



Peripheral-Central Neuroimmune Crosstalk in Parkinson's Disease: What Do Patients and Animal Models Tell Us?

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The brain is no longer considered an immune privileged organ and neuroinflammation has long been associated with Parkinson's disease. Accumulating evidence demonstrates that innate and adaptive responses take place in the CNS. The extent to which peripheral immune alterations impacts on the CNS, or vice and versa, is, however, still a matter of debate. Gaining a better knowledge of the molecular and cellular immune dysfunctions present in these two compartments and clarifying their mutual interactions is a fundamental step in understanding and preventing Parkinson's disease (PD) pathogenesis. This review provides an overview of the current knowledge on inflammatory processes evidenced both in PD patients and in toxin-induced animal models of the disease. It discusses differences and similarities between human and animal studies in the context of neuroinflammation and immune responses and how they have guided therapeutic strategies to slow down disease progression. Future longitudinal studies are necessary and can help gain a better understanding on peripheral-central nervous system crosstalk to improve therapeutic strategies for PD.

Keywords: inflammasomes, cytokine, toxin-induced models, LRRK2, lymphocytes, blood-brain barrier, MPTP, 6-OHDA

INTRODUCTION

Innate and adaptive immunity are crucial for the survival of all organisms (1). The innate system as we know it today is the result of a long evolutionary period. Innate immunity promotes inflammation as an immediate, non-specific response to infection, insults and/or biological stressors through a limited set of germline-encoded receptors expressed on specialized cells: macrophages, dendritic cells, natural killer cells, or neutrophils (2). While it does not provide long-lasting immunity it is pivotal to the overall immune response. Adaptive immunity possibly developed and evolved as a complementary plug-in system to strengthen innate immunity in complex organisms (3). Adaptive immunity requires activation of the innate system and subsequent antigen presentation to adaptive immune cells and is based on unlimited somatic diversification of receptors present on lymphoid cells and their selective expansion to match pathogens (4). The adaptive immunity repertoire is specific for each individual, shaped by individual life history, and is the foundation of a strong memory response that allows rapid reaction to repeated infections. Combination of innate and adaptive immunity is required for the comprehensive immune protection observed in humans.

The capacities of the central nervous system (CNS), recalling those provided by the adaptive immune system, evolves in response to each individual's life experience. In the timeline of evolution, the CNS has developed amidst the innate and adaptive immune systems, combining characteristics to allow the appearance and development of increasingly more complex organisms. Throughout evolution the CNS and the two arms of the immune system have co-evolved through constant crosstalk and communication, persistently improving their ability to respond and adapt to the environment. Today, the brain is no longer considered an immune privileged organ. Innate and adaptive responses take place in the CNS (5), and peripheral immune alterations can impact on the CNS. Gaining a better knowledge of the molecular and cellular immune dysfunctions present in these two compartments, clarifying and understanding their mutual interactions represents a fundamental step in the development of alternative therapeutic strategies for neurodegenerative diseases, including Parkinson's disease (PD). PD is not considered an immune disease, but it is now widely accepted that inflammation and neuroinflammation are important players in the etiology and/or the progression of the disease; the triad, inflammation, neuroinflammation, and neurodegeneration, likely intervening in a vicious, each one sustaining the other. A possible role of viral infection in PD etiology has been extensively addressed but is still a matter of debate (6).

Here we will review some inflammatory processes that take place both in the central and peripheral compartments. In particular, we will look at communication barriers that limit passage of information, as well as the regulation of inflammatory markers and cells that may transit from the periphery to the brain, and vice versa. We will summarize data on the inflammasome, an important player in both inflammatory and neuro-inflammatory processes, which has gained considerable attention in the past decade and that may represent a key factor in peripheral-central neuro-immune crosstalk. Due to space limitations, we will not review the fundamental importance of alpha-synuclein in immune and neuro-immune processes and crosstalk but will sometimes introduce it where appropriate. The subject is complex and deserves a space on its own to be properly addressed and has been reviewed elsewhere (7–10). Finally, we will consider the importance of LRRK2, a major genetic risk factor for developing PD that is expressed by both neurons and immune cells. For each point we will present and compare data obtained from human and animal studies and underline how they converge to help us improve our understanding of immune crosstalk.

NEUROINFLAMMATION AND MICROGLIA IN PD

The CNS, long considered an immune-privileged organ, has developed a tightly regulated immune reactivity (11). We now know that insults, such as endogenous danger signals or pathogens, can trigger an immune response in the CNS. Neuroinflammation is the combined response of immune cells

present in the brain, including microglia, astrocytes, infiltrating lymphocytes as well as inflammatory factors. Microglial cells and microgliosis seem to play a particular important function in the initiation of neuroinflammation (12, 13). If not controlled or terminated immune reactions may alter brain homeostasis and cause cellular cell death and chronic inflammation (14). Degenerating neurons may themselves release molecules that will spark inflammation (15), triggering a deleterious feedforward loop.

McGeer and collaborators first evidenced the presence of microglial activation in postmortem brains of PD patients suggesting that neuroinflammation may promote neurodegeneration in PD (16, 17). Population-based prospective data has also indicated that the chronic low-dose consumption of non-steroidal anti-inflammatory drugs (NSAID) reduced the risk of developing PD although the protective effect depended on the type of NSAID molecule (18–22). Anti-inflammatory drugs have, however, not yet proven efficacious as anti-symptomatic or disease-modifying treatments (23). Over the past decades neuroinflammatory processes have undeniably been linked to PD but whether they may be a cause, or a consequence of neuronal degeneration remains unanswered (13). Intrinsic damage in degenerating neurons also referred to as cell-autonomous pathological mechanisms may drive their death and was long considered the sole causes of neurodegeneration. Neuronal degeneration may also be a secondary event induced by pathological interactions or signals from neighboring glial cells or immune cell infiltrating from peripheral compartments. The discovery of Lewy bodies containing alpha-synuclein aggregates (24) and the subsequent development of transgenic mouse models expressing alpha-synuclein in astrocytes and displaying PD-like phenotypic dysfunctions (25) supported the existence of non-cell autonomous mechanisms in the disease.

Microglia cells do not originate from blood-derived cells but are established during early prenatal period from yolk-sac-derived progenitors. They remain segregated in and are shaped by the CNS, maintaining self-renewal abilities throughout life (26, 27) without the contribution of peripheral myeloid cells (28, 29). Under physiological conditions microglia constantly surveil the brain parenchyma and provide trophic support to neurons (30–32). Physiological brain homeostasis, including intact barriers that separate CNS from peripheral compartments, regulated expression of soluble factors (TGF- β , Il-4, Il-13, BDNF, NGF) and receptor-mediated cell-cell interactions, all intervene in maintaining microglia under a surveillance-competent phenotype (33). Microglia cells are equipped with receptors to sense endogenous as well as pathogen danger signals (34). Immune mechanisms combine to confer a tight regulation of microglia function in the brain parenchyma. These include, separation from the blood by barriers, soluble factors such as TGF- β , specific interleukins, BDNF etc., direct contact with neighboring cells through receptors, such as the fractaline receptor CX3CR1, CD200R, MHC II, as well as transcription factors that may regulate activation phenotypes (33). Under pathological conditions, microglia undergo morphological and functional changes and become "activated" (35); they acquire phagocytic phenotype, increase the expression of chemokine and

cytokine receptors and are themselves a constant supplier of inflammatory factors (32). Recent evidence clearly indicates that microglia can assume a large variety of phenotypic changes upon activation and show significant regional variability in terms of gene expression profile and functionality that goes well-beyond the simple definition of M1/M2 classification (36).

PD Patients

Activated microglia express major histocompatibility class II (MHC-II) markers that present peptides to effector cells including T lymphocytes. In humans these include human leukocyte antigen (HLA)-DR, HLA-DQ, and HLA-DP molecules. Presentation is key to the engagement of adaptive immune, which in turn can further sustain inflammatory processes. In postmortem PD brains, HLA-DR⁺ microglia were observed in the SNc and striatum (16, 17) (**Figure 1**), mainly associated with neurons containing LB and damaged neurons (37). They also expressed intracellular adhesion molecule (ICAM), the scavenger receptor TLR2 and the lysosomal marker CD68 (37, 38). Interestingly, pro-inflammatory factors, including IL-6 and TNF- α , were expressed in MHCII⁺ cells (37) (**Figure 2**).

Single nucleotide polymorphism in the MHC-II locus has been associated with increased risk of developing PD (39) and genome-wide association studies (GWA) (39) have noticeably implicated HLA cell-surface complexes as fundamental to trigger the adaptive immune system in the frame of PD pathology (40).

Positron emission tomography (PET) using ¹¹C-(R)-PK11195, a radioligand that binds to the 18-kDa translocator protein (TSPO) mainly expressed on “activated” microglia (41), evidenced increased binding in various brain regions in PD patients compared to healthy controls (36, 42–44). Inconsistent data was obtained with a panel of radioligands, possibly as a consequent of polymorphism-linked difference in TSPO binding affinity of the ligands (45, 46). Thus, while PET analysis can be used to confirm microgliosis in PD, ligands do not have the ability to distinguish among the phenotypic diversity of activation states and do not allow correlation between imaging and disease severity or progression.

Astrocytes are the most abundant cells in the brain. They regulate many brain processes including glucose metabolism (47). They play a fundamental role in maintaining brain homeostasis and providing energy and support to neurons (48). Their role in PD pathology still not well-understood but an elevated cell density and phenotypic changes are observed in astrocytes in postmortem PD brains (49, 50). Astrocytes also contribute to the blood-brain-barrier that is disrupted in patients with PD (51).

PD Animal Models

Glial activation, both astrocytes and microglia, has been consistently observed in toxic animal models of PD, including the 6-OHDA rats and mice (52–54), LPS (55), MPTP treated animals (56, 57), and rotenone models (58–60) (**Figure 1**).

Intracerebral injection of the neurotoxin 6-hydroxydopamine (6-OHDA) in rodents (rats and mice) causes nigrostriatal neurodegeneration and induces a strong glial activation (microglia and astrocytes) in the striatum and substantia nigra

(SN). Profile, localization and time of neuroinflammation depend on the site of injection. Increased MHC-II and CD68 expression is detected rapidly after 6-OHDA injection in the medial forebrain bundle, in particular in microglia located nearby neuronal cell loss (61, 62). In 6-OHDA models, microgliosis seems to be a transient phenomenon that peaks shortly before neurodegeneration and then slowly reverts to an apparently normal phenotype. Intrastriatal injection of 6-OHDA in mice causes a rapid increase of TNF- α in microglia indicating an inflammatory-prone phenotype (54).

The MPTP neurotoxin induces persistent microgliosis in non-human primates (NHP) evidenced by enhanced HLA-DR⁺ microglia (56) reminiscent of phenotypes observed in PD brains (16, 17). In MPTP-treated NHP chronic microglial activation is still present years after MPTP intoxication (56, 63).

A more transient activation of microglia cells is observed in rodents depending on the MPTP regimen and paradigm (56). In a chronic rodent model of intoxication microglia activation is detected well-before neurodegeneration when non-motor dysfunctions, including hyposmia are already present and persists for at least 6 months (64). Upregulation of MHC-I, MHC-II, and ICAM-1 are detected transiently in MPTP mice (65). Increased CD68 expression in microglia located close to neuronal cell death is also observed in MPTP mice (66). Interestingly, the neuro-toxin induces a down regulation of anti-inflammatory markers, including CD206, Arg-1, and YM-1, in the SN suggesting a shift toward a more inflammatory-prone phenotype of microglial cells (67).

Rotenone, a naturally occurring substance largely used in organic agriculture until its prohibition in 2008, has been linked to the development of PD (60) and has been used to develop rodent models of the disease through different administration paradigm including intracerebral or intraperitoneal injection and intragastric administration (68, 69). Consistent neuroinflammation and microglial activation is observed in rotenone models (58–60, 70).

Peripheral or intracerebral injection of the bacterial endotoxin lipopolysaccharide (LPS) causes microgliosis that precedes neuronal cell death (71). LPS acts through interaction with the Toll-like receptor 4 (TLR-4) and is a potent inducer of peripheral (72) and central immune cells (73, 74) but has no direct effect on neuron. LPS injection has been used in numerous toxic-induced or transgenic models of PD and accentuates neurodegeneration and neuroinflammation (48, 49). Recent data indicated that peripheral injection of LPS induces microglial activation that precedes and peaked just before neurodegeneration and then slowly decreased. Interestingly, at later time points a shift toward a more anti-inflammatory profile was observed in microglia (Arg-1⁺ cells) corresponded to cessation of neurodegenerative processes (75).

Numerous transgenic models of PD have been developed in particular model overexpressing wild type or mutant forms of the protein alpha-synuclein using different promoters (25). The thy-1 a-syn transgenic model, the best characterized syn model (61), shows early and progressive increase of activated microglia specifically detected in the SN and striatum and that precedes nigrostriatal neurodegeneration (76, 77). Similarly,

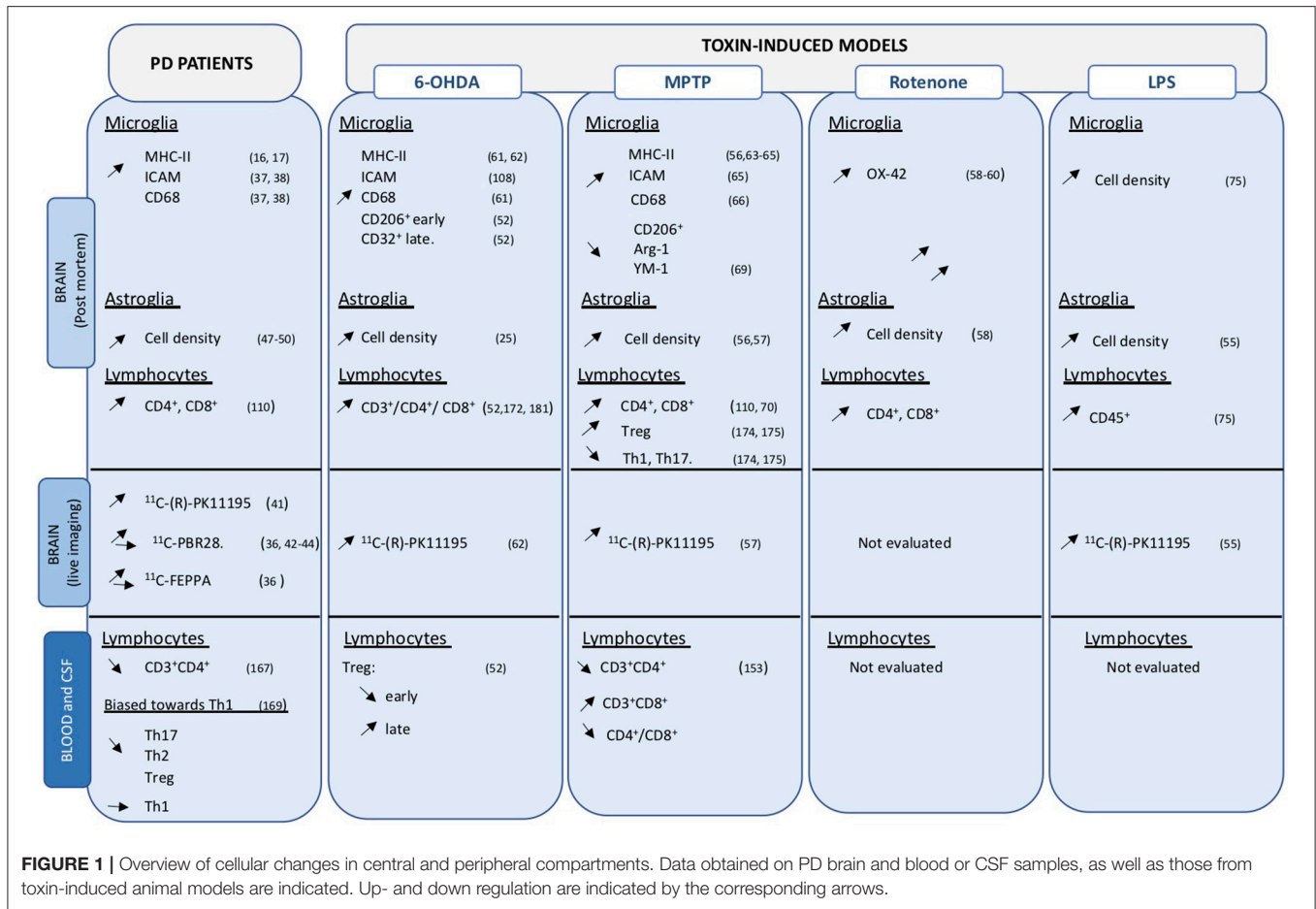


FIGURE 1 | Overview of cellular changes in central and peripheral compartments. Data obtained on PD brain and blood or CSF samples, as well as those from toxin-induced animal models are indicated. Up- and down regulation are indicated by the corresponding arrows.

viral vector-driven overexpression of a-syn models (AAV a-syn models) have been developed in rodents (78) and primates (79). Robust microglial activation is also observed in AAV a-syn models in rodents (80–82) and in primates (83) and are consistent with neuroinflammatory features observed in PD patients including MHC-II upregulation. A paper by Ferreira and Romero-Ramos (84) extensively reviews the role and crosstalk between a-syn and microglia in PD and because a space limitation this topic will not be further addressed here.

Evidence and data obtained in PD patients and animal models of PD (Figure 1) clearly converge and sustain the importance of neuroinflammation in the disease.

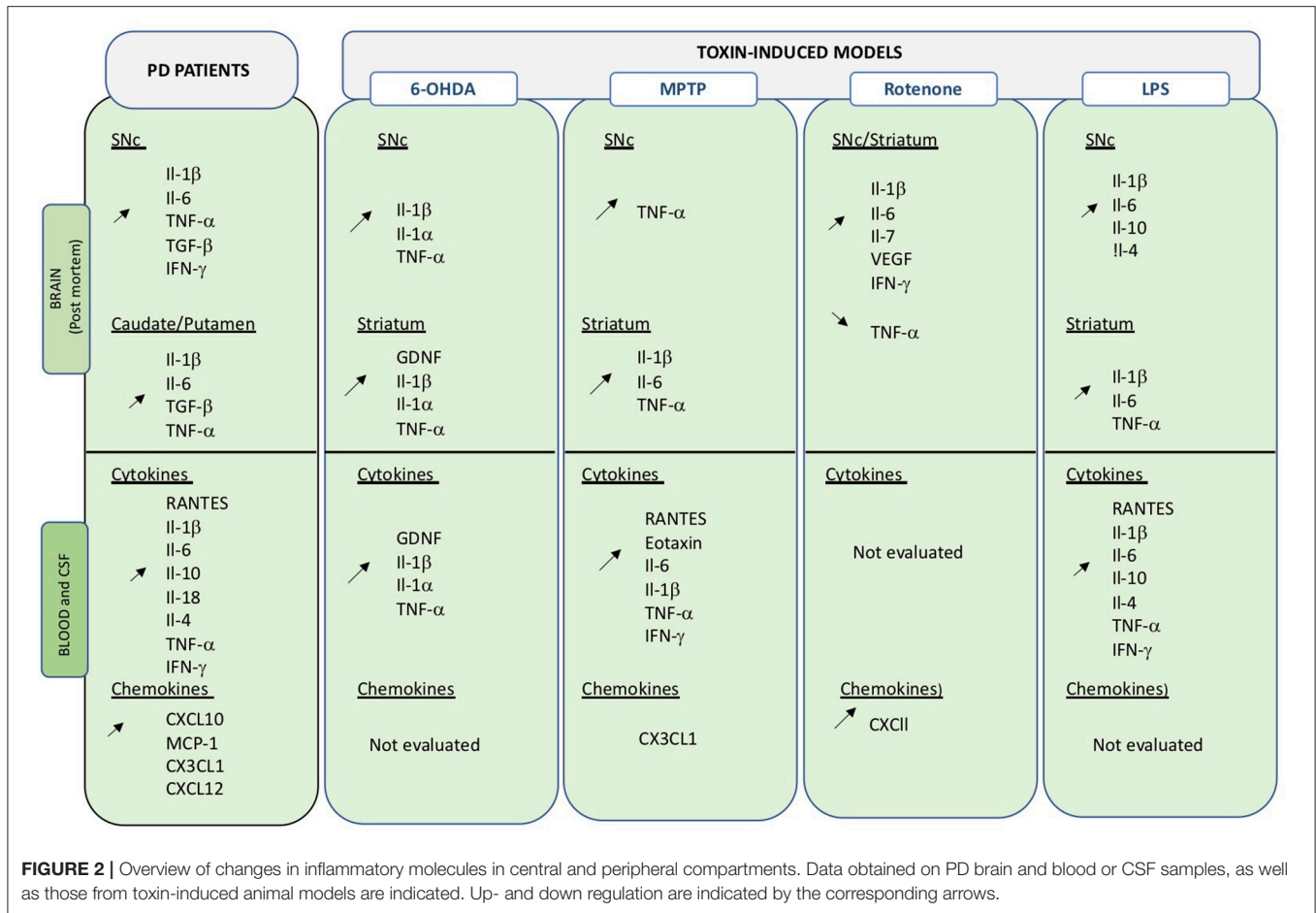
COMMUNICATION ROUTES BETWEEN THE PERIPHERY AND THE BRAIN

Crosstalk between systems implies and requires the existence of communication routes. Neurons in the brain are protected from adverse effects of peripherally borne insults by several barriers, including the blood-brain barrier (BBB), the blood CSF barrier (BCSFB) and the meninges. They have different permeability to substance and cells. Under physiological conditions only few leukocytes are observed in the CNS. These

barriers represent physiological and selective entrance to the CNS, yet at the same time they are also a niche where blood-derived immune cell may distantly modulate or affect brain homeostasis (85).

The BBB is formed of endothelial cell tight junctions and a layer astrocytes end-foot. BBB alterations may be linked to aging, by far the most relevant risk factor for developing PD. Astrocytes are important players in maintaining an intact BBB and age-related changes in astrocytes may modify BBB permeability (86, 87). Astrocytes also release numerous soluble factors, including monocyte chemoattractant protein-1 (MCP-1), which favors the recruitment and infiltration of monocytes from the periphery into the brain. The CSF, filling the space in between, contains self-maintained resident myeloid cells of embryonic origin (88). Under physiological conditions, the BBB allows the passive diffusion of water and lipophilic molecules and the selective transport of molecules necessary for neural function, such as glucose and amino acids, but does not permit cellular infiltration to the brain. Dysfunction or disruption of tight junctions can cause leaky BBB and exposes the brain to blood-borne substances.

The BCSF is formed by the choroid plexus (CP) that produces and distributes the CSF throughout the CNS (89). It is formed of tight junctions and epithelial cells, which express trafficking



molecules (85, 90, 91) These may sense and response to signals secreted by immune cells present both in the CNS and the stroma. The presence of epithelial vs. endothelial cells renders the BCSF less impermeable than the BBB and trafficking of a low number of T cells, in particular CD4⁺ memory T cells, is possible even under physiological conditions (92).

The meninges surround the brain and the spinal cord and contain the myeloid- and T-cell-populated CSF in the subarachnoid space (88, 93). Similarly to the BCSF, they have a different anatomical structure than the BBB that could allow migration of immune cells into the brain parenchyma (94).

Recent evidence indicates that a selected population of resident cells, including T cell subsets, NK cells, B cells and dendritic cells, are present in those brain boundaries, the “brain interface,” mostly located in the meninges and the BCSF. These cells may serve as communication bridges to and from the brain (95) and have been defined in depth recently (96). Expression of CD44 is crucial for cell motility and is not present in brain resident myeloid cells (96).

Pathological events, in the CNS or in peripheral systems, may modulate barrier integrity leading to important functional dysregulation and opening of tightly regulated communication routes causing unwanted crosstalk and passage of noxious molecules or cells that may sensitize or worsen existing

conditions. Leakage could potentiate existing neuroinflammatory processes by allowing infiltration of peripheral cells into the brain parenchyma. It could also be caused by neuroinflammation itself.

PD Patients

BBB disruption has been reported in PD patients (97, 98). Post-mortem brain samples show accumulation of blood-derived proteins (fibrinogen, IgG) in the striatum and globus pallidus (51, 99). Microvascular degeneration, disrupted and damaged tight junctions, changes in the capillary basement membrane of the subthalamic nucleus, as well as red blood cell extravasation in striatum have been documented. Aberrant angiogenesis in the SN, locus coeruleus and putamen also support alterations in BBB (100, 101). Increased of blood-derived albumin in CSF and of IgG CSF: serum ratio (102, 103) are also indicative of barrier dysfunction. Live neuroimaging studies have evidenced disruption of BBB integrity in basal ganglia (104) and deep cortical gray matter regions and white matter (105), as well as diminished P-glycoprotein function (97).

PD Animal Models

Existing data in animal models confirm the presence of barrier alteration although this pathological data has not been systematically evaluated in all models. Injection of LPS causes

BBB disruption and loss of TH-positive cells in rodents (23, 106). When present, BBB disruption occurs mostly at the site of dopaminergic cell loss but the causes and sequence of events leading to BBB permeability changes are still a matter of debate.

Altered expression of cerebral adhesion molecules, possibly reflecting BBB alterations have been detected in 6-OHDA rats (105, 107) and have been associated with concomitant alterations of peripheral molecules (108). Increased BBB permeability has also been observed in the striatum and SNC following intra-striatal injection of 6-OHDA (109). It has also been suggested that brain accumulation of iron measured in 6-OHDA animals is partly due to altered BBB (107).

Upregulation of adhesion molecules is important for infiltration of cells has been observed in MPTP models (rodents and NHP) (110, 111). Peripheral inflammation itself may cause BBB alterations, thus favoring or sustaining neurodegeneration. Inflammatory mediators, produced systemically, or within the brain, can signal through the endothelial cells causing alteration in tight junctions' structure thus modifying BBB permeability. Increased number of blood vessels and endothelial cells have been described in proximity of degenerating neurons in MPTP-treated NHP (112). Changes in phospho-glycoprotein functionality suggestive of BBB alterations have also been observed in MPTP-treated NHP (113). Therapeutic strategies that prevent BBB leakage through activation of CB2 receptors have been shown to reduce dopamine neuron loss in the MPTP model (114). However, it remains unclear whether increased BBB integrity is a causal effect or the result of reduced neuronal cell loss.

No clear evidence of BBB alteration, measured by fluorescein leakage to the brain, has been detected in the rotenone model (115).

Globally, evidence obtained from human and animal studies clearly points to a dysregulation of barriers between the peripheral and central compartment. It remains to be determined if increased BBB integrity is a causal effect or the result of neuronal cell loss and neuroinflammation.

INFLAMMATORY MARKERS

Peripheral inflammatory markers including cytokines and chemokines are critical signaling molecules in the modulation of the immune system and can affect both peripheral and central systems. Cytokines and chemokines are actively transported across the BBB by saturable transport and any variations in expression levels in the blood may directly or indirectly impact on CNS function (116). Peripheral inflammation could thus be an important contributor in the etiology of PD as well as in disease progress (Figure 2).

PD Patients

Increased levels of inflammatory markers were already detected in PD post-mortem samples in the late 1990's (Figure 2) (117–121). Changes in cytokine/chemokine levels have then been largely evaluated in PD patients biofluids (blood, serum plasma, CSF) and measurements show divergences of pro-inflammatory and anti-inflammatory profiles compared to healthy subjects (122–126). Qin and collaborators have recently

performed a systemic review and meta-analysis of published data to investigate alterations of peripheral cytokines in PD patients (127). Findings from 25 peer-reviewed publications, including 1,547 PD patients, and 1,107 healthy controls, confirmed that patients present an increased inflammatory-prone response and allowed the identification of elevated levels of pro-inflammatory factors, including RANTES Il-1 β , Il-2, Il-6, TNF- α , and C-reactive protein. Interestingly, Il-1 β is an important central downstream effector of inflammasome activation, an inflammatory mediator that is attracting considerable attention in neurodegenerative diseases (see below section Inflammasome). Altered levels of IFN- γ and Il-8 were also detected, although in a limited number of small studies (122, 128). Similarly, alterations in levels of the anti-inflammatory cytokines Il-4 and Il-10 were detected (118, 122). Il-10 is thought to oppose action of proinflammatory cytokines but may also be involved in B cell survival and activation as well as IFN- γ production. Recently, some of the above-mentioned cytokines have been correlated with specific PD phenotypes (129). High Il-10 was related to non-tremor and late onset PD, while Il-6 correlated with longer disease duration and TNF- α with disease progression. Correlation between RANTES and disease severity (130) as well as TNF- α blood levels and non-motor symptoms have also been suggested.

Chemokines have been less commonly assessed in blood or CSF of PD patients, but recent data suggest that elevated CXCL10 levels may be related to worsening of cognitive functions in PD patients (131). Similarly, changes in MCP1 (CCL2), CXCL10 and CX3CL1 have been detected (132, 133). Changes are also observed in the CSF, in particular increased levels of Il-2, Il-6, TNF- α and MCP-1 have been measured (134). Importantly, increased levels of Il-1 β , Il-6, and TNF- α , have also been detected in PD brains (135, 136), suggesting that changes in both systems may be correlated.

PD Animal Models

Few studies have addressed the modulation of inflammatory factors in peripheral compartments, including blood and CSF, in animal models of PD. Nonetheless, results obtained in animal models also recapitulate the convergence of peripheral and central changes in inflammatory molecules.

In 6-OHDA rodents blockage of TNF- α or Il-4 can reduce neurodegeneration (23, 137), while it is exacerbated by treatment with systemic Il-1 β (138, 139). Interestingly, a similar worsening effect was observed in DJ-1 KO (140) and Parkin KO mice (141) for which neurodegeneration of dopaminergic neurons is usually absent (25). A delayed increase of striatal Il-1 β mRNA levels is observed following 6-OHDA administration (142). Modulation of Il-1 α , Il-1 β , Il-6, and GDNF levels is observed at different time points both in serum CSF and brain extract of 6-OHDA rats (53, 143) It is possible that the time course analyses (24 h, 7 days, 4 and 8 weeks after toxic insult) in the various studies does not allow the detection of transient up- or down-regulation of the inflammatory markers.

CSF and serum concentration of TNF- α and IFN- γ are elevated in MPTP-treated NHP, even several years after intoxication (144, 145). Confirming the importance of the two

cytokines, KO mice lacking IFN- γ or TNF- α receptors are protected from MPTP neurotoxicity (144, 146–148). Elevated levels of IL-1 β , TNF- α and IL-6 are also consistently observed in serum and brain following MPTP administration in mice (67, 149–153).

More recent evidence from the acute MPTP mouse model, indicates a transient increase in both brain and serum levels of RANTES and eotaxin (154, 155). RANTES is known to induce migration and homing of lymphoid cells (156) and as indicated above is also increased in serum of PD patients (127). Eotaxin is an important factor involved in infiltration of mononuclear cells at inflammation sites (157). Biweekly injection of RANTES and eotaxin induced a continuous activation of neuroinflammation and T-cell infiltration as well as persistent neurodegeneration, while functional blocking antibodies to the two factors reduced T-cell infiltration, neuroinflammation and neurodegeneration. Interestingly, increased RANTES and eotaxin levels, as well as T cell infiltration have also been detected in the serum of MPTP-treated NHP (158). Blocking RANTES and eotaxin expression could significantly reduce neuroinflammation. Unfortunately, effect on neurodegeneration of RANTES blockade was not assessed in this study.

Animals that received repeated i.p. injection of LPS presented with a significant loss of dopaminergic neurons that peaked at 19 days and remained stable thereafter. An immediate increase in pro-inflammatory cytokines, IL-1 β , IL-6, and TNF- α was detected in the brain. Interestingly, this pro-inflammatory upregulation preceded neurodegeneration, was then reduced when maximal neuronal cell loss was detected, and switched to a more anti-inflammatory profile (IL-10) as cell loss ceased and stabilized (75). This sequential modulation from a pro- to an anti-inflammatory phenotype may represent an interesting target to arrest and resolve chronic neuro-inflammation.

LYMPHOCYTE INFILTRATION

In a normal adult brain, the crosstalk between the peripheral immune system and the brain is transient, and there is no evidence that it may lead to the central neuroinflammation. As mentioned above under physiological conditions, only few leukocytes are observed in the CNS. A growing body of evidence suggests that in chronic neurodegeneration, not only are the brain-resident microglia activated (159, 160), but they may be “primed” by previous or ongoing systemic inflammation, leading to the exaggerated synthesis of pro-inflammatory molecules (161–163). Numerous studies showed that microglial cells can be activated by the chronic infiltration of peripheral inflammatory T cells (164, 165), as well as various toxic molecules circulating from the peripheral tissue to the brain (166). T lymphocytes are an essential component of adaptive immunity and collaborate with B cells to produce an immune response.

PD Patients

T cell populations are altered in peripheral compartments and invade the CNS in PD and may contribute to neuronal degeneration and disease progression. Infiltration of CD4⁺ and

CD8⁺ cells have been observed in post-mortem analyses of PD brains (110) (**Figure 1**).

In peripheral blood of PD patients, alterations of the adaptive system are detected showing a decrease in both B and T lymphocytes, together with alterations in components of innate immunity including increased natural killer cells and neutrophils levels. In particular, a reduction in CD3⁺/CD4⁺ lymphocytes is consistently described, while the number of CD8⁺ cells remains largely unchanged in blood of PD patients (167).

CD4⁺ T cells can acquire different phenotypes corresponding to different inflammatory states. Pro-inflammatory T helper (Th) cells include Th1 that produce IFN- γ and TNF- α , and Th17 cells, producing IL-17 and IL-22. Anti-inflammatory cells include Th2 that release IL-4, IL-5, and IL-13, and regulatory T cells (Treg) that are fundamental modulators of T cell activation. Kustrimovic and collaborators have recently indicated that the balance among different T-cell phenotypes in the blood of PD patients is biased toward a more Th1-response, with a reduction in the number of Th17, Th2, and Treg, but not Th1 cells (168). This imbalance was further reflected by a Th-1-prone polarization in response to specific inflammatory stimuli, observed *in vitro* in lymphocytes from PD patients but not healthy volunteers. The reduced efficacy of PD Treg cells in controlling the release of pro-inflammatory cytokines by effector T cells (169) is a likely contributing factor that further amplifies this Th1-prone profile of peripheral T cells in PD.

PD Animal Models

Evidence in toxin-induced animal models corroborates data obtained in PD patients and sustains the important function of T cell subsets in neurodegenerative processes in PD (**Figure 1**). Infiltration of T cells, in particular CD4⁺ and CD8⁺ infiltration in the brain parenchyma, has been documented in numerous animal models of PD, including MPTP mice (110, 170), intragastric rotenone PD model (171), as well as in 6-OHDA PD models (52, 172). Much information on T-cell infiltration has been obtained using the MPTP mouse model combined to a variety of transgenic models. Rag1^{-/-} mice, which lack mature lymphocytes, and Tcrb^{-/-} mice, which lack T cell receptor β , are more resistant to acute MPTP toxicity compared to control mice (173, 174). Similarly, administration of MPTP to CD4^{-/-} mice induced less prominent dopaminergic cell loss compared to that observed in CD8^{-/-} animals (110). Altogether, these data indicate the importance of T lymphocyte infiltration and sustain a prevalent function of CD4⁺ over CD8⁺ lymphocytes in the MPTP-induced neurodegeneration processes.

The Th1-prone imbalance together with the reduced Treg efficacy observed in PD patient blood, combined with the importance of anti-inflammatory action and regulation of Treg in neurodegeneration is further sustained by experiments involving adoptive transfer of T cell subsets in MPTP mice. Transfer of Treg cells reduced neuronal cell loss, while transfer of Th1 or Th17 increased neurodegeneration (174, 175). In the same line, immunization with bacillus Calmette-Guerrin that favors Treg activation had a protective potential in MPTP mice insult (176). Chung and collaborators also reported that neuroprotective potential of bee venom immunization in MPTP mice could be

linked to a global reduction of CD4⁺ infiltration accompanied by a relative increased proportion of Treg cells in the brain parenchyma (177). Reduction in the number of lymphocytes in MPTP mice has been reported as early as 1992 (178) and confirmed by recent data reporting a global reduction in the number of CD3⁺ with reduced CD3⁺CD4⁺ but increased CD3⁺CD8⁺ cells (153).

Infiltration of T-lymphocytes has also been observed in 6-OHDA mice and rats PD models together with time-dependent neuroinflammation (52, 179). Blood of 6-OHDA animals showed an initial decrease in Treg cells that progressively returned to normal values. Interestingly, reduced Treg levels at the peripheral level corresponded to a phenotypic shift in microglial activation, from an anti-inflammatory phenotype (CD206⁺) to a more pro-inflammatory (CD32⁺) phenotype, as well as with the reduction of neuronal cell loss in the SNc, further suggesting an important modulatory role of Treg cells in the neuronal cell loss and neuroinflammation (53).

Considering the close interrelationship between T cells and microglia cells (180), therapies that change T cells may directly modulate microglial phenotype and vice versa. For example, stimulation of the regulatory function of CD4⁺ cells infiltrating the brain may represent a therapeutic strategy to limit neurodegeneration.

MONOCYTE/MACROPHAGES

As described above the presence of infiltrating lymphocytes in the CNS is well-documented both in animal models of PD and in post-mortem analyses of PD brains. Differently, a role for monocytes/macrophages in PD remains unclear but evidence suggests that they may also be contributing actors to the disease. Macrophages and monocytes are important players in the regulation of immune reaction in peripheral compartments and can pass the BBB to enter the brain where they may participate in regulation of central neuroinflammatory process (181).

Monocytes are short-lived myeloid-derived cells that continuously generated from bone marrow precursors (182). Monocytes circulate in the blood and tissues and do not proliferate under physiological conditions. They are key components of the innate immune system, express cell surface receptors as well as pathogen recognition receptors, and can produce cytokines. During inflammation they may migrate to inflamed tissues and differentiate into dendritic cells or macrophages (27, 183). Under physiological conditions, monocytes are constantly renewed from the myeloid repertoire while microglia renew themselves without the contribution of peripheral myeloid cells (28, 35).

Circulating monocytes can be found in the brain parenchyma only following BBB disruption caused for example by irradiation and bone marrow transplantation (184). Parabiosis experiments (26, 185) indicate that there is no infiltration of monocytes in the brain under physiological conditions. In neurodegenerative diseases, monocytes may infiltrate the brain and join microglia. As microglia they also undergo phenotypic changes, rapidly acquire a macrophage-like phenotype but never fully gain a

microglial identity (186). Until recently, it was difficult to distinguish infiltration monocytes from endogenous microglia. Recent data indicates that the chemokine receptor CCR2, required for cellular infiltration, is expressed on blood monocytes but not on resting or activated microglia and that the reverse is true for the fractaline receptor CX3CR1 (187, 188). This differential expression of cell surface markers favors the distinction between monocytes and microglia population in the brain parenchyma during a short time-window before infiltrating monocytes turn into tissue macrophages and downregulate CCR2 (189).

A specific population of macrophages are located at the brain interface, including meninges and CP; they have the same ontogenetic origin as microglia and differentiate through fine-tuned processes to give rise to separate cellular population with distinct profiles (190). Brain interface macrophages can be replenished by circulating cells but mostly originate from embryonic yolk sac and are maintained by self-renewal (88). They express microglia markers including CD11b, CX3CR1 and are different than circulating monocytes. The role of these perivascular macrophages is still under study.

PD Patients

Recent data indicates that, in early stage PD patients, disease-specific gene expression in peripheral monocytes may correlate with disease severity (191). Interestingly, genes relating to leukocyte migration and regulation of immune responses were found to be enriched in PD monocytes. Of particular interest, LRRK2 expression was highly upregulated in monocytes (see the section LRRK2: a genetic factor and an immune mediator in PD). Different gene expression patterns in monocytes are observed when looking at distinct disease stages (192) suggesting that monocytes may represent an important population to identify disease progression markers in PD.

PD Animal Models

MPTP treatment in mice increases the number of circulating monocytes (193). Infiltration of CCR2⁺ monocytes has been detected in the brain parenchyma of CCR2-GFP reporter mice following acute MPTP treatment (194). Interestingly, monocyte infiltration was transient and occurred before infiltration of T cells. In this acute model, blocking CCR2⁺ had no effect on MPTP-induced neurodegeneration. Precise contribution of monocytes infiltration to neuronal cell death still needs to be clearly demonstrated and more chronic states of infiltration may be needed.

INFLAMMASOMES AND PARKINSON'S DISEASE

Innate immunity is the first line of defense of the organism. It has evolved to recognize conserved pathogen molecular sequence (pathogen-associated molecular pattern—PAMP) through a set of receptors, the pattern recognition receptors (PRR). PRR can also be activated by damage-associated molecular patterns (DAMP). Recognition of PAMP or DAMP by PRR normally triggers transcriptional activation and neo-synthesis of proteins.

Inflammasomes react to specific PRR signal, trigger caspase 1 activation, which in turn causes the maturation and release of the pro-inflammatory cytokines IL-1 β and IL-18.

The inflammasome is a macromolecular complex formed through the oligomerization of a receptor, an adaptor, and caspase-1, the effector of the complex. Inflammasome receptors belong to several families, including the nucleotide-binding domain and leucine-rich repeats containing receptor family (NLR). In the past years NLRs have emerged as key sensors and regulators responding to PAMP and in particular DAMP produced under non-microbial inflammatory conditions (195). NLRP3 is the most characterized and studied inflammasome receptor and NLRP3 alterations have been linked to several pathologies, including neurodegenerative diseases (196). Evidence indicates that inflammasomes are important players in both peripheral and central innate immunity (197) and need to be tightly controlled to avoid overt inflammatory activation (198, 199).

PD Patients

Post-mortem analysis of confirmed idiopathic PD brains revealed high NLRP3 protein expression in surviving neurons (200). Downstream effectors of NLRP3, namely IL-18 and IL-1 β are increased in CSF and serum of PD patients (201). IL-1 β is a key cytokine in PD and increased levels are detected in central and peripheral compartments both in PD patients and in animal models of the disease (**Figure 2**). Considering the close link between NLRP3 and IL-1 β maturation, inflammasomes may be an important linking bridge between peripheral inflammation and central PD pathology (**Figure 3**).

A SNPs variant (rs7525979) of NLRP3, linked to altered stability of inflammasome assembly, is associated with significantly lower risk of developing PD (200). Interestingly, NLRP3 polymorphism has recently been associated with inflammatory bowel disease [IBD (202)]; IBD being a recently identified risk factor for PD development (203). Sustaining this link, recent retrospective analyses indicate that anti-TNF- α therapy to treat IBD reduces the incidence of PD, with a 78% reduction of risk in treated compared to non-treated patients (204). Thus, peripheral and central inflammation may be linked through activation of inflammasomes. Thus, a specific genetic susceptibility bridges PD and inflammation in the gut. The importance and involvement of the gut-brain axis PD pathogenesis has drawn considerable attention in the past decades. The Braak theory suggests that PD pathology may initially be triggered in the gastrointestinal (GI) tract and then spread to the brain via the vagus nerve. While the Braak theory is still a matter of debate (205, 206), the dysregulation of the gut-brain axis is well-established (207). A majority of patients suffer GI disorders that often appear before the onset of any motor symptoms (208). Today, there is no consensus on whether GI disturbances occur as a consequence of neurodegeneration in the CNS, the enteric nervous system, or both, or because of a yet unknown pathological process. Evidence supporting a contribution of chronic intestinal inflammation in PD has been covered elsewhere (207, 209, 210) and will not be reviewed here.

Several pathologic features characteristic of PD are linked to inflammasome regulation and activation further sustaining its importance. Indeed, dopamine (DA), the key neurotransmitter in PD, acts on almost all peripheral blood cells, which knowingly express dopamine receptors (211). DA has been shown to be an endogenous modulator of inflammasome by promoting NLRP3 ubiquitination and degradation (212). DA can inhibit LPS-induced NLRP3 activation in mice (212). Inflammasome can also be triggered by α -syn (213). Mitochondrial alteration is a common defect normally observed in most cell compartments in PD patients (214). Mitochondrial stress induced by rotenone can prime the activation of NLRP3 pointing out a link between mitochondrial defect and inflammasome activation (215, 216).

PD Animal Models

Evidence in an animal model of PD indicates that IL-1 β is primarily induced by NLRP3 activation in brain and microglia (217). Multiple studies in animals have shown that blocking NLRP3 can block development of PD phenotypes. Inhibition of inflammasome in MPTP-treated mice can reduce neuronal cell death (218). NLRP3^{-/-} mice are less susceptible to MPTP compared to wild type animals and show reduced IL-1 β and IL-18 production in serum (212). On the same line, mice lacking Caspase-1, the inflammasome effector, are less susceptible to MPTP (219). Inhibition of caspase-1 also reduces susceptibility to intracerebral administration of LPS or 6-OHDA in rats (220). Intragastric and ip exposure to rotenone increases striatal NLRP3 levels in treated mice (171, 221) and leads to caspase 1 cleavage, as well as neuroinflammation. Interestingly, the same treatment in mice lacking NLRP3 does not induce an inflammatory response and reduced neuronal cell death, typically induced by the neurotoxin, is detected (171) (**Figure 3**).

A large number of cytokines can be produced by the liver, which seems to be an active indirect participant in inflammatory processes. Aside from increased NLRP3 activation in the brain, MPTP-treated mice also present NLRP3 changes in liver and bone marrow-derived macrophages (BMDM) (222). In these mice, the selective liver-directed downregulation of NLRP3 reduced hepatic NLRP3 levels, as well as levels of proinflammatory cytokines in serum and brain. Specifically, IL-1 β and IL-18, but not the anti-inflammatory IL-4 and IL-10 cytokines, were impacted, suggesting the induction of an anti-inflammatory prone environment. Decreased hepatic inflammasome activation was accompanied by reduced neurodegenerative and neuroinflammatory processes. Interestingly, hepatic alterations have been previously described in 6-OHDA treated animals (143) and it was suggested that brain-liver axis may intervene in a feedforward loop in which neurodegeneration caused hepatic alteration that in turn exacerbated neurodegeneration. Inflammasome components have not been evaluated in this study but could represent an important mediator in peripheral-to-central transmission of inflammation and vice versa. Interestingly, BMDM isolated from animals receiving hepatic inhibitory vectors displayed reduced release of IL-1 β and caspase 1 in the absence of changes in NLRP3 expression suggesting an indirect effect produced by hepatic inhibition.

positive or negative, were observed in monocytes from PD patients and control subjects, respectively (230). SNPs in the HLA-DR region have been associated with increased risk of developing PD (39, 225, 231, 232). The combination of specific HLA polymorphisms and pesticide exposure seem to favor the induction of a more pro-inflammatory-prone CD4⁺ activation (233). Thus, LRRK2 may be an important factor that intervenes at the immune interface and may favor a pro-inflammatory-prone environment in PD patients as well as in animal models (Figure 2).

PD Animal Models

LRRK2 deficient rats show significantly increased percentage of CD4⁺ and CD3⁺ cells, but not CD8⁺ in the spleen, as well as a reduced percentage of B cells compared to wild type animals (234). Interestingly, LRRK2 KO rats challenged with α -syn overexpression or intracerebral LPS administration are protected from neurodegeneration normally occurring in wild type animals (235). Transgenic mice overexpressing pathogenic LRRK2 mutations, R1441G or G2019S, do not normally present any evidence of neuronal cell loss or neuroinflammation in the SNc. Recently, Kozina and collaborators showed that systemic LPS-induced inflammation triggered significant loss of TH-positive cells only in mice overexpressing a mutant form of the human LRRK2 protein (236). No neurodegeneration was induced by LPS in mice overexpressing the human wild type LRRK2 protein, strongly suggesting a role of LRRK2 mutations in pathological mechanisms leading to cell loss. Interestingly, no lymphocyte infiltration was detected in transgenic LRRK2 mutant animals. Analysis of peripheral immune reaction indicated that systemic LPS administration in the context of mutant LRRK2 triggered significant increase in peripheral cytokines that exacerbated neuroinflammation in the brain, increased LRRK2 expression in neurons and caused neurodegeneration. Interestingly, time-dependent increase of peripheral expression of numerous immune factors, including IL-1 β , IL-6, IL-10, RANTES, CXCL1, were detected in LPS-treated mutant LRRK2 mice factors. These factors are reminiscent of alterations observed in the blood of PD patients (see the section "Inflammatory markers" above).

DISCUSSION

The etiology of PD pathogenesis is still largely unknown, and evidence strongly indicates that combinations of multiple factors are involved in triggering neurodegeneration. Neuroinflammation and systemic inflammation have been implicated in PD pathogenesis and appear as key aggravating factors. Yet it remains unknown if inflammation and immune dysfunctions mediate PD or if PD mediate immune dysfunction in both peripheral and central systems. Evidence obtained from patients and animal models of the disease gives clues of pathological alterations but does not as yet clearly answer this question.

Our current knowledge on pathological mechanisms involved in PD etiology and progression in humans is a consequence of the limited access to *in vivo* brain data. Cerebral imaging, while

rapidly evolving in more powerful tools, has yet failed to give clear cut correlations between central dysfunctions and disease stage or progression, or with peripheral biological markers. Notwithstanding the development of improved radioligands for *in vivo* PET analyses, a clear understanding of the role of neuroinflammation in PD progression is still lacking. The comprehension of the complex nature of microglia cells, which can embrace a diversity of phenotype throughout the course of the disease, has guided the development of therapeutic strategies that would help mitigate their deleterious effect and modulate them toward a more "protective" phenotype rather than just inhibiting microglia activation. Exenatide, a GLP-1 receptor agonist, is a perfect example of a promising therapeutic alternative that may slow down disease progression through modulation of inflammation and neuroinflammation. GLP-1 receptors are highly expressed in microglia (237). In animals, exenatide has been shown to reduce MPTP-induced activation of microglia as well as the levels of inflammatory molecules including TNF- α and IL- β (238). Similar effects have been obtained in the rotenone model (239). The molecule, already available in the market for the treatment of insulin-resistant diabetes, has rapidly advanced in clinical trials for PD treatment. After a positive proof of concept open-label study that suggested significant improvement in both motor and non-motor PD features (240), researchers moved to a double-blind, placebo-controlled trial (241). Results indicate a significant improvement in motor scores in exenatide treated patients vs. the placebo group. Improvement in non-motor symptoms have also been reported for the same patients (242, 243). While the action of exenatide and how it may slow down PD progression is not clear, a recent evidence indicates that another GLP-1 agonist, NLY01, may limit microglia activation and reduce release of inflammatory molecules thus limiting neuroinflammation.

Preclinical models, in particular MPTP-treated mice, have also been used to evaluate the effect of minocycline, a tetracycline derivative, and showed that the molecule also possess anti-inflammatory properties, reducing microglia activation and IL-1 β production in the SN (244). NET-PD FS 1, a futility trial in early untreated PD patients suggested that prolonged minocycline treatment caused no major safety concerns (245). Another antibiotic tetracycline molecule, doxycycline, has also shown promising results in animal models of PD, including 6-OHDA-treated mice (246), the LPS rat model (247). Doxycycline effect is associated with reduced microglia activation and may regulate inflammasome signaling (248). Today, large efforts are being made to modify the tetracycline molecules and separate their antimicrobial and anti-inflammatory properties to reduce any bacterial resistance that may occur after chronic use of antibiotics.

The inflammasome and its importance in neurodegenerative disease has attracted a lot of attention in the past years. All animal models of PD present upregulated levels of IL-1 β both in peripheral and central compartment (Figure 3) and IL-1 β is a major downstream activator of the inflammasome. Evidence indicates that blocking inflammasome with a small molecule called MCC950, which can readily cross the BBB,

reduced Il-1 β and caspase 1 levels and neurodegeneration in 6-OHDA animals and improved motor features in treated animals (249). MCC950 is being developed by a drug company that is hoping to start a Phase 1 clinical trial to determine the safety features in humans. Interestingly, many natural compounds with known anti-inflammatory properties have inhibitory activities on various components of the NLRP3 inflammasome pathway. Curcumin, resveratrol, and quercetin have all been shown to reduce levels of caspase-1 and Il-1 β (250–252).

To date, most brain data still refer to postmortem pathology and thus only give a snapshot information, at a given and often advanced disease time point, on processes that may have been ongoing and have been evolving for years or decades. In the search for therapies that may slow down disease progression it is important to grasp the evolution of pathological mechanisms that are likely different at different disease stages. Current challenges and unmet needs in PD is the development of biomarkers that allow assessing ongoing dysregulated process in humans. Animal models largely contribute to the current knowledge of peripheral and central dysregulations that accompany neuronal cell loss. Numerous animal models have been developed in different organisms (25). While none of them fully recapitulate the multifactorial deficits observed in humans, they have, in particular, toxic transgenic rodent models, greatly helped address unanswered questions and are ideal for studying early and progressive neurodegenerative processes.

The perfect animal model that recapitulates all PD features does not exist. Yet animal models allow the evaluation of relevant genetic and environmental factors involved in PD pathology. Many immune alterations detected in PD patients have also been observed in animal models (see **Figures 1–3**). They have the advantage of presenting a homogeneous population, all individuals sharing identical genotype, and because they show high anatomical and physiological similarities to humans, they can be readily analyzed to understand the interrelationships and crosstalk between different body compartments. Importantly, animal models allow for relatively easy longitudinal studies. To date, few studies have assessed alterations in systemic compartments in available models. In the future, more systematic time-course evaluations of potential changes in peripheral immune factors are warranted. Similarly, the crossing of existing transgenic models or the combination of genetic and environmental factors in models to generate multiple hit triggers, will improve our knowledge on peripheral-central inflammation crosstalk.

Similarly, studies on patients have mostly concentrated on single point evaluation of immune alterations. Post-mortem studies give clear but static indication of late stage neuroinflammation alterations in PD brain, including infiltration of T or B lymphocytes infiltration or microglial activation. Similarly, analyses of levels of soluble factors and immune cells describe alterations at single time points. These studies have generated valuable information and have advanced our knowledge and understanding of PD. Yet, they represent a time point snapshot and barely or do

not take into account the progressive nature of PD or the heterogeneity of the PD patient population. Longitudinal studies and patient stratification are desperately needed to gain a more comprehensive understanding of PD pathogenesis and disease progression.

In the past decades, biorepository resources and studies that allow collecting, processing, storing and distributing biospecimens have been developed to support research. These include the BioFIND study (completed in 2015), the Parkinson's Progression marker Initiative (PPMI), the Parkinson's Disease biomarker program (PDBP), the De Novo Parkinson (DeNoPa) in Germany, the ICEBERG study in France, the Norwegian Parkwest study, COPPADIS 2015 in Spain, the Oxford Parkinson's disease Centre and many more. These repositories aim at establishing a comprehensive follow up and collection of bio samples that will permit a better understanding of factors involved in disease progression, in particular in immune systems. The parallel development of both more precise imaging markers and more potent imaging equipment will allow a more precise *in vivo* quantification of neuroinflammatory processes, in particular microglial activation, that take place in affected brain structures, and allow correlation of ongoing immune alterations taking place in the brain and in peripheral systems.

CONCLUSION

In the past decades, the development of animal models of PD has greatly contributed to expand our understanding of the disease. Animal models, transgenic, toxin- or viral induced, permit the analyses of more specific pathways and their impact on PD genotype. Today, the role of inflammation and neuroinflammation in the etiology and progression of PD, as well as the knowledge that both must closely interact is well-accepted. However, our understanding on how they communicate and combine to trigger and sustain neuronal cell death still needs to be refined. Comparing longitudinal data from patients and models will help us unravel the complicated mechanisms involved in peripheral-central inflammation crosstalk and open new ways of developing alternative therapeutic strategies to slow down disease progression.

DATA AVAILABILITY

All datasets generated for this study are included in the manuscript and/or the supplementary files.

AUTHOR CONTRIBUTIONS

MF-A reviewed the literature and wrote the first draft of the manuscript. SC and FB reviewed the literature and critically reviewed the manuscript.

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