



# Neurodegeneration and Neuroinflammation in Parkinson's Disease: a Self-Sustained Loop

G. Arena<sup>1</sup> · K. Sharma<sup>2</sup> · G. Agyeah<sup>1</sup> · R. Krüger<sup>1,3,4</sup> · A. Grünewald<sup>1,5</sup> · J. C. Fitzgerald<sup>2</sup>

Accepted: 2 May 2022 / Published online: 8 June 2022  
© The Author(s) 2022

## Abstract

**Purpose of Review** Neuroinflammation plays a significant role in Parkinson's disease (PD) etiology along with mitochondrial dysfunction and impaired proteostasis. In this context, mechanisms related to immune response can act as modifiers at different steps of the neurodegenerative process and justify the growing interest in anti-inflammatory agents as potential disease-modifying treatments in PD. The discovery of inherited gene mutations in PD has allowed researchers to develop cellular and animal models to study the mechanisms of the underlying biology, but the original cause of neuroinflammation in PD is still debated to date.

**Recent Findings** Cell autonomous alterations in neuronal cells, including mitochondrial damage and protein aggregation, could play a role, but recent findings also highlighted the importance of intercellular communication at both local and systemic level. This has given rise to debate about the role of non-neuronal cells in PD and reignited intense research into the gut-brain axis and other non-neuronal interactions in the development of the disease. Whatever the original trigger of neuroinflammation in PD, what appears quite clear is that the aberrant activation of glial cells and other components of the immune system creates a vicious circle in which neurodegeneration and neuroinflammation nourish each other.

**Summary** In this review, we will provide an up-to-date summary of the main cellular alterations underlying neuroinflammation in PD, including those induced by environmental factors (e.g. the gut microbiome) and those related to the genetic background of affected patients. Starting from the lesson provided by familial forms of PD, we will discuss pathophysiological mechanisms linked to inflammation that could also play a role in idiopathic forms. Finally, we will comment on the potential clinical translatability of immunobiomarkers identified in PD patient cohorts and provide an update on current therapeutic strategies aimed at overcoming or preventing inflammation in PD.

**Keywords** Parkinson's disease · Inflammation · Gut microbiome · Protein aggregation · Mitochondrial dysfunction

---

This article is part of the Topical Collection on *Genetics*

---

✉ G. Arena  
giuseppe.arena@uni.lu

<sup>1</sup> Luxembourg Center for Systems Biomedicine (LCSB),  
University of Luxembourg, Esch-sur-Alzette, Luxembourg

<sup>2</sup> Department of Neurodegenerative Diseases, Hertie Institute  
for Clinical Brain Research, University of Tübingen,  
Tübingen, Germany

<sup>3</sup> Transversal Translational Medicine, Luxembourg Institute  
of Health, Strassen, Luxembourg

<sup>4</sup> Centre Hospitalier de Luxembourg (CHL), Luxembourg,  
Luxembourg

<sup>5</sup> Institute of Neurogenetics, University of Lübeck, Lübeck,  
Germany

## Introduction

Parkinson's disease (PD) is characterized by the cardinal signs of the movement disorder such as tremor and postural instability, as well as the histopathological hallmarks of alpha-synuclein ( $\alpha$ -syn) accumulation and loss of dopaminergic neurons in the *substantia nigra* (SN). Aggregated  $\alpha$ -syn is the main component of Lewy bodies, which are proteinaceous neuronal inclusions found in the SN of PD brains [1, 2]. PD is clinically, pathologically and genetically heterogeneous, and the absence of LBs in some genetic cases has led to an ongoing discussion about the overlap between PD, parkinsonism and other neurodegenerative diseases. Other brain pathologies in PD include vascular pathology [3, 4], gliosis [5•] and brain lesions [6, 7].

Finding causative treatments for PD is a major challenge because the underlying pathobiology is complex, multifactorial and may differ from person to person. This has led researchers to explore whether there are common or converging pathways that could be exploited for pharmacological intervention (e.g. kinase activity, protein aggregation and inflammation). But there are further challenges; most of the dopaminergic neurons in the SN are often already lost at the point of clinical presentation, and therefore a lot of effort is being put into early disease detection and reliable biomarkers. Finally, many known PD pathomechanisms do not specifically affect the dopaminergic neurons of the SN and in some cases—including inflammation—are associated with a plethora of other diseases such as dementia, irritable bowel syndrome (IBS) and diabetes [8–10]. Today, dopamine replacement is still the mainstay treatment for PD, and the disease prevalence is drastically rising [11]. Finding causative treatments may reduce the disease prevalence or improve prognosis. Identification of markers at different stages of disease progression in different patient subtypes would help in predicting causative agents and drastically help in the search for a treatment strategy.

In the following sections, we will summarize current mechanistic concepts on the role of inflammation in PD. Based on the evidence provided by monogenic forms, we will first review the main cellular dysfunctions and molecular determinants that locally trigger CNS inflammation; moreover, we will examine more closely the pathophysiological mechanisms and metabolites that control peripheral dysbiosis-induced inflammation and their contribution to the development of PD. Finally, we will discuss potential controversies and provide future directions with a focus on the emerging fields, biomarkers and therapeutic strategies.

## Inflammation in PD

Sustained inflammatory processes are largely recognized as major patho-etiological mechanisms underlying neurodegeneration [12]. In contrast to acute inflammation, which is usually beneficial and contributes to the immediate repair of brain tissues exposed to various environmental insults (e.g. traumatic injury, viral infection, toxins), chronic inflammation is typically associated to the development and progression of neurodegenerative disorders [13]. Whether there is a trigger for neuroinflammation in PD is not fully understood, but conditions such as  $\alpha$ -syn misfolding [14, 15], polymorphisms in immune-related genes [16, 17] and mitochondrial dysfunction [18, 19] have been suggested.

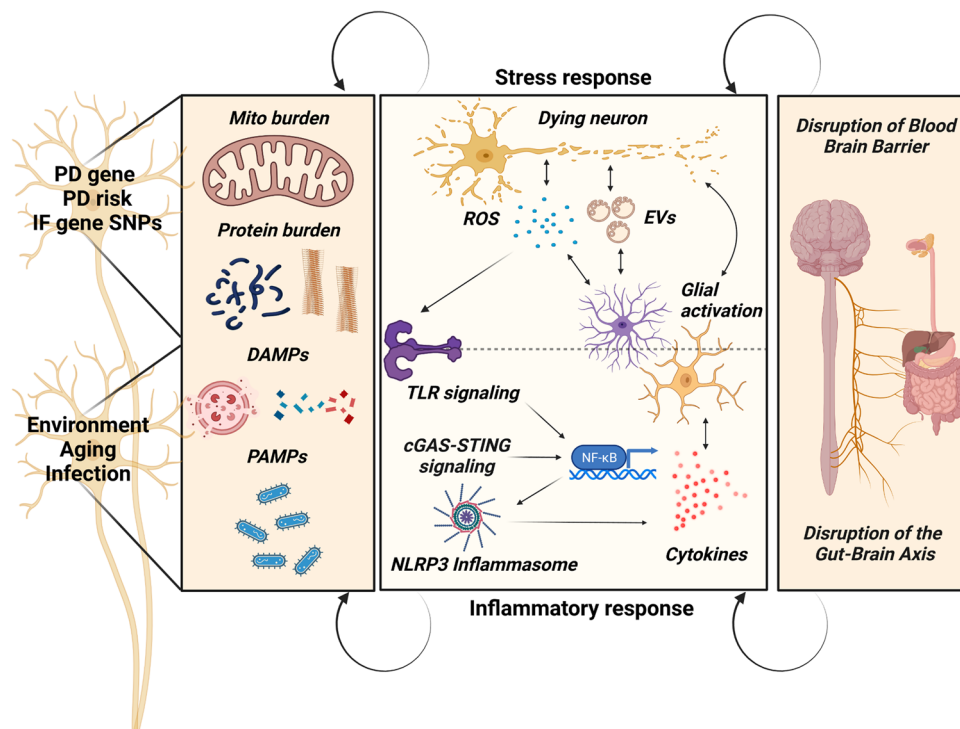
The thin line between the physiological role of acute neuroinflammation and the pathological consequences of persistent neuroinflammatory responses is defined by the activity of multiple cell types involved in both innate and adaptive

immunity [20]. These include not only the central nervous system (CNS)-resident glial cells (i.e. microglia, astrocytes and oligodendrocytes), but also peripheral circulating myeloid cells (i.e. monocytes, macrophages and dendritic cells) and T lymphocytes that actively participate to the neuroinflammatory process by infiltrating into the brain [21]. Mechanistically, following neuronal damage, the CNS-resident glial cells release signaling molecules (i.e. cytokines, chemokines, growth factors and other metabolites) that attract peripheral myeloid cells to the site of injury; in turn, myeloid cells have the ability to recruit other immune cells (T lymphocytes) within the CNS, thus amplifying the inflammatory response [22, 23]. Of note, not only glial cells, but also neurons can directly release inflammatory mediators that activate immune cells. This is a crucial notion to take into account to understand the temporal sequence of events (neurodegeneration vs neuroinflammation) that lead to irreversible cell death in PD. In fact, cell autonomous alterations inside SNpc DA neurons (e.g. mitochondrial dysfunction, defective protein clearance,  $\alpha$ -synuclein release) can trigger, via the secretion of signaling molecules, an inflammatory response in the surrounding microenvironment or even at a systemic level, affecting other neuronal and non-neuronal cell types involved in the neuroinflammatory process [24•, 25] (Fig. 1).

## Environmental Triggers of Immune Response—the Gut Microbiome

It is worth noting that neuroinflammation-induced DA loss can be also triggered by peripheral non-cell autonomous mechanisms, as well illustrated by activation of the immune system in response to abnormalities in the gut microbiota [26]. A close connection between the CNS and the gut has been extensively described, the so-called gut-brain axis, and dysbiosis-induced inflammation could even represent the primary cause of neurodegeneration based on recent studies [6, 27•, 28, 29]. In PD, gastrointestinal symptoms such as constipation and increased gut membrane permeability often precede the motor symptoms, raising the possibility that gut inflammation triggered by a pathogen could play a role in the onset and progression of PD pathogenesis [30, 31].

If, on the one hand, brain can regulate gut activity through the parasympathetic and sympathetic nervous systems, by means of hormones and neurotransmitters that control digestive secretions and gut motility, on the other hand the gut microbiota also produces molecules able to influence activity of the host immune system and CNS function [32, 33]. Among these, pathogen-associated molecular patterns (PAMPs), including, e.g. bacterial lipopolysaccharides (LPS), peptidoglycans, CpG oligonucleotides and viral double-stranded RNAs (dsRNAs), can trigger the innate immune system by acting as ligands for the corresponding



**Fig. 1. Sustained loop of neurodegeneration and inflammation in Parkinson's disease.** Parkinson's disease (PD) gene mutations, PD-associated gene variants (PD risk), inflammatory gene single nucleotide polymorphisms (IF gene SNPs) plus environmental factors such as infection and aging can all trigger stress responses (upper, middle panel) and inflammatory responses (lower, middle panel) via mitochondrial damage (overall mitochondrial burden), protein burden (including impaired proteostasis but also impaired function) and the

damage associated molecular patterns (DAMPs) as a result. Pathogen associated molecular patterns (PAMPs) also contribute to the triggering of stress and inflammatory responses. These self-supporting responses create a loop that facilitates further inflammatory signaling coupled with glial activation, production of reactive oxygen species (ROS) and changes to extracellular vesicle (EVs) release, which aggravates neuronal pathology. Disruption of the blood-brain barrier and gut-brain axis can further aggravate the self-sustained loop

pattern recognition receptors (PRRs) on the surface of host cells [33]. PRRs are usually members of the Toll-like receptor (TLR) family, expressed on the plasma membrane of several cell types, including gut epithelial cells, myeloid cells, T lymphocytes, neurons and glial cells [34]. Under homeostatic conditions, a balanced gut microbiota results in a fine-tuned activation of TLR signaling in the gut epithelial cells, preventing induction of inflammatory pathways and maintaining the gut barrier intact. Conversely, modifications in the composition of microorganisms that populate the gut, also known as dysbiosis, may lead to dysregulated TLR signaling, persistent production of proinflammatory cytokines and disruption of the gut epithelial barrier. In turn, this results in a leakage of microbial-derived products and inflammatory mediators into the bloodstream, through which they can cross the blood-brain barrier (BBB) and finally reach the brain [34] (Fig. 1). Of note, in PD as well as in other brain diseases, neuroinflammation also dampens BBB integrity, making it more porous to substances, including toxins and bacterial metabolites, which may otherwise not be permitted through [35]. Other products of microbial metabolism, such as short-chain fatty acids (SCFAs),

tryptophan metabolites and the amyloid *curli*, can have an impact of neuronal activity and modulate neuroinflammation [36–38]. Most SCFAs have anti-inflammatory properties (e.g. butyrate, valerate) and contribute to maintain the integrity of intestinal barrier; as a consequence, a low abundance of SCFA-producing bacteria may cause leakiness of the gut epithelium thus promoting the passage of intestinal pathogens into the bloodstream and systemic inflammation [39, 40]. Accordingly, reduced levels of the SCFA acetate, propionate and butyrate were detected in the stool of PD patients compared to age-matched controls and paralleled by a decreased amount of SCFA-producing bacteria, in particular from the families *Prevotellaceae* and *Lachnospiraceae* [40, 41]. In support of these observations, transplantation of fecal microbiota from healthy donors as well as butyrate supplementation improved dopamine deficiency and motor impairment in different animal models of PD [38]. In parallel, we and others recently reported increased levels of *Lactobacillus*, *Christensenella* and *Akkermansia* in stool samples from PD patients [40]. Higher levels of *Akkermansia* could account for most of the metabolic alterations we predicted based on the different microbiota composition

between healthy individuals and PD cases [41]. The neurotransmitter gamma-aminobutyric acid (GABA), the amino acid methionine and hydrogen sulfide ( $H_2S$ ) are the microbial metabolites with the highest predicted secretion potential we found [41]. To this regard, it is worth noting that GABA receptors have been found not only in the CNS but also in the ENS, where they could transduce signals regulating gastric motility and secretion. Importantly, GABAergic dysfunctions have been reported both in prodromal PD (mostly linked to gastrointestinal symptoms) and at later disease stages, but GABA contribution to neurodegeneration is still debated, as demonstrated by multiple studies showing controversial results [42, 43]. Interestingly, our study also highlighted a higher abundance of *Bifidobacteria* but only in constipated PD cases, thus suggesting a link between microbiota composition and intestinal non-motor symptoms in PD [41]. Of note, also pathogens that belong to the families *Enterococcaceae* and *Enterobacteriaceae* significantly increased in fecal samples from PD patients, and this positively correlated with disease duration and severity [44, 45]. Last but not the least, *Helicobacter pylori* infection has been also associated to an increased risk to develop PD. Indeed, *H. pylori*-positive PD patients displayed higher mortality rate and motor dysfunction compared to healthy controls, a clinical phenotype significantly improved following *Helicobacter* eradication [46].

### The Role of Microglia

Different from macroglia (e.g. astrocytes, oligodendrocytes), which arise from the neuroectoderm as do neurons, microglia arise from the peripheral mesoderm [13]. Microglia are the most relevant CNS-resident immune cells (mononuclear phagocytes) of the brain. While at rest, they are involved in synaptic pruning and remodeling thereby regulating brain connectivity [47]. By contrast, in case of a pathological insult, microglia change their morphology into an amoeboid shape and start to secrete inflammatory cytokines (activated state) [47]. Activated microglia engulf debris from surrounding cells such as degenerating dopaminergic neurons [47]. Accordingly, microgliosis is a typical histopathological hallmark of PD that was discovered as early as in 1988 [48]. The upregulation of proinflammatory enzymes and cytokines creates a microenvironment that is hostile for the survival of neurons [49, 50]. By contrast, it remains uncertain whether microgliosis is purely a consequence of neuronal demise in PD or whether microglial dysregulation can trigger neurodegeneration in the first place. In support of the latter hypothesis, PET studies using the 11C-(R)-PK11195 ligand that specifically binds to active microglia revealed that microgliosis can be observed during the early stages of the disease [51]. Recent advances in our understanding of the complex

interplay between glia and neuronal cells in PD have come from single-cell studies [52, 53, 54, 55•]. Assessing the cellular diversity in murine brain tissue revealed an unexpected glial heterogeneity. Comparing mouse striatum and midbrain sections, the authors identified a microglia cluster with an “activated signature” specifically in the latter tissue. These cells overexpressed inflammatory genes as well as antigen presenting cell markers and shared transcriptional features of reactive microglia [53]. Recently, we also demonstrated, by means of single-nuclei sequencing, a specific upregulation of microglia in the midbrain tissue from sporadic PD (sPD) patients compared to controls [55•]. In particular, pseudo-time ordering identified an activation trajectory that branches out from resting microglia into two activated subpopulations—cells overexpressing *GPNMB* or such with high levels of *HSP90AA1* and *IL1B*. In addition, quantitative imaging analysis of sPD and control midbrain sections revealed a reduction in microglial branching exclusively in the SN of PD patients [55•]. Further strengthening the role of microglia in neurodegeneration, we observed an enrichment of PD risk variants specifically in these cells [55•]. Thereby the strongest association was detected for the PD-associated protein LRRK2, which has been intensively studied in the context of inflammation in PD as detailed in the coming sections. In light of the recent development of human microglial differentiation protocols, the findings from human post-mortem tissue can now be validated and extended in induced pluripotent stem cell (iPSC)-derived models.

### Evidence from Genetic PD

The inheritance of specific gene mutations in autosomal dominant (e.g. SNCA, LRRK2) and autosomal recessive (e.g. PINK1, PRKN, DJ-1) manner has been associated with the development of familial PD. PD caused by a known alteration to a single gene is collectively referred to as monogenic PD and accounts for about 10–15% of cases [56]. Most cases of PD have no known cause and are named ‘sporadic’ or ‘idiopathic’ PD (sPD). However, this terminology is currently being challenged, due to the involvement of gene variants or common genetic risk factors (e.g. GBA) in PD onset and progression [57]. The large body of mechanistic evidence suggesting that inflammation plays a significant role in PD pathogenesis has mostly come from studies of monogenic forms of the disease, where the emerging topics are aggregation or buildup of toxic proteins (including insoluble  $\alpha$ -syn) in the brain as a trigger of inflammatory responses and wild-type PD proteins protecting dopaminergic neurons by suppressing inflammation in the surrounding cells.



## SNCA

Duplication, triplication and point mutations in *SNCA*, the gene which codes for  $\alpha$ -syn, are equally linked with late and early onset PD [58].  $\alpha$ -syn is a small protein capable of binding to membranes via its N-terminus. In the brain, the function of  $\alpha$ -syn is to aid neurotransmission via the regulation of the synaptic vesicles and synaptic membranes [59]. In contrast, insoluble aggregates of  $\alpha$ -syn, which are also a feature of sporadic PD, can trigger neuroinflammation [60]. Not only aggregation, but also the overexpression and post-translational modifications (e.g. nitration) of  $\alpha$ -syn are linked to sustained microglial activation [61–66], an effect likely mediated by the NF $\kappa$ B and MAPK signaling pathways [64, 67]. Accordingly, the levels of neuroinflammatory markers, TNF, ICAM, IL-6 and IL-1 $\alpha$ , are increased in the *SN* of mouse brain overexpressing  $\alpha$ -syn [66]. Other studies have shown an activation of NLRP3 inflammasome in distinct  $\alpha$ -syn PD models, including primary monocytes and primary microglia exposed to fibrillar  $\alpha$ -syn, mouse striatum subjected to 6-OHDA treatment,  $\alpha$ -syn pre-formed fibrils (PFF)-injected mice, post-mortem *SN* sections from PD brains and also blood and CSF samples from PD patients [68, 69, 70•]. Conversely, Piancone et al. recently showed that neither monomeric nor aggregated  $\alpha$ -syn significantly activated the NLRP3 inflammasome in peripheral blood mononuclear cells (PBMCs) from PD patients [71]. Recent studies suggested that  $\alpha$ -syn aggregation at nerve terminals as well as its capability to leave the cell into exosomes can trigger neuroinflammation and could be used as a potential biomarker for early PD diagnosis and a prognostic tool for disease progression [72, 73].

Interestingly, also  $\alpha$ -syn silencing may cause neuroinflammation, suggesting that not only excessive  $\alpha$ -syn concentrations but also perturbation of physiological  $\alpha$ -syn levels could support PD pathogenesis [74].

## LRRK2

Mutations in LRRK2 can cause autosomal dominant PD [75, 76]. LRRK2 is known to phosphorylate substrates in the endosomal-lysosomal pathway. The expression of LRRK2 is increased in monocytes activated by IFN $\gamma$ , suggesting that it could play a role in monocyte maturation [77]. LPS-treated R1141G LRRK2 transgenic mice showed increased secretion of pro-inflammatory TNF $\alpha$ , IL-1b and IL-6, as well as a decreased expression of anti-inflammatory IL-10. mRNA levels of the pro-inflammatory cytokines TNF, IL-1, IL-12, CCL4, CXCL1, CCL3L1 were also increased, suggesting an upstream regulation by LRRK2 [78].

Higher LRRK2 kinase activity has been shown to be detrimental in normal cellular processes. The expression and kinase activity of LRRK2 were increased in LPS-treated

lymphoblasts. LPS-dependent activation of TLR signaling pathway, increase in LRRK2/TRAF6 interaction and increased phosphorylation of both MAPK and I $\kappa$ B were reduced upon treatment with a LRRK2 inhibitor, leading to reduced TNF $\alpha$  secretion and thus confirming the involvement of LRRK2 in the generation of pro-inflammatory responses in lymphoblasts [79•].

## PINK1 and Parkin

Mutations in the *PARK6* gene encoding PINK1 can cause autosomal recessive PD [80]. PINK1 phosphorylates ubiquitin, regulates mitochondrial quality control and plays a key role in mitophagy (the removal of damaged mitochondria from cells). PINK1 is involved in the recruitment of cytosolic Parkin to damaged mitochondria [81]. Mutations in the *PARK2* gene encoding Parkin also cause autosomal recessive PD [82]. Parkin is an E3-ubiquitin ligase that is responsible for the ubiquitylation and degradation of mitochondrial proteins and the recruitment of autophagy receptors that facilitate the removal of damaged mitochondria during mitophagy [83]. Parkin is known to regulate oxidative stress and maintain mitochondrial function within the cell and, together with PINK1, was originally shown to provide neuroprotection by activating the NF $\kappa$ B transcription factor that regulates immune response among others [84–87]. However, both increased and reduced activation of NF $\kappa$ B signaling have been observed in PINK1 KO mice and mouse macrophage cultures subjected to PINK1 knockdown [88, 89]. Parkin also suppresses inflammation by degrading TRAF2/6 and preventing the activation of NF $\kappa$ B and JNK signaling pathways [90]. Of note, many of these studies have shown that downregulation of either PINK1 or Parkin does not induce inflammation unless an external stressor like LPS or IFN $\gamma$  is applied [85, 88, 91]. Several studies have suggested that wild type PINK1 inhibits peripheral inflammation [92], and both PINK1 and Parkin repress mitochondrial antigen presentation thereby preventing adaptive inflammation [93]. Accordingly, PINK1 deficiency triggers an innate immune response mediated by mitochondrial dysfunction and a dysregulation in anti-microbial defense mechanisms [94]. When subjected to exhaustive exercise, both PINK1- and Parkin-deficient mice trigger the pro-inflammatory cGAS-STING mediated Type-1 interferon response to foreign DNA [95•], resulting in increased serum levels of IL-6, IFN- $\beta$ 1, IL-12(p70), IL-13, CXCL1, CCL2 and CCL4 [96]. A similar response was observed in Parkin-KO mice genetically engineered to accumulate high levels of mtDNA mutations (*PARK2*<sup>-/-</sup>; mutator mice). Importantly, these mice display a motor deficit accompanied by the progressive loss of *SN* DA neurons with age, a phenotype rescued by the loss of STING [96]. Collectively, these findings revealed a functional link between mitophagy impairment caused by

PINK1/Parkin loss and neurodegeneration in PD, which appears to be facilitated by systemic inflammation. Interestingly, reduction of STING pathway did not help to rescue PD phenotypes in Parkin-deficient *drosophila* models [97], highlighting that evidence for inflammation in PD is also subject to species differences. Since PINK1 only accumulates on depolarized mitochondria and substrates of the PINK1/Parkin pathway beyond mitophagy remain elusive, it is unclear by which mechanism PINK1 and Parkin inhibit inflammation under normal conditions. Recent proteomic studies have focused extensively on substrates of the PINK1-Parkin pathway [98], which does not suggest direct interaction with inflammatory proteins at least in human and mouse neurons during mitophagy. Perhaps, the integrity or quality of mitochondria rather than any direct action by PINK1 or Parkin is relevant for inflammation in PD. Underlying mitochondrial burden in sporadic PD may also play a role, involving small effect size variants in multiple nuclear-encoded mitochondrial genes affecting the same downstream molecular network (i.e. PINK1/Parkin-mediated mitophagy).

More recently, it was shown that intestinal infection/dysfunction in PINK1-KO mice and PINK1-mutant flies also leads to neuroinflammation and neurotoxicity [27•, 86]. These studies are important because until this point, researchers struggled to find significant Parkinson phenotypes in PINK1 or Parkin loss-of-function models in vivo. Also, several studies at that time showed that PINK1 and Parkin were not required for basal mitophagy nor in tissues of high energy demand in mice and flies [99–101]. These findings have reignited the discussion about whether PINK1 and Parkin could protect against inflammation via some form of evolved mitochondrial resistance. For example, Parkin was shown to mediate the response of mice to intracellular pathogens already a decade ago [102]. It is possible that the role of Parkin in mitochondrial clearance is tied to its suppression of inflammation via the mtROS-NLRP3 axis [103]. It is not known whether PINK1 (which is thought to act upstream of Parkin) is a necessity for evolved mitochondrial resistance or whether deficient PINK1-Parkin surveillance worsens mitochondrial dysfunction which then aggravates inflammation. The consensus is that the wild type PD proteins PINK1 and Parkin contribute to an overall inflammatory defense. Corti and others have gone further to suggest that the PINK1-Parkin mediated mitochondrial quality control in the glia is particularly important for protecting dopaminergic neurons [104].

## DJ-1

Mutations in DJ-1 cause autosomal recessive PD [105]. DJ-1 has multiple neuroprotective functions, including the regulation of oxidative stress [106], but the link with

inflammation is less clear. In Zebrafish, overexpression of DJ-1 in astrocytes was found to upregulate HMGB1 and Cyclophilin-A [107], which have both anti-inflammatory and pro-inflammatory functions. Proteomic analysis in the brain of DJ-1 knockout (KO) fish revealed downregulation of some inflammatory regulators, including the complement proteins c3a and c3b [108]. RNA sequencing analysis in the midbrain of DJ-1 KO mice also allowed to identify several genes potentially involved in neuroinflammation (e.g. *Parp1*, *Mmp8*, *Hmgn1*, *IL-1*, *Nfkbid*), most of which were significantly upregulated [109•]. Recently, DJ-1 was shown to suppress NFkB signaling by directly interacting with its p65 subunit [110] and to mitigate inflammation mediated by the STING pathway [111]. Finally, a link between DJ-1 and regulation of gut microbiome was also described. In particular, DJ-1 KO mice display a significant increase in *Rikenella* and *Alistipes*, accompanied by higher levels of malonate in stool and serum, and elevated expression of fecal inflammatory proteins calprotectin and MCP-1. Importantly, expression of PD-related inflammatory genes in the midbrain of DJ-1 KO mice was significantly increased, suggesting a possible link between alteration of gut microbiome, metabolism and neuroinflammation in DJ-1 associated PD [109•].

## GBA

Biallelic homozygous and compound heterozygous mutations in the GBA gene are known to cause Gaucher Disease, whereas individuals with heterozygous GBA mutations have a risk to develop PD which is 5 to 20 times higher compared to non-carriers [112, 113].

The GBA gene encodes Beta-glucocerebrosidase (GCase), which helps the breakdown of glucosylceramide into ceramide and glucose into lysosomes [114]. Knocking down GBA leads to  $\alpha$ -syn aggregation, which in turn further impinges on GCase activity [115]. As described above, accumulation of  $\alpha$ -syn itself can trigger a pro-inflammatory response; therefore, one can argue that inflammation observed in GBA-PD is simply mediated by  $\alpha$ -syn pathology and not a direct consequence of GBA mutations. However, two independent studies carried out in mice carrying the homozygous GBA D409V mutation observed no inflammatory response, even in the presence of typical signs of  $\alpha$ -syn pathology [116, 117]. In contrast, specific inhibition of GCase in mice resulted in  $\alpha$ -syn neuropathology and inflammation, as revealed by elevated GFAP levels that are indicative of astrogliosis [118].

## The Importance of Intercellular Transmission

Based on recent studies, the cell-to-cell spreading of  $\alpha$ -syn aggregates, and in particular the fibrillar forms of  $\alpha$ -syn, can trigger an inflammatory response that contributes to

PD progression [68, 119]. In fact,  $\alpha$ -syn fibrils are able to induce the TLR2-NF $\kappa$ B signaling pathway in glial cells, resulting in microglia activation and release of proinflammatory cytokines [119, 120]. Several mechanisms have been proposed which may account for this  $\alpha$ -syn spreading in a “prion-like” manner, including direct diffusion, exocytosis/endocytosis and uptake of EVs/exosomes [121–124]. In a very recent study, Heneka and colleagues showed that  $\alpha$ -syn fibrils were readily taken up by microglial cells in a phagocytosis-dependent fashion and activate a transcriptional program related to pro-inflammatory and proapoptotic pathways [125]. Interestingly, microglial cells were not able to promptly degrade  $\alpha$ -syn aggregates but transferred  $\alpha$ -syn to surrounding cells to reduce the degradation burden, which indeed resulted in improved  $\alpha$ -syn clearance. The authors also demonstrated that, upon  $\alpha$ -syn exposure, the number of intercellular microglial connections (i.e. tunneling nanotubes and gap junctions) dramatically increased, and this was accompanied by efficient transfer of  $\alpha$ -syn aggregates from donor to acceptor cells [125]. In particular, tunneling nanotubes (TNT) seem to play a crucial role in this process, as suggested by impaired  $\alpha$ -syn transfer after treatment with a potent inhibitor of actin polymerization. Importantly, intercellular transfer via TNT also interested mitochondria, which are donated from healthy microglial cells to reduce inflammatory profile and cell death of dysfunctional, fibrillary  $\alpha$ -syn-loaded, microglia. LRRK2 mutation impairs this ‘double-rescue’ strategy, as demonstrated by less efficient redistribution of  $\alpha$ -syn between microglial cells from LRRK2 G2019S mice, thereby amplifying neuroinflammation [125]. Finally, it is worth noting that transfer of fibrillary  $\alpha$ -syn is not restricted to microglia but may also involve other cell types, such as astrocytes. To this regard, Rostami and colleagues recently showed in co-culture experiments that microglia can absorb and clear protein aggregates from the astrocytes [126], thus highlighting the importance of glial cell communication in the development of neuroinflammation and neurodegeneration in PD.

Extracellular vesicles (EVs) are small vesicles secreted by cells. Vesicles can arise from the budding of the endosomal membranes and can either fuse with the lysosome or with the plasma membrane and thereby be secreted into the extracellular space. Once in the extracellular space, they are commonly referred to as exosomes, which have a diameter of ~100nm [127]. EVs can circulate in the periphery (although the presence of neuronal EVs in blood is controversial) and have been shown to be taken up by other cells as a means of cell communication or sequestration of unwanted cargo. EVs are also involved in gene expression and contain non-coding RNA and proteins [127]. The possibility that EVs could harbor damaged or unwanted cargo from neurons in PD has led to extensive research into

peripheral EVs as a potential window into the brain pathologic process [128] and as material for biomarker discovery in PD [129–131].

EVs contain both chromosomal and mitochondrial DNA, and recent work has shown distinct mitochondrial signatures in the EVs of PD patients [132]. Damaged or dysfunctional mitochondria are the main source of damage-associated molecular patterns (DAMPs), which play additional functions outside the organelle and are recognized by the immune system in a similar way to PAMPs (see above). They often stimulate an inflammatory response and any necessary regeneration. DAMPs have long been associated with dead and dying cells but can also arise following cellular stress. Mitochondrial DAMPs induce cytotoxicity, and cells have been shown to use the secretion of harmful molecules via EVs for cell homeostasis. Cytoplasmic release of damaged mitochondria DNA (mtDNA) is an important DAMP that initiates multiple inflammatory pathways, including STING, NLRP3 inflammasome and NF $\kappa$ B signaling [133]. MtDNA can also leave the cell (presumably via EVs) and cause damage to other cells and tissues. There is also a correlation between cell free mtDNA and neurological diseases with the presence of inflammation [134].

## Potential Biomarkers in PD Patient Cohorts

Starting from the 1990s, PD patient cohorts have provided biomaterials for inflammation studies on a large scale, thus allowing researchers to account for differences between individuals in the absence of isogenic controls. Early findings mainly looked at cytokines and other inflammatory markers in the cerebral spinal fluid (CSF) of PD patients, revealing increased levels of IL-1 $\beta$  and IL-6 [135, 136]. By the early 2000s, there were several genetic studies showing that inflammation could play a role in PD, as suggested for instance by the positive association with IL-1 $\beta$  polymorphisms [137, 138]. Based on growing evidence including the pioneering studies showing reactive microglia in the SN of PD patients [48], it has now been accepted that chronic inflammation in the basal ganglia of PD brains can contribute to the progressive loss of dopaminergic neurons.

Despite the early findings, few studies have convincingly shown increased inflammation in sporadic PD patients compared to healthy individuals [14, 139–141], and no inflammatory blood marker has been recommended as a potential biomarker for PD. So far, the most reliable biomarkers are limited to IL-1 $\beta$  and NLRP3 levels in genetic PD models. However, despite their significance, these innate immunity markers are also closely tied to the development of chronic diseases such as type 2 diabetes, obesity, retinal degeneration and other neurodegenerative

diseases including Alzheimer's disease and multiple sclerosis [142], suggesting that inflammation might only facilitate or aggravate PD pathogenesis rather than cause it. This is supported by work on T-cells isolated from PD patients, which are able to recognize  $\alpha$ -syn peptides thus suggesting a role of adaptive immunity in PD [143]. Another study observed a defective meningeal lymphatic drainage in sporadic PD patients [144], known to impair clearance of toxic CSF waste from the brain leading to an aggravated inflammatory response [145].

Studies focused on either genetic risk or monogenic PD have supported the involvement of inflammation, but still no direct or unique inflammation biomarker for PD is evident that could be clinically translated. Increased plasma levels of IL-8, MCP-1, MIP-1-a, IL-1 $\beta$  and TNF $\alpha$  were shown to be associated with GBA-PD compared to sporadic PD [146, 147]. In a separate study, GBA mutation carriers without PD were found to have increased microglial activation compared to age matched healthy controls, suggesting that inflammation could be an early event. However, it cannot be predicted prematurely if the GBA mutation carriers will eventually develop PD. A thorough time course study in these carriers would be beneficial in correlating GBA mutations associated to inflammation to PD [148]. Plasma levels of ferritin, CCL18 and MIP1a were increased in PD patients with biallelic GBA mutations. Nevertheless, they were not increased in GBA-PD patients with heterozygous mutations suggesting that these markers are not promising to predict PD onset [149].

Serum of PD patients with biallelic PINK1 and Parkin mutations have high levels of IL-6 [24•, 96]. Increased circulating cell free levels of mtDNA (discussed as an inflammation trigger) were also observed in PD patients with PINK1 mutations. The study describes IL-6 as a PD state marker and circulating cell free mtDNA as a PD progression marker [24•]. Studies in the serum and cerebral spinal fluid (CSF) of asymptomatic LRRK2 mutation carriers, showing increased levels of IL-1 $\beta$ , PDGF, VEGF and IL-8 compared to healthy controls, have suggested these molecules as pre-clinical markers of PD onset and development [150]. Conversely, another study did not observe any difference in asymptomatic LRRK2 cohort and healthy controls arguing against inflammation as an early event in PD pathogenesis [151]. Interestingly, LRRK2 expression was upregulated in B cells, T cells and CD16 monocytes from sporadic PD patients compared to healthy controls [152], highlighting cell type specificity as an important factor in biomarker studies. Enrichment or separation of immune cells in blood could provide an opportunity to discover good biomarkers for PD even if the markers themselves are not cytokines or inflammatory proteins.

## Conclusions and Future Therapeutic Strategies

In developing useful treatments for PD, one major hurdle is the inconclusive and variable mechanistic data available, especially for sporadic forms of PD, which are difficult to model in vitro. Studies using patient-derived or isogenic iPSC-derived neuronal models as well as 3D brain organoids are still quite limited.

In this respect, focusing on patient-based biosamples and clinical data from large PD cohorts will be crucial for the identification and validation of novel and relevant biomarkers for different stages of PD and subsets of patients.

Overall, there is increasing evidence for the involvement of immune mechanisms and related inflammatory processes in the initiation and/or propagation of the neurodegenerative process in PD. Therefore, future neuroprotective treatment strategies need to account for these mechanistic insights, which are partially already reflected in available epidemiological data. In this context, an increasing body of evidence supported a protective role of anti-inflammatory medication in terms of risk to develop PD. It was shown that regular intake of nonsteroidal anti-inflammatory drugs (NSAID) was associated with a reduced risk for PD [153]. Interestingly, the LRRK2 gene, in which mutations are the most common cause of autosomal dominantly inherited PD, is encoding a protein that is highly expressed in immune cells, including blood cells and microglia. Therefore, it was speculated that the same LRRK2 gene that is also associated with inflammatory bowel disease [154] may modulate inflammatory pathways related to neurodegeneration. Recently, it was shown that indeed the LRRK2-related pro-inflammatory pathway can be modulated by regular NSAID intake. Here, it was shown that the penetrance of PD-linked LRRK2 mutations was reduced based on NSAID treatment [155]. These results may justify first clinical trials examining the potential modulatory effect of NSAID exposure on LRRK2-related PD.

An alternative potentially disease-modifying approach based on the increasing understanding of the role of the microbiome in PD pathogenesis relates to targeting the gut-brain-axis via acting on dysbiosis. It was shown that dysbiosis was associated with alterations of the protective mucus barrier within the gut and may favor the aggregation and propagation of the misfolded PD-associated protein alpha-synuclein [156, 157]. Therefore, interventions that may help to re-equilibrate the altered gut microbiota are currently investigated and include stool transplantation from healthy donors, which may prevent chronic inflammation and finally the pathology related to alpha-synuclein aggregation [156]. In mice, it was shown that indeed stool samples from PD patients can aggravate alpha-synuclein pathology and motor symptoms.



If alpha-synuclein pathology is not only triggered within the brain, but a more systemic degenerative process with contribution from chronic inflammation in the gut and mediated via the peripheral nerve system may play a role, systemic therapies targeting alpha-synuclein were further justified. Indeed, first clinical trials using antibodies raised against human alpha-synuclein are currently underway and may provide access to a causative treatment slowing disease progression in PD [159].

Future studies may integrate different pharmacological and lifestyle interventions aiming at positively modulating chronic inflammation and pathological alpha-synuclein aggregation as tightly interwoven processes in the pathogenesis of Parkinson's disease and may focus on specific patient strata that can be defined genetically (e.g. LRRK2) or based on environmental factors (e.g. dysbiosis) and are enriched for the underlying chronic inflammatory process.

**Funding** Work of GAR is supported by the Luxembourg Fonds National de Recherche (FNR), grant number C21/BM/15850547/PINK1-DiaPDs. KS and JF are supported by Deutsche Forschungsgemeinschaft (DFG, German Research Foundation)—Research Training Group MOMbrane 654651/GRK2364. GAg obtained funding from the FNR within the framework of the i<sub>2</sub>TRON DTU (PRIDE19/14254520/i<sub>2</sub>TRON). Work of RK is supported by the FNR within the following projects MotaSYN (grant number 12719684), MAMaSyn (INTER/LEIR/18/12719318), MiRisk (grant number C17/BM/11676395), i<sub>2</sub>TRON DTU, by the Michael J Fox Foundation and the European Union's Horizon2020 research and innovation program (Orchestra). AG was supported by the FNR within the ATTRACT program (Model-IPD, FNR9631103). In addition, AG and GAR are supported by an FNR CORE grant (MiRisk-PD, C17/BM/11676395).

## Declarations

**Conflict of Interest** Rejko Krüger has received research grants from Fonds National de Recherche de Luxembourg (FNR) as Coordinator of the National Centre for Excellence in Research on Parkinson's disease (NCER-PD), Coordinator of the Study on COvid-19 National survey for assessing Viral spread by Non-affected Carriers (CON-VINCE), received speaker's honoraria and/or travel grants from Abbvie, Bial, Desitin, Medtronic and Zambon, participated as PI or site-PI for industry sponsored clinical trials without receiving honoraria.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

**Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will

need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>.

## References

Papers of particular interest, published recently, have been highlighted as: • Of importance

1. Spillantini MG, Schmidt ML, Lee VM-Y, Trojanowski JQ, Jakes R, Goedert M.  $\alpha$ -Synuclein in Lewy bodies. *Nature*. 1997;388:839–40.
2. Moors TE, Maat CA, Niedereker D, et al. The subcellular arrangement of alpha-synuclein proteoforms in the Parkinson's disease brain as revealed by multicolor STED microscopy. *Acta Neuropathol*. 2021;142:423–48.
3. Rektor I, Goldmund D, Sheardová K, Rektorová I, Michálková Z, Dufek M. Vascular pathology in patients with idiopathic Parkinson's disease. *Parkinsonism & Related Disorders*. 2009;15:24–9.
4. Jellinger KA. Prevalence of cerebrovascular lesions in Parkinson's disease. A postmortem study. *Acta Neuropathol*. 2003;105:415–9.
5. • Kam T-I, Hinkle JT, Dawson TM, Dawson VL. Microglia and astrocyte dysfunction in Parkinson's disease. *Neurobiology of Disease*. 2020;144:105028 **Comprehensive review discussing the implication of glial cells in PD pathogenesis, with a particular focus on monogenic forms.**
6. Braak H, Tredici KD, Rüb U, de Vos RAI, Jansen Steur ENH, Braak E. Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiol Aging*. 2003;24:197–211.
7. Fang E, Fartaria MJ, Ann CN, et al. Clinical correlates of white matter lesions in Parkinson's disease using automated multimodal segmentation measures. *J Neurol Sci*. 2021;427:117518.
8. Zhang X, Svn Z, Liv M, Yang Y, Zeng R, Huang Q, Sun Q. Association between irritable bowel syndrome and risk of Parkinson's disease: a systematic review and meta-analysis. *Front Neurol*. 2021;12:720958.
9. De Pablo-Fernandez E, Goldacre R, Pakpoor J, Noyce AJ, Warner TT. Association between diabetes and subsequent Parkinson disease: a record-linkage cohort study. *Neurology*. 2018;91:e139–42.
10. Liu G, Bao X, Jiang Y, et al. Identifying the association between Alzheimer's disease and Parkinson's disease using genome-wide association studies and protein-protein interaction network. *Mol Neurobiol*. 2015;52:1629–36.
11. Dorsey ER, Bloem BR. The Parkinson pandemic—a call to action. *JAMA Neurol*. 2018;75:9.
12. Walker KA. Inflammation and neurodegeneration: chronicity matters. *Aging*. 2018;11:3–4.
13. Kwon HS, Koh S-H. Neuroinflammation in neurodegenerative disorders: the roles of microglia and astrocytes. *Transl Neurodegener*. 2020;9:42.
14. Chatterjee K, Roy A, Banerjee R, Choudhury S, Mondal B, Halder S, Basu P, Shubham S, Dey S, Kumar H. Inflammasome and  $\alpha$ -synuclein in Parkinson's disease: a cross-sectional study. *Journal of Neuroimmunology*. 2020;338:577089.
15. Puentes LN, Lengyel-Zhand Z, Lee JY, Hsieh C-J, Schneider ME, Edwards KJ, Luk KC, Lee VM-Y, Trojanowski JQ, Mach RH. Poly (ADP-ribose) interacts with phosphorylated  $\alpha$ -synuclein in post mortem PD samples. *Front Aging Neurosci*. 2021;13:704041.

16. Ulhaq ZS, Garcia CP. Inflammation-related gene polymorphisms associated with Parkinson's disease: an updated meta-analysis. *Egypt J Med Hum Genet.* 2020;21:14.
17. Wang J, Liu Y, Liu Y, Zhu K, Xie A. The association between TLR3 rs3775290 polymorphism and sporadic Parkinson's disease in Chinese Han population. *Neuroscience Letters.* 2020;728:135005.
18. Missirolis S, Genovese I, Perrone M, Vezzani B, Vitto VAM, Giorgi C. The role of mitochondria in inflammation: from cancer to neurodegenerative disorders. *JCM.* 2020;9:740.
19. de Oliveira LG, de Angelo YS, Iglesias AH, JPS P. Unraveling the link between mitochondrial dynamics and neuroinflammation. *Front Immunol.* 2021;12:624919.
20. Kannarkat GT, Boss JM, Tansey MG. The role of innate and adaptive immunity in Parkinson's disease. *J Parkinson's Disease.* 2013;3:493–514.
21. MacMahon Copas AN, McComish SF, Fletcher JM, Caldwell MA. The pathogenesis of Parkinson's disease: a complex interplay between astrocytes, microglia, and T lymphocytes? *Front Neurol.* 2021;12:666737.
22. Chitnis T, Weiner HL. CNS inflammation and neurodegeneration. *J Clin Investig.* 2017;127:3577–87.
23. Greenhalgh AD, David S, Bennett FC. Immune cell regulation of glia during CNS injury and disease. *Nat Rev Neurosci.* 2020;21:139–52.
24. ● Borsche M, König IR, Delcambre S, et al. Mitochondrial damage-associated inflammation highlights biomarkers in PRKN/PINK1 parkinsonism. *Brain.* 2020;143:3041–51 **This study reported increased levels of inflammatory biomarkers (IL-6, ccf-mtDNA) in the serum of PD patients carrying homozygous mutations in PINK1 and Parkin, suggesting a causal link between impaired mitophagy and neuroinflammation in PD.**
25. Harms AS, Ferreira SA, Romero-Ramos M. Periphery and brain, innate and adaptive immunity in Parkinson's disease. *Acta Neuropathol.* 2021;141:527–45.
26. Roy Sarkar S, Banerjee S. Gut microbiota in neurodegenerative disorders. *J Neuroimmunol.* 2019;328:98–104.
27. ● Matheoud D, Cannon T, Voisin A, et al. Intestinal infection triggers Parkinson's disease-like symptoms in Pink1<sup>-/-</sup> mice. *Nature.* 2019;571:565–9 **This study demonstrated that bacterial infection in the gut of PINK1 knockout mice is able to trigger autoimmune mechanisms that lead to neuroinflammation and human-like L-DOPA responsive parkinsonism. Altogether, these findings highlight the importance of the gut-brain axis in PD pathogenesis, with intestinal infection acting as a primary event.**
28. Kim S, Kwon S-H, Kam T-I, et al. Transneuronal propagation of pathologic  $\alpha$ -synuclein from the gut to the brain models Parkinson's disease. *Neuron.* 2019;103:627–641.e7.
29. Van Den Berge N, Ferreira N, Gram H, et al. Evidence for bidirectional and trans-synaptic parasympathetic and sympathetic propagation of alpha-synuclein in rats. *Acta Neuropathol.* 2019;138:535–50.
30. Fasano A, Visanji NP, Liu LWC, Lang AE, Pfeiffer RF. Gastrointestinal dysfunction in Parkinson's disease. *Lancet Neurol.* 2015;14:625–39.
31. Wallen ZD, Appah M, Dean MN, Sesler CL, Factor SA, Molho E, Zabetian CP, Standaert DG, Payami H. Characterizing dysbiosis of gut microbiome in PD: evidence for overabundance of opportunistic pathogens. *npj Parkinsons Dis.* 2020;6:11.
32. Sharon G, Sampson TR, Geschwind DH, Mazmanian SK. The central nervous system and the gut microbiome. *Cell.* 2016;167:915–32.
33. Zhu S, Jiang Y, Xu K, Cui M, Ye W, Zhao G, Jin L, Chen X. The progress of gut microbiome research related to brain disorders. *J Neuroinflammation.* 2020;17:25.
34. Semin I, Ninnemann J, Bondareva M, Gimaev I, Kruglov AA. Interplay between microbiota, toll-like receptors and cytokines for the maintenance of epithelial barrier integrity. *Front Med.* 2021;8:644333.
35. Galea I. The blood–brain barrier in systemic infection and inflammation. *Cell Mol Immunol.* 2021;18:2489–501.
36. Wang C, Lau CY, Ma F, Zheng C. Genome-wide screen identifies curli amyloid fibril as a bacterial component promoting host neurodegeneration. *Proc Natl Acad Sci USA.* 2021;118:e2106504118.
37. Kaur H, Bose C, Mande SS. Tryptophan metabolism by gut microbiome and gut-brain-axis: an in silico analysis. *Front Neurosci.* 2019;13:1365.
38. Silva YP, Bernardi A, Frozza RL. The role of short-chain fatty acids from gut microbiota in gut-brain communication. *Front Endocrinol.* 2020;11:25.
39. Luu M, Pautz S, Kohl V, et al. The short-chain fatty acid pentanoate suppresses autoimmunity by modulating the metabolic-epigenetic crosstalk in lymphocytes. *Nat Commun.* 2019;10:760.
40. Huang Y, Liao J, Liu X, Zhong Y, Cai X, Long L. Review: The role of intestinal dysbiosis in Parkinson's disease. *Front Cell Infect Microbiol.* 2021;11:615075.
41. Baldini F, Hertel J, Sandt E, et al. Parkinson's disease-associated alterations of the gut microbiome predict disease-relevant changes in metabolic functions. *BMC Biol.* 2020;18:62.
42. Song Y, Gong T, Xiang Y, Mikkelsen M, Wang G, Edden RAE. Single-dose L-dopa increases upper brainstem GABA in Parkinson's disease: a preliminary study. *J Neurol Sci.* 2021;422:117309.
43. Błaszczyk JW. Parkinson's disease and neurodegeneration: GABA-collapse hypothesis. *Front Neurosci.* 2016. <https://doi.org/10.3389/fnins.2016.00269>.
44. Scheperjans F, Aho V, Pereira PAB, et al. Gut microbiota are related to Parkinson's disease and clinical phenotype. *Mov Disord.* 2015;30:350–8.
45. Li W, Wu X, Hu X, Wang T, Liang S, Duan Y, Jin F, Qin B. Structural changes of gut microbiota in Parkinson's disease and its correlation with clinical features. *Sci China Life Sci.* 2017;60:1223–33.
46. Lolekha P, Sriphanom T, Vilaichone R-K. Helicobacter pylori eradication improves motor fluctuations in advanced Parkinson's disease patients: a prospective cohort study (HP-PD trial). *PLoS ONE.* 2021;16:e0251042.
47. Ho MS. Microglia in Parkinson's Disease. In: Verkhatsky A, Ho MS, Zorec R, Parpura V, editors. *Neuroglia in neurodegenerative diseases.* Singapore: Springer Singapore; 2019. p. 335–53.
48. McGeer PL, Itagaki S, Boyes BE, McGeer EG. Reactive microglia are positive for HLA-DR in the substantia nigra of Parkinson's and Alzheimer's disease brains. *Neurology.* 1988;38:1285–5.
49. Subbarayan MS, Hudson C, Moss LD, Nash KR, Bickford PC. T cell infiltration and upregulation of MHCII in microglia leads to accelerated neuronal loss in an  $\alpha$ -synuclein rat model of Parkinson's disease. *J Neuroinflammation.* 2020;17:242.
50. Hoban DB, Connaughton E, Connaughton C, Hogan G, Thornton C, Mulcahy P, Moloney TC, Dowd E. Further characterisation of the LPS model of Parkinson's disease: a comparison of intra-nigral and intra-striatal lipopolysaccharide administration on motor function, microgliosis and nigrostriatal neurodegeneration in the rat. *Brain, Behavior, and Immunity.* 2013;27:91–100.
51. Gerhard A, Pavese N, Hotton G, Turkheimer F, Es M, Hammers A, Eggert K, Oertel W, Banati RB, Brooks DJ. In vivo imaging

- of microglial activation with [11C](R)-PK11195 PET in idiopathic Parkinson's disease. *Neurobiol Disease*. 2006;21:404–12.
52. Badanjak K, Fixemer S, Smajić S, Skupin A, Grünewald A. The contribution of microglia to neuroinflammation in Parkinson's disease. *IJMS*. 2021;22:4676.
  53. Uriarte Huarte O, Kyriakis D, Heurtaux T, Pires-Afonso Y, Grzyb K, Halder R, Buttini M, Skupin A, Mittelbronn M, Michelucci A. Single-cell transcriptomics and in situ morphological analyses reveal microglia heterogeneity across the nigrostriatal pathway. *Front Immunol*. 2021;12:639613.
  54. Lang C, Campbell KR, Ryan BJ, et al. Single-cell sequencing of iPSC-dopamine neurons reconstructs disease progression and identifies HDAC4 as a regulator of Parkinson cell phenotypes. *Cell Stem Cell*. 2019;24:93–106.e6.
  55. • Smajić S, Prada-Medina CA, Landoulsi Z, et al (2021) Single-cell sequencing of human midbrain reveals glial activation and a Parkinson-specific neuronal state. *Brain* awab 446. **By means of single-nuclei RNA sequencing, the authors identified a significant upregulation of glial cells in postmortem midbrain tissues from idiopathic PD patients. Disease trajectory analyses identified stress related to accumulation of misfolded proteins as a major trigger of the observed pro-inflammatory phenotype.**
  56. Tran J, Anastacio H, Bardy C. Genetic predispositions of Parkinson's disease revealed in patient-derived brain cells. *npj Parkinsons Dis*. 2020;6:8.
  57. Nalls MA, Blauwendraat C, Vallerga CL, et al. Identification of novel risk loci, causal insights, and heritable risk for Parkinson's disease: a meta-analysis of genome-wide association studies. *Lancet Neurol*. 2019;18:1091–102.
  58. Day JO, Mullin S. The genetics of Parkinson's disease and implications for clinical practice. *Genes*. 2021;12:1006.
  59. Burré J. The synaptic function of  $\alpha$ -synuclein. *JPD*. 2015;5:699–713.
  60. Lema Tomé CM, Tyson T, Rey NL, Grathwohl S, Britschgi M, Brundin P. Inflammation and  $\alpha$ -synuclein's prion-like behavior in Parkinson's disease—is there a link? *Mol Neurobiol*. 2013;47:561–74.
  61. Croisier E, Moran LB, Dexter DT, Pearce RK, Graeber MB. Microglial inflammation in the parkinsonian substantia nigra: relationship to alpha-synuclein deposition. *J Neuroinflammation*. 2005;2:14.
  62. Zhang W, Wang T, Pei Z, et al. Aggregated  $\alpha$ -synuclein activates microglia: a process leading to disease progression in Parkinson's disease. *FASEB j*. 2005;19:533–42.
  63. Thomas MP, Chartrand K, Reynolds A, Vitvitsky V, Banerjee R, Gendelman HE. Ion channel blockade attenuates aggregated alpha synuclein induction of microglial reactive oxygen species: relevance for the pathogenesis of Parkinson's disease. *J Neurochem*. 2007;100:503–19.
  64. Reynolds AD, Glanzer JG, Kadiu I, et al. Nitrated alpha-synuclein-activated microglial profiling for Parkinson's disease: Synuclein-induced microglia activation. *J Neurochem*. 2008;104:1504–25.
  65. Su X, Maguire-Zeiss KA, Giuliano R, Prifti L, Venkatesh K, Federoff HJ. Synuclein activates microglia in a model of Parkinson's disease. *Neurobiol Aging*. 2008;29:1690–701.
  66. Theodore S, Cao S, McLean PJ, Standaert DG. Targeted overexpression of human  $\alpha$ -synuclein triggers microglial activation and an adaptive immune response in a mouse model of Parkinson disease. *J Neuropathol Exp Neurol*. 2008;67:1149–58.
  67. Hoenen C, Gustin A, Birck C, Kirchmeyer M, Beaume N, Felten P, Grandbarbe L, Heuschling P, Heurtaux T. Alpha-synuclein proteins promote pro-inflammatory cascades in microglia: stronger effects of the A53T mutant. *PLoS ONE*. 2016;11:e0162717.
  68. Codolo G, Plotegher N, Pozzobon T, Brucale M, Tessari I, Bubacco L, de Bernard M. Triggering of inflammasome by aggregated  $\alpha$ -synuclein, an inflammatory response in synucleinopathies. *PLoS ONE*. 2013;8:e55375.
  69. Gordon R, Albornoz EA, Christie DC, et al. Inflammasome inhibition prevents  $\alpha$ -synuclein pathology and dopaminergic neurodegeneration in mice. *Sci Transl Med*. 2018;10:eaah4066.
  70. • Pike AF, Varanita T, Herrebout MAC, Plug BC, Kole J, Musters RJP, Teunissen CE, Hoozemans JJM, Bubacco L, Veerhuis R.  $\alpha$ -Synuclein evokes NLRP3 inflammasome-mediated IL-1 $\beta$  secretion from primary human microglia. *Glia*. 2021;69:1413–28 **This study demonstrated that exposure of primary human microglia to  $\alpha$ -synuclein fibrils activates the NLRP3 inflammasome, suggesting that this pathway can play a crucial role in PD pathogenesis.**
  71. Piancone F, Saresella M, La Rosa F, Marventano I, Meloni M, Navarro J, Clerici M. Inflammatory responses to monomeric and aggregated  $\alpha$ -synuclein in peripheral blood of Parkinson disease patients. *Front Neurosci*. 2021;15:639646.
  72. Niu M, Li Y, Li G, Zhou L, Luo N, Yao M, Kang W, Liu J. A longitudinal study on  $\alpha$ -synuclein in plasma neuronal exosomes as a biomarker for Parkinson's disease development and progression. *Eur J Neurol*. 2020;27:967–74.
  73. Jiang C, Hopfner F, Katsikoudi A, et al. Serum neuronal exosomes predict and differentiate Parkinson's disease from atypical parkinsonism. *J Neurol Neurosurg Psychiatr*. 2020;91:720–9.
  74. Benskey MJ, Sellnow RC, Sandoval IM, Sortwell CE, Lipton JW, Manfredsson FP. Silencing alpha synuclein in mature nigral neurons results in rapid neuroinflammation and subsequent toxicity. *Front Mol Neurosci*. 2018;11:36.
  75. Zimprich A, Biskup S, Leitner P, et al. Mutations in LRRK2 cause autosomal-dominant Parkinsonism with pleomorphic pathology. *Neuron*. 2004;44:601–7.
  76. Paisán-Ruiz C, Jain S, Evans EW, et al. Cloning of the gene containing mutations that cause PARK8-linked Parkinson's disease. *Neuron*. 2004;44:595–600.
  77. Thévenet J, Pescini Gobert R, Hooft van Huijsduijnen R, Wiessner C, Sagot YJ. Regulation of LRRK2 expression points to a functional role in human monocyte maturation. *PLoS ONE*. 2011;6:e21519.
  78. Gillardon F, Schmid R, Draheim H. Parkinson's disease-linked leucine-rich repeat kinase 2 (LRRK2) mutation increases proinflammatory cytokine release from activated primary microglial cells and resultant neurotoxicity. *Neuroscience*. 2012;208:41–8.
  79. • Li T, Ning B, Kong L, Dai B, He X, Thomas JM, Sawa A, Ross CA, Smith WW. A LRRK2 GTP binding inhibitor, 68, reduces LPS-induced signaling events and TNF- $\alpha$  release in human lymphoblasts. *Cells*. 2021;10:480 **Findings from this study indicate that LRRK2 is implicated in pro-inflammatory pathways in human lymphoblasts, whereas LRRK2 pharmacological inhibition reduces inflammation.**
  80. Valente EM, Abou-Sleiman PM, Caputo V, et al. Hereditary early-onset Parkinson's disease caused by mutations in PINK1. *Science*. 2004;304:1158–60.
  81. Zheng X, Hunter T. Pink1, the first ubiquitin kinase. *EMBO J*. 2014;33:1621–3.
  82. Kitada T, Asakawa S, Hattori N, Matsumine H, Yamamura Y, Minoshima S, Yokochi M, Mizuno Y, Shimizu N. Mutations in the parkin gene cause autosomal recessive juvenile parkinsonism. *Nature*. 1998;392:605–8.
  83. Lazarou M, Sliter DA, Kane LA, Sarraf SA, Wang C, Burman JL, Sideris DP, Fogel AI, Youle RJ. The ubiquitin kinase PINK1 recruits autophagy receptors to induce mitophagy. *Nature*. 2015;524:309–14.

84. Henn IH, Bouman L, Schlehe JS, et al. Parkin mediates neuroprotection through activation of I B kinase/nuclear factor-B signaling. *J Neurosci*. 2007;27:1868–78.
85. Sun L, Shen R, Agnihotri SK, Chen Y, Huang Z, Büeler H. Lack of PINK1 alters glia innate immune responses and enhances inflammation-induced, nitric oxide-mediated neuron death. *Sci Rep*. 2018;8:383.
86. Fedele G, Loh S, Celardo I, Lehmann S, Costa A, Martins LM (2020) Gut-brain axis neurodegeneration in a *Drosophila* model of Parkinson's disease is linked to mitochondrial dysfunction. <https://doi.org/10.21203/rs.3.rs-100637/v1>
87. Kim J, Byun J-W, Choi I, Kim B, Jeong H-K, Jou I, Joe E. PINK1 deficiency enhances inflammatory cytokine release from acutely prepared brain slices. *Exp Neurobiol*. 2013;22:38–44.
88. Akundi RS, Huang Z, Eason J, Pandya JD, Zhi L, Cass WA, Sullivan PG, Büeler H. Increased mitochondrial calcium sensitivity and abnormal expression of innate immunity genes precede dopaminergic defects in Pink1-deficient mice. *PLoS ONE*. 2011;6:e16038.
89. Zhou J, Yang R, Zhang Z, Liu Q, Zhang Y, Wang Q, Yuan H. Mitochondrial protein PINK1 positively regulates RLR signaling. *Front Immunol*. 2019;10:1069.
90. Chung J-Y, Park HR, Lee S-J, et al. Elevated TRAF2/6 expression in Parkinson's disease is caused by the loss of Parkin E3 ligase activity. *Lab Invest*. 2013;93:663–76.
91. Frank-Cannon TC, Tran T, Ruhn KA, et al. Parkin deficiency increases vulnerability to inflammation-related nigral degeneration. *Journal of Neuroscience*. 2008;28:10825–34.
92. Yunfu W, Guangjian L, Ping Z, et al. PINK1 and its familial Parkinson's disease-associated mutation regulate brain vascular endothelial inflammation. *J Mol Neurosci*. 2014;53:109–16.
93. Matheoud D, Sugiura A, Bellemare-Pelletier A, et al. Parkinson's disease-related proteins PINK1 and Parkin repress mitochondrial antigen presentation. *Cell*. 2016;166:314–27.
94. Torres-Odio S, Key J, Hoepken H-H, et al. Progression of pathology in PINK1-deficient mouse brain from splicing via ubiquitination, ER stress, and mitophagy changes to neuroinflammation. *J Neuroinflammation*. 2017;14:154.
95. ● Decout A, Katz JD, Venkatraman S, Ablasser A. The cGAS–STING pathway as a therapeutic target in inflammatory diseases. *Nat Rev Immunol*. 2021;21:548–69 **Very recent and comprehensive review article discussing the emerging role of the cGAS–STING signalling pathway in inflammation and neurodegeneration.**
96. Sliter DA, Martinez J, Hao L, et al. Parkin and PINK1 mitigate STING-induced inflammation. *Nature*. 2018;561:258–62.
97. Lee JJ, Andrezza S, Whitworth AJ. The STING pathway does not contribute to behavioural or mitochondrial phenotypes in *Drosophila* Pink1/parkin or mtDNA mutator models. *Sci Rep*. 2020;10:2693.
98. Antico O, Ordureau A, Stevens M, et al. Global ubiquitylation analysis of mitochondria in primary neurons identifies endogenous Parkin targets following activation of PINK1. *Sci Adv*. 2021;7:eabj0722.
99. McWilliams TG, Prescott AR, Montava-Garriga L, Ball G, Singh F, Barini E, Muqit MMK, Brooks SP, Ganley IG. Basal mitophagy occurs independently of PINK1 in mouse tissues of high metabolic demand. *Cell Metabolism*. 2018;27:439–449.e5.
100. Allen GFG, Toth R, James J, Ganley IG. Loss of iron triggers PINK1/Parkin-independent mitophagy. *EMBO Rep*. 2013;14:1127–35.
101. Lee JJ, Sanchez-Martinez A, Zarate AM, Benincá C, Mayor U, Clague MJ, Whitworth AJ. Basal mitophagy is widespread in *Drosophila* but minimally affected by loss of Pink1 or parkin. *J Cell Biol*. 2018;217:1613–22.
102. Manzanillo PS, Ayres JS, Watson RO, Collins AC, Souza G, Rae CS, Schneider DS, Nakamura K, Shiloh MU, Cox JS. The ubiquitin ligase parkin mediates resistance to intracellular pathogens. *Nature*. 2013;501:512–6.
103. Li J, Ma C, Long F, et al. Parkin impairs antiviral immunity by suppressing the mitochondrial reactive oxygen species-Nlrp3 Axis and antiviral inflammation. *iScience*. 2019;16:468–84.
104. Mouton-Liger F, Jacoupy M, Corvol J-C, Corti O. PINK1/Parkin-dependent mitochondrial surveillance: from pleiotropy to Parkinson's disease. *Front Mol Neurosci*. 2017;10:120.
105. Bonifati V, Rizzu P, van Baren MJ, et al. Mutations in the *DJ-1* gene associated with autosomal recessive early-onset parkinsonism. *Science*. 2003;299:256–9.
106. Ariga H, Takahashi-Niki K, Kato I, Maita H, Niki T, Iguchi-Ariga SMM. Neuroprotective function of DJ-1 in Parkinson's disease. *Oxidative Med Cell Longevity*. 2013;2013:1–9.
107. Frøyset AK, Edson AJ, Gharbi N, et al. Astroglial DJ-1 overexpression up-regulates proteins involved in redox regulation and is neuroprotective in vivo. *Redox Biol*. 2018;16:237–47.
108. Edson AJ, Hushagen HA, Frøyset AK, Elda I, Khan EA, Di Stefano A, Fladmark KE. Dysregulation in the brain protein profile of zebrafish lacking the Parkinson's disease-related protein DJ-1. *Mol Neurobiol*. 2019;56:8306–22.
109. ● Singh Y, Trautwein C, Dhariwal A, et al. DJ-1 (Park7) affects the gut microbiome, metabolites and the development of innate lymphoid cells (ILCs). *Sci Rep*. 2020;10:16131 **This study provides evidence that DJ-1 is implicated in the regulation of mouse gut microbiome. Indeed, DJ-1 knockout mice display signs of intestinal inflammation and altered metabolic profile, likely due to higher abundance of specific gut microbial species. Notably, expression of PD-related inflammatory genes was increased in the midbrain of these mice, suggesting that bacterial metabolites and inflammatory mediators could trigger neuroinflammation and play a role in PD pathogenesis.**
110. Lin Z, Chen C, Yang D, Ding J, Wang G, Ren H. DJ-1 inhibits microglial activation and protects dopaminergic neurons in vitro and in vivo through interacting with microglial p65. *Cell Death Dis*. 2021;12:715.
111. Zhao M, Wang B, Zhang C, Su Z, Guo B, Zhao Y, Zheng R. The DJ1–Nrf2–STING axis mediates the neuroprotective effects of Withaferin A in Parkinson's disease. *Cell Death Differ*. 2021;28:2517–35.
112. Sidransky E, Nalls MA, Aasly JO, et al. Multicenter analysis of glucocerebrosidase mutations in Parkinson's disease. *N Engl J Med*. 2009;361:1651–61.
113. Balestrino R, Tunesi S, Tesei S, Lopiano L, Zecchinelli AL, Goldwurm S. Penetrance of glucocerebrosidase (GBA) mutations in Parkinson's disease: a kin cohort study. *Mov Disord*. 2020;35:2111–4.
114. Velayati A, Yu WH, Sidransky E. The role of glucocerebrosidase mutations in Parkinson disease and Lewy body disorders. *Curr Neurol Neurosci Rep*. 2010;10:190–8.
115. Mazzulli JR, Xu Y-H, Sun Y, Knight AL, McLean PJ, Caldwell GA, Sidransky E, Grabowski GA, Krainc D. Gaucher disease glucocerebrosidase and  $\alpha$ -synuclein form a bidirectional pathogenic loop in synucleinopathies. *Cell*. 2011;146:37–52.
116. Sardi SP, Clarke J, Kinnecom C, et al. CNS expression of glucocerebrosidase corrects  $\alpha$ -synuclein pathology and memory in a mouse model of Gaucher-related synucleinopathy. *Proc Natl Acad Sci*. 2011;108:12101–6.
117. Polinski NK, Martinez TN, Gorodinsky A, et al. Decreased glucocerebrosidase activity and substrate accumulation of glycosphingolipids in a novel GBA1 D409V knock-in mouse model. *PLoS ONE*. 2021;16:e0252325.
118. Fredriksen K, Aivazidis S, Sharma K, Burbidge KJ, Pitcairn C, Zunke F, Gelyana E, Mazzulli JR. Pathological  $\alpha$ -syn



- aggregation is mediated by glycosphingolipid chain length and the physiological state of  $\alpha$ -syn in vivo. *Proc Natl Acad Sci USA*. 2021;118:e2108489118.
119. Gustot A, Gallea JI, Sarroukh R, Celej MS, Ruysschaert J-M, Raussens V. Amyloid fibrils are the molecular trigger of inflammation in Parkinson's disease. *Biochem J*. 2015;471:323–33.
  120. Dutta D, Jana M, Majumder M, Mondal S, Roy A, Pahan K. Selective targeting of the TLR2/MyD88/NF- $\kappa$ B pathway reduces  $\alpha$ -synuclein spreading in vitro and in vivo. *Nat Commun*. 2021;12:5382.
  121. Emmanouilidou E, Melachroinou K, Roumeliotis T, Garbis SD, Ntzouni M, Margaritis LH, Stefanis L, Vekrellis K. Cell-produced-synuclein is secreted in a calcium-dependent manner by exosomes and impacts neuronal survival. *J Neurosci*. 2010;30:6838–51.
  122. Flavin WP, Bousset L, Green ZC, Chu Y, Skarpathiotis S, Chaney MJ, Kordower JH, Melki R, Campbell EM. Endocytic vesicle rupture is a conserved mechanism of cellular invasion by amyloid proteins. *Acta Neuropathol*. 2017;134:629–53.
  123. Freundt EC, Maynard N, Clancy EK, Roy S, Bousset L, Sourigues Y, Covert M, Melki R, Kirkegaard K, Brahic M. Neuron-to-neuron transmission of  $\alpha$ -synuclein fibrils through axonal transport. *Ann Neurol*. 2012;72:517–24.
  124. Masuda-Suzukake M, Nonaka T, Hosokawa M, Oikawa T, Arai T, Akiyama H, Mann DMA, Hasegawa M. Prion-like spreading of pathological  $\alpha$ -synuclein in brain. *Brain*. 2013;136:1128–38.
  125. Scheiblich H, Dansokho C, Mercan D, et al. Microglia jointly degrade fibrillar alpha-synuclein cargo by distribution through tunneling nanotubes. *Cell*. 2021;184:5089–5106.e21 **In this paper, the authors demonstrated that microglia make use of tunneling nanotubes to dilute the burden of excessive  $\alpha$ -synuclein accumulation and attenuate inflammation. At the same time, healthy microglia are able to donate mitochondria to  $\alpha$ -synuclein overloaded cells to improve their bioenergetic efficiency.**
  126. Rostami J, Mothes T, Kolahdouzan M, et al. Crosstalk between astrocytes and microglia results in increased degradation of  $\alpha$ -synuclein and amyloid- $\beta$  aggregates. *J Neuroinflammation*. 2021;18:124.
  127. Colombo M, Raposo G, Théry C. Biogenesis, secretion, and intercellular interactions of exosomes and other extracellular vesicles. *Annu Rev Cell Dev Biol*. 2014;30:255–89.
  128. Mustapic M, Eitan E, Werner JK, Berkowitz ST, Lazaropoulos MP, Tran J, Goetzl EJ, Kapogiannis D. Plasma extracellular vesicles enriched for neuronal origin: a potential window into brain pathologic processes. *Front Neurosci*. 2017;11:278.
  129. Gui Y, Liu H, Zhang L, Lv W, Hu X. Altered microRNA profiles in cerebrospinal fluid exosome in Parkinson disease and Alzheimer disease. *Oncotarget*. 2015;6:37043–53.
  130. Hong Z, Shi M, Chung KA, et al. DJ-1 and  $\alpha$ -synuclein in human cerebrospinal fluid as biomarkers of Parkinson's disease. *Brain*. 2010;133:713–26.
  131. Hong Z, Tian C, Stewart T, et al. Development of a sensitive diagnostic assay for Parkinson disease quantifying  $\alpha$ -synuclein-containing extracellular vesicles. *Neurology*. 2021;96:e2332–45.
  132. Picca A, Guerra F, Calvani R, et al. Mitochondrial signatures in circulating extracellular vesicles of older adults with Parkinson's disease: results from the EXosomes in PARKinson's Disease (EXPAND) Study. *JCM*. 2020;9:504.
  133. De Gaetano A, Solodka K, Zanini G, Sella V, Mattioli AV, Nasi M, Pinti M. Molecular mechanisms of mtDNA-mediated inflammation. *Cells*. 2021;10:2898.
  134. Gambardella S, Limanaqi F, Ferese R, Biagioni F, Campopiano R, Centonze D, Fornai F. ccf-mtDNA as a potential link between the brain and immune system in neuro-immunological disorders. *Front Immunol*. 2019;10:1064.
  135. Blum-Degen D, Müller T, Kuhn W, Gerlach M, Przuntek H, Riederer P. Interleukin-1 $\beta$  and interleukin-6 are elevated in the cerebrospinal fluid of Alzheimer's and de novo Parkinson's disease patients. *Neurosci Lett*. 1995;202:17–20.
  136. Müller T, Blum-Degen D, Przuntek H, Kuhn W. Short communication interleukin-6 levels in cerebrospinal fluid inversely correlate to severity of Parkinson's disease. *Acta Neurologica Scandinavica*. 2009;98:142–4.
  137. McGeer PL, Yasojima K, McGeer EG. Association of interleukin-1 $\beta$  polymorphisms with idiopathic Parkinson's disease. *Neurosci Lett*. 2002;326:67–9.
  138. McGeer PL, McGeer EG. Inflammation and neurodegeneration in Parkinson's disease. *Parkinsonism & Related Disorders*. 2004;10:S3–7.
  139. Wang X, Chi J, Huang D, Ding L, Zhao X, Jiang L, Yu Y, Gao F.  $\alpha$ -synuclein promotes progression of Parkinson's disease by upregulating autophagy signaling pathway to activate NLRP3 inflammasome. *Exp Ther Med*. 2019. <https://doi.org/10.3892/etm.2019.8297>.
  140. Fan Z, Pan Y-T, Zhang Z-Y, Yang H, Yu S-Y, Zheng Y, Ma J-H, Wang X-M. Systemic activation of NLRP3 inflammasome and plasma  $\alpha$ -synuclein levels are correlated with motor severity and progression in Parkinson's disease. *J Neuroinflammation*. 2020;17:11.
  141. Solini A, Rossi C, Santini E, Giuntini M, Raggi F, Parolini F, Biancalana E, Del Prete E, Bonuccelli U, Ceravolo R. P2X7 receptor/NLRP3 inflammasome complex and  $\alpha$ -synuclein in peripheral blood mononuclear cells: a prospective study in neurodiagnosed, treatment-naïve Parkinson's disease. *Eur J Neurol*. 2021;28:2648–56.
  142. Deleidi M, Jäggle M, Rubino G. Immune aging, dysmetabolism, and inflammation in neurological diseases. *Front Neurosci*. 2015. <https://doi.org/10.3389/fnins.2015.00172>.
  143. Sulzer D, Alcalay RN, Garretti F, et al. T cells from patients with Parkinson's disease recognize  $\alpha$ -synuclein peptides. *Nature*. 2017;546:656–61.
  144. Ding X-B, Wang X-X, Xia D-H, et al. Impaired meningeal lymphatic drainage in patients with idiopathic Parkinson's disease. *Nat Med*. 2021;27:411–8.
  145. Zou W, Pu T, Feng W, Lu M, Zheng Y, Du R, Xiao M, Hu G. Blocking meningeal lymphatic drainage aggravates Parkinson's disease-like pathology in mice overexpressing mutated  $\alpha$ -synuclein. *Transl Neurodegener*. 2019;8:7.
  146. Chahine LM, Qiang J, Ashbridge E, et al. Clinical and biochemical differences in patients having Parkinson disease with vs without *GBA* mutations. *JAMA Neurol*. 2013;70:852.
  147. Miliukhina IV, Usenko TS, Senkevich KA, Nikolaev MA, Timofeeva AA, Agapova EA, Semenov AV, Lubimova NE, Totolyan AA, Pchelina SN. Plasma cytokines profile in patients with Parkinson's disease associated with mutations in *GBA* gene. *Bull Exp Biol Med*. 2020;168:423–6.
  148. Mullin S, Stokholm MG, Hughes D, Mehta A, Parbo P, Hinz R, Pavese N, Brooks DJ, Schapira AHV. Brain microglial activation increased in glucocerebrosidase (*GBA*) mutation carriers without Parkinson's disease. *Mov Disord*. 2021;36:774–9.
  149. Galper J, Balwani M, Fahn S, Waters C, Krohn L, Gan-Or Z, Dzamko N, Alcalay RN. Cytokines and Gaucher biomarkers in glucocerebrosidase carriers with and without Parkinson disease. *Mov Disord*. 2021;36:1451–5.
  150. Dzamko N, Rowe DB, Halliday GM. Increased peripheral inflammation in asymptomatic leucine-rich repeat kinase 2 mutation carriers: inflammatory biomarkers for Parkinson's disease. *Mov Disord*. 2016;31:889–97.
  151. Brockmann K, Apel A, Schulte C, et al. Inflammatory profile in LRRK2-associated prodromal and clinical PD. *J Neuroinflammation*. 2016;13:122.
  152. Cook DA, Kannarkat GT, Cintron AF, et al (2017) LRRK2 levels in immune cells are increased in Parkinson's disease. *npj Parkinson's Disease* 3:11

153. Gagne JJ, Power MC. Anti-inflammatory drugs and risk of Parkinson disease: a meta-analysis. *Neurology*. 2010;74:995–1002.
154. Hui KY, Fernandez-Hernandez H, Hu J, et al. Functional variants in the *LRRK2* gene confer shared effects on risk for Crohn's disease and Parkinson's disease. *Sci Transl Med*. 2018;10:eaai7795.
155. San Luciano M, Tanner CM, Meng C, et al. Nonsteroidal anti-inflammatory use and LRRK2 Parkinson's disease penetrance. *Mov Disord*. 2020;35:1755–64.
156. Brown EG, Goldman SM. Modulation of the microbiome in Parkinson's disease: diet, drug, stool transplant, and beyond. *Neurotherapeutics*. 2020;17:1406–17.
157. Sampson TR, Debelius JW, Thron T, et al. Gut microbiota regulate motor deficits and neuroinflammation in a model of Parkinson's disease. *Cell*. 2016;167:1469–1480.e12.
158. Pagano G, Boess FG, Taylor KI, et al. A phase II study to evaluate the safety and efficacy of prasinezumab in early Parkinson's disease (PASADENA): rationale, design, and baseline data. *Front Neurol*. 2021;12:705407.
159. Wojewska DN, Kortholt A. LRRK2 targeting strategies as potential treatment of Parkinson's disease. *Biomolecules*. 2021;11:1101.

**Publisher's Note** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.