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Review

Neuroinflammation as an Integral Component of Neurodegeneration in Parkinson's Disease

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Abstract: Parkinson's disease (PD) is a progressively advancing neurodegenerative disorder, the pathogenetic mechanisms of which remain poorly understood. The disease is characterized by the degeneration of dopaminergic neurons in the substantia nigra of the midbrain. Given the improvement in the quality of medical care provided to the population, it is projected that the total number of patients diagnosed with PD worldwide will rise to 8.7 million by 2030. This review addresses the fundamental aspects of neuroinflammation in the context of PD pathogenesis. There is no doubt that pro-inflammatory immunological mechanisms play a critical role in the onset and progression of the disease. Neuronal-derived cells, such as microglia and astrocytes, act as inducers of neuroinflammation, affecting the permeability of the blood-brain barrier to peripheral immune-competent cells. Furthermore, cytokine patterns of the immune response in PD appear to exist. Potential therapeutic approaches for mitigating neuroinflammation in PD, which have been studied in experimental and in vitro models, are also discussed.

Keywords: *neuroinflammation, cytokines, Parkinson's disease, neurodegeneration, immunotherapy*

1. INTRODUCTION

Parkinson's disease (PD) is the most common neurodegenerative disorder, second only to Alzheimer's disease [1]. PD is a multisystem alpha-synucleinopathy that leads to the death of dopaminergic neurons in the substantia nigra of the midbrain [2]. Currently, approximately 6.1 million people worldwide are affected by PD, and by 2030, the number of patients is projected to increase by 1.5 times [1, 3]. The rising prevalence of the disease can be attributed to the increasing average lifespan and the improvement in the quality of medical care for patients diagnosed with PD [2]. PD symptoms can be divided into motor symptoms, which include bradykinesia, gait disturbances, tremor, rigidity, and hypomimia [4], and non-motor symptoms such as depression, hyposmia, cognitive impairments, sleep disturbances, and constipation [5]. However, there exists a prodromal phase of PD during which the disease is asymptomatic or manifests with other symptoms that do not fall into the standard diagnostic markers for PD. For example, one of the symptoms with the highest risk of developing PD is idiopathic REM sleep behavior disorder, and it has been shown that 80% of individuals with idiopathic REM sleep behavior disorder will eventually develop PD [6].

Etiologically, PD can be divided into two main forms: familial and idiopathic. Familial cases account for 5-10% of all cases, whereas the remaining majority are idiopathic [7]. For the familial form, 13 loci and 9 genes have been implicated in the manifestation and progression of the disease. In idiopathic PD, a combination of genetic aberrations and environmental risk factors such as pesticides, neurotoxins, and traumatic brain injury is in-

volved [7]. Current data on the pathophysiology of neurodegeneration in PD is ambiguous and sometimes even contradictory. Recently, there has been an increasing body of evidence regarding the role of neuroinflammation in the development of PD.

From a pathophysiological perspective, inflammation is a typical pathological process that develops in response to local damage of any origin, characterized by phenomena of alteration, microcirculatory disturbances (including exudation and emigration), and proliferation aimed at localizing, destroying, and removing the damaging agent, as well as restoring or replacing the damaged tissues. Following an analysis of data from studies conducted in the broader field of neurodegenerative diseases, primarily Alzheimer's disease, neurobiologists have identified a link between neurodegeneration and inflammation [8]. It is important to note that the brain is an immunoprivileged organ, shielded from effector immune cells by the blood-brain barrier. Under normal conditions, immune system cells cannot enter brain tissue, and microglia play a crucial role in the permeability of the blood-brain barrier to immune cells.

Microglia constitute 0.5–16.6% of the total cell population in the brain and represent the most prevalent type of cells involved in immune responses within the central nervous system (CNS) [9, 10]. Interacting with neurons and the extracellular matrix, microglia exhibit various functions, including synaptic balancing, regulation of neovascularization, and phagocytosis [11]. Research has demonstrated that microglial density varies across different regions of the brain, with a higher concentration of microglia found in gray matter compared to white matter. Additionally, areas such as the hippocampus, olfactory bulb, basal ganglia, and substantia nigra exhibit denser microglial populations compared to the cerebellum and brainstem [12]. In a healthy brain, microglia continuously monitor the CNS for potential threats while striving to maintain homeostasis by secreting neurotrophic factors such as nerve growth factor and basic fibroblast growth factor. A wide array of antigens can activate microglia, ranging from infectious agents and foreign pathogens to prions, as well as pathologically altered proteins, aggregates, and apoptotic cells. Other common stimuli for microglial activation, both in vitro and in vivo, include interferon (IFN)-γ, β-amyloid (Aβ), lipopolysaccharides, and alpha-synuclein, the latter of which is characteristic of Parkinson's disease [14].

2. MATERIAL AND METHODS

We analyzed more than 60 articles in English focused on neuroinflammation and neurodegeneration. The inclusion criteria for the search were as follows: 1) full original articles and reviews cited in databases such as PubMed, MedLine, Web of Science, and Scopus, 2) articles in English, 3) a search time frame of 20 years, 4) keywords: neuroinflammation, Parkinson's disease, neurodegeneration, cytokines, neuroprotective effect, immune response, and immunity. The exclusion criteria included abstracts, monographs, manuals, and guidelines. The review was conducted in accordance with the PRISMA 2020 statement.

3. RESULTS

3.1. Neuroinflammation in Parkinson's Disease

Neuroinflammation can be defined as the process by which the brain's immune system is activated in response to ischemia, trauma, infection, exposure to toxins, neurodegenerative processes, stress, or aging [13]. Neuroinflammation appears to be a part of the complex pathogenesis of PD. However, the precise causal relationships between neuroinflammation and neurodegeneration remain unclear. Activated microglia are involved in neuroinflammation associated with PD, as demonstrated by various studies conducted in tissue cultures and animal models of the disease [15]. Significant activation of microglia has been observed in the post-mortem brains of patients with PD, indicated by the abnormal overexpression of human leukocyte antigen (HLA) and major histocompatibility

complex class II (MHC-II) in the affected brain regions, predominantly in the substantia nigra [16]. These multiple HLA molecules were expressed by dopaminergic neurons and presented processed antigenic peptides on the surfaces of neurons to be recognized by CD4+ T lymphocytes [17]. MHC-II-expressing microglia and CD4+ and CD8+ T cells have been documented in the substantia nigra of rat models of PD [18]. Similar results have been obtained through positron emission tomography analysis in living patients with PD [19, 20].

Alpha-synuclein aggregates are primarily detected in the substantia nigra in PD, but they can also be found in neurons throughout the central nervous system, peripheral nervous system, sympathetic ganglia, and the mesenteric plexus of the intestines [22]. Many animal studies and in vitro experiments have clearly demonstrated that alpha-synuclein acts as a potent stimulant of neuroinflammation [23]. Specifically, following the injection of short alpha-synuclein fibrils, chemokines are produced, and the induction of MHC class II (MHCII) in microglia is stimulated, accompanied by the recruitment of peripheral macrophages and monocytes. The induction of MHCII persists over time and appears to spread to other areas of the brain (e.g., the striatum) up to six months post-injection. The activation of microglia and the subsequent immune response propagate throughout the brain alongside alpha-synuclein inclusions, ultimately leading to dopaminergic neurodegeneration. This process underscores the role of the innate immune system in the course of the disease, particularly the notion that alpha-synuclein fibrils may be involved in the development of early prodromal stages of Parkinson's disease (PD), thus positioning them as promising candidates for biomarkers of preclinical PD [23, 24]. Another promising feature in the preclinical and early stages of PD, according to a recently published case-control study, is the specific T-cell responses to alpha-synuclein [25]. In this study, samples of peripheral blood mononuclear cells from an individual were analyzed before and after the diagnosis of motor stage PD. Remarkably, a strong CD4+ T-cell response against alpha-synuclein epitopes was detected more than 10 years prior to diagnosis, whereas in samples taken post-diagnosis, T-cell reactivity was significantly lower. In a further investigation, two additional cohorts of patients suspected of having PD were examined, and it was found that T-cell responses to alpha-synuclein were most robust shortly after diagnosis, producing high levels of cytokines (IFN-γ, IL-5, and IL-10), after which reactivity declined. The specific T-cell reactivity to epitopes derived from alpha-synuclein suggests autoimmune features in PD [33].

The potential involvement of the adaptive immune system in the pathogenesis of neurodegeneration in Parkinson's disease (PD) has also been investigated. Experiments using animal models have shown that both CD8+ and CD4+ T cells infiltrate the substantia nigra of patients with PD [26, 27]. More specifically, experimental data obtained from a mouse model suggest a PD-associated shift towards a Tc1/Th1 immune response, characterized by an increased ratio of CD8+ cytotoxic T cells (Tc) to CD4+ helper T cells (Th) and an elevated ratio of interferon-gamma (IFN-γ) producing T cells to interleukin-4 (IL-4) producing T cells [28]. This imbalance favoring pro-inflammatory Th cells (primarily Th1) over anti-inflammatory cells (Th2, regulatory T cells) is likely a contributing factor to the persistent neuroinflammation leading to neuronal degeneration. Accordingly, a case-control study was designed to investigate whether PD is associated with T-cell recognition of alpha-synuclein epitopes presented by a specific MHC class II allele [29]. Sulzer et al. demonstrated a T-cell response predominantly mediated by CD4+ T cells producing IL-4 or IFN-γ, with a potential contribution from CD8+ T cells producing IFN-γ. They also found that T cells respond to alpha-synuclein epitopes present in both extracellular native alpha-synuclein and fibrillar alpha-synuclein. The response of T cells to alpha-synuclein antigenic peptides is largely mediated by IL-5 or IFN-γ-secreting CD4+ T cells, as well as IFN-γ-secreting CD8+ T cells [24].

As for the involvement of B cells, the results are conflicting. Several studies have shown a decrease in the population of B lymphocytes, while others have found no changes in the peripheral blood of patients with Parkinson's disease (PD) [30, 31]. Recent research

focused on natural antibodies (IgG) targeting the pathology of PD. The researchers isolated memory B cells that produce antibodies against alpha-synuclein and found that these antibodies inhibited the seeding of intracellular alpha-synuclein aggregation. In this case, IgG played a protective role in the pathogenesis of PD [32].

3.2. Genes associated with neuroinflammation in Parkinson's disease

Many recent studies indicate a particular connection between certain genes linked to PD and the immune response of microglia and astrocytes in the central nervous system (CNS) [34]. Mutations in the *LRRK2* gene serve as risk factors for both familial and idiopathic PD. Furthermore, LRRK2 has been found in B lymphocytes and macrophages, suggesting its active involvement in the immune response [35]. Numerous studies have presented intriguing findings regarding *LRRK2* expression in primary microglial cells from adult mice and the secretion of pro-inflammatory cytokines from these activated microglia in response to pro-inflammatory stimuli such as lipopolysaccharides (LPS) [36]. Transgenic LRRK2 microglia stimulated with LPS have been shown to induce cell death when added to neuronal cultures [37]. These data indicate that patients with LRRK2 mutations exhibit heightened neuroinflammation, leading to excessive neurodegeneration and disease progression. Variants of the *LRRK2* gene have also been associated, beyond PD, with Crohn's disease, which is one of the most common forms of inflammatory bowel disease [38].

Mutations in the Parkin gene are the most common cause of autosomal recessive inherited PD. This gene typically encodes an E3 ubiquitin ligase [42]. Research in mice with *PARK* gene mutations has demonstrated excessive degeneration of dopaminergic neurons following the administration of lipopolysaccharides (LPS) and increased vulnerability of neurons to rotenone toxicity. Notably, microglia with mutations in the Parkin gene produced higher levels of pro-inflammatory cytokines, such as TNF-α, IL-6, and inducible nitric oxide synthase (iNOS), after LPS administration [43].

Missense mutations in the PINK1 gene are responsible for early familial forms of PD, which are inherited in an autosomal recessive manner [39]. The primary disruption caused by PINK1 mutations is mitochondrial damage, as PINK1 directly phosphorylates Parkin, enhancing its activity [40]. Studies have shown that PINK1-mutant mice produce elevated levels of IL-1β, IL-12, IL-10, and TNF-α in the striatum following systemic administration of LPS, thereby modeling the inflammatory response [41].

Another gene associated with PD that has been studied for its potential connection to inflammation is DJ-1, which is primarily expressed in astrocytes and microglia. Studies in DJ-1 mutant mice have revealed elevated levels of pro-inflammatory molecules, such as cyclooxygenase-2 and IL-6, in astrocytes following LPS administration [44]. This suggests that DJ-1 may play a significant role in the inflammatory response in the context of PD, highlighting its importance in the pathophysiology of the disease.

3.3. Cytokine profile of neuroinflammation in Parkinson's disease

Expression levels of cytokines such as IL-1α, IL-2, IL-1β, TNF-α, IL-6, TGF-β, and IFN-γ have been implicated in the degeneration of dopaminergic neurons in the substantia nigra following microglial activation [45]. Increased levels of these pro-inflammatory cytokines suggest an immune response to neuronal damage. Studies examining cerebrospinal fluid (CSF) and peripheral blood from patients with PD have primarily shown elevated serum levels of IL-1β and IL-6, along with increased levels of TGF-β in the CSF [46]. Additionally, the expression of IL-6 was significantly higher in the hippocampus of PD patients, as well as in those suffering from dementia [47]. Furthermore, in the case of TNF-α, inhibition of soluble TNF signaling through the administration of the recombinant dominant-negative TNF inhibitor XENP345 resulted in approximately 50% neuroprotection of substantia nigra neurons in various animal models of PD [48].

Another important cytokine involved in the pathogenesis of PD is IL-9. IL-9 is a pleiotropic cytokine with both pro-inflammatory and regulatory functions, depending on the context in which it is induced and the nature of the producing cells. IL-9 affects the activity of various cell lines in both the immune system and CNS. Notably, the production of IL-9 by Th9 cells has been associated with neurodegeneration and autoimmune diseases of the CNS [49]. Moreover, a distinguishing feature of IL-9, compared to other cytokines, is its neuroprotective role and support for recovery functions [50]. Recently, it was discovered that lower serum concentrations of IL-9 are present in patients with PD, which may indicate a dysregulation of IL-9 signaling, contributing to impaired neuroprotective processes in PD [51].

Thus, there appears to be a pattern of systemic inflammatory markers in patients with PD, characterized by lower levels of IL-9 and higher concentrations of IL-1β, IL-6, TGF-β, and TNF-α. This pattern underscores the existence of a specific inflammatory response [52, 53]. Furthermore, the levels of these markers correlate with the clinical stage of the disease, providing evidence of their contribution to neuroinflammation and the progression of PD [46]. These findings suggest that monitoring these cytokines could be beneficial for understanding disease progression and potentially guiding therapeutic interventions aimed at modulating inflammation in PD.

4. DISCISSION

Although the impact of neuroinflammation on the pathogenesis and progression of PD is well-established, concerns remain regarding potentially effective therapeutic strategies. Firstly, experimental data and animal studies have shown promising results for non-steroidal anti-inflammatory drugs, particularly ibuprofen and piroxicam, which appear to reduce the risk of developing PD [54, 55, 56]. However, epidemiological studies and meta-analyses have not confirmed a beneficial effect of these medications on either risk reduction or disease progression [57, 58].

Another potential immunomodulatory therapy, based on in vitro studies, is anti-TNF-α therapy. TNF-α has been shown to cause significant damage to dopaminergic neurons in vitro, and the use of non-specific TNF-α inhibitors, such as thalidomide, has yielded positive outcomes in some experiments with mouse and rat models of PD [59, 60]. Additionally, an epidemiological study revealed a lower incidence of PD among patients with inflammatory bowel disease receiving anti-TNF-α therapy compared to those who did not undergo this specific treatment [58]. These findings suggest that while the therapeutic potential of targeting neuroinflammation in PD is promising, further investigation and clinical trials are necessary to establish the efficacy and safety of such approaches in patients with PD.

Recently, several methodologies have emerged in the field of immunomodulatory therapy targeting α-synuclein, aimed at eliminating α-synuclein from the extracellular space and consequently reducing its aggregates in the brain. Similar clinical trials are being conducted for Alzheimer's disease, focusing on β-amyloid, and more recently on intracellular tau protein [59]. Immunotherapeutic approaches targeting α-synuclein have steadily advanced, encompassing both active and passive immunotherapy methods [60]. Active immunization involves the generation of antibodies against α-synuclein produced by the immune systems of animals. The first developed vaccine was capable of eliciting high titers of antibodies against aggregated α-synuclein, successfully reducing α-synuclein deposition and degeneration in the striatum [61]. In passive immunization, antibodies against various domains of α-synuclein are administered [61, 62]. The goal is to stimulate microglia via these specific antibodies, facilitating the clearance of extracellular α-synuclein and preventing intercellular transmission of α-synuclein.

5. CONCLUSION

Thus, neuroinflammation serves as a fundamental immune response that protects neurons from damage and compensates for neuronal injury occurring in the early stages of disease. However, the neurotoxic effects of neuroinflammation exacerbate neurodegeneration. Additionally, the neuroinflammatory response is regulated not only by peripheral immune cells but also by cells of the nervous system, including microglia and astrocytes. Cellular cooperation in the immune response in the context of PD is mediated by a specific cytokine pattern (IL-1β, IL-6, TGF-β, and TNF-α), which correlates with clinical symptoms and the stage of the disease. Reviews have indicated that neuroinflammation plays a key role in the pathogenesis of the prodromal stage of PD. In the immunopathology of PD, neuroinflammation is closely associated with α-synuclein, which triggers excessive activation of microglia. Contemporary immunotherapeutic approaches to PD involve both active and passive immunization with antibodies against α-synuclein.

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