrocytes, which may be elicited by pathological α-syn or signals from affected neurons and other cell types, and are directly linked to neurodegeneration and disease development. Apart from the prominent immune alterations seen in the CNS, including the infiltration of T cells into the brain, more recent studies have demonstrated important changes in the peripheral immune profile within both the innate and adaptive compartments, particularly involving monocytes, $CD4^+$ and $CD8^+$ T cells.

This review aims to integrate the consolidated understanding of immune-related processes underlying the pathogenesis of Parkinson's disease, focusing on both central and peripheral immune cells, neuron-glia crosstalk as well as the central-peripheral immune interaction during the development of Parkinson's disease. Our analysis seeks to provide a comprehensive view of the emerging knowledge of the mechanisms of immunity in Parkinson's disease and the implications of this for better understanding the overall pathogenesis of this disease.

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Introduction

Parkinson's disease: clinical and pathological hallmarks

Parkinson's disease (PD) is a chronic progressive neurodegenerative disease, whose main clinical diagnostic features are motor defects, which may be preceded by well-established non-motor symptoms by more than a decade.[1] Advanced age is the main risk factor for developing PD, affecting nearly 1% of the population over age 60. The prevalence and incidence of PD is reported to peak after 80 years of age.[2] Other risk factors include male sex, family history of PD, exposure to toxicants and genetic susceptibility.[3,4]

The core pathological feature of PD is the prominent and progressive loss of dopaminergic neurons in the substantia nigra (SN) pars compacta.[5] Other neuronal subtypes are also affected in PD, contributing to its heterogenous manifestations.[6] Another key pathological hallmark of PD is the presence of Lewy bodies in neurons, consisting mainly of fibrillar aggregates of α-synuclein (α-syn).[7] The exact cause of the α-syn misfolding and accumulation remains uncertain. Genetic mutations and post-translational modifications may initiate misfolding, affecting cellular clearance systems like ubiquitin-proteasome and autophagy.[8] α-syn accumulation is thought to be a primary driver of PD pathogenesis, impacting mitochondria, generating reactive oxygen species (ROS), activating immune cells and ultimately altering neuronal function. It is proposed that α-syn pathology propagates from cell to cell in a prion-like manner.[9,10]

Recently, significant attention has been drawn to the relevance of the immune response in the pathogenesis and prognosis of PD motivated by multiple lines of evidence from patients with PD and from PD preclinical models.[11] Epidemiological studies revealed a higher PD risk in people with autoimmune disorders[12] and a lower PD risk in people who have taken immunosuppressive therapies,[13] and multiple animal studies support a driving role for inflammation in the disease (see later). Based on this and because current PD therapies are symptomatic,[14] immunomodulation has been proposed as a disease-modifying therapy. However, to achieve this a clear understanding of the immune response in PD is needed. This is a core aim of the European Cooperation of Science and Technology (COST) Action IMMUPARKNET, which all authors are members of (Supplementary material). Thus, in an attempt to reflect the current consensus in the field, here we review the literature so far regarding the immune system in PD and the relevance of this in the PD neurodegenerative process. We discuss and relate clinical and basic research findings, and we highlight some of those factors which remain unknown and questions yet to be addressed.

Genetic clues linking Parkinson's disease with immune dysfunction

Currently, more than 20 causative genetic variants with high penetrance such as mutations or copy number variations in *SNCA*, *LRRK2*, *PRKN*, *PINK1*, *PARK7*/DJ1 and *VPS35* are associated with familial PD, enlightening the multiple molecular pathways involved in PD pathogenesis.[14] The *LRRK2* gene is linked to both monogenic and sporadic PD with the most common pathological variant being G2019S.[15] LRRK2 is highly expressed in myeloid-lineage peripheral cells and microglia[16] and has been recently implicated in immune responses in PD[17] (see later). Additionally, PINK1 and parkin have been associated with mitochondrial antigen presentation[18] and other immune relevant processes (discussed later).

Genome-wide association studies (GWAS) have yielded more than 90 commonly occurring variants linked to PD risk. These include variants within human leucocyte antigen (*HLA*), highlighting the relevance of the adaptive immune response in PD.[19] Heterozygous variants in *GBA* (whose homozygous mutations cause the lysosomal storage disorder Gaucher's disease) are the most common genetic risk factor for PD,[20] with more than 350 *GBA1* variants that account for 5%–10% of PD cases.[21] Lysosomal membrane dysfunction with associated immune abnormalities has been recently proposed as a critical pathological process in GBA-PD.[22]

Analysis of GWAS data supports common genetic pathways between PD and autoimmune diseases,[23] particularly inflammatory bowel disease.[24] This supports the relevance of a gut-immune-brain interaction in PD, which is reinforced by the finding that functional variants of LRRK2 are associated both to risk of PD and to Crohn's disease.[25] Moreover, LRRK2 was upregulated in colonic biopsies obtained from people with PD and Crohn's disease and correlated with disease severity.[26,27] Consistent with the overlapping risk susceptibility observed in humans, mice harbouring the LRRK2 G2019S variant treated with dextran sodium sulphate (DSS, used to model colitis) showed increased severity of inflammatory colitis, higher colonic expression of α-syn, as well as enhanced neuroinflammation, dopaminergic neurodegeneration and motor impairment compared to wild-type *LRRK2* mice.[28,29] Interestingly,

intestinal TNFα was also increased, and both PD- and colitis-associated symptomatology were alleviated, when treated with an anti-TNFα antibody.[28] Moreover, wild-type bone marrow transplantation into LRRK2 G2019S mice alleviated the colitis symptomatology, indicating that the G2019S-driven pathogenicity is mediated at least in part by haematopoietic cells.[29]

Disruption of the gut–brain axis may also relate to gut dysbiosis, which has been well-described in persons with PD, and may ultimately modify the immune environment in the brain and promote disease.[30,31] Changes in the gut microbiome can compromise gut barrier permeability, leading to a leaky gut[32] and infiltration of bacterial toxins into the gut mucosa and systemic circulation.[33] Importantly, this could promote disease both through a local inflammatory microenvironment leading to α-syn aggregation within enteric neurons and spreading via the vagus nerve,[34] and a systemic inflammatory response influencing central pathology via mechanisms, which are further discussed later. Further discussion of the gut–brain axis and the role of microbiota in PD are beyond the scope of this review but we refer the reader to recently published articles elsewhere.[35,36]

CNS immunity and neuroinflammation in Parkinson's disease

Clinical evidence

The cellular immune process in the brain involves microglia and infiltrating peripheral immune cells

The immune response in the brain of people with PD has been shown in multiple post-mortem studies, evidencing upregulation of immune relevant proteins such as HLA-DR, CD68 and TLR in microglia.[37-42] Higher expression of these proteins suggest pro-inflammatory activation, phagocytic activity, and activation of the adaptive immune system. A PD-related microglial signature has also been seen in more recent single cell-nucleus RNA sequencing studies (scRNAseq; reviewed by Badanjak*et al.*[43]), where elevated levels of IL-1β and GPNMB were described.[44] It is expected that such studies will contribute to the definition of novel key molecular players in the immune response. Several studies describe activated microglia not only in SN or striatum but also in other areas where α-syn pathology occurs, such as the amygdala,[45] supporting the capability of α-syn as an inflammogen (see later).

Microglial activation in the brain of PD patients *in vivo* has been demonstrated in PET studies using ligands for the 18 kDa translocator protein TSPO, which is upregulated in activated microglia (and astrocytes). Increased TSPO signal has been shown in multiple brain regions in PD[46,47] and confirmed in a meta-analysis of 15 studies.[48] Remarkably, recent TSPO PET studies suggest increased microglial activation may already be present in prodromal stages of the disease, including in people with REM sleep behaviour disorder (RBD), who are at high risk of converting to PD[49] or non-manifested GBA-mutation carriers.[50] However, more research is needed in prodromal disease to confirm the current findings (reviewed by Terkelsen *et al.*[51]).

Supporting a peripheral immune component in PD, increased monocytes[52] and T cells[53] are found in the CSF. Infiltrating T cells have also been detected using immunohistochemical staining in the brain parenchyma in PD with both $CD4^+$ and $CD8^+$ T cells being implicated.[45,54,55] Infiltration of peripheral monocytes into the brain has not yet been definitively proven in humans due to a lack of efficient markers to distinguish monocytes from microglia. Nevertheless, cells expressing CD163, considered a monocyte-specific protein, have been observed in PD brain.[56] Moreover, soluble CD163, produced by monocytes/macrophages on activation, was found to be increased in CSF samples from people with PD. This elevation correlated with neurodegeneration markers such as α-syn and Tau, as well as with cognitive decline.[57] Microglial activation in cognition-relevant brain areas has also been shown to be increased in PD dementia cases at post-mortem,[45] and TSPO PET imaging studies have demonstrated an association between binding in multiple cortical and subcortical regions and cognitive scores[58,59] and with dementia risk.[60] All of this supports a role for myeloid cells (microglia and macrophages) in the neurodegenerative process and particularly in the cognitive component of PD.

The ongoing brain inflammatory process in PD is supported by augmented levels of cytokines and chemokines in the brain[45,61,62] and CSF (meta-analysis)[63] in PD. TGF-β1, IL-6, and IL-1β have been consistently shown to be increased, supporting a pro-inflammatory neurotoxic environment and involvement of the inflammasome. It is unclear, however, which cells are the main contributors to this elevation: microglia, neurons, astroglia, CNS associated macrophages (CAMs) or infiltrating peripheral immune cells.

In vitro and preclinical evidence

Neuroinflammation and neurodegeneration

During the past two decades, accumulated evidence from *in vitro* and *in vivo* studies has established neuroinflammation, mostly driven by microglia and astrocytes, as a key contributor to PD pathogenesis.[64] Seminal works in rodent models demonstrated that inducing microglia reactivity with brain-injected LPS or peripheral injections of neurotoxicants, rotenone and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), contributes to dopaminergic neuronal death via the production and release of pro-inflammatory factors (e.g. TNFα, IL-1β, NO, ROS).[65,66] In this process, toll-like receptor 4 (TLR4) seems to be crucial as MPTP-induced neuroinflammation and neurodegeneration were suppressed in TLR4-knockout (KO) mice.[67,68] Importantly, more recent studies based on chronic MPTP-mouse models, which compared to acute models may better reflect the pathology of human PD, have also shown early and progressive neuroinflammation.[69,70]

In vitro evidence supports a role for abnormal α-syn species in driving CNS immune responses in PD (Fig. 1).[64] Exogenously added or endogenous α-syn released from neurons are internalized by neighbouring neuronal and glial cells[71-73] and *in vitro* exposure of microglial cells to α-syn aggregates or to PD-linked α-syn variants leads to increased levels of pro-inflammatory cytokines, including IL-1β, TNFα, IL-6, chemokines and ROS production.[74-77] Pioneering studies *in vivo* based on α-syn overexpression have shown early microglial activation and microglia-mediated neuroinflammation in rodents[71,78,79] and in non-human primates.[80] These findings, which demonstrate that altered α-syn can be a trigger of microgliosis and neuroinflammation *in vivo*, have been reproduced when using other α-syn-based rodent models achieved by intracerebral injection of α-syn preformed fibrils (PFF)[81,82] or infusion of α-syn oligomers.[83] It is notable that the brain immune response in a number of α-syn-based *in vivo* studies preceded dopaminergic neuronal death,[71,79,84] and has been associated to cognitive decline[85] strongly suggesting that microglia-mediated neuroinflammation may play a driving role in PD pathogenesis.

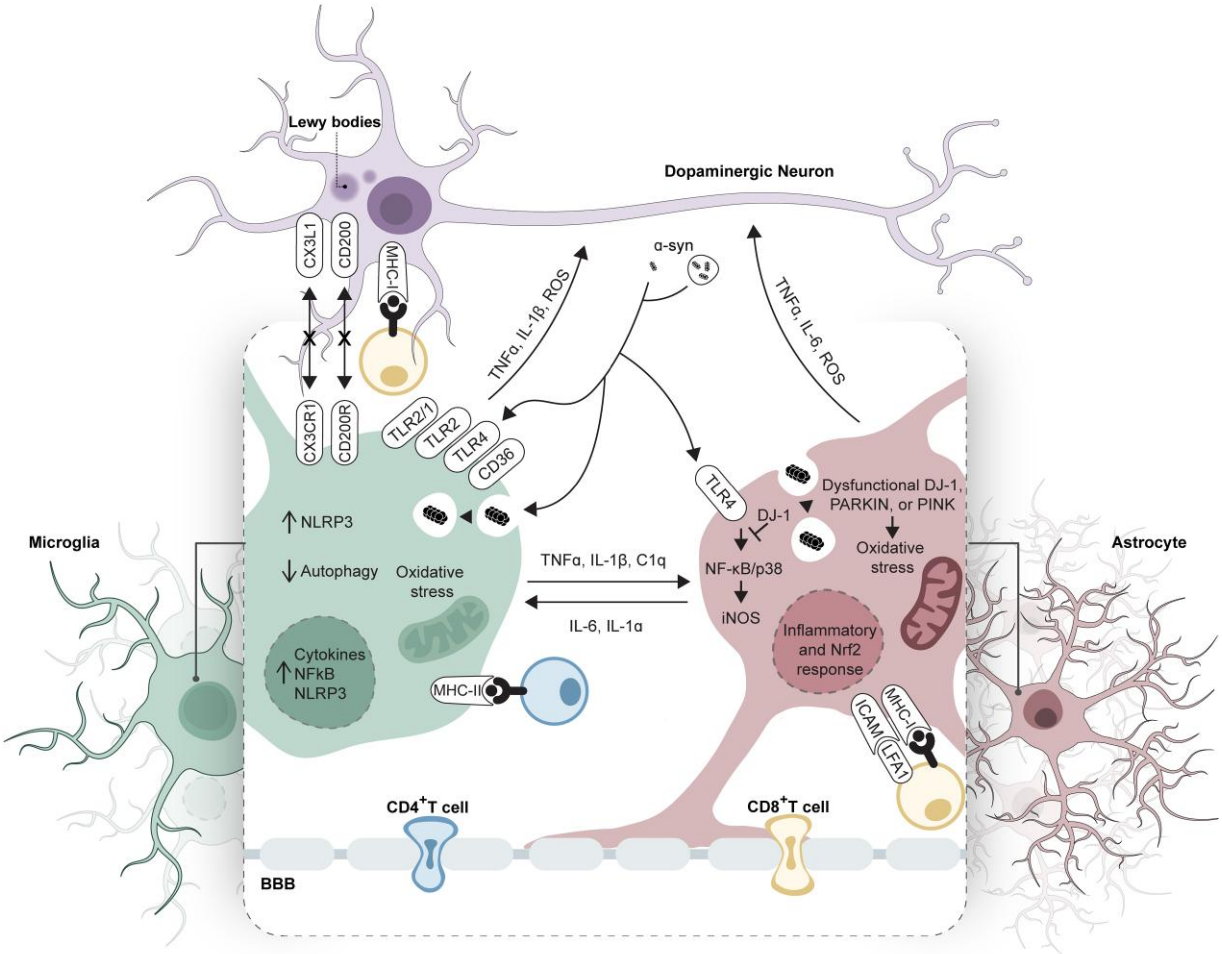

Figure 1 Immune mechanisms in the CNS in Parkinson's disease. During Parkinson's disease (PD), α-synuclein (α-syn) undergoes post-translational modification and aggregation, forming oligomeric species and finally insoluble fibrils that accumulate within dopaminergic neurons in the Lewy bodies. As a result of cell death or exocytosis, abnormal α-syn species released from neurons activate microglia acting as a damage-associated molecular pattern (DAMP) via different cell receptors including TLRs and CD36. This results in activation of the NF-κB and NLRP3 pathways, leading to the release of pro-inflammatory cytokines and reactive oxygen species (ROS), which will further promote neurodegeneration by direct action towards neurons or indirectly by supporting neurotoxic astrocyte differentiation. Such reactive astrocytes favour the damage and permeabilization of the blood–brain barrier (BBB), which enables the infiltration of peripheral immune cells, particularly CD4+ and CD8+ T lymphocytes, into the CNS. Dysfunction in key cellular processes, such as autophagy, mitochondrial respiration and the response to oxidative stress may lead to abnormal immune responses in glial cells, in an α-syn-dependent or -independent manner. The intracellular degradation of pathological α-syn leads to α-syn antigen presentation, which activates $CD8^+$ T cells (CTLs) via class-I MHC, and $CD4^+$ (Th and Treg) cells via class-II MHC. Th1 and Th17 T cells typically potentiate pro-inflammatory and neurotoxic events, whereas Th2 and Treg T cells support the resolution of inflammation and neuroprotection.

Microglia: mechanisms, receptors and signalling pathways

Microglia have been shown to take up extracellular α-syn via phagocytosis in several studies *in vitro* and in *in vivo* in mouse models.[74,86-88] A number of receptors in glia have been linked to α-syn recognition, transport into the cell and signalling activation, thereby triggering pro-inflammatory responses and ultimately leading to neurotoxicity. In particular, TLR4,[89,90] TLR2[91-93] and the TLR2/1 heterodimer[94-96] have been implicated and display concentration- and conformation-sensitive reactivity to α-syn. TLR2 recognizes α-syn aggregates released from neurons and fibrillar α-syn species[92,96-98] but also monomeric α-syn[92,99]; whereas TLR2/1 and TLR4 have been shown to recognize α-syn and respond more strongly to oligomers and fibrils,[95,96] likewise eliciting inflammatory responses. Interestingly, microglial TLR4 seems to also mediate α-syn clearance and to suppress neurotoxicity *in vitro*, and *in vivo*. Accordingly, when using AAV-α-syn overexpression[93] or α-syn PFF[100] to model PD in TLR4-defficient mice, an increase in α-syn propagation and neurodegeneration was observed, whereas the opposite effect was seen as a result of TLR4 stimulation.[89,90] This duality in the impact of TLR4 in neuroinflammation and neurodegeneration may reflect different TLR4-mediated mechanisms involved at different stages of PD pathogenesis.

According to studies *in vitro* and *in vivo*, engagement of both TLR4[89,90] and TLR2[91,92,98] in α-syn-elicited microglial responses has been linked to activation of NF-κB/p65 and p38 MAPK pathways. Moreover, α-syn overexpression in the vagus nerve was shown to induce prodromal features of PD via activation of TLR2/MyD88/NF-κB signalling in Schwann cells in a rat model[101]; whereas the selective targeting of this pathway reduced α-syn spreading, NF-κB activation and neurodegeneration *in vitro* and *in vivo* in a PFF mouse PD model.[102] Another receptor shown by *in vitro* and *in vivo* studies to participate in the uptake of extracellular α-syn species by

microglia is the class B scavenger receptor CD36,[71,103,104] a fatty acid transporter that regulates immune cell responses, including activation of the NOD-like receptor pyrin domain containing 3 (NLRP3) inflammasome. Indeed, studies *in vitro* have identified NLRP3 activation as a downstream effect of CD36 engagement[104] and of TLR2-mediated microglial responses to α-syn species.[98,99]

Multiple recent studies in murine and human microglia as well as in mouse models have demonstrated α-syn-triggered activation of the NLRP3 inflammasome and caspase-1, leading to TNFα and IL-1β secretion, production of ROS and dopaminergic degeneration.[92,99,105-107] In addition, (CX3CR1-mediated) microglia-specific expression of an active NLRP3 mutant exacerbated motor dysfunction and dopaminergic degeneration in the MPTP model *in vivo*.[108] Importantly, inhibition of the NLRP3 or its downstream mediators has been consistently shown to mitigate neuroinflammation and neurodegeneration in PD rodent models.[109-111]

The triggering receptor expressed on myeloid cells 2 (TREM2), an immune membrane receptor with known relevance in Alzheimer's disease, is upregulated in PD brain, including microglia.[112,113] *In vitro* TREM2 supports anti-inflammatory responses by negatively regulating the MAPK and NF-κB pathways.[114,115] Moreover, TREM2 overexpression in the striatum of MPTP-treated mice attenuated neuroinflammation and neurodegeneration,[114] whereas genetic deletion of TREM2 in the AAV-α-syn mouse PD model resulted in a shift from anti-inflammatory towards pro-inflammatory activation of microglia and led to exacerbated dopaminergic loss.[113]

As mentioned, LRRK2 is highly expressed in immune cells such as microglia (and monocytes/macrophages) and is thought to play a key role in innate immunity by engaging in various cellular processes. LRRK2 has been implicated in phagocytosis through the autophagy/lysosomal degradation pathway, microglial motility, antigen presentation and in activation inflammatory pathways.[116] Indeed, microglial cells from mice carrying the PD-linked LRRK2 R1441G[117] and LRRK2 G2019S[118] mutations displayed increased inflammatory and neurotoxic responses to LPS together with increased phagocytic capacity, respectively, whereas microglial cells from *LRRK2*-KO mice or *LRRK2*-KO human-derived monocytes showed impaired phagocytosis.[118,119] In addition, *LRRK2* deletion attenuated oxidative stress-related pathways triggered by exposure of primary microglia to α-syn fibrils,[120] while pharmacological inhibition of LRRK2 diminished α-syn-mediated neuroinflammation and microglial neurotoxicity in murine, rat and human cells in culture and in two α-synucleinopathy mouse models.[121,122]

In addition, microglial and peripheral immune responses in PD seem to be closely interconnected. For example, microglial MHCII has been found to mediate α-syn-induced activation and CD4+ T-cell proliferation, *in vitro* and *in vivo*[123] (read further in the 'Evidence from *in vitro* and preclinical studies' section). In view of the wealth of data supporting highly relevant roles played by microglia in multiple pathogenic mechanisms linked to PD, it seems clear that harnessing microglial function in a timely manner, could be of benefit in PD. It is however, to be determined at what stage and in which patients this will be most beneficial.

Astrocytes: role and mechanisms

There is growing evidence that astrocytes play an important role in the development and progression of PD (for an in-depth review, see Liddelow *et al.*[124]). Disease-affected areas of post-mortem PD brains show reactive astrocytes that have acquired a pro-inflammatory and neurotoxic phenotype,[44,125] which might hinder their ability to maintain homeostasis. For example, the astrocytic uptake of glutamate—crucial to avoid excitotoxicity—seems compromised in PD as suggested by the downregulation of the astrocytic glutamate transporters observed in PD rodent models and LRRK2 G2019S PD patients.[126-128]

Astrocytes also play an important role in the clearance and phagocytosis of pathological α-syn species. In both animal PD models and post-mortem PD brain tissue, astrocytes have been shown to internalize and accumulate α-syn within inclusions.[129-132] Astrocytes might take up extracellular α-syn released by neurons,[73,133] or that is transferred from microglia[134] or from other astrocytes[133,135] via nanotunnels.[135] As with microglia, extracellular α-syn can activate astrocytes via the TLR4 receptor, which in turn activates the NF-κB and p38 MAPK pathways,[89,136,137] leading to the release of IL-1α, IL-1β, and IL-6 and increase in ROS production, resulting in non-cell autonomous death of dopaminergic neurons.[89,138] However, internalization of α-syn can also occur via a TLR4-independent endocytosis pathway[136] and it leads to the formation of lysosomal inclusions.[73,89,133] On the other hand, α-syn-overexpression in cultured astrocytes (reflecting a scenario of persistent pathological α-syn accumulation) resulted in autophagy impairment and neuronal death.[139] Consistent with those results, astrocytic expression of PD-related α-syn variants led to neurodegeneration both *in vitro* and *in vivo*.[140,141] Moreover, astrocytes may also acquire a pro-inflammatory and neurotoxic reactive phenotype in response to activated microglia-secreted signals, e.g. IL-1α, TNFα and C1q,[125] and administration of a GLP1R agonist could block this conversion, and was neuroprotective in both the PFF and A53Tα-syn transgenic mouse PD models.[142]

Disruption of blood–brain barrier (BBB) integrity has been demonstrated both in animal models and in PD patients,[143-145] while astrocytes have proven necessary to maintain BBB integrity and function.[146] LRRK2 G2019S PD patient-derived astrocytes have altered angiogenetic and inflammatory profiles.[147] Alterations in the BBB might provide peripheral immune cells, such as T cells and monocytes/macrophages, with the opportunity to infiltrate the brain,[55,78,148-150] enabling interactions between infiltrating leucocytes and CNS cells. Moreover, astrocytes can function as antigen-presenting cells and MHC-II expressing astrocytes are in close proximity to CD4+ T cells in post-mortem PD brain tissue and in animal models.[151,152] Furthermore, spatial proximity between ICAM-1$^+$-reactive astrocytes and LFA-1$^+$-infiltrating leucocytes was detected in the SN of MPTP intoxicated non-human primates,[153] suggesting a complex interplay between CNS-resident and infiltrating immune cells, which needs to be further explored.

Emerging mechanisms in pathophysiology of glial responses

In addition to undergoing chronic activation and developing pro-inflammatory phenotypes in the context of PD, glial cells may be affected by PD-associated mutations in genes which regulate key cellular processes in microglia and astrocytes. These include, among others, the antioxidant response, mitochondrial respiration and autophagy. For example, mutations in *PARK7* lead to deficiency of DJ-1, a protein which protects cells against oxidative stress, regulates mitochondrial function and autophagy, and has been related to innate and adaptive immunity.[154] Accordingly, DJ-1-KO rodent microglia and astrocytes display constitutive cell activation and exacerbated pro-inflammatory responses in culture.[155-157] In line with these findings, *in vivo* neurotoxicant- and LPS-induced dopaminergic loss are amplified in DJ-1 KO mice.[157-159] These and other findings suggest that, even though lack of DJ-1 alone does not

recapitulate typical parkinsonian features in mice, people with DJ-1-associated PD may be more susceptible to neuroinflammation. In sporadic PD, on the other hand, DJ-1 is upregulated in reactive astrocytes, presumably as a protective mechanism.[160] Accordingly, astrocyte-specific overexpression of DJ-1 attenuates the neurotoxicant-induced neurodegeneration and inflammation in zebrafish and rats.[161,162]

Several recent studies have demonstrated a role for mitochondrial impairment in neurodegenerative disorders, via induction of NLRP3 inflammasome-mediated neuroinflammation. Exposure of rodent and human astrocytes and microglia in culture to α-syn aggregates has been shown to induce mitochondrial dysfunction.[104,107,132,163] Studies *in vitro* and *in vivo* have demonstrated that rotenone aggravates NLRP3 pro-inflammatory signalling and dopaminergic neuronal loss via mitochondrial damage in microglia.[164] Moreover, MPTP—which induces mitochondrial damage—contributes to microglial NLRP3 inflammasome activation and neurodegeneration.[108] Conversely, pharmacological inhibition of mitochondrial damage could attenuate such effects.[165] In addition, reduction of striatal dopamine levels may itself favour neuroinflammation by promoting changes in the type of dopamine receptors stimulated in microglia and astrocytes.[166-168]

The cyclic GMP-AMP synthase (cGAS)/stimulator of interferon genes (STING) pathway is the driver of type-I IFN immunity, which can be activated upon mitochondrial damage. This pathway has recently been implicated in exacerbated inflammation caused by loss-of-function mutations in *PRKN* (parkin) and *PINK1*.[169] A role for this pathway in PD pathogenesis is further supported by three recent studies, one using mutant STING-overexpressing animals and two based on α-syn-PFF and MPTP models, which showed that cGAS/STING signalling promotes glial activation, microglia-mediated neuroinflammation, α-syn pathology, higher mitochondrial ROS and degeneration of dopaminergic neurons.[170-172] Remarkably, a study using microglial co-culture demonstrated that healthy microglia are able to transfer mitochondria to α-syn overloaded cells via direct intercellular contact to escape from ROS-induced cytotoxicity, and found that this mechanism is impaired in microglia carrying the *LRRK2* G2019S mutation.[173]

In recent years, various experimental models support a role for glial autophagy in maintenance of brain health and homeostasis in the context of PD.[174] Studies *in vitro* and in α-syn-overexpression mouse models showed that microglia clear extracellular α-syn released from neurons by p62- and TLR4-dependent selective autophagy, leading to neuroprotection.[93] However, high concentrations of extracellular α-syn result in microglial autophagy impairment also via a p62- and TLR4-dependent mechanism, which led to dopaminergic neuronal loss.[175] Furthermore, microglia-specific overexpression of α-syn resulted in α-syn intracellular accumulation and microglial reactivity with phagocytic exhaustion and impaired autophagy, leading to neuroinflammation and dopaminergic neuronal degeneration *in vitro* and *in vivo*.[176] A converging conclusion by several studies was that pharmacologic or genetic disruption of microglial autophagy in mice aggravates α-syn accumulation and neuroinflammatory responses and ultimately causes dopaminergic neurodegeneration.[93,175,177,178]

Neuron-glia crosstalk

In the past few years, major attention has been given to the role of α-syn in the neuron-glia crosstalk. In addition to free α-syn, neurons can release extracellular vesicles or exosomes, capable of transferring α-syn to neighbouring neurons, where they can form aggregates and induce cell death.[72,179-182] Other cell types in the CNS are also able to take up exosomal α-syn. Microglial cells exposed to α-syn-containing plasma exosomes derived from PD patients became activated and displayed impaired autophagy flux, leading to the accumulation of intracellular α-syn and accelerated secretion of α-syn-containing exosomes.[183,184] Intracerebral administration of microglia-released exosomes containing α-syn, enhanced protein aggregation in recipient neurons, ultimately inducing motor impairment and dopaminergic neurodegeneration in mice.[88,183,184] Conversely, suppressing microglia-mediated exosomal α-syn communication or depletion of microglia ameliorated neuroinflammatory responses, dopaminergic degeneration and motor dysfunction.[184] Recently, astrocytes-astrocytes, microglia-microglia, astrocytes-microglia and neuron–microglia communication via tunnelling nanotube mechanisms,[134,135,173,185] in addition to neuron–astrocyte intercellular crosstalk,[133] were shown in cells and organotypic brain slices to enable distribution of α-syn cargo and to increase clearance of α-syn aggregates.

The CX3CR1-CX3CL1 and CD200-CD200R axes, which are crucial to maintain neuronal homeostasis and to prevent microglia reactivity, are also altered in PD. CX3CR1 and CD200R are expressed in microglia and their respective ligands CX3CL1 (fractalkine) and CD200 are produced in neurons, astrocytes, and oligodendrocytes. Excess of CX3CL1 using recombinant proteins or genetic models prevented dopaminergic neuronal loss and inhibited microglia reactivity induced by neurotoxins or α-syn.[186-188] Along this line, a time-dependent downregulation of CX3CL1 was found in the serum of PD patients.[189] However, the evidence about the role of the CX3CR1 receptor in PD is contradictory[190,191] and needs further investigation. Regarding the CD200-CD200R axis, it was found to be downregulated in PD models, whereas inducing CD200-CD200R genetic dysfunction exacerbated microglial activation and dopaminergic neurodegeneration, thus supporting a neuroprotective and anti-inflammatory function.[192-195]

Astrocytes are able to boost dopaminergic neuronal survival by secreting neurotrophic molecules and extracellular vesicles.[196,197] Notably, extracellular vesicles derived from *LRRK2* G2019S-mutant astrocytes failed to provide full neurotrophic support to dopaminergic neurons.[197] Extracellular vesicles containing α-syn aggregates can also be transferred between neurons and astrocytes. Astrocytes and microglia are able to take up free or exosomal α-syn aggregates by endocytosis or phagocytosis for subsequent degradation and clearance of α-syn.[73,133,198,199] Nevertheless, *in vitro* studies have also shown that prolonged exposure to α-syn aggregates can lead to accumulation and induction of inflammatory responses in astrocytes[73] and further transfer to dopaminergic neurons, thus propagating α-syn pathology and neuronal degeneration.[198,200]

Peripheral immunity in Parkinson's disease

Evidence from clinical studies

Increased neutrophil to lymphocyte ratio

In addition to cellular immune activation within the brain, multiple studies have shown changes in peripheral immune cells in blood from people with PD. These include alterations in the frequency of immune cell subsets, as well as transcriptomic and functional changes. Simple measures of peripheral immune balance can be derived from the full blood count, a routine clinical blood test. Specifically, the neutrophil/lymphocyte ratio (NLR) provides an

indication of the balance between the innate and adaptive immune cells. There is consensus from several studies that higher NLR is associated with increased PD risk. Importantly, the increase in NLR seems to occur many years before diagnosis, and while some studies attribute this change to increased neutrophil numbers, others describe this as a result of decreased lymphocyte counts.[201-203] NLR was found to correlate positively with disease duration[204] and motor symptom severity[205] and inversely with olfaction[206] in PD, suggesting that it is disease-relevant. However, elevated NLR is not universal in PD and may be dependent on disease subtype. Two studies report that it was not increased in people with PD-mild cognitive impairment (PD-MCI), whom in fact showed a higher number of lymphocytes than those without cognitive problems.[207,208] Moreover, patients with tremor-dominant or mixed-type PD were reported to a lower NLR than those with the akinetic rigid type.[206] To date, the underlying cause of changes in NLR in PD is unclear. One possibility is that it is driven by a decrease in lymphocytes numbers due to their migration to the diseased brain. On the other hand, a rise in neutrophils may occur due to systemic inflammation, in keeping with the observed rise in pro-inflammatory cytokines in the blood in PD (discussed later). Notably, research on the role of neutrophils in PD is lacking due to the standard approach of isolating peripheral blood mononuclear cells (PBMCs), which discards multinucleated cells. Therefore, the research community should assess the possibility of isolating granulocytes (including neutrophils) from blood to enable a more comprehensive assessment of peripheral immune effectors in PD.

Monocytes in Parkinson's disease display altered expression of relevant proteins

Monocytes are divided into three subtypes: (i) classical monocytes (pro-inflammatory/highly phagocytic), which mature into (ii) intermediate monocytes (involved in antigen presentation/T cell activation) and ultimately into (iii) non-classical monocytes (which patrol vascular endothelium and play a role in vascular and tissue repair).[209] Studies measuring monocyte balance in PD are conflicting: whilst some observed no difference,[53,210-214] several others have reported increased classical monocytes in early PD.[215-217] This inconsistency may reflect heterogeneity of cohorts, as changes in monocyte balance and activation may be dependent on disease type and stage. Increased intermediate monocytes have been reported at later disease stages[218,219] and in people with higher PD severity,[220] and increased C52 expression (monocyte activation marker) has been correlated with worse motor defects [Unified Parkinson's Disease Rating Scale, (UPDRS)-III] in PD.[221] In addition, monocyte activation has been reported to be more pronounced in early PD cases at higher risk of dementia (increased classical, reduced non-classical, increased TLR4$^+$ cells), compared to those at low dementia risk[216] and changes in CCR2 and CD11b expression (markers of migratory capacity) have been found to be associated with cognitive impairment.[219]

Monocytes also show transcriptomic changes in PD[222] which are different between males and females.[223] Increased expression of proteins including TLR4, HLA-DR and CCR2[216,218,219,224] suggest pro-inflammatory activation, increased antigen presentation and monocyte migration in PD. On the other hand, *ex vivo* functional analysis of blood monocytes from people with PD has produced conflicting data, with studies showing increased,[215] decreased[217,225] or unchanged[226] responses to different immune activators. This could be due to technical differences in the various *in vitro* approaches and/or the use of heterogenous cohorts that might include patients at different disease stages. Moreover, studies do not truly replicate the *in vivo* environment, as the use of autologous serum was seen to be crucial to show enhanced monocyte phagocytic activity in PD patients.[226] Thus, *ex vivo* studies of immune cell responses should be interpreted with caution.

Increased levels of effector and inflammatory T cells

Lower T-cell numbers have been reported in the blood in PD and seem to mostly reflect reduction in the CD4$^+$ cells, although decreased CD8$^+$ numbers have also been reported, particularly in later stages of the disease[203,227] (meta-analysis[228]). There is limited evidence for association with disease severity/progression, but deviation from the reference range for CD8$^+$ was reported to be associated with higher UPDRS-III scores[203] and lymphocyte count was correlated negatively with Hoehn and Yahr scores.[204]

The T-cell compartment is also altered in terms of CD4$^+$ and CD8$^+$ subsets and effector status. Several studies have reported a diminished immunoregulatory compartment in PD, and Treg cells with a lower regulatory/suppressive capacity, associated with an increase in pro-inflammatory effector T cells.[210,220,229-233] In addition, a Th1/Th17 pro-inflammatory bias has been suggested.[210,220] However, a parallel increase in both Th17 and also Th2 has been reported in *de novo* PD (<2 years).[234] Changes in the differentiation status of both CD8 and CD4 have also been reported including decreased naïve cells and increased memory cells, activated and/or terminally differentiated cells.[234-238] In contrast, other studies have found evidence of reduced terminally differentiated CD8$^+$ T cells and reduced immunosenescence markers in early PD.[239-241] These inconsistencies in the literature may relate to differences in disease stage and clinical phenotype, which warrants further exploration.

A correlation between lower blood lymphocyte count and lower CSF total α-syn levels has been reported in PD, supporting a link between peripheral lymphocyte changes and neurodegenerative α-syn pathology.[204] In this regard, it has been proposed that α-syn has an autoantigenic ability: α-syn-specific CD4$^+$ and CD8$^+$ T cells have been identified to occur at higher frequency in early PD compared to controls.[242,243] A recent scRNAseq T-cell receptor (TCR) study suggests that α-syn peptides could indeed be responsible for the clonal T-cell expansion seen in PD.[238] However, α-syn-specific T-cell reactivity is not found in all PD patients, suggesting again a heterogeneity in the immune response.[244] Further research addressing the relevance of α-syn specific T cells in different subtypes and across disease stages is needed.

B cells and humoral response: protective or deleterious?

B-cell numbers are also consistently reported to be reduced in the blood in PD,[236,245-247] with some studies reporting lower naïve B cells and increased memory B cells.[234,248] Similar to T cells, a pro-inflammatory B-cell bias is also seen in PD with increased pro-inflammatory B cells and lower levels of regulatory and anti-inflammatory B cells.[210,234,248,249] Furthermore, higher numbers of regulatory B cells have been found to correlate with better motor scores in PD, indicating that they may have a protective role.[250,251]

With respect to the humoral antibody response in PD, the data are conflicting, but meta-analysis indicates that α-syn antibodies in serum are elevated in early disease[252] and are elevated in patients with RBD.[251] Similarly, antibodies against neuromelanin were found to be inversely correlated to disease progression, suggesting a higher relevance of the humoral response at early

stages.[251,253] However, it remains unclear whether disease-specific antibodies are deleterious,[254] or protective by supporting the clearance of pathogenic proteins, including α-syn. Studies measuring high-affinity anti-α-syn antibodies have reported that these are reduced in PD even at prodromal stages, suggesting that there may be a decrease of putative protective antibodies prior to disease onset.[255,256] In keeping with this evidence, several pharma companies are pursuing development of α-syn antibodies as a therapy in PD.

Cytokines and chemokines analysis: pro-inflammatory and migratory environment

These described immune cellular changes in the periphery results in a pro-inflammatory landscape in the blood of people with PD as shown by the increase in IL-6, and IL-1β in addition to TNFα, IL-2, IL-10, CRP and RANTES/CCL5 (meta-analysis[257]). It has been suggested that the relevance of these cytokines is time/stage-dependent, with, for example, TNFα being more relevant at the onset rather than at later disease stages.[258] A more pro-inflammatory profile in the blood at time of diagnosis in PD was associated with a more rapid subsequent motor progression and worse cognitive function,[259] and blood CRP has been shown to predict cognitive decline,[260] supporting a deleterious role for the inflammation occurring in PD. Chemotaxis and migration of immune cells are also important in disease as chemokines CCL3 and CCL4—involved on immune cell recruitment—were reported to predict motor decline in a longitudinal study in PD.[261] These changes might be due to the putative presence of oligomeric forms of α-syn in the blood that can induce pro-inflammatory activation of monocytes.[262] Although the literature suggests an abnormal monocytic response to aggregated α-syn or LPS in PD, there is no consensus about this, nor on the cytokine profile of such response.[225,263,264] Alternatively the cytokine response in PD may be a consequence of peripheral and/or central neuronal changes that may induce a cellular immune response through neuro-immune relevant signals (see review by Dantzer[265]).

Crosstalk between peripheral immune changes and central pathology

The infiltration of peripheral immune cells into the brain and CSF in PD (see the 'The cellular immune process in the brain involves microglia and infiltrating peripheral immune cells' section) provides a mechanism of direct communication between peripheral and central immunity and neuronal processes ongoing in the brain. Cytokines generated systemically may also cross the BBB. Whilst correlation between blood and CSF cytokine levels is poor (likely reflecting local cytokine production within the CNS), plasma IL-1β and IL-8 have been found to be associated with CSF tau levels, suggesting that peripherally generated cytokines may influence or be influenced by central neurodegenerative processes.[266] On the other hand, drainage of brain derived antigen to lymph nodes can occur through meningeal lymphatic vessel, thus informing periphery on the events occurring in CNS.[267] Notably, recent research has highlighted the relevance of immunological niches in choroid plexus, meninges, and skull bone marrow in brain immunity,[268] although this remains practically unexplored in PD.

Recent studies show correlation between brain imaging measures and peripheral immune markers. Although such data require confirmation, they support a coordinated brain-periphery response. For example in prodromal PD stages, monocyte markers correlated with increased inflammation (TSPO-PET) in brain and dopaminergic degeneration (F-DOPA-PET) in RBD patients.[218] In *de novo* PD cases, regional increases in TSPO signal in brain were correlated with cognitive scores and CCL22 (attractant for monocytes, and T cells) in CSF, and with eotaxin 3/CCL26 (attractant for basophils and eosinophils) in plasma.[59] Another recent study in newly-diagnosed PD cases reported significant associations between cognitive performance and whole brain TSPO-PET signal and serum inflammatory cytokines: IFNγ, IL-1β and IL-6.[60] NLR was also found to be correlated with the TSPO binding in the SN,[59] and with dopaminergic neurodegeneration [dopamine transporter (DAT) scans] in PD.[205,269] Another study in *de novo* PD showed a paradoxical relationship between higher number of (immunoregulatory/anti-inflammatory) Treg and Th2 cells and increased dopaminergic degeneration (FP-CIT SPECT).[270] Clearly, more research of this type is needed to better comprehend the reciprocal influence between peripheral immune changes and central neuroinflammation and neurodegeneration in PD and how this might evolve over time across disease stages.

Evidence from *in vitro* and preclinical studies

Involvement of T cells

Several studies conducted by different laboratories in rodent PD models have consistently shown that $CD4^+$ and $CD8^+$ T cells infiltrate the brain during the disease development, including genetic-,[149] toxicant-induced[55] and virus-induced models (usually rAAV).[271] Genetic deficiency of $CD4^+$ T cells in the MPTP and the rAAV-hαSyn mouse models abrogated the development of neurodegeneration, while $CD8^+$ T-cell deficiency was negligible for the SN neurodegeneration.[55,272] In keeping with this, α-syn upregulates MHCII in microglia/macrophages *in vitro* and *in vivo*, facilitating antigen presentation to $CD4^+$ T cells.[123,273] Nevertheless, several recent publications also support a role for $CD8^+$ T-lymphocytes. Systemic depletion of either $CD8^+$ or $CD4^+$ T cells—using anti-CD8 or anti-CD4 antibodies—significantly reduced the neurodegeneration and the motor impairment in the MPTP model.[274] In the rAAV-A53T hαSyn mouse model, either $CD4^+$ or $CD8^+$ T cells infiltrating the SN play a detrimental non-redundant role by promoting neurodegeneration.[275] Furthermore, a study addressing the role of gut inflammation in the loss of dopaminergic nigral neurons showed that the antibody-mediated depletion of $CD8^+$ T cells abolished the potentiation of dopaminergic neurodegeneration induced by experimental colitis in mice.[276] Altogether, these findings indicate that both $CD4^+$ and $CD8^+$ T cells play a relevant role by promoting nigral dopaminergic neurodegeneration in PD rodent models (Fig. 2).

Several studies have explored mechanisms by which $CD4^+$ T cells influence neurodegeneration. When stimulated by microglia presenting α-syn-derived antigens on MHCII, $CD4^+$ lymphocytes produce pro-inflammatory cytokines (i.e. IFNγ, TNFα, IL-17), which induce the production of high levels of neurotoxic factors by microglia, including ROS, glutamate and TNFα and consequent neuronal death.[64,277,278] Involvement of $CD8^+$ T cells and MHCI in PD was suggested many years ago,[279] and upregulation of MHCI in neurons has been shown to be induced by conditioned media from microglia[279] or by exposure to MPP^+.[280] Moreover, rAAV mediated MHCI knockdown significantly reduced the number of $CD8^+$ T cells infiltrating the SN of the MPTP model.[280] Importantly, Pink1 was found to repress MHCI expression in neurons[280] and Pink1-deficiency triggered the presentation of mitochondrial autoantigens on MHCI and the subsequent activation of autoreactive $CD8^+$ T cells.[281] Moreover, infection of *Pink1*-KO mice with gram-negative bacteria

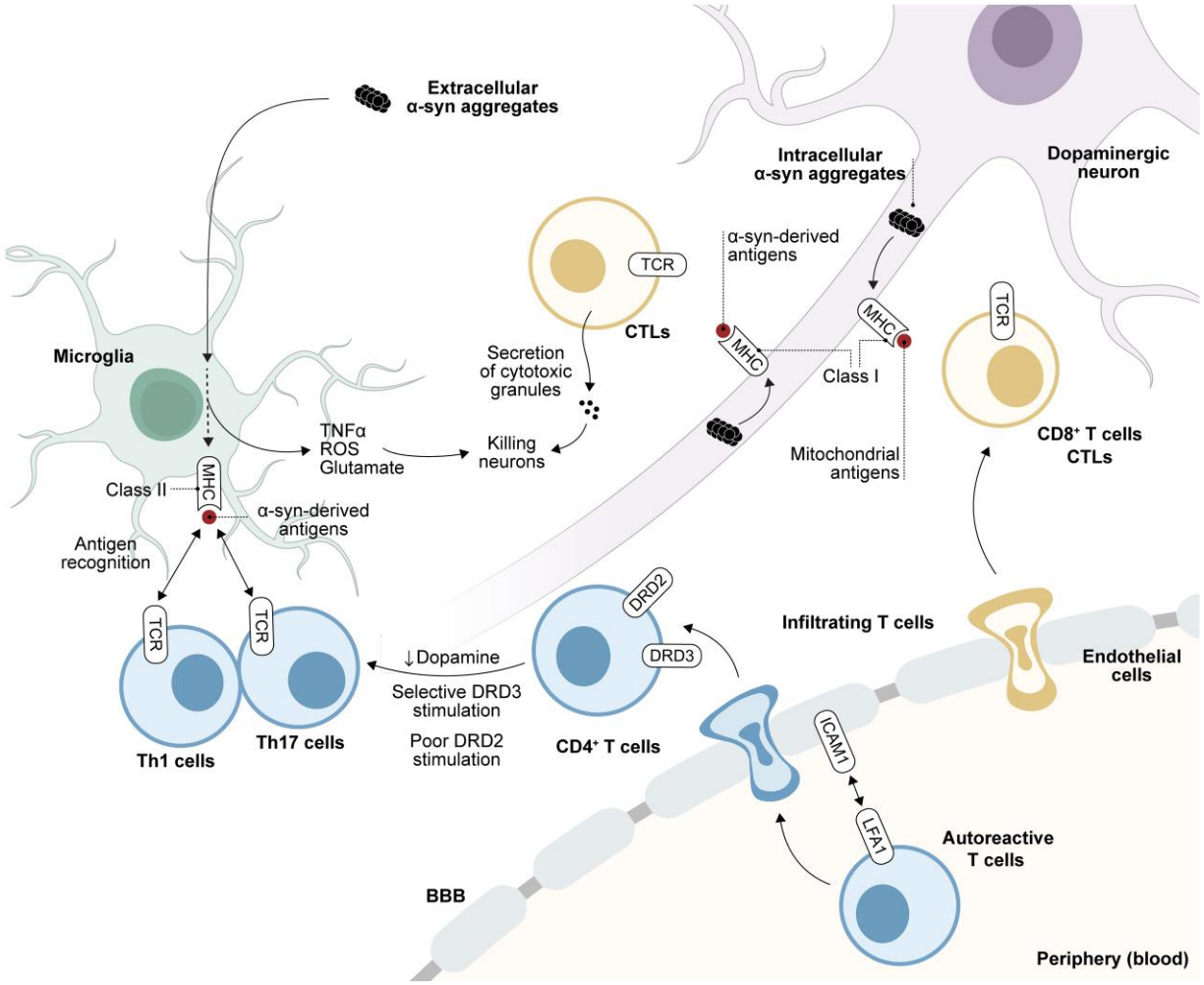

Figure 2 Putative mechanisms of peripheral T-lymphocyte involvement in Parkinson's disease. Autoreactive T cells might be activated in the periphery and then infiltrate into the brain, a process supported by the interaction of LFA1 expressed on the T-cell surface with ICAM1 expressed on the surface of the blood–brain barrier (BBB) endothelial cells. CD8+ T cells (cytotoxic T lymphocytes; CTLs) infiltrating into the brain might recognize their cognate antigens (α-syn-derived or mitochondrial-derived antigens) on class-I MHC molecules expressed on the surface of dopaminergic neurons, triggering the direct killing of neurons by CTLs. CD4+ T cells infiltrating the brain are exposed to low dopamine levels, which promotes poor DRD2-signalling and strong DRD3-signalling, favouring the acquisition of a strong pro-inflammatory profile (Th1 and Th17). These autoreactive Th1 and Th17 cells recognize α-syn-derived antigens presented on class-II MHC by microglia, leading to release of inflammatory cytokines directly onto microglia. In response to this, microglia produce high levels of neurotoxic factors, including TNFα, reactive oxygen species (ROS) and glutamate, thus inducing the killing of dopaminergic neurons by CTLs. TCR = T-cell receptor.

promoted a $CD8^+$ T cell-mediated autoimmune response to mitochondrial antigens that resulted in dopaminergic neurodegeneration.[281] Hence $CD8^+$ T cell-mediated responses to mitochondrial autoantigens might be important in the pathogenesis of *Pink1* associated PD, but the relevance of this to idiopathic PD is not known.

Although the vast majority of studies indicate a detrimental role for T cells in PD, some evidence indicates that T-cell response might be beneficial under certain circumstances. The adoptive transfer of T cells specific to A53T-hαSyn, in the M83 A53T α-syn transgenic mouse injected with PFF α-syn in the leg muscle, ameliorated motor impairment, α-syn pathology, astrogliosis and microgliosis and prolonged the survival of mice.[282] Moreover, the transfer of T cells into immunocompromised (NSG) mice decreased the phospho-S129-α-syn pathology in the intra-striatal PFF-PD model.[283] Another study showed that genetic lymphocyte deficiency enhances the motor decline and the dopaminergic neurodegeneration induced by 6-OHDA in *Rag1*$^{-/-}$ mice.[284] In addition, a number of studies have observed protective effects resulting from active immunization of rodents with α-syn. Immunization with low dose of α-syn in a mix with complete Freund's adjuvant induced the generation of antigen-specific Treg and the reduction of the α-syn pathology in the rAAV-hαSyn-induced PD model.[285] Direct immunization of mice with α-syn in combination with the chaperone Grp94 redirected the peripheral T-cell response and suppressed microglial activation in the MPTP PD model.[286] More recently, a combination of active α-syn immunization with rapamycin and an antigen-presenting cell-targeting glucan-microparticle vaccine delivery system, achieved a robust neuroprotection in the PDGF-α-syn transgenic mice that was associated with high number of Treg cells in brain and lower levels of TNF and IL6.[287] Importantly, the AFFITOPE immunotherapy approach using α-syn peptides, which is currently in clinical trials,[288] has been shown *in vivo* to decrease pathology and neurodegeneration in both the PLP- and PDGF-α-syn transgenic mice.[289] Alternatively, DNA vaccines targeting B-cell α-syn epitopes—which avoid harmful T-cell responses—have also been shown to be neuroprotective in the

PDGF-α-syn transgenic mice.[290] This suggest that the protective capacity of the immune system can be harnessed to slow disease progression.

T-cell subsets involved in neurodegeneration

With regards to functional phenotypes relevant to the disease process, several studies in animal PD models have shown a higher frequency of Th1 and Th17 cells and lower levels of Treg.[272,291-293] Importantly, the infiltration of IFN-γ-producing $CD8^+$ T cells (cytotoxic T lymphocytes, CTLs) into the brain has been described in the MPTP mouse model[276] and in *Pink1*-deficient mice.[281] Highlighting the relevance of the reduction of Treg frequency in the physiopathology of PD, Treg depletion (by an anti-CD25 antibody) exacerbated neurodegeneration in the MPTP mouse model.[294] Conversely, several approaches that increase the polyclonal or the α-syn-induced Treg response show amelioration of neurodegeneration and motor defects in both neurotoxin and α-syn-based PD models (reviewed by Machhi *et al.*[295]). Similarly, the relevance of Th17 cells in PD has been suggested by evidence from animal studies. Indeed, pharmacological inhibition of RORγt (the transcription factor controlling the Th17 phenotype) ameliorated the neurodegeneration and motor decline in MPTP-treated mice.[292] Conversely, the adoptive transfer of Th17 cells from mice immunized with nitrated α-syn into MPTP-treated mice exacerbated nigral dopaminergic neurodegeneration.[296] Altogether, the current evidence points to the involvement of Th1, Th17 and CTLs in the autoimmune response in animal models of PD, and a therapeutic potential of Tregs. Several studies analysing how T cells infiltrate the CNS suggest that Th17 cells predominantly use the surface lymphocytic molecule LFA-1 which might bind to its endothelial ligand ICAM-1,[78,274,293,297] but other mechanisms might also be involved.

Of note, the early aggregation of α-syn in SN neurons might impair the trafficking of presynaptic vesicles, thus reducing the levels of striatal dopamine even before neurodegeneration is established,[298] which might affect T-cell behaviour since they express dopamine receptors. Addressing this issue, a group of studies has provided genetic and pharmacologic evidence indicating that stimulation of DRD2 (low-affinity; ≈1700 nM) induced by high dopamine levels exerts anti-inflammatory effects in T cells and reduces neurodegeneration in mice,[291] while low dopamine levels stimulate DRD3 (high-affinity; ≈20 nM), selectively promoting inflammatory behaviour in T cells and favouring neuroinflammation and neurodegeneration.[299,300] Therefore, it is important to keep in mind that both reduced brain dopamine but also dopaminergic drugs might affect the local and peripheral immune response in PD.

Involvement of B cells

Most studies have found no changes in B-cell infiltration into the brain in rodent PD models.[149,287,301,302] However, two studies by the same lab showed B-cell infiltration in both neurotoxicant and α-syn based models.[78,303] In an effort to analyse the aetiological relevance of B cells, two studies from different authors and different experimental approaches evaluated the development of the PD-like neurodegeneration in B cell-deficient mice and found no change compared to control animals.[275,283] However, another study in the 6-OHDA toxin model found that B-cell deficiency (μMT mice) or B-cell depletion (using CD20 antibodies) resulted in attenuated neurodegeneration, suggesting that B cells may play a protective role in early PD development.[251] Further studies are needed to clarify the role of different B-cell subsets in α-syn based models.

Involvement of other peripheral innate immune cells

Studies conducted in PFF-injected mice,[304] 6-OHDA rats,[150] MPTP mice[305] and rAAV-hαSyn mice[306] have all shown that peripheral monocytes infiltrate the striatum through a mechanism involving the recruitment of CCR2+ monocytes by CCL2 produced in astrocytes. Genetic *Ccr2* deficiency abrogated neuroinflammation and neurodegeneration in rAAV-hαSyn mice[306] but not in MPTP mice,[305,307] indicating this mechanism may be most relevant in α-syn-mediated neurodegeneration. Besides astrocytic CCL2, Th1-mediated responses can also promote the recruitment of peripheral monocytes. Furthermore, when restimulated by MHCII antigen-presentation, Th1 cells release IFN-γ, further exacerbating the local inflammatory response. Interestingly, using the rAAV-hαSyn mouse model, a recent study analysing the relative relevance of tissue resident macrophages (microglia and CAMs) found that CAMs, but not microglia, were essential for restimulation of $CD4^+$ T cells in the brain.[308] Still, these recent findings should be confirmed by further studies.

On the other hand, Th17-mediated responses are known to recruit peripheral blood neutrophils into the target tissue to promote inflammation. Despite some studies having confirmed an association between neuroinflammation and neutrophils in animal models of PD,[272,309] there is no causal evidence indicating a significant role of these leucocytes in the development of neuroinflammation. Regarding the role of natural killer (NK) cells, a number of studies have shown higher percentage of $CD56^+$ NK cells in people with PD (reviewed by Menees and Lee[310]). In the α-syn PFF mouse model, NK cell antibody-mediated depletion resulted in exacerbated motor impairment and enhanced deposition of α-syn aggregates.[311] Moreover, using human NK cells *in vitro*, they provided evidence suggesting that the beneficial effects exerted by NK cells were mediated by the uptake and degradation of α-syn aggregates.[311] Altogether, these studies suggest the relevance of peripheral innate immune cells in the PD pathophysiology. However, the research in this area is still incipient and needs further exploration.

Conclusion

In conclusion, a wealth of data from human and animal studies strongly support the relevance of the immune system in PD. It is now accepted that microglia respond early during disease, and while these cells can remove toxic molecules such as misfolded α-syn, based on the results from studies in rodents, microglia might later acquire a pro-inflammatory status that promotes neuronal death. Accumulated evidence suggests that α-syn plays a central role by initiating such inflammatory processes through interaction with immune receptors and subsequent activation of the NF-κB pathway and NLRP3 inflammasome. Other molecular pathways such as the STING related pathway have also recently been implicated. In addition to microglia-mediated inflammation in the brain, immune cells are also altered in the peripheral blood in PD, with changes in both the innate and adaptive immune compartments, and infiltration of peripheral immune cells into the CNS. However, changes in peripheral immune cell subsets are somewhat inconsistent across studies, possibly due to differences in clinical phenotype and disease stage. Further longitudinal studies in larger patient cohorts are needed to establish changes throughout the disease course and their relevance to disease progression. Whilst there are inconsistencies in human studies, animal research strongly supports a significant role for peripheral immune cells in the neuronal death associated with PD. While lymphocytes and

monocytes might infiltrate the brain and modify the local immune response, it is unclear how much influence they can exert from the periphery. The possibility of modifying immune cells in blood and in turn modulating the immune environment in the brain holds a very attractive potential, and indeed this is already being explored in clinical trials (ISRCTN14616801[312]). However, more evidence is needed from human studies regarding which immune cell types and mechanisms are most relevant, and at what stage of the disease, in order to better understand when, and how, to modulate the immune response in a targeted way to achieve neuroprotection without unwanted off-target effects.

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Competing interests

The authors report no competing interests.

Supplementary material

Supplementary material is available at *Brain* online.

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