BJCMR Brazilian Journal of Clinical Medicine and Review

PCAA PUBLICAÇÕES CIENTÍFICAS DE ACESSO ABERTO

Health Review

The Role of Microglia in Parkinson's Disease and Possible Therapeutic Targets

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Abstract: Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by the degeneration of dopaminergic neurons in the substantia nigra pars compacta, leading to significant motor and non-motor symptoms. Recent research highlights the critical role of microglia, the resident immune cells of the central nervous system, in the pathogenesis and progression of PD. Microglia contribute to neuroinflammation through the release of pro-inflammatory cytokines and reactive oxygen species, exacerbating neuronal damage. Moreover, α-synuclein aggregates, a hallmark of PD, activate microglia, further promoting inflammation and neurodegeneration. This review explores the dual role of microglia in PD, encompassing both their neuroprotective functions and their contribution to neuroinflammation. We discuss the molecular mechanisms underlying microglial activation and their interactions with astrocytes, another crucial glial cell type. The review also examines potential therapeutic targets aimed at modulating microglial activity to mitigate neuroinflammation and slow the progression of PD. Current therapeutic strategies predominantly focus on symptomatic relief through dopaminergic medications. However, emerging therapies targeting microglial activation, such as anti-inflammatory drugs, immunomodulators, and novel agents like metabotropic glutamate receptor 5 (mGluR5) modulators, offer promising avenues for disease modification. Understanding the complex interplay between microglia and other cellular components in the PD brain is essential for developing effective treatments that address the underlying pathophysiological mechanisms of the disease.

Keywords: Parkinson's disease; Microglia; Neuroinflammation; α-synuclein; Therapeutic targets; Astrocytes; mGluR5.

Citation: Gomes GF, Galvão SL, Ventura C, Lessa YPN, Santos JCC. The Role of Microglia in Parkinson's Disease and Possible Therapeutic Targets. Brazilian Journal of Clinical Medicine and Review. 2025:Jan-Dec;03(1): bjcmr11.

https://doi.org/10.52600/2763-583X.bjcmr.2025.3.1.bjcmr11

Received: 12 June 2024
Accept: 17 July 2024
Published: 31 July 2024

1. Introduction

Neurodegenerative diseases are chronic, progressive, and multisystem pathologies that are typically incurable and debilitating [1-3], which mitigate normal brain activity and may or may not be associated with brain tissue atrophy and reduced cognition [4]. With an estimated presence in 0.3% of the global population [5], and an incidence rate ranging from 5/100,000 to over 32/100,000 new cases per year, PD is the second most prevalent neurodegenerative disease, second only to Alzheimer's disease [6]. Thus, although the pathogenesis of PD is not fully understood, there is a consensus [2] on the presence of alpha-synuclein-containing Lewy bodies in the substantia nigra of the brain with the loss of dopaminergic neurons in the substantia nigra pars compacta being the hallmark of the changes responsible for the motor deficiencies of the pathology [7-9].

It is also worth highlighting the physiological role of astrocytes and microglia; these human cells are part of the nervous tissue, constantly monitoring the brain parenchyma to perform homeostatic and neurotrophic roles, ensuring the balance in the functioning, maintenance, and growth of neuronal cells [8, 10-12]. Therefore, the dysfunction of these cells may be linked to neurodegenerative disorders present in many brain diseases, including Parkinson's disease [8, 13].

The most abundant type of glial cell in the central nervous system and surrounding neurons are astrocytes [2]. With direct connections between their cytoplasmic extensions, neurons, and blood vessels, they can act as metabolic support by providing lactate for mitochondrial respiration, participating in the maintenance and permeability of the blood-brain barrier, assisting in tissue repair by occupying spaces left by dead neurons, producing antioxidants, discarding waste products, and secreting neurotrophic molecules necessary for neuron survival [2, 8, 10]. Microglia are the main cells of the brain's innate immune system [14], which participate in the maintenance of the CNS to maintain homeostasis, secrete neurotrophic factors, eliminate toxic substances, and also participate in neuronal remodeling, repair, and synaptic pruning [10]. In addition to phagocytizing dead cells and helping eliminate alpha-synuclein aggregates, which are a prominent feature of Parkinson's disease (PD) [14, 15].

On the other hand, alpha-synuclein also activates microglia [14] through Pathogen-Associated Molecular Patterns (PAMPs) and Damage-Associated Molecular Patterns (DAMPs), which are factors secreted by damaged neurons from injuries such as ischemia, infection, inflammatory diseases, brain trauma, and neurodegenerative diseases [15] or protein aggregates (alpha-synuclein), culminating in the release of pro-inflammatory cytokines that will further damage neurons [10, 14], mainly dopaminergic neurons [10, 15, 16], leading to persistent neuroinflammation and degeneration, thus being associated with the progression of PD, and not the initial stimulus [10, 14, 15].

Neurodegenerative diseases are increasingly frequent causes of global morbidity and mortality. Keeping this in mind, and considering the chronicity of these pathologies, it is essential that they are properly diagnosed, so the prognosis will be more favorable, and specific treatments and management will be more efficient [6]. Currently, the therapies used for PD are only symptomatic, focusing on providing the dopamine precursor (levodopa or dopamine agonists) or maintaining dopamine levels by inhibiting the degradation of endogenous dopamine (monoamine oxidase B inhibitors and catechol-O-methyl transferase inhibitors) [10]. Focusing on PD, we have a multifactorial disease, meaning a wide range of factors are necessary for the development of the disease, with the dominant risk factor being aging, with a sharp increase in incidence after the age of 60. Thus, there are different predominant factors in different patients [17]. Therefore, treatments are generally targeted therapies for pathophysiologically defined subtypes [18].

In this review, we discuss the role of microglia in the progression of Parkinson's Disease and the possible therapeutic targets. In this way, this study will contribute to a better understanding of the role of microglia and astroglia in Parkinson's Disease, contributing to the pathogenesis of the disease, and elucidating new therapies and their respective therapeutic targets, which are the focus of recent studies in the field.

2. Review

2.1 Neuroinflammation in PD

PD, as previously mentioned, is the deterioration of dopaminergic neurons in the substantia nigra pars compacta caused by inflammation [2, 7, 16, 19], which, in turn, is a mechanism aimed at protecting the host from an agent that causes damage and subsequently restoring the tissue [10]. This neuroinflammation is mainly driven by the activation of cerebral microglial cells (M1), infiltration of T lymphocytes, and the presence of pro-inflammatory cytokines such as tumor necrosis factor (TNF-alpha), gamma inter-

feron (IFN-gamma), NF-KB, interleukin 6 (IL-6), and interleukin 1 (IL-1), which are consistently observed in the brains of PD patients [2, 10, 13, 14, 16, 16, 20]. Additionally, HLA variants, namely HLA-DRA and HLA-DRB1, are also associated with neuroinflammation in PD. Finally, the activation of microglial cells can be triggered by harmful products that cause PD, such as alpha-synuclein [19, 21]. Although not yet identified as infiltrating cells, B lymphocytes also play a role in neuroinflammation as IgG deposits have been found in dopaminergic neurons and Lewy bodies [19].

Similarly, neuroinflammation mediated by microglial cells is also accompanied by metabolic changes from oxidative phosphorylation to aerobic glycolysis [22, 23], mitochondrial dysfunction, and proteasomal dysfunction [22], which are caused by PAMPs and DAMPs and, together with the factors described above, can alter the permeability of the blood-brain barrier (BBB) and induce brain infiltration by circulating leukocytes, increasing local inflammation [10, 19].

All these changes increase oxidative stress, leading to apoptosis of nerve cells, which, through positive feedback, intensifies the abnormal aggregation of alpha-synuclein in the brain [13, 20]. In other words, oxidative stress, which is derived from the inflammatory process and the toxicity of pro-inflammatory cytokines, influences the degeneration of the substantia nigra by decreasing neurogenesis, neuronal loss, and alterations in synaptic plasticity, leading to the progression of PD [19, 20]. Therefore, it is indeed the case that neuroinflammation exacerbates neurotoxicity, promoting greater abnormal accumulation of alpha-synuclein and continuous degeneration of the substantia nigra [13, 14, 23].

2.2. The role of microglia in PD

Microglia are the primary brain cells derived from the immune system [14], which can also be called brain macrophages [10, 24, 25]. They communicate with neurons to maintain the function and structure of the parenchyma [8], promoting CNS homeostasis [10, 11], in addition to their neurotrophic role [10, 11], removal of toxic substances (such as alpha-synuclein), remodeling, and synaptic pruning [10, 21, 26]. Furthermore, they represent about 5 to 10-12% of all CNS cells [8, 15], being more abundant in gray matter than in white matter [15]. On the other hand, their dysfunction is an ally for the neurodegeneration of various brain diseases, including PD [8, 12], due to their role in neuroinflammation [14, 23], leading to decreased neurogenesis, neuronal loss, and altered patterns of synaptic plasticity [19, 27].

M1 microglia are related to the pro-inflammatory process, meaning they are related to neurodegenerative diseases by causing neurodegeneration through establishing inflammatory environments in the CNS by secreting inflammatory mediators [11, 28] such as TNF-alpha, IL-1beta, and IL-6 [14, 26, 29, 30,], while M2 are related to the anti-inflammatory process, i.e., homeostasis [11, 28]. Additionally, M1 activation can transmit neural changes, among them inducing astrocytes to adopt neurotoxic functions or lose their neurotrophic or synaptotrophic functionality [8]. Moreover, cytokines can alter the blood-brain barrier and recruit more immune cells to the brain parenchyma through chemokine receptor CCR2 signaling, increasing neuroinflammation [19]. Another change they can induce is the transmission of alpha-synuclein to neurons via exosomes, which are efficiently secreted as an antigen presentation mechanism and cargo release, leading to neuronal apoptosis [31]. Additionally, it has been identified that pro-inflammatory cytokines released by M1 microglia increased alpha-synuclein aggregation and its dissemination through exosomes [14, 21], which enter the microglial cytoplasm via Toll-like Receptor 2 (TLR2) receptors [13, 30, 32], and that alpha-synuclein binds to the microglial Fc gamma IIB receptor, leading to reduced phagocytosis and impairing its elimination [8].

Microglia activation is driven by Pathogen-Associated Molecular Patterns (PAMPs) and Damage-Associated Molecular Patterns (DAMPs), which are factors secreted by damaged neurons from injuries such as ischemia, infection, inflammatory diseases, brain

trauma, and neurodegenerative diseases [1], such as PD, for instance, whose primary inflammation mechanism is the accumulation of protein aggregates, alpha-synuclein [10, 33], which is secreted by neurons [28]. In an inflammatory response, microglia are polarized into M1 or M2, depending on the type of inflammation [10].

Alpha-synuclein, a pathological hallmark of PD, is encoded by the SNCA gene, being a genetic risk factor, both sporadic and familial, leading to uncontrolled mutations and multiplications [8, 34, 35]. It activates microglia through the NF-Kbeta pathway, which is the center of inflammatory microglial activity [8], increasing the production of pro-inflammatory cytokines, chemokines, inducible nitric oxide synthase (iNOS), and COX-2, leading to neuroinflammation. On the other hand, NF-Kbeta activated by neurons promotes survival and plasticity [13]. This pathway also activates the NLRP3 inflammasome, responsible for the maturation of IL-18 and primarily IL-1beta cytokines secreted by microglia, suggesting that alpha-synuclein, besides inducing pro-inflammatory microglial behaviors, also interacts with intracellular signaling cascades [8, 36].

It is worth noting that glucose metabolism is related to inflammatory responses through microglial activation [23], and that alpha-synuclein overexpression increases microglial activation [13, 28, 34, 37], leading to greater release of pro-inflammatory cytokines that damage neurons and further activate microglia, resulting in a vicious positive feedback loop [10].

2.3. The role of astrocytes in PD

Recent studies demonstrate that astroglia have a very important heterogeneous role in the pathogenesis of PD, being associated with factors that protect against the development of the disease and with factors that accentuate neurodegeneration and the evolution of the pathology [38, 39]. On one hand, as previously mentioned, under physiological conditions, astrocytes are responsible for neuroprotection, secreting neutrophil factors, being fundamental for homeostasis, survival, and information processing in the central nervous system. On the other hand, there is emerging evidence that dysfunctions of both microglia and astrocytes contribute to the pathogenesis and progression of PD [13, 8, 40, 41, 35, 28]. In the brains of patients with neurodegenerative diseases, when activated by a harmful stimulus, they migrate and transform into hypertrophic forms, that is, a "reactive or activated" form with a controversial role, as they can act in favor of neuroprotection or neurotoxicity when releasing cells and inflammatory factors associated with neurodegeneration and eventual development of PD. It is also worth mentioning that a dramatic accumulation of astrogliosis (reactive astrocytes) has been identified in the brains of patients with Parkinsonism [2, 42, 30].

New discoveries in the field delve into the pathological effects of this inflammatory response caused by astrocytes, as astrocytes respond to damage with this reactivity promoting the pathogenesis of PD. During this process, astroglia release a wide range of chemokines and cytokines such as interleukin-1 beta (IL-1β) and tumor necrosis factor-alpha (TNF-α), which are neurotoxic. Moreover, aggregated or misfolded α-synucleins are captured and degraded by astrocytes as mentioned, suggesting that α-synuclein released by neurons ends up accumulating in astrocytes and forming immunoreactive inclusion bodies [2, 31, 38, 39, 43]. Due to their cell-to-cell transmission function, this process results in a pro-inflammatory response dependent on the Toll-like receptor 4 (TLR4), which produces pro-inflammatory cytokines such as IL-1, IL-6, and TNF-α, as well as chemokines like CXC motif ligand 1 (CXCL1) [44, 32]. Finally, this accumulation of α-synuclein ends up disrupting astrocytic functions, causing significant dopaminergic neuronal death and neuroinflammation, contributing to neurodegeneration in PD, meaning that the presence of inclusions and neuronal loss are accompanied by astrogliosis [2, 8, 45].

It suggests that inhibiting the function of LRRK2 kinase normalizes lysosomal dysfunction and inflammatory responses [32, 46]. Additionally, attenuated monocyte infil-

tration and decreased C-C motif chemokine 2 (CCL2) because of defective astrogliosis in DJ-1 KO, observed in mice, indicate a failure in brain injury repair and contribute to the neurodegeneration seen in the development of PD. Conversely, astrocytes also exhibit functionalities that hinder the development of PD. A significant reduction in neuron death, α-synuclein accumulation, and microglial activation was observed when DJ-1 overexpression occurred in astrocytes, verifying rotenone-induced protection [38, 33, 45]. Astrocytes release molecules such as glial cell-derived neurotrophic factor (GDNF), mesencephalic astrocyte-derived neurotrophic factor (MANF), and ciliary neurotrophic factor (CNTF). Astrocyte activation also prevents the loss of dopaminergic neurons from MPP+-induced neuronal toxicity via Wnt1/β-catenin signaling activation [8, 13].

2.4. Interactions between microglia and astrocytes

The interaction between microglia and astrocytes occurs through various molecular signals, including adenosine triphosphate (ATP) and the cytokines IL-1alpha, C1q, and TNF-alpha [47-51], which are released by M1 microglia [49] in response to PAMPs or DAMPs [45, 47] to activate A1 astrocytes, thereby contributing to neuronal death in neurodegenerative diseases [49], as they do not respond to PAMPs or DAMPs without microglia [47]. However, A1 astrocytes recruited by microglia exhibit reduced phagocytic activity and expression of neurotrophic factors (48). On the other hand, astrocytes also release cytokines such as CCL2, CXCL1, CXCL10, GM-CSF, and IL-6, which stimulate microglia, dendritic cells, macrophages, and T cells at the site of inflammation [31, 40, 49], creating a bidirectional positive feedback communication that accelerates the progression of neurodegenerative diseases, including PD [50].

M1 microglia are primarily activated by TLR4 receptors in response to PAMPs or DAMPs, while astrocytes are activated by TLR2, TLR3, and TLR4 receptors, indicating a partial dependence on microglia, as TLR4 activation in microglia triggers an astrocytic response. This response involves the release of the aforementioned cytokines, but primarily TNF-alpha and IL-1, which are not only pro-inflammatory mediators but also signals to activate astrocytes [44, 45, 47].

During disease progression, there is communication between M2 microglia and A2 astrocytes, promoting neuronal survival and repair through the anti-inflammatory cytokine IL-10 produced by M2, which binds to IL-10R receptors expressed on A2, subsequently secreting TGF-Beta and reducing microglial activation [47]. Therefore, microglia initiate the inflammatory process through the release of immune cascades, inflammatory mediators, and network regulation formation, while astrocytes amplify neuroinflammation [39, 47].

2.5. PD multifactoriality and possible therapeutic targets

The interaction between microglia and astrocytes occurs through various molecular signals, including adenosine triphosphate (ATP) and cytokines IL-1alpha, C1q, and TNF-alpha [47-51], which are released by M1 microglia [49] from PAMPs or DAMPs [45, 47], to activate A1 astrocytes, thus contributing to neuronal death in neurodegenerative diseases [49], as they do not respond to PAMPs or DAMPs without microglia [47]. However, A1 astrocytes recruited by microglia have reduced phagocytic activity and expression of neurotrophic factors [48]. On the other hand, astrocytes also release cytokines such as CCL2, CXCL1, CXCL10, GM-CSF, and IL-6, which will stimulate microglia, dendritic cells, macrophages, and T cells at the site of inflammation [31, 40, 49], creating a bidirectional positive feedback communication that will accelerate the progression of neurodegenerative diseases, including PD [50].

M1 microglia are primarily activated by TLR4 receptors in the presence of PAMPs or DAMPs, while astrocytes are activated by TLR2, TLR3, and TLR4 receptors, meaning they almost depend on microglia. When TLR4 is activated in microglia, it triggers an astrocytic response. This response is mediated by the release of the aforementioned cyto-

kines, but mainly TNF-alpha and IL-1, which are not only pro-inflammatory mediators but also signals to activate astrocytes [45, 47].

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2.6. New Therapies

Currently, the existing therapies for PD treatment are symptomatic, revolving around maintaining dopamine levels, either by inhibiting the degradation of endogenous dopamine or providing dopamine agonists or the dopamine precursor. On one hand, these treatments do alleviate symptoms, but they are also associated with severe irreversible side effects such as drug resistance and dyskinesias, which greatly limit the management of the pathology [10, 13, 41, 44, 42]. Therefore, the need for developing therapies that alter the course of the disease or make its incidence more difficult becomes evident, as the available options to date do not represent a substantial alteration in the course of the pathology [15, 42].

As seen, inflammation is a significant pathogenetic factor in the progression of PD, hence, immunomodulatory therapies are increasingly being studied. Recent studies show that non-steroidal anti-inflammatory drugs do not have consistent results in reducing PD, but other alternatives are being tested and will be discussed in this topic [10]. Patients suffering from inflammatory bowel disease and undergoing anti-TNF therapy have had a considerable reduction in the incidence of PD. Another measure to slow the pathology is to resolve inflammation caused by astroglia and microglia. In this regard, studies in rodents have proven the efficacy of resolvin D1 (a pro-resolving molecule) in preventing both central and peripheral inflammation, as well as preventing neuronal dysfunction and motor deficits [10, 39].

On the other hand, neurodegeneration exacerbated by microglial activation is the target of several studies: adipose-derived stem cells (ADSCs) prevent dopaminergic loss by inhibiting microglial activation, and inhibition with nitric oxide (NO) also reduces microglial activation and prevents dopaminergic degeneration (13).

Furthermore, another line of studies considers the nature of α-synucleins associated with PD progression, with studies focusing either on using the patient's own immune system to generate antibodies against α-synucleins seeking active immunization or on the direct administration of antibodies against α-synucleins for passive immunization [10, 37]. An example of active immunization is the vaccine called AFFITOPE ®AFF1, which is based on the administration of short fragments of α-synucleins, resulting in a proven reduction in neuropathy and increased expression of anti-inflammatory cytokines [10].

As previously addressed, the interaction between mGluR5 and α-synucleins results in inflammatory dysfunction and consequent microglial activation. Therefore, an effective therapeutic strategy for neuroprotection would be to abort this interaction. In this regard, evidence shows that the activation of mGluR5 with CHPG nullifies the existing association between the receptors and α-synucleins, as there will be a decrease in lysosome-dependent degradation. This results in a reduction in α-synuclein-induced inflammatory signaling, and concomitantly, there will be an inhibition of inflammatory microglia, thus protecting neurons against cytotoxicity induced by microglial activation. Additionally, a treatment for urate for anti-inflammation achieved the same dissociative results [28, 37].

Lastly, another line of study that has gained strength in recent years is integrative medicine, primarily focusing on acupuncture. In tests with PD mice, improvements in

motor functions, anxiety, and increased levels of dopaminergic fibers and neurons in the substantia nigra and striatum were observed when treated at the acupoints GB34 and ST36. There were also indications that inflammatory responses and apoptosis were blocked when microglial and astrocyte overexpression was restored [52].

3. Conclusion

In this article, we reviewed the role of neuroinflammation in neurodegenerative diseases, focusing on microglia and astrocytes. Additionally, clinical or experimental studies on treatments associated with neuroinflammation in neurodegenerative diseases were discussed. A balance between pro-inflammatory and neuroprotective glial cells can be critical in the progression of neurodegenerative diseases. Furthermore, it has been reported that activated microglia and reactive astrocytes influence each other. Due to the complexity of microglial and astrocyte phenotypes and the various types of drugs, the stages of neurodegenerative diseases (more pro-inflammatory than neuroprotective) and the patients' conditions (confirmed disease pathology and likely to progress in a few years) can be crucial to demonstrating the benefits of anti-inflammatory treatments in clinical trials. The functions of microglia and astrocytes at specific stages of specific diseases in specific patients need to be identified. The next step for trials is to determine a standard method for evaluating each phenotype of microglia and astrocytes to standardize subsequent assessment.

Funding: None.

Research Ethics Committee Approval: None.

Acknowledgments: None.

Conflicts of Interest: The authors declare no conflict of interest.

Supplementary Materials: None.

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