Ashdin Publishing
Journal of Drug and Alcohol Research
Vol. 14 (2025), Article ID 171062, 15 pages
DOI: 10.4303/JDAR/236457

Review Article

Neuroinflammatory Pathways in Parkinson's Disease: Understanding Triggers and Treatment Approaches

Anastasia V. Poznyak[1*], Aleksey Aleksandrovich Vatlin[2], Elizaveta Romanovna Korchagina[1], Olga Nikolaevna Maltseva[3], Aleksandra Sergeevna Utkina[4] and Alexander N. Orekhov[1]

[1]*Institute for Atherosclerosis Research, Osennyaya 4-1-207, 121609 Moscow, Russia*

[2]*Laboratory of Angiopathology, Institute of General Pathology and Pathophysiology, 8 Baltiiskaya Street, Moscow 125315, Russia*

[3]*Institute of Experimental Medicine, 12, Academician Pavlov Street Street, 197022, Saint Petersburg, Russia*

[4]*Department of Commodity Expertise and Customs Business, Plekhanov Russian University of Economics, 36, Stremyanny Lane, 115054 Moscow, Russia*

**Address Correspondence to: Anastasia V. Poznyak, Email: tehhy_85@mail.ru*

Received: 16 September 2025; Manuscript No: JDAR-25-171062; **Editor assigned:** 18 September 2025; PreQC No: JDAR-25-171062 (PQ); **Reviewed:** 02 October 2025; QC No: JDAR-25-171062; **Revised:** 09 October 2025; Manuscript No: JDAR-25-171062 (R); **Published:** 16 October 2025; DOI: 10.4303/JDAR/236457

Abstract

Parkinson's Disease (PD) is a prevalent neurodegenerative disorder characterized by a complex interplay of motor and non-motor symptoms, primarily resulting from the loss of dopaminergic neurons and the accumulation of pathological α-synuclein aggregates. Recent research underscores the significant role of neuroinflammation in the pathophysiology of PD, where chronic inflammatory processes contribute to neuronal degeneration. This review comprehensively examines the mechanisms underlying neuroinflammation in PD, highlighting the involvement of microglia, astrocytes, and peripheral immune responses. Various triggers, including α-synuclein aggregation, genetic predispositions, mitochondrial dysfunction, and gut microbiome dysbiosis, are discussed as potential instigators of neuroinflammatory cascades. Therapeutic strategies aimed at mitigating neuroinflammation, such as immunotherapy targeting α-synuclein, nonsteroidal anti-inflammatory medications, and lifestyle interventions, are also explored. Understanding the intricate relationship between neuroinflammation and PD is crucial for the development of effective therapeutic approaches to alleviate disease progression and improve patient outcomes. This review emphasizes the necessity for a multi-faceted approach to unravel the complexities of PD and leverage neuroinflammatory pathways for therapeutic intervention.

Keywords: Parkinson's disease; Therapeutic strategies; Neuroinflammatory; Astrocytes

Introduction

PD is the second most prevalent neurodegenerative disorder globally, with approximately 90% of cases being occasional and only 10% linked to genetic mutations. In recent years, both the occurrence and death rates of PD have risen significantly, making it a main health concern, particularly for individuals aged 45 to 70, who show a notably higher occurrence of the disease [1-3].

The hallmark symptoms that facilitate the diagnosis of PD include asymmetric, gradually worsening resting tremors, cogwheel rigidity, bradykinesia, and impaired postural reflexes. Non-motor symptoms may also emerge years before the onset of motor issues, such as anosmia, constipation, depression or apathy, sleep disturbances, and memory impairment. As the disease progresses, additional symptoms may develop, including autonomic dysfunction, pain, cognitive decline, language difficulties, and psychosis [4].

The onset and advancement of PD symptoms are primarily linked to a substantial loss of Dopaminergic neurons (DA neurons) in the Substantia Nigra Pars Compacta (SNPc), coupled with the presence of Lewy bodies (LBs) intracytoplasmic inclusions composed of insoluble and misfolded aggregates of α-synuclein (α-syn) [5-7]. The presence of LBs and α-syn aggregates is considered a key molecular hallmark of PD. These pathological changes are more commonly observed in regions such as the basal ganglia, locus coeruleus, raphe nuclei, thalamus, amygdala, and cerebellum [8-10].

Although PD being first characterized over 200 years ago, its underlying causes remain incompletely understood. Nevertheless, the role of neuroinflammation in the pathophysiology of PD has gained increasing recognition [11-13]. Neuroinflammation refers to the inflammatory processes occurring within the Central Nervous System (CNS), involving both inborn and adaptive immune replies. This process is complex, as it can simultaneously activate

neuroprotective and neurodevelopmental mechanisms while also contributing to neuronal damage, thereby playing a role in the neurodegeneration seen in diseases like PD [14-16].

In this context, a multi-level approach to studying PD is crucial for deepening our understanding of the disease and its link to neuroinflammation, along with the developing of new therapeutic methods.

Inflammation in PD

Persistent inflammatory processes are widely acknowledged as key pathogenic and etiological factors driving neurodegeneration. Unlike acute inflammation, which is generally protective and aids in the immediate repair of brain tissue following environmental stressors (such as traumatic injuries, viral infections, or toxins), chronic inflammation is more commonly linked to the onset and progression of neurodegenerative diseases [17-19]. While the exact triggers of neuroinflammation in PD remain unclear, factors like α-synuclein misfolding, immune-related gene polymorphisms, and mitochondrial dysfunction have been proposed as potential contributors [20,21].

The delicate balance between the physiological influence of acute neuroinflammation and the pathological outcomes of prolonged neuroinflammatory replies is regulated by the activity of various cell types engaged either in inborn or adaptive immunity [22-24]. These include not only Central Nervous System (CNS)-resident glial cells (such as microglia, astrocytes, and oligodendrocytes), but also peripheral circulating myeloid cells (including monocytes, macrophages, and dendritic cells) and T lymphocytes, which strongly contribute to the neuroinflammatory procedure by penetrating into the brain. Automatically, succeeding neuronal injury, CNS-resident glial cells liberate signaling molecules (such as cytokines, chemokines, growth factors, and other metabolites) that captivate peripheral myeloid cells to the place of injury [25-28]. Sequentially, these myeloid cells can engage additional immune cells, like T lymphocytes, into the CNS, thereby increasing the inflammatory reply. It's important to highlight that not only glial cells, but also neurons can bluntly output inflammatory agents that stimulate immune cells. This is a key point to consider when understanding the sequence of events (neurodegeneration vs. neuroinflammation) that cause unchangeable cell death in Parkinson's disease [29-31]. Actually, independent changes within SNpc dopaminergic neurons (such as mitochondrial dysfunction, impaired protein clearance, and α-synuclein release) can initiate an inflammatory reply in the surrounding environment, or even at a systemic grade, through the release of signaling molecules. This can impact other neuronal and non-neuronal cell types engaged in the neuroinflammatory course [32-36].

Factors contributing to neuroinflammation in PD

Neuroinflammation is a key feature of various neurological conditions, including PD. Immune cells in the Central Nervous System (CNS), equal to microglia and astrocytes, manage inflammation by discharging agents such as Interleukins (IL), Tumor Necrosis Factor-α (TNF-α), NF-κB, inducible Nitric Oxide Synthase (iNOS), NOD-Like Receptor Family Pyrin domain-containing 3 (NLRP3) inflammasome, and Reactive Oxygen Species (ROS) [37,38]. The secretion of these agents triggers an inflammatory reply that is harmful to neurons. As a result, superfluous and unregulated microglial stimulation significantly contributes to PD pathology by promoting the discharge of pro-inflammatory cytokines, IL, and ROS, initiating apoptosis, and leading to the degeneration of dopaminergic neurons [39-41].

Microglia

Microglia make up about 10% of the general brain cell population. Apart from their homeostatic roles, they serve as the first line of protection in the brain's immune system. The density of microglia varies across different brain regions, with the highest concentrations found in the hippocampus, olfactory bulb, basal ganglia, and Substantia Nigra (SN), while lower densities are observed in the putamen, transentorhinal, cingulate, and temporal cortices [42,43].

Microglial cells emit neurotrophic elements, clear toxic substances, and play a role in neuronal improvement, remodeling, and synaptic pruning. In the normal physiological circumstances, microglial stimulation supports brain evolution by removing programmed neural cells and promoting neuronal survival+the production of trophic and anti-inflammatory factors [44-47]. However, when microglia become overactive, they can exert significant neurotoxic effects by immoderately liberating harmful factors like superoxide, Nitric Oxide (NO), and Tumor Necrosis Factor-α (TNF-α). The dysregulated expression of α-syn or duplications in the SNCA gene in PD lead to the accumulation of toxic α-syn fibrils that are the primary components of Lewy bodies and neurites. These Lewy bodies and neurites are harmful and contribute to the loss of dopaminergic neurons in PD [48,49]. Additionally, α-syn pathology can activate microglia by stimulating Toll-Like Receptors (TLR) on the microglial surface, triggering an inflammatory reply. This reply causes the production of pro-inflammatory cytokines and stimulates the NF-KB signaling pathway, further amplifying the inflammatory process [50-53].

α-Synuclein (α-syn) is an endogenous protein primarily located at the presynaptic terminal, though its exact physiological function remains unclear. Various *in vitro* and *in vivo* studies under pathological conditions have

demonstrated that incorrect folding or accumulation of α-syn plays a key role in the pathogenesis of PD [54-57]. Extracellular α-syn oligomers activate immune receptors on the surface of microglia, involving Toll-Like Receptor 2 (TLR-2), which subsequently stimulates NF-κB and p38 a protein engaged in the Mitogen-Activated Protein Kinase (MAPK) signaling pathway *via* TLR-2 signaling. Stimulation of the TLR 1/2 receptor by α-syn also enhances the activity of the IL-1 Receptor-Associated Kinase (IRAK) complex, leading to the activation of TNF Receptor-Associated Factor 6 (TRAF6). These chronological processes result in the activation of Inhibitory Kappa Kinases (IKKs), which trigger the degradation of inhibitory kappa B alpha (IκB-α) [58-60]. Consequently, pro-inflammatory cytokines are produced through the MAPK pathway and the nuclear displacement of NF-κB, c-Jun N-terminal Kinase (JNK), and p38 activation. The generation and emission of pro-inflammatory cytokines following the phagocytosis of α-synuclein fibrils contribute to cell death and quicken the development of Parkinson's disease. Furthermore, the cooperation of α-synuclein fibrils, TLR, and NF-κB enhances NLRP3 upregulation [61-63].

Activation of the NF-κB pathway *via* TLRs or cytokines escalates the expression of NLRP3 by promoting pro-IL-1β and pro-IL-18, resulting the activation of the NLRP3 inflammasome. Once activated, NLRP3 converts procaspase-1 into active caspase-1, which then processes pro-IL-1β and pro-IL-18 into their active forms, IL-1β and IL-18, both of which contribute to neuroinflammation. In addition, caspase-1 plays a role in pyroptosis, an inflammatory model of cell death [64-66].

Injured dopaminergic neurons emit Matrix Metalloproteinase 3 (MMP3), a proteinase that breaks down the extracellular matrix, α-synuclein, and neuromelanin, leading to microglial activation. Overactivated microglia produce Reactive Oxygen Species (ROS) and liberate pro-inflammatory cytokines, which contribute to the death of dopaminergic neurons. This self-perpetuating cycle accelerates the progression of Parkinson's disease [67-69].

Astrocytes

Astrocytes are the most plentiful type of glial cell in the central nervous system. Their cytoplasmic additions connect neurons to blood vessels, facilitating substance exchange between them. Astrocytes provide metabolic support to neurons by supplying lactate for mitochondrial respiration, assisting in tissue recovery, and exuding trophic factors essential for neuronal viability and synaptogenesis [70-72]. Additionally, they play a crucial role in regulating Blood-Brain Barrier (BBB) permittivity, defending cerebral blood flow, and maintaining ion homeostasis [73].

Astrogliopathy in the Substantia Vigra (SN) and striatum has been observed in the 1-Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine (MPTP) form of Parkinson's disease. As astrocytes lose their usual characteristics, such as providing nutrients to neurons and regulating synaptic activity, they begin exuding IL-1α, complement Component 1q (C1q), and TNF-α. In their reactive state, astrocytes release neurotoxic factors that lead to the death of neurons and oligodendrocytes. However, astrocytes also upregulate several neurotrophic factors, which are thought to have neuroprotective effects [74-77].

Reactive astrocytes are commonly observed in Parkinson's disease. α-synuclein-positive inclusions are found both in neurons and in astrocytes in postmortem brain tissue of PD patients. Neuronal α-synuclein aggregates are transferred to neighboring astrocytes, where they create pathological inclusion bodies. The accumulation of α-synuclein in astrocytes results in increased production of pro-inflammatory cytokines (such as IL-6 and TNF-α) *via* TLR4 signaling, along with elevated expression of Intercellular Adhesion Molecule 1 (ICAM1) and Reactive Oxygen Species (ROS), further exacerbating the disease pathology [78-81].

Leukotrienes

Leukotrienes (LTs) are a class of lipid mediators based on arachidonic acid through the 5-Lipoxygenase (5-LOX) enzyme. After the 5-LOX enzyme synthesizes LTA4 from free arachidonic acid, LTA4 is further metabolized into LTB4, LTC4, LTD4, and LTE4. LTC4, LTD4, and LTE4 are together known as Cysteinyl Leukotrienes (CysLTs) due to the presence of an additional cysteinyl group, primarily activating two receptors, CysLT1R and CysLT2R [82-85]. LTs play key roles in inflammatory replies, including leukocyte chemotaxis, vascular permeability, and cell proliferation. Under normal physiological conditions, CysLT1R and CysLT2R activation in the brain is restricted. Nevertheless, their levels rise in different conditions such as Alzheimer's Disease (AD) and PD. Connecting CysLTs with microglial CysLT1R enhances the inflammatory response *via* upregulation of the NF-κB-mediated MAPK pathway, leading to increased emission of cytokines like IL-1β and TNF-α [86-89].

What triggers neuroinflammation in PD?

The development of PD is multifaceted, including various cases and processes. There is no unified agreement on what exactly provokes neuroinflammation in PD. Earlier studies have suggested that damaged dopaminergic neurons can initiate microglia, leading to neuroinflammation. Nonetheless, more recent research on PD pathogenesis points to factors such as aberrant α-synuclein, immune-related gene polymorphisms, mitochondrial dysfunction, and gut microbiome dysbiosis as potential triggers for neuroinflammation [90-93]. This suggests that microglial activation may occur prior to neuronal degeneration. The following sections outline the common materials and processes that contribute to neuroinflammation.

A summary of the main triggers and molecular mechanisms of neuroinflammation in PD is provided in Table 1.

Table 1: Triggers and mechanisms of neuroinflammation in Parkinson's disease.

Trigger/Factor	Key Mechanisms	Consequences in PD
α-Synuclein aggregation	Activates microglia *via* TLR2/TLR4/CD36 → NF-κB, MAPK, NLRP3 inflammasome path-ways; promotes cytokine release (IL-1β, TNF-α)	Microglial overactivation, apoptosis, pyroptosis, dopaminergic neuron loss
Genetic factors (e.g., LRRK2, PINK1, PRKN, HLA polymor-phisms)	Altered microglial oxidative stress signaling, im-paired autopha-gy/mitophagy, STING-mediated IFN responses, antigen presentation *via* MHC-II	Chronic inflammation, immune overactivation, increased susceptibility to PD
Mitochondrial dysfunction	ROS overproduction, release of mtDNA/ DAMPs, activation of TLRs, NLRP3, and cGAS-STING pathways	Oxidative stress, persistent innate immune acti-vation, neurodegeneration
Gut microbiome dysbiosis	Reduced SCFA signaling → impaired microglial maturation; pro-inflammatory dysbiosis; α-synu-clein accumulation in enteric nervous system	Peripheral-to-central immune activation, en-hanced neuroinflammation
Astrocyte reactivity	α-Synuclein inclusions transferred from neurons; TLR4 signaling; release of IL-6, TNF-α, ROS	BBB dysfunction, neuronal and oligodendrocyte death
Leukotrienes (LTs)	Activation of CysLT1R/CysLT2R → NF-κB and MAPK signaling → cytokine release	Amplification of microglial inflammatory re-sponse

α-Synuclein aggregation and neuroinflammation

Microglia are essential innate immune cells that play a key role in the central nervous system's first border of protection. They support homeostasis by negotiating phagocytosis and inflammatory responses. The accumulation of aberrant α-synuclein can trigger microglial activation. When excessively initiated, microglia can stimulate other innate immune elements within the central nervous system and provoke peripheral adaptive immune responses, ultimately leading to significant neuronal damage [94-96]. This phenomenon was first observed in cell culture and animal examples of PD. In a mouse case of PD, where human α-synuclein was amplified using a recombinant Adeno-Associated Virus Vector, serotype 2 (AAV2), a significant growth in CD68-positive microglia was noted four weeks after injecting AAV2 and human α-synuclein into the substantia nigra. In cultivated BV-2 microglia, exposure to extracellular α-synuclein was shown to induce an NF-κB positive response and the manufacture of pro-inflammatory cytokines [97-99]. Additionally, the existence of α-synuclein-reactive T cells was verified, with the highest levels observed shortly after PD diagnosis. Later, it was proved that morbid α-synuclein activated a strong inflammatory reply in human monocytes from PD patients [100-102]. Recent advances in understanding the molecular mechanisms behind microglial activation have revealed the following key pathways: (1) Membrane receptor pathway: α-synuclein (α-syn) can specifically connect with TLR2, TLR4, and CD36 receptors on the surface of microglial membranes, triggering receptor-mediated inflammatory signaling pathways. (2) Intracellular signaling pathway: α-syn can elevate STAT3 levels and initiate the JAK/STAT signaling pathway in microglia, causing the expression of MHC-II molecules and pro-inflammatory genes. (3) Inflammasome route: α-syn can trigger the NLRP3 inflammasome *via* the Fyn signaling pathway, resulting in enhanced IL-1β secretion. (4) RNA-connecting protein route: α-syn can also stimulate the appearance of the RNA-connecting protein Caspase8, which promotes further release of IL-1β [103-105].

Genetic factors and neuroinflammation

Genetic forms of PD represent approximately 5% to 10% of cases and are typically associated with early-onset. Genes generally connected with PD include *LRRK2*, *SNCA*, *VPS35*, *PRKN*, *DJI*, *PINK1*, and *PARK7*. Of these, *LRRK2*, *VPS35*, *PRKN*, and *PINK1* have a significant meaning in the immune system. *LRRK2*, in particular, is not only a key gene in autosomal dominant PD but also associated with sporadic forms of the disease. Additionally, *LRRK2* is highly represented in peripheral blood mononuclear cells [106-108]. Preceding research has demonstrated that *LRRK2* influences microglial role in various ways. Transcriptomic analysis of *LRRK2* knock-out microglial cells revealed a reduced induction of mitochondrial SOD2 in response to α-synuclein pre-formed fibrils, suggesting that microglial *LRRK2* may promote PD pathogenesis through altered oxidative stress signaling [109,110]. In a manganese exposure animal model, activated microglia were shown to liberate numerous inflammatory cytokines, with an upregulation in *LRRK2* expression. Moreover, inhibiting *LRRK2* reduced the expression of inflammatory cytokines and restored microglial autophagic function. Additionally, last findings suggest *LRRK2* plays a role in vesicular trafficking, being vital to the autophagy/lysosomal pathway and necessary for proper lysosomal role. *LRRK2* can associate with the intracellular sorting protein VPS35 to regulate the phosphorylation of RabGTPases, which in turn intercede phagocytosis, extracellular secretion, and autophagy in immune cells by controlling vesicle transport [111-113]. Autophagy, sequentially, affects inflammation by facilitating the transport of disintegrative material

to the lysosome. *LRRK2* mutations may contribute to inflammatory responses by affecting intracellular dealing. Similarly, *PRKN* and *PINK1* are generally associated with Parkinson's disease. Research has shown that both acute and chronic mitochondrial stress *in vivo* can trigger a STING-mediated type I interferon response in mice lacking parkin or *PINK1* [114,115]. Moreover, raised cytokine levels have been observed in the serum of asymptomatic PRKN mutation carriers, suggesting that parkin and *PINK1* help to impede inflammation by releasing harmed mitochondria. Co-expression of parkin and *PINK1* has been found to hinder the antigen introduction of MHC-I molecules, which can activate CD8+ T cells. Mutations in these genes may result in an overactivation of immune cells. These findings indicate that *LRRK2*, *PRKN*, and *PINK1* play significant roles in regulating the immune system [116-118].

In last years, Genome-Wide Association Studies (GWAS) have revealed that polymorphisms in definite gene loci enhance receptivity to sporadic PD. In 2017, a GWAS determined 17 different PD loci and discovered that a few recently determined PD risk genes are involved in lysosomal function and autophagy. To further expand the understanding of genetic risk in PD, a 2019 GWAS identified 90 autonomous standard genetic risk factors, almost doubling the previously recognized risk variants [119]. This study also highlighted intracranial and putaminal volume as potential future PD biomarkers and determined cognitive performance as a PD dangerous factor. The majority of gene loci are associated with autoimmunity, and polymorphisms in HLA alleles have been strongly linked to the danger of PD. Several Single Nucleotide Polymorphisms (SNPs) within the HLA class II gene locus have been reported to increase genetic receptivity to PD, along with rs3129882, rs75855844, rs2395163, rs660895, and rs4248166 [120-123]. It was identified a connection between the rs3129882 polymorphism and PD risk. This variant, located in the noncoding area of the HLA-DRA gene, can control the expression of HLA-DR and HLA-DQ genes. A meta-analysis of genome-wide following studies further confirmed that the rs75855844 polymorphism in the HLA-DRB5 gene is connected with PD [124,125].

A meta-analysis conducted in 2012 identified the rs660895 polymorphism in the *HLA-DRB1* gene as a defensive agent against PD [126]. MHC-II particles, codified by HLA genes, are expressed on the surface of various activated immune cells and identify epitopes, which trigger adaptive immune responses through antigen presentation. Single nucleotide substitutions in the coding regions of the HLA-DR, HLA-DQ, and HLA-DP genes can impair the function of MHC-II molecules. The expression of HLA class II genes is regulated by sequences in the noncoding regions, which can influence the expression of multiple structural genes simultaneously [127,128]. Consequently, changes in both coding and noncoding regions of HLA class II genes can impact MHC-II molecule functionality. In the central nervous system, MHC-II molecules are primarily emerged from microglia, with astrocytes and vascular endothelial cells demonstrating miserable grades of expression [129-131].

Initiated microglia express MHC-II molecules, which can trigger adaptive immune replies and cause neuronal destruction by stimulating T cells. These researches suggest that polymorphisms in the HLA gene locus can control the expression of MHC-II molecules on the surface of microglia, leading to a neuroinflammatory response in Parkinson's disease [132,133].

Mitochondrial dysfunction and neuroinflammation

Mitochondrial disorder and increased oxidative stress have been observed in the Substantia Nigra (SN) of PD patients and animal examples. In tissues from patients with the LRRK2 (G2019S) mutation, mitochondrial membrane potential and intracellular ATP grades were reduced, while mitochondrial elongation and interconnectivity raised, suggesting that the *LRRK2* mutation may impact both mitochondrial function and morphology [134-136]. The DJ1 protein is located in the mitochondrial matrix and intermembrane space, and its removal results in impaired mitochondrial dynamics and triggers cell apoptosis. Mutations in PINK1 can also disturb mitochondrial morphology and work. Additionally, α-synuclein aggregation can impede proteasome complex 1 activity, disturb calcium homeostasis within the mitochondrial matrix, support mitochondrial fragmentation, restrain fusion, and ultimately lead to mitochondrial dysfunction [137-140]. When mitochondrial function is endangered, huge amounts of Reactive Oxygen Species (ROS), mitochondrial fragments, and mitochondrial DNA (mtDNA) fragments are generated. ROS act as a main pro-inflammatory trigger by stimulating nuclear factor κB. Additionally, mtDNA fragments can initiate inflammation by cooperating with Toll-Like Receptors (TLRs), Nucleotide-binding Oligomerization Domain (NOD)-like receptor family pyrin domain containing 3 (NLRP3) inflammasomes, and the cytosolic cyclic GMP-AMP Synthase (cGAS)-Stimulator Of Interferon Genes (STING) DNA-sensing pathway [141-143].

Once liberated, these substances can operate as Damage-Associated Molecular Patterns (DAMPs), provoking an innate immune inflammatory response by joining danger signal receptors, with mtDNA fragments playing a particularly significant role. Mitochondria are unique organelles with their own genetic material. The proteins codified by mtDNA form four proteasome compounds on the interior mitochondrial membrane, which are crucial for electron transfer and ATP synthesis. Destruction of mtDNA and proteasome compounds can lead to mitochondrial trouble. The frequency of mtDNA mutations, removals, duplications, and alterations in PD is considerably higher compared to standard controls, showing that mtDNA is damaged in PD. Consequently, mitochondrial disorder can trigger a neuroinflammatory response [144-146].

Gut microbiome dysbiosis and neuroinflammation

The Gut Microbiome (GM) has an important meaning in the development, distinction, and role of microglia. Research in 2015 demonstrated that colonization with a complex microbiota modulates microglial activation and maturation, whereas in the absence of intestinal microbes, the innate immune response of microglia is weakened. In Germ-Free (GF) mice, supplementation with short-chain fatty acids microbial metabolites was able to restore impaired microglial maturation, highlighting the importance of gut microbiota and metabolites for proper microglial development and activation [147-150]. Gut microbiome dysbiosis, persistent intestinal mucosal inflammation, and α-synuclein accumulation in the enteric nervous system have been observed in PD patients. The microbial communities in the mucosal and fecal samples of PD patients show a proinflammatory dysbiosis distinct from that of control subjects. In α-synuclein-overexpressing mouse cases, colonization with microbiota from PD patients led to a greater motor dysfunction in contrast with transplants from healthy human donors [151-154]. Moreover, managing specific microbial metabolites to germ-free mice induced neuroinflammation and motor symptoms. This suggests that signals from gut microbes are necessary to trigger neuroinflammatory responses in PD models. Therefore, gut microbiome dysbiosis may drive neuroinflammation [155].

Therapeutic strategies to target neuroinflammation in PD

Several drugs have shown promise in preclinical and clinical investigations for potentially treating or delaying PD. However, the absence of truly effective treatments has driven the search for new therapeutic approaches. Notably, neuroinflammation is emerging as a key characteristic that can be purposed in PD. This section will explore advanced pharmacological methods aimed at treating PD by addressing neuroinflammation [156-158].

Immunotherapy for alpha-synuclein aggregation

As earlier mentioned, toxic forms of α-Syn can impair neuronal role and initiate various immune pathways and cells. These detrimental effects may arise due to the breakdown in liquidation of α-Syn aggregates. Given that PD patients exhibit insignificant grades of α-Syn antibodies, it appears that the clearance mechanisms are compromised. An immunotherapeutic strategy could potentially impede the development of extracellular α-Syn assemblies, thereby inhibiting oligomerization, fibrillization, and/or conglomeration of α-Syn, which would stop its multiplication between cells [159-161]. Targeting neuroinflammatory issues in PD, passive immunization (introducing antibodies from an external source) or active immunization (stimulating the body to produce antibodies through antigens) have shown promise as therapeutic methods. Notably, the first vaccine developed, PD01A, showed promising results, leading to the production of antibodies against aggregated α-Syn, decreased deposition, and better memory and motor feature in mouse examples. In PD patients, PD01A was found to be harmless and well-tolerated in a phase I clinical trial, though further trials are required to confirm its productiveness [162,163].

Vagotomy and appendectomy

The communication between the gut and brain, along with the subsequent accumulation of α-Synuclein (α-Syn) from the gastrointestinal tract to the lower brainstem, suggests that procedures like vagotomy and appendectomy could potentially mitigate the jeopardy of advancing Parkinson's disease. Some accessory researches have indicated that truncal vagotomy, but not selective vagotomy, may offer a protective effect against PD [164,165]. Specifically, Svensson and colleagues reported that individuals who experienced truncal vagotomy had a 15% lower risk of advancing PD [166]. These findings suggest that the vagus nerve plays a role in the transmission of pathological α-Syn along the gut-brain axis, and that vagotomy may postpone, but not completely annihilate, the risk of PD. Furthermore, another accessory research showed that the appendix could play a key role in PD through its influence on inflammation and the microbiota, as it serves as a long-term channel of aberrant α-Syn. Early removal of the appendix was associated with a reduced risk of developing PD. Overall, a deeper understanding of the relationship between the gut-brain axis, gut microbiota, and PD could pave the way for new diagnostic and therapeutic approaches [167-169].

Nonsteroidal anti-inflammatory agents

Anti-inflammatory tools like Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) can potentially slow the progression of the inflammatory response, reducing the risk of exacerbated feedback in PD. Among the most promising NSAIDs is ibuprofen, which exerts its anti-inflammatory effects by nonselectively inhibiting Cyclooxygenase (COX), an enzyme involved in the synthesis of prostaglandins that is elevated in the dopaminergic neurons of PD patients [170-173]. Additionally, ibuprofen appears to possess antioxidant properties that offer neuroprotection through a mechanism independent of COX inhibition. In animal model studies, ibuprofen reduced dopaminergic neurodegeneration by restricting the development of oxidative types. Nonetheless, this pharmacological strategy has yet to undergo clinical validation in the case of PD [174,175].

In addition to ibuprofen, other NSAIDs like aspirin and celecoxib have demonstrated protective effects in PD pathology. Aspirin, another COX obstacle, impacts neuroinflammatory processes and neuronal degeneration, helping to restrain the exhaustion of striatal dopamine. Consequently, further investigation into the use of NSAIDs as a therapeutic approach could enhance the modulation of neuroinflammatory events linked to PD [176].

Dietary interventions and physical activity

Dietary interventions appear to help reduce gut permeability, oxidative stress, and intestinal inflammation, eventually restoring microbiota balance. Utilizing probiotics (such as Lactobacillus and Bifidobacterium), prebiotics (including inulin, galactooligosaccharides, fructooligosaccharides, and short-chain fatty acids), and synbiotics (a combination of probiotics and prebiotics) to aim the gut-brain axis and regulate gut microbiome homeostasis offers a favourable approach. Additionally, consuming high levels of polyunsaturated fatty acids may have anti-inflammatory benefits and could reduce NLRP3 inflammasome initiators, such as α-Syn accumulation and mitochondrial disorder [177-179].

A nutritious diet that includes fresh vegetables, fruits, nuts, seeds, non-fried fish, olive oil, wine, coconut oil, fresh herbs, and spices characteristic of the Mediterranean diet—along with foods rich in flavonoids such as tea, apples, oranges, and red wine, may help to prevent or slow the progression of PD. Furthermore, studies suggest that caffeine intake is associated with a lower risk of developing PD [180].

In addition to a healthy diet, engaging in physical activity enhances both motor and non-motor symptoms of PD. It helps to stanch the disease progression, reduces neuroinflammation, delays the deprival of Dopaminergic neurons (DAn), and promotes synaptic bond. Studies have shown that aerobic exercise in PD patients can elevate serum grades of Brain-Derived Neurotrophic Factor (BDNF) while lowering inflammatory markers such as VCAM and TNFα [181-183]. This results in reduced microglial activation and oxidative stress, along with increased levels of dopamine and neuroplasticity. Furthermore, physical exercise lessens the impact of key molecular features of PD, such as the accumulation of α-synuclein and mitochondrial dysfunction, which helps preserve DAn in rodent models of the disease, enhances antioxidative capacity, and decreases the pro-inflammatory cytokine IL-1β. Overall, exercise has neuroprotective properties and reduces inflammation associated with PD.

It is important to note that several clinical trials have been conducted to address the debilitating conditions of patients with Parkinson's disease (PD) [184-186]. Most of these trials have focused on reducing or inhibiting extracellular α-synuclein, increasing autophagy, or stimulating molecular chaperones related to the lysosomal enzyme GCase. Lately, modern clinical tests have utilized PET ligands like GE180 (NCT03702816) and [18F] DPA-714 (NCT03457493), which bind to the mitochondrial Translocator Protein (TSPO) connected with inflammation. TSPO is found in the mitochondria of activated microglia, allowing for the noninvasive analysis of regional and global inflammation in living patients through PET imaging. The primary objective of these studies is to determine whether PD patients exhibit higher levels of neuroinflammation compared to healthy individuals. So far, no publicly available results have been reported, but these studies could enhance our knowledge of inflammation in Parkinson's disease [187-188].

Table 2: Therapeutic strategies targeting neuroinflammation in PD.

Strategy	Mechanism of Action	Evidence/Clinical Status
Immunotherapy (active and passive)	Antibodies/vaccines against α-synuclein aggregates → reduce oligomerization, fibrillization, intercellular spread	PD01A vaccine: Safe in Phase I trial; improved outcomes in preclinical models
NSAIDs (ibuprofen, aspirin, celecoxib)	Inhibit COX enzymes → reduce prostaglandin synthesis; ibuprofen also has antioxidant properties	Preclinical evidence of neuroprotection; limited clinical validation in PD
Vagotomy and appendectomy	Interrupt gut-brain α-synuclein transmission; appendix removal reduces α-syn reservoir	Epidemiological studies: Truncal vagotomy and early appendectomy linked to lower PD risk
Dietary interventions (Mediterranean diet, probiotics, prebiotics, polyunsaturated fatty acids)	Restore gut microbiota balance; reduce intestinal inflammation and NLRP3 activation	Observational and experimental support; associated with reduced PD progression risk
Physical activity	Increases BDNF; reduces TNF-α, VCAM, IL-1β; improves synaptic plasticity, dopamine signaling	Clinical and preclinical evidence of neuroprotection and symptom improvement
PET imaging biomarkers (TSPO ligands)	Noninvasive assessment of microglial activation and neuroinflammation in PD	Ongoing clinical trials (e.g., GE180, [18F]DPA-714); no published results yet

An overview of current and emerging therapeutic strategies targeting neuroinflammation in PD is presented in Table 2.

Conclusion

PD remains a complex and multifaceted neurodegenerative disorder, intricately linked to neuroinflammation and its diverse driving factors. This review highlights that neuroinflammatory processes play a pivotal role in the onset and progression of PD, contributing to dopaminergic neuron degeneration and the subsequent emergence of both motor and non-motor symptoms. Understanding the various triggers of neuroinflammation ranging from α-synuclein accumulation and genetic predispositions to mitochondrial dysfunction and gut microbiome dysbiosis reveals critical insights into the disease's pathophysiology.

The exploration of therapeutic strategies targeting neuroinflammation, including immunotherapy, nonsteroidal anti-inflammatory drugs, and lifestyle modifications, offers promising avenues for managing PD. As researchers continue to unravel the complexities of neuroinflammatory pathways, it is essential to adopt a holistic approach integrating pharmacological, dietary, and lifestyle interventions. This multidisciplinary strategy not only aims to mitigate inflammation but also seeks to enhance neuroprotection and improve the quality of life for PD patients.

Continued research into the intricate connections between neuroinflammation and PD will be vital for identifying novel therapeutic targets and advancing personalized treatment options. Ultimately, a deeper understanding of these mechanisms will pave the way for effective interventions, potentially altering the trajectory of this debilitating disease and offering hope for millions affected worldwide.

Funding

This research was funded by Russian Science Foundation, grant number 25-75-10016.

References

1. A. Kouli, K.M. Torsney, W.L. Kuan. Parkinson's disease: Etiology, neuropathology, and pathogenesis, In: Stoker T. B., Greenland J. C., eds. Parkinson's disease: Pathogenesis and clinical aspects [Internet], Codon Publications, Brisbane (AU), (2018).
2. F. Jia, A. Fellner, K. R. Kumar. Monogenic Parkinson's disease: Genotype, phenotype, pathophysiology, and genetic testing, Genes (Basel), 13(2022):471.
3. J. Tran, H. Anastacio, C. Bardy. Genetic predispositions of Parkinson's disease revealed in patient-derived brain cells, NPJ Parkinsons Dis, 6(2020):8.
4. J.C. Greenland, R.A. Barker. The differential diagnosis of Parkinson's disease, In: Stoker T. B., Greenland J. C., eds. Parkinson's disease: Pathogenesis and clinical aspects [Internet], Codon Publications, Brisbane (AU), (2018).
5. S. Yi, L. Wang, H. Wang, M.S. Ho, S. Zhang. Pathogenesis of α-synuclein in Parkinson's disease: From a neuron glia crosstalk perspective, Int J Mol Sci, 23(2022):14753.
6. P. Calabresi, A. Mechelli, G. Natale, L.V. Daley, G.D. Lazzaro, et al. Alpha-synuclein in Parkinson's disease and other synucleinopathies: From overt neurodegeneration back to early synaptic dysfunction, Cell Death Dis, 14(2023):176.
7. J. Jankovic, E.K. Tan. Parkinson's disease: Etiopathogenesis and treatment, J Neurol Neurosurg Psychiatry, 91(2020):795-808.
8. A. Jan, N.P. Gonçalves, C.B. Vaegter, P.H. Jensen, N. Ferreria. The prion-like spreading of alpha-synuclein in Parkinson's disease: update on models and hypotheses, Int J Mol Sci, 22(2021):8338.
9. M. Gómez-Benito, N. Granado, P. García-Sanz, M.A. De la Fuente, J.M. Castillo, et al. Modeling Parkinson's disease with the alpha-synuclein protein, Front Pharmacol, 11(2020):356.
10. K. Nordengen, C. Morland. From synaptic physiology to synaptic pathology: The enigma of α-synuclein, Int J Mol Sci, 25(2024):986.
11. W. Zhang, D. Xiao, Q. Mao. Role of neuroinflammation in neurodegeneration development, Sig Transduct Target Ther, 8(2023):267.
12. B. Araújo, R. Caridade-Silva, C. Soares-Guedes, L. Alves, P. Pereira, et al. Neuroinflammation and Parkinson's disease: from neurodegeneration to therapeutic opportunities, Cells, 11(2022):2908.
13. M.G. Tansey, R.L. Wallings, M.C. Houser, J.P. Herrera, T.E. Colonna, et al. Inflammation and immune dysfunction in Parkinson's disease, Nat Rev Immunol, 22(2022):657-673.
14. L. Muzio, A. Viotti, G. Martino. Microglia in neuroinflammation and neurodegeneration: from understanding to therapy, Front Neurosci, 15(2021):742065.
15. C. Gao, J. Jiang, Y. Tan, S. Chen. Microglia in neurodegenerative diseases: Mechanism and potential therapeutic targets, Sig Transduct Target Ther, 8(2023):359.
16. A.V. Poznyak, V.A. Orekhova, V.N. Sukhorukov, T.A. Nikiforov, E.N. Kartashov, et al. Atheroprotective aspects of heat shock proteins, Int J Mol Sci, 24(2023):11750.

17. R.J. Boyd, D. Avramopoulos, L.L. Jantzie, J.R. Smith, A.S. McCallion, et al. Neuroinflammation represents a common theme amongst genetic and environmental risk factors for Alzheimer and Parkinson diseases, J Neuroinflammation, 19(2022):223.

18. A. Adamu, S. Li, F. Gao, G. Xue. The role of neuroinflammation in neurodegenerative diseases: current understanding and future therapeutic targets, Front Aging Neurosci, 16(2024):1347987.

19. J. Sian-Hulsmann, P. Riederer. Virus-induced brain pathology and the neuroinflammation-inflammation continuum: the neurochemist's view, J Neural Transm, (2024).

20. A. Heidari, N. Yazdanpanah, N. Rezaei. The role of Toll-like receptors and neuroinflammation in Parkinson's disease, J Neuroinflammation, 19(2022):135.

21. A. Grünewald, K.R. Kumar, C.M. Sue. New insights into the complex role of mitochondria in Parkinson's disease, Prog Neurobiol, 177(2019):73-93.

22. Y. Rajesh, T.D. Kanneganti. Innate immune cell death in neuroinflammation and Alzheimer's disease, Cells, 11(2022):1885.

23. R. Kölliker-Frers, L. Udovin, M. Otero-Losada, T. Kobiec, M.I. Herrera, et al. Neuroinflammation: An integrating overview of reactive-neuroimmune cell interactions in health and disease, Mediators Inflamm, 2021(2021):9999146.

24. S.T.T. Schetters, D. Gomez-Nicola, J.J. Garcia-Vallejo, Y.V. Kooyk. Neuroinflammation: Microglia and T cells get ready to tango, Front Immunol, 8(2018):1905.

25. M. Prinz, T. Masuda, M.A. Wheeler, F.J. Quintana. Microglia and central nervous system-associated macrophages from origin to disease modulation, Annu Rev Immunol, 39(2021):251-277.

26. N. Abe, T. Nishihara, T. Yorozuya, J. Tanaka. Microglia and macrophages in the pathological central and peripheral nervous systems, Cells, 9(2020):2132.

27. E. Lee, J.C. Eo, C. Lee, J.W. Yu. Distinct features of brain-resident macrophages: Microglia and non-parenchymal brain macrophages, Mol Cells, 44(2021):281-291.

28. Y. Hu, W. Tao. Current perspectives on microglia-neuron communication in the central nervous system: Direct and indirect modes of interaction, J Adv Res, (2024).

29. H.S. Kwon, S.H. Koh. Neuroinflammation in neurodegenerative disorders: The roles of microglia and astrocytes, Transl Neurodegener, 9(2020):42.

30. M. Bouras, K. Asehnoune, A. Roquilly. Immune modulation after traumatic brain injury, Front Med (Lausanne), 9(2022):995044.

31. N.G. Nikiforov, T.V. Kirichenko, M.V. Kubekina, Y.S. Chegodaev, A.D. Zhuravlev, et al. Macrophages derived from LPS-stimulated monocytes from individuals with subclinical atherosclerosis were characterized by increased pro-inflammatory activity, Cytokine, 172(2023):156411.

32. G. Arena, K. Sharma, G. Agyeah, A. Grünewald, J.C. Fitzgerald, et al. Neurodegeneration and neuroinflammation in Parkinson's disease: a self-sustained loop, Curr Neurol Neurosci Rep, 22(2022):427-440.

33. K. Saramowicz, N. Siwecka, G. Galita, A.K. Lusina, W.R. Kamińska, et al. Alpha-synuclein contribution to neuronal and glial damage in Parkinson's disease, Int J Mol Sci, 25(2023):360.

34. H.R. Morris, M.G. Spillantini, C.M. Sue, C.H.W. Gray. The pathogenesis of Parkinson's disease, Lancet, 403(2024):293-304.

35. A.V. Poznyak, V.N. Sukhorukov, M.A. Popov, Y.S. Chegodaev, A.Y. Postnov, et al. Mechanisms of the Wnt pathways as a potential target pathway in atherosclerosis, J Lipid Atheroscler, 12(2023):223-236.

36. G. Forloni. Alpha synuclein: Neurodegeneration and inflammation, Int J Mol Sci, 24(2023):5914.

37. K. Chen, H. Wang, I. Ilyas, A. Mahmood, L. Hou, et al. Microglia and astrocytes dysfunction and key neuroinflammation-based biomarkers in Parkinson's disease, Brain Sci, 13(2023):634.

38. A.V. Poznyak, D.A. Kashirskikh, A.Y. Postnov, M.A. Popov, V.N. Sukhorukov, et al. Sialic acid as the potential link between lipid metabolism and inflammation in the pathogenesis of atherosclerosis, Braz J Med Biol Res, 56(2023):e12972.

39. S. Guo, H. Wang, Y. Yin. Microglia polarization from M1 to M2 in neurodegenerative diseases, Front Aging Neurosci, 14(2022):815347.

40. S. Isik, B. Y. Kiyak, R. Akbayir, R. Seyhali, T. Arpaci, et al. Microglia mediated neuroinflammation in Parkinson's disease, Cells, 12(2023):1012.

41. M. Lin, H. Yu, Q. Xie, Z. Xu, P. Shang, et al. Role of microglia autophagy and mitophagy in age-related neurodegenerative diseases, Front Aging Neurosci, 14(2023):1100133.

42. Y. Sun, J. Che, J. Zhang. Emerging non-proinflammatory roles of microglia in healthy and diseased brains, Brain Res Bull, 199(2023):110664.

43. S. Bachiller, I. Jiménez-Ferrer, A. Paulus, Y. Yang, M. Swanberg, et al. Microglia in neurological diseases: A road map to brain-disease dependent-inflammatory response, Front Cell Neurosci, 12(2018):488.

44. J. Cornell, S. Salinas, H.Y. Huang, M. Zhou. Microglia regulation of synaptic plasticity and learning and memory, Neural Regen Res, 17(2022):705-716.

45. H. Ward, S.J. West. Microglia: Sculptors of neuropathic pain? R Soc Open Sci, 7(2020):200260.

46. Y. Xiong, J. Chen, Y. Li. Microglia and astrocytes underlie neuroinflammation and synaptic susceptibility in autism spectrum disorder, Front Neurosci, 17(2023):1125428.

47. M. Kiraly, J.F. Foss, T. Giordano. Neuroinflammation, its role in Alzheimer's disease and therapeutic strategies, J Prev Alzheimers Dis, 10(2023):686-698.

48. D. Béraud, H.A. Hathaway, J. Trecki, S. Chasovskikh, D.A. Johnson, et al. Microglial activation and antioxidant responses induced by the Parkinson's disease protein α-synuclein, J Neuroimmune Pharmacol, 8(2013):94-117.

49. J. García-Revilla, I.M. Alonso-Bellido, M.A. Burguillos, A. J. Herrera, A.M. Espinosa-Oliva, et al. Reformulating pro-oxidant microglia in neurodegeneration, J Clin Med, 8(2019):1719.

50. J.S. Deyell, S. Sriparna, M. Ying, X. Mao. The interplay between α-synuclein and microglia in α-synucleinopathies, Int J Mol Sci, 24(2023):2477.

51. Y. Li, Y. Xia, S. Yin, F. Wan, J. Hu et al. Targeting microglial α-synuclein/TLRs/NF-κB/NLRP3 inflammasome axis in Parkinson's disease, Front Immunol, 12(2021):719807.

52. L. Li, C. Acioglu, R.F. Heary, S. Elkabes. Role of astroglial Toll-Like Receptors (TLRs) in central nervous system infections, injury and neurodegenerative diseases, Brain Behav Immun, 91(2021):740-755.

53. K. Colleselli, A. Stierschneider, C. Wiesner. An update on toll-like receptor 2, its function and dimerization in pro- and anti-inflammatory processes, Int J Mol Sci, 24(2023):12464.

54. X.Y. Du, X.X. Xie, R.T. Liu. The role of α-synuclein oligomers in Parkinson's disease, Int J Mol Sci, 21(2020):8645.

55. M.J. Benskey, R.G. Perez, F.P. Manfredsson. The contribution of alpha-synuclein to neuronal survival and function-implications for Parkinson's disease, J Neurochem, 137(2016):331-359.

56. Z.A. Sorrentino, B.I. Giasson. The emerging role of α-synuclein truncation in aggregation and disease, J Biol Chem, 295(2020):10224-10244.

57. J. Burré, R.H. Edwards, G. Halliday, A.E. Lang, H.A. Lashuel, et al. Research priorities on the role of α-synuclein in Parkinson's disease pathogenesis, Mov Disord, 39(2024):1663-1678.

58. S. Kwon, M. Iba, E. Masliah, C. Kim. Targeting microglial and neuronal toll-like receptor 2 in synucleinopathies, Exp Neurobiol, 28(2019):547-553.

59. Y. Li, Y. Xia, S. Yin, F. Wan, J. Hu et al. Targeting microglial α-synuclein/TLRs/NF-κB/NLRP3 inflammasome axis in Parkinson's disease, Front Immunol, 12(2021):719807.

60. A.V. Blagov, V.N. Sukhorukov, S. Guo, D. Zhang, M.A. Popov, et al. Impaired mitochondrial function in T-lymphocytes as a result of exposure to HIV and ART, Cells, 12(2023):1072.

61. A.D. Bachstetter, L.J. Van Eldik. The p38 MAP kinase family as regulators of proinflammatory cytokine production in degenerative diseases of the CNS, Aging Dis, 1(2010):199-211.

62. A. Bellucci, L. Bubacco, F. Longhena, E. Parrella, G. Faustini, et al. Nuclear factor-κB dysregulation and α-synuclein pathology: Critical interplay in the pathogenesis of Parkinson's disease, Front Aging Neurosci, 12(2020):68.

63. Q. Wang, Y. Liu, J. Zhou. Neuroinflammation in Parkinson's disease and its potential as therapeutic target, Transl Neurodegener, 4(2015):19.

64. C. Jiang, S. Xie, G. Yang, N. Wang. Spotlight on NLRP3 inflammasome: Role in pathogenesis and therapies of atherosclerosis, J Inflamm Res, 14(2021):7143-7172.

65. S. Unterberger, L. Mullen, M.S. Flint, S. Sacre. Multiple TLRs elicit alternative NLRP3 inflammasome activation in primary human monocytes independent of RIPK1 kinase activity, Front Immunol, 14(2023):1092799.

66. M. Islamuddin, X. Qin. Renal macrophages and NLRP3 inflammasomes in kidney diseases and therapeutics, Cell Death Discov, 10(2024):229.

67. T. Behl, G. Kaur, A. Sehgal, S. Bhardwaj, S. Singh, et al. Multifaceted role of matrix metalloproteinases in neurodegenerative diseases: Pathophysiological and therapeutic perspectives, Int J Mol Sci, 22(2021):1413.

68. M. Brkic, S. Balusu, C. Libert, R.E. Vandenbroucke. Friends or foes: Matrix metalloproteinases and their multifaceted roles in neurodegenerative diseases, Mediators Inflamm, 2015(2015):620581.

69. S.F. Darwish, A.M.M. Elbadry, A.S. Elbokhomy, G.A. Salama, R.M. Salama, et al. The dual face of microglia

(M1/M2) as a potential target in the protective effect of nutraceuticals against neurodegenerative diseases, Front Aging, 4(2023):1231706.

70. E. Beard, S. Lengacher, S. Dias, P.J. Magistretti, C. Finsterwald, et al. Astrocytes as key regulators of brain energy metabolism: New therapeutic perspectives, Front Physiol, 12(2022):825816.

71. S.V. Gudkov, D.E. Burmistrov, E.V. Kondakova, R.M. Sarimov, R.S. Yarkov, et al. An emerging role of astrocytes in aging/neuroinflammation and gut-brain axis with consequences on sleep and sleep disorders, Ageing Res Rev, 83(2023):101775.

72. A. Verkhratsky, A. Butt, B. Li, P. Illes, R. Zorec, et al. Astrocytes in human central nervous system diseases: A frontier for new therapies, Sig Transduct Target Ther, 8(2023):396.

73. C. Menaceur, F. Gosselet, L. Fenart, J.S. Pol. The blood-brain barrier, an evolving concept based on technological advances and cell-cell communications, Cells, 11(2021):133.

74. I. Miyazaki, M. Asanuma. Neuron-astrocyte interactions in Parkinson's disease, Cells, 9(2020):2623.

75. Y. Lu, X. Zhang, L. Zhao, C. Yang, L. Pan, et al. Metabolic disturbances in the striatum and substantia nigra in the onset and progression of MPTP-induced parkinsonism model, Front Neurosci, 12(2018):90.

76. S. Takahashi, K. Mashima. Neuroprotection and disease modification by astrocytes and microglia in Parkinson disease, Antioxidants (Basel), 11(2022):170.

77. S. Yi, L. Wang, H. Wang, M.S. Ho, S. Zhang, et al. Pathogenesis of α-synuclein in Parkinson's disease: From a neuron-glia crosstalk perspective, Int J Mol Sci, 23(2022):14753.

78. H.D.E. Booth, W.D. Hirst, R. Wade-Martins. The role of astrocyte dysfunction in Parkinson's disease pathogenesis, Trends Neurosci, 40(2017):358-370.

79. R. Patani, G.E. Hardingham, S.A. Liddelow. Functional roles of reactive astrocytes in neuroinflammation and neurodegeneration, Nat Rev Neurol, 19(2023):395-409.

80. Z. Krejciova, G.A. Carlson, K. Giles, S.B. Prusiner. Replication of multiple system atrophy prions in primary astrocyte cultures from transgenic mice expressing human α-synuclein, Acta Neuropathol Commun, 7(2019):81.

81. N.C. Gilbert, M.E. Newcomer, O. Werz. Untangling the web of 5-lipoxygenase-derived products from a molecular and structural perspective: The battle between pro- and anti-inflammatory lipid mediators, Biochem Pharmacol, 193(2021):114759.

82. N.A. Orekhov, V.I. Summerhill, V.A. Khotina. Role of mitochondria in the chronification of inflammation: Focus on dysfunctional mitophagy and mitochondrial DNA mutations, Gene Expression, 22(2023):329-344.

83. J.Z. Haeggström. Leukotriene biosynthetic enzymes as therapeutic targets, J Clin Invest, 128(2018):2680-2690.

84. B. Wang, L. Wu, J. Chen, L. Dong, C. Chen, et al. Metabolism pathways of arachidonic acids: Mechanisms and potential therapeutic targets, Sig Transduct Target Ther, 6(2021):94.

85. E. Çınar, B.C. Tel, G. Şahin. Neuroinflammation in Parkinson's disease and its treatment opportunities, Balkan Med J, 39(2022):318-333.

86. R.G. Biringer. The role of eicosanoids in Alzheimer's disease, Int J Environ Res Public Health, 16(2019):2560.

87. W. Tian, X. Jiang, D. Kim, T. Guan, M.R. Nicolls, et al. Leukotrienes in tumor-associated inflammation, Front Pharmacol, 11(2020):1289.

88. Y.X. Luo, L.L. Yang, X.Q. Yao. Gut microbiota-host lipid crosstalk in Alzheimer's disease: Implications for disease progression and therapeutics, Mol Neurodegener, 19(2024):35.

89. K. Badanjak, S. Fixemer, S. Smajić, A. Skupin, A. Grünewald, et al. The contribution of microglia to neuroinflammation in Parkinson's disease, Int J Mol Sci, 22(2021):4676.

90. A.C. Müller-Nedebock, M.C.J. Dekker, M.J. Farrer, N. Hattori, S. Y. Lim, et al. Different pieces of the same puzzle: A multifaceted perspective on the complex biological basis of Parkinson's disease, NPJ Parkinsons Dis, 9(2023):110.

91. F. Lind-Holm Mogensen, A. Scafidi, A. Poli, A. Michelucci. PARK7/DJ-1 in microglia: implications in Parkinson's disease and relevance as a therapeutic target, J Neuroinflammation, 20(2023):95.

92. K. Xu, Y. Li, Y. Zhou, Y. Zhang, Y. Shi, et al. Neuroinflammation in Parkinson's disease: Focus on the relationship between miRNAs and microglia, Front Cell Neurosci, 18(2024):1429977.

93. B.T. Casali, E.G. Reed-Geaghan. Microglial function and regulation during development, homeostasis and Alzheimer's disease, Cells, 10(2021):957.

94. M. Colonna, O. Butovsky. Microglia function in the central nervous system during health and neurodegeneration, Annu Rev Immunol, 35(2017):441-468.

95. G.J. Harry. Microglia in neurodegenerative events-an initiator or a significant other? Int J Mol Sci,

22(2021):5818.

96. S. Bido, S. Muggeo, L. Massimino, M.J. Marzi, S.G. Giannelli, et al. Microglia-specific overexpression of α-synuclein leads to severe dopaminergic neurodegeneration by phagocytic exhaustion and oxidative toxicity, Nat Commun, 12(2021):6237.

97. M. Bérard, L. Martínez-Drudis, R. Sheta, O.M.A. El-Agnaf, A. Oueslati, et al. Non-invasive systemic viral delivery of human alpha-synuclein mimics selective and progressive neuropathology of Parkinson's disease in rodent brains, Mol Neurodegeneration, 18(2023):91.

98. A. Fajardo-Serrano, A.J. Rico, E. Roda, A. Honrubia, S. Arrieta, et al. Adeno-associated viral vectors as versatile tools for Parkinson's research, both for disease modeling purposes and for therapeutic uses, Int J Mol Sci, 22(2021):6389.

99. C.S. Lindestam Arlehamn, R. Dhanwani, J. Pham, R. Kuan, A. Frazier, et al. α-Synuclein-specific T cell reactivity is associated with preclinical and early Parkinson's disease, Nat Commun, 11(2020):1875.

100. B. Zhu, D. Yin, H. Zhao, L. Zhang. The immunology of Parkinson's disease, Semin Immunopathol, 44(2022):659-672.

101. F. Piancone, M. Saresella, F. La Rosa, I. Marventano, M. Meloni, et al. Inflammatory responses to monomeric and aggregated α-synuclein in peripheral blood of Parkinson disease patients, Front Neurosci, 15(2021):639646.

102. D. Béraud, M. Twomey, B. Bloom, A. Mittereder, V. Ton, et al. α-Synuclein alters Toll-like receptor expression, Front Neurosci, 5(2011):80.

103. R. Wang, H. Ren, E. Kaznacheyeva, X. Lu, G. Wang et al. Association of glial activation and α-synuclein pathology in Parkinson's disease, Neurosci Bull, 39(2023):479-490.

104. Y. Pei, R.W. Maitta. Alpha synuclein in hematopoiesis and immunity, Heliyon, 5(2019):e02590.

105. C.Y. Kim, R.N. Alcalay. Genetic forms of Parkinson's disease, Semin Neurol, 37(2017):135–146.

106. F. Jia, A. Fellner, K.R. Kumar. Monogenic Parkinson's disease: genotype, phenotype, pathophysiology, and genetic testing, Genes (Basel), 13(2022):471.

107. J.O. Day, S. Mullin. The genetics of Parkinson's disease and implications for clinical practice, Genes (Basel), 12(2021):1006.

108. I. Russo, A. Kaganovich, J. Ding, N. Landeck, A. Mamais, et al. Transcriptome analysis of LRRK2 knock-out microglia cells reveals alterations of inflammatory- and oxidative stress-related pathways upon treatment with α-synuclein fibrils, Neurobiol Dis, 129(2019):67-78.

109. A.I. Ravinther, H.D. Dewadas, S.R. Tong, C.N. Foo, Y.E. Lin, et al. Molecular pathways involved in LRRK2-linked Parkinson's disease: A systematic review, Int J Mol Sci, 23(2022):11744.

110. E. Pajarillo, S.H. Kim, A. Digman, M. Dutton, D.S. Son et al. The role of microglial LRRK2 in manganese-induced inflammatory neurotoxicity via NLRP3 inflammasome and RAB10-mediated autophagy dysfunction, J Biol Chem, 299(2023):104879.

111. M. Zhang, C. Li, J. Ren, H. Wang, F. Yi, et al. The double-faceted role of leucine-rich repeat kinase 2 in the immunopathogenesis of Parkinson's disease, Front Aging Neurosci, 14(2022):909303.

112. A. Jurcau, F.L. Andronie-Cioara, D.C. Nistor-Cseppento, N. Pascalau, M. Rus, et al. The involvement of neuroinflammation in the onset and progression of Parkinson's disease, Int J Mol Sci, 24(2023):14582.

113. M.G. Williamson, M. Madureira, W. McGuinness, R. H. Roberts, E. D. Mock, et al. Mitochondrial dysfunction and mitophagy defects in LRRK2-R1441C Parkinson's disease models, Hum Mol Genet, 32(2023):2808-2821.

114. L. Nechushtai, D. Frenkel, R. Pinkas-Kramarski. Autophagy in Parkinson's disease, Biomolecules, 13(2023):1435.

115. M. Borsche, I.R. König, S. Delcambre, et al. Mitochondrial damage-associated inflammation highlights biomarkers in PRKN/PINK1 parkinsonism, Brain, 143(2020):3041-3051.

116. A.F. Magnusen, S.L. Hatton, R. Rani, et al. Genetic defects and pro-inflammatory cytokines in Parkinson's disease, Front Neurol, 12(2021):636139.

117. P.M.J. Quinn, P.I. Moreira, A.F. Ambrósio. PINK1/PARKIN signalling in neurodegeneration and neuroinflammation, Acta Neuropathol Commun, 8(2020):189.

118. D. Chang, M.A. Nalls, I.B. Hallgrímsdóttir, J. Hunkapiller, M. van der Brug, et al. A meta-analysis of genome-wide association studies identifies 17 new Parkinson's disease risk loci, Nat Genet, 49(2017):1511-1516.

119. L.M. García-Marín, P. Reyes-Pérez, S. Diaz-Torres, A. Medina-Rivera, N.G. Martin, et al. Shared molecular genetic factors influence subcortical brain morphometry and Parkinson's disease risk, NPJ Parkinsons Dis, 9(2023):73.

120. A.F. Magnusen, S.L. Hatton, R. Rani, M.K. Pandey. Genetic defects and pro-inflammatory cytokines in

Parkinson's disease, Front Neurol, 12(2021):636139.

121. A. Hall, S. Bandres-Ciga, M. Diez-Fairen, J.P. Quinn, K.J. Billingsley, et al. Genetic risk profiling in Parkinson's disease and utilizing genetics to gain insight into disease-related biological pathways, Int J Mol Sci, 21(2020):7332.

122. T.A. Yacoubian, Y.D. Fang, A. Gerstenecker, A. Amara, N. Stover, et al. Brain and systemic inflammation in de novo Parkinson's disease, Mov Disord, 38(2023):743-754.

123. R.L. Zhu, X.C. Lu, L.J. Tang, B.S. Huang, W. Yu, et al. Association between HLA rs3129882 polymorphism and Parkinson's disease: A meta-analysis, Eur Rev Med Pharmacol Sci, 19(2015):423-432.

124. Z.G. Ma, T.W. Liu, Y.L. Bo. HLA-DRA rs3129882 A/G polymorphism was not a risk factor for Parkinson's disease in Chinese-based populations: A meta-analysis, Int J Neurosci, 125(2015):241-246.

125. Y.H. Chuang, P.C. Lee, T. Vlaar, C. Mulot, M.A. Loriot, et al. Pooled analysis of the HLA-DRB1 by smoking interaction in Parkinson disease, Ann Neurol, 82(2017):655-664.

126. H. Macmillan, M.J. Strohman, S. Ayyangar, W. Jiang, N. Rajasekaran, et al. The MHC class II cofactor HLA-DM interacts with Ig in B cells, J Immunol, 193(2014):2641-2650.

127. A. Sanchez-Mazas. A review of HLA allele and SNP associations with highly prevalent infectious diseases in human populations, Swiss Med Wkly, 150(2020):w20214.

128. P. Prapas, M. Anagnostouli. Macrophages and HLA-Class II Alleles in Multiple Sclerosis: Insights in therapeutic dynamics, Int J Mol Sci, 25(2024):7354.

129. D.A. Lipski, R. Dewispelaere, V. Foucart. MHC class II expression and potential antigen-presenting cells in the retina during experimental autoimmune uveitis, J Neuroinflammation, 14(2017):136.

130. D. Matias, J. Balça-Silva, G.C. da Graça, C.M. Wanjiru, L.W. Macharia, et al. Microglia/Astrocytes-glioblastoma crosstalk: Crucial molecular mechanisms and microenvironmental factors, Front Cell Neurosci, 12(2018):235.

131. R. Gu, J. Pan, M.U.N. Awan, X. Sun, F. Yan, et al. The major histocompatibility complex participates in Parkinson's disease, Pharmacol Res, 203(2024):107168.

132. B. Huang, Y. Zhenxin, S. Chen, Z. Tan, Z. Zong, et al. The innate and adaptive immune cells in Alzheimer's and Parkinson's diseases, Oxid Med Cell Longev, 2022(2022):1315248.

133. H.E. Moon, S.H. Paek. Mitochondrial dysfunction in Parkinson's disease, Exp Neurobiol, 24(2015):103-116.

134. J. Walter, S. Bolognin, P.M.A. Antony, S.L. Nickels, S.K. Poovathingal, et al. Neural stem cells of Parkinson's disease patients exhibit aberrant mitochondrial morphology and functionality, Stem Cell Reports, 12(2019):878–889.

135. S.R. Subramaniam, M.F. Chesselet. Mitochondrial dysfunction and oxidative stress in Parkinson's disease, Prog Neurobiol, 106-107(2013):17-32.

136. A.M. Pickrell, R.J. Youle. The roles of PINK1, parkin, and mitochondrial fidelity in Parkinson's disease, Neuron, 85(2015):257-273.

137. E.H. Clark, A. Vázquez de la Torre, T. Hoshikawa, T. Briston. Targeting mitophagy in Parkinson's disease, J Biol Chem, 296(2021):100209.

138. P. Ge, V.L. Dawson, T.M. Dawson. PINK1 and Parkin mitochondrial quality control: A source of regional vulnerability in Parkinson's disease, Mol Neurodegeneration, 15(2020):20.

139. N.J. Thorne, D.A. Tumbarello. The relationship of alpha-synuclein to mitochondrial dynamics and quality control, Front Mol Neurosci, 15(2022):947191.

140. Y. Zhao, B. Liu, L. Xu, S. Yu, J. Fu, et al. ROS-induced mtDNA release: the emerging messenger for communication between neurons and innate immune cells during neurodegenerative disorder progression, Antioxidants (Basel), 10(2021):1917.

141. G.E. Moya, P.D. Rivera, K.E. Dittenhafer-Reed. Evidence for the role of mitochondrial DNA release in the inflammatory response in neurological disorders, Int J Mol Sci, 22(2021):7030.

142. D. Hu, H. Sheeja Prabhakaran, Y.Y. Zhang. Mitochondrial dysfunction in sepsis: Mechanisms and therapeutic perspectives, Crit Care, 28(2024):292.

143. S. Cicchinelli, G. Pignataro, S. Gemma, A. Piccioni, D. Picozzi, et al. PAMPs and DAMPs in sepsis: A review of their molecular features and potential clinical implications, Int J Mol Sci, 25(2024):962.

144. Y. Lyu, T. Wang, S. Huang, Z. Zhang. Mitochondrial damage-associated molecular patterns and metabolism in the regulation of innate immunity, J Innate Immun, 15(2023):665-679.

145. M. Garg, S. Johri, K. Chakraborty. Immunomodulatory role of mitochondrial DAMPs: A missing link in pathology? FEBS J, 290(2023):4395-4418.

146. J. Cook, M. Prinz. Regulation of microglial physiology by the microbiota, Gut Microbes, 14(2022):2125739.

147. G. Sharon, T.R. Sampson, D.H. Geschwind, S.K. Mazmanian. The central nervous system and the gut microbiome, Cell, 167(2016):915-932.

148. S. Dash, Y.A. Syed, M.R. Khan. Understanding the role of the gut microbiome in brain development and its association with neurodevelopmental psychiatric disorders, Front Cell Dev Biol, 10(2022):880544.

149. W. Hao, Q. Ma, L. Wang. Gut dysbiosis induces the development of depression-like behavior through abnormal synapse pruning in microglia mediated by complement C3, Microbiome, 12(2024):34.

150. N.U. Mahbub, M.M. Islam, S.T. Hong, H.J. Chung. Dysbiosis of the gut microbiota and its effect on α-synuclein and prion protein misfolding: consequences for neurodegeneration, Front Cell Infect Microbiol, 14(2024):1348279.

151. Q. Lei, T. Wu, J. Wu, X. Hu, Y. Guan, et al. Roles of α-synuclein in gastrointestinal microbiome dysbiosis-related Parkinson's disease progression (Review), Mol Med Rep, 24(2021):734.

152. B. Huang, S.W.H. Chau, Y. Liu. Gut microbiome dysbiosis across early Parkinson's disease, REM sleep behavior disorder and their first-degree relatives, Nat Commun, 14(2023):2501.

153. S. Salim, F. Ahmad, A. Banu, F. Mohammad. Gut microbiome and Parkinson's disease: Perspective on pathogenesis and treatment, J Adv Res, 50(2023):83-105.

154. T.R. Sampson, J.W. Debelius, T. Thron, S. Janssen, G.G. Shastri, et al. Gut microbiota regulate motor deficits and neuroinflammation in a model of Parkinson's disease, Cell, 167(2016):1469-1480.

155. A. Bougea. Some novel therapies in Parkinson's disease: A promising path forward or not yet? A systematic review of the literature, Biomedicines, 12(2024):549.

156. S.P. Sardi, J.M. Cedarbaum, P. Brundin. Targeted therapies for Parkinson's disease: From genetics to the clinic, Mov Disord, 33(2018):684-696.

157. T.B. Stoker, K.M. Torsney, R.A. Barker. Emerging treatment approaches for Parkinson's disease, Front Neurosci, 12(2018):693.

158. M.J. Benskey, R.G. Perez, F.P. Manfredsson. The contribution of alpha synuclein to neuronal survival and function-Implications for Parkinson's disease, J Neurochem, 137(2016):331-359.

159. M. Upcott, K.D. Chaprov, V.L. Buchman. Toward a disease-modifying therapy of alpha-synucleinopathies: New molecules and new approaches came into the limelight, Molecules, 26(2021):7351.

160. C.R. Fields, N. Bengoa-Vergniory, R. Wade-Martins. Targeting alpha-synuclein as a therapy for Parkinson's disease, Front Mol Neurosci, 12(2019):299.

161. F. De Marchi, I. Munitic, L. Vidatic, E. Papić, V. Rački, et al. Overlapping neuroimmune mechanisms and therapeutic targets in neurodegenerative disorders, Biomedicines, 11(2023):2793.

162. A.M. Castonguay, C. Gravel, M. Lévesque. Treating Parkinson's disease with antibodies: Previous studies and future directions, J Parkinsons Dis, 11(2021):71-92.

163. E. Schaeffer, A. Kluge, M. Böttner, F. Zunke, F. Cossais, et al. Alpha synuclein connects the gut-brain axis in Parkinson's disease patients-A view on clinical aspects, cellular pathology and analytical methodology, Front Cell Dev Biol, 8(2020):573696.

164. P. Lyra, V. Machado, S. Rota, K.R. Chaudhuri, J. Botelho, et al. Revisiting alpha-synuclein pathways to inflammation, Int J Mol Sci, 24(2023):7137.

165. E. Svensson, E. Horváth-Puhó, R.W. Thomsen, J.C. Djurhuus, L. Pedersen, et al. Vagotomy and subsequent risk of Parkinson's disease, Ann Neurol, 78(2015):522-529.

166. J.C. Claudino Dos Santos, L.F. Oliveira, F.M. Noleto, C.T.P. Gusmão, G.A.C. Brito, et al. Gut-microbiome-brain axis: The crosstalk between the vagus nerve, alpha-synuclein and the brain in Parkinson's disease, Neural Regen Res, 18(2023):2611-2614.

167. H.R. Morris, M.G. Spillantini, C.M. Sue, C.H. Williams-Gray. The pathogenesis of Parkinson's disease, Lancet, 403(2024):293-304.

168. R. Yang, G. Gao, H. Yang. The pathological mechanism between the intestine and brain in the early stage of Parkinson's disease, Front Aging Neurosci, 14(2022):861035.

169. T.N. Poly, M.M.R. Islam, H.C. Yang, Y.J. Li. Non-steroidal anti-inflammatory drugs and risk of Parkinson's disease in the elderly population: A meta-analysis, Eur J Clin Pharmacol, 75(2019):99-108.

170. D. Belvisi, R. Pellicciari, G. Fabbrini, M. Tinazzi, A. Berardelli, et al. Modifiable risk and protective factors in disease development, progression and clinical subtypes of Parkinson's disease: What do prospective studies suggest? Neurobiol Dis, 134(2020):104671.

171. A. Tsoupras, D.A. Gkika, I. Siadimas, I. Christodoulopoulos, P. Efthymiopoulos, et al. The multifaceted effects of non-steroidal and non-opioid anti-inflammatory and analgesic drugs on platelets: Current knowledge, limitations, and future perspectives, Pharmaceuticals (Basel), 17(2024):627.

172. A.M. Badawoud, L.S. Ali, M.S. Abdallah, R.M. El Sabaa, M.M. Bahaa, et al. The relation between Parkinson's disease and non-steroidal anti-inflammatories: A systematic review and meta-analysis, Front Pharmacol, 15(2024):1434512.

173. M. Świątkiewicz, M. Zaremba, I. Joniec, A. Członkowski, I. Kurkowska-Jastrzębska, et al. Potential neuroprotective effect of ibuprofen: Insights from the mice model of Parkinson's disease, Pharmacol Rep, 65(2013):1227-1236.

174. A. Varesi, L.I.M. Campagnoli, A. Carrara, I. Pola, E. Floris, et al. Non-enzymatic antioxidants against Alzheimer's disease: Prevention, diagnosis and therapy, Antioxidants (Basel), 12(2023):180.

175. A.L. Bartels, K.L. Leenders. Cyclooxygenase and neuroinflammation in Parkinson's disease neurodegeneration, Curr Neuropharmacol, 8(2010):62-68.

176. S. Roy, S. Dhaneshwar. Rloe of prebiotics, probiotics, and synbiotics in management of inflammatory bowel disease: Current perspectives, World J Gastroenterol, 29(2023):2078-2100.

177. H. Jiang, M. Cai, B. Shen, Q. Wang, T. Zhang, et al. Synbiotics and gut microbiota: New perspectives in the treatment of type 2 diabetes mellitus, Foods, 11(2022):2438.

178. S. Selvamani, V. Mehta, H. Ali El Enshasy, S. Thevarajoo, H. El Adawi, et al. Efficacy of probiotics-based interventions as therapy for inflammatory bowel disease: A recent update, Saudi J Biol Sci, 29(2022):3546-3567.

179. J. Godos, F. Scazzina, C. Paternò Castello, F. Giampieri, J.L. Quiles, et al. Underrated aspects of a true Mediterranean diet: Understanding traditional features for worldwide application of a "Planeterranean" diet, J Transl Med, 22(2024):294.

180. K.S. Bhalsing, M.M. Abbas, L.C.S. Tan. Role of physical activity in Parkinson's disease, Ann Indian Acad Neurol, 21(2018):242-249.

181. D.M. Cammisuli, U. Bonuccelli, S. Daniele, C. Martini, J. Fusi, et al. Aerobic exercise and healthy nutrition as neuroprotective agents for brain health in patients with Parkinson's disease: A critical review of the literature, Antioxidants (Basel), 9(2020):380.

182. J.A. Santiago, J.A. Potashkin. Physical activity and lifestyle modifications in the treatment of neurodegenerative diseases, Front Aging Neurosci, 15(2023):1185671.

183. V.A. Ruiz-Pozo, R. Tamayo-Trujillo, S. Cadena-Ullauri, E. Frias-Toral, P. Guevara-Ramírez, et al. The molecular mechanisms of the relationship between insulin resistance and Parkinson's disease pathogenesis, Nutrients, 15(2023):3585.

184. H. Quan, E. Koltai, K. Suzuki, A.S. Aguiar Jr, R. Pinho, et al. Exercise, redox system and neurodegenerative diseases, Biochim Biophys Acta Mol Basis Dis, 1866(2020):165778.

185. M.F. Beal, J. Chiluwal, N.Y. Calingasan, G.L. Milne, M.S. Shchepinov, et al. Isotope-reinforced polyunsaturated fatty acids improve Parkinson's disease-like phenotype in rats overexpressing α-synuclein, Acta Neuropathol Commun, 8(2020):220.

186. M.E. Gegg, G. Verona, A.H.V. Schapira. Glucocerebrosidase deficiency promotes release of α-synuclein fibrils from cultured neurons, Hum Mol Genet, 29(2020):1716-1728.

187. D. Sepúlveda, M. Cisternas-Olmedo, J. Arcos, M. Nassif, R.L. Vidal. Contribution of autophagy-lysosomal pathway in the exosomal secretion of alpha-synuclein and its impact in the progression of Parkinson's disease, Front Mol Neurosci, 15(2022):805087.