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Immunopathogenesis of Parkinson's Disease: From Peripheral Inflammation to Neurodegeneration

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ABSTRACT

Parkinson's disease (PD) is increasingly recognized as a multifactorial disorder in which immune dysfunction and chronic inflammation play critical pathogenic roles. This review synthesizes evidence from clinical, genetic, and experimental studies on the contribution of innate and adaptive immune responses to PD. It discusses the roles of microglia, T cells, and peripheral immune cells; the influence of autoimmune processes and gut inflammation; and the therapeutic potential of targeting immune pathways. Both central and peripheral immune alterations are implicated in PD onset and progression. Dysregulated microglial activation, abnormal T-cell responses to α-synuclein, and systemic inflammation may drive dopaminergic neurodegeneration. Moreover, autoimmune diseases, gut dysbiosis, and infections have been associated with increased PD risk. Understanding immune-mediated mechanisms offers new avenues for early diagnosis and disease-modifying treatments. Emerging immunotherapies—such as α-synuclein antibodies, inflammasome inhibitors, and TNF-targeting agents—hold promise for modifying disease trajectory and improving patient outcomes.-

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1. INTRODUCTION

Parkinson's disease (PD) stands as the second most prevalent and rapidly expanding neurodegenerative disorder among the elderly, affecting 1–3% of individuals over 65 years old. Currently, it impacts over 6.2 million people globally, with projections suggesting this number will rise to over 12 million by 2040. PD is a long-term, diverse, and advancing neurodegenerative condition, pathologically marked by the accumulation of α-synuclein (α-syn) within Lewy bodies (LBs) and neurites, alongside the deterioration of dopaminergic (DA) neurons in the substantia nigra (SN). This degeneration is crucial for the emergence of PD's motor symptoms [1].

Furthermore, PD affects multiple systems, with α-syn pathology and neuronal loss also occurring in both the central and peripheral nervous systems outside of dopaminergic pathways. This broader impact can lead to various non-motor symptoms, such as loss of smell, constipation, fatigue, depression, and sleep issues, which may manifest before SN degeneration [2,3]. Motor dysfunction, a key pathological sign of PD, includes a range of movement and posture issues (such as slowness of movement, stiffness, resting tremor, and instability in posture and gait). These are mainly due to the progressive loss of DA neurons in the SN pars compacta (SNpc) and the resulting decrease in striatal DA levels, typically occurring when DA neuron loss is between 60–80%. This late manifestation restricts the effectiveness of medical treatments [4,5]. However, the pathology of PD extends beyond the loss of DA pathways, encompassing alterations in the serotonergic, noradrenergic, cholinergic, GABAergic, and glutamatergic systems. These changes are linked to the non-motor symptoms of PD, which can appear years or even decades before motor symptoms, offering a critical window for studying PD's progression, identifying early markers, conducting presymptomatic research, and potentially initiating early therapeutic interventions [6,7].

Currently, the initial source of α-synuclein aggregates, which seem to spread between cells in a manner similar to prions,

is not well understood. Recent theories suggest the existence of two types of PD: a "brain-first" type where neurodegeneration starts in the central nervous system (CNS), and a "body-first" type where it begins in the peripheral nervous system (PNS). The Synaptic Organizing Complex (SOC) model for Lewy body disease proposes that for most

patients, the initial α-synuclein pathology starts at a single location and then spreads [8,9]. The olfactory system and the enteric nervous system are believed to be the most common starting points. According to the SOC model, pathology starting in the olfactory system leads to the "brain-first" subtype of PD, which presents fewer non-motor symptoms before diagnosis, whereas pathology originating in the gut leads to a "body-first" subtype. This latter subtype is associated with older patients, symmetrical degeneration of dopamine neurons, a higher risk of dementia, autonomic symptoms before diagnosis, and REM sleep behavior disorders (RBDs) [10,11].

Though the "brain-first" and "body-first" PD subtypes have been proposed, there are no clear diagnostic criteria for the early stages of PD beyond non-motor risk markers. These include isolated RBD (iRBD) confirmed by polysomnography, loss of smell, constipation, orthostatic hypotension, erectile dysfunction, urinary issues, and depression. iRBD, a sleep disorder where dreams are physically acted out due to the failure of muscle paralysis, is considered the most significant early marker for PD and other diseases involving synuclein [12,13].

At this time, treatment for PD is limited to managing symptoms, making the development of early diagnostic methods and therapies that could delay or prevent disease progression critical. While non-motor symptoms have become a key focus for identifying individuals in the early stages of PD, new animal models that mimic this early stage with minimal loss of dopaminergic cells are vital for creating therapies that can modify the disease's course [14,15].

Furthermore, due to the challenges in replicating the full spectrum of early, middle, and late stages of PD within a single animal model, it is crucial to choose the most appropriate model based on the specific goals of the research [16,17].

Over the past two decades, there has been a significant increase in our understanding of how neuroinflammation and changes in the peripheral immune system contribute to the pathology of PD. It is now recognized as a complex disorder that involves neuroinflammation and immune system dysfunction, accompanied by a range of non-motor symptoms that can appear many years before the disease is officially diagnosed [18,19].

Given that PD is a disease associated with aging, immunosenescence, which refers to the decline in immune function and increased inflammation seen with aging, plays a critical role in its development. Both the innate and adaptive immune systems deteriorate with age and undergo changes in PD. This condition, known as inflammaging, is marked by the chronic release of inflammatory mediators or cytokines, such as C-reactive protein (CRP), interleukin 6 (IL6), and tumor necrosis factor (TNF), at low levels by persistently activated immune cells [20,21].

Extensive research, including postmortem studies, in vitro experiments, and animal models, has demonstrated that neuroinflammation is a key factor in the development of PD, involving both the innate and adaptive immune responses. Therefore, gaining insights into the immune-related mechanisms could unlock new therapeutic avenues for managing PD.

2. PERIPHERAL AND CNS IMMUNE RESPONSES IN PD

In patients with PD, there is a disruption in both cellular and humoral immune responses in the body's peripheral tissues, affecting individuals of various ages, disease durations, and levels of motor or psychiatric symptoms. Studies have found that monocytes from the blood of PD patients show increased phagocytic activity compared to those from healthy individuals. Furthermore, treating these monocytes with extracellular vesicles derived from the red blood cells of PD patients leads to an inflammatory response and a rise in LRRK2 expression [22,23].

There is also evidence suggesting the involvement of Toll-like receptors (TLRs) in the immune cells of the periphery in the development of PD. Specifically, TLR4 expression is reduced in women with PD, while TLR2 expression seems to be linked with the severity of motor symptoms. Importantly, monocytes have the capability to break down α-syn using their lysosomal system [24]. Mutations in the GBA gene, which affect lysosomal function, have been found to increase the risk of developing PD. Additionally, peripheral monocytes can serve as antigen-presenting cells by displaying MHC class I and II molecules, some of which are associated with PD [25,26].

On top of that, differences have been observed in the populations of immune cells in the periphery, such as CD8 T-cells and natural killer (NK) cells, in the blood of individuals with early-onset PD compared to those with late-onset PD, which is categorized by a disease duration of either less than or more than five years, respectively. NK cells are known as primary defenders in the immune system, crucial for initiating immune defense through their cytotoxic actions and cytokine production [27,28]. In studies examining the brains of deceased PD patients, NK cells were detected in the substantia nigra, with an observed increase in NK cell percentages in the CNS tissue before the loss of dopaminergic neurons. This suggests that NK cells may move from the blood to the brain, possibly aiming at and contributing to the loss of dysfunctional dopaminergic neurons as PD progresses. The interaction between immune responses in the periphery and the CNS represents a complex element of PD's underlying mechanisms. Disrupted peripheral immune responses, involving monocytes, TLRs, and certain immune cells like NK cells, may influence PD's onset and progression [29,30]. Deviations

in the adaptive immune response, particularly affecting peripheral blood lymphocytes, have been linked to PD's development. Studies have shown distinct immune profiles in PD patients compared to healthy individuals, highlighting potential immune-related mechanisms of the disease. Notably, people with PD have a significantly lower percentage of CD3 T-cells in their blood compared to healthy individuals, resulting in an altered ratio of CD4 to CD8 T-cells. This finding points to a significant alteration in T-cell populations in PD patients, underscoring the importance of the immune aspect in understanding the disease [31,32].

Moreover, the immune profile found in patients with PD differs significantly from the expected changes associated with normal aging. Instead of the usual CD8 T-cell replicative senescence seen with aging, this condition is conspicuously missing in PD patients. This unusual immune response hints at specific immune processes in PD that are different from those occurring due to aging. Interestingly, studies have shown that peripheral CD4 and CD8 T-cells in PD patients produce Th1/Th2 cytokines in reaction to α-synuclein, indicating a sustained memory T-cell response that might be contributing to persistent neuroinflammation in PD [33-35]. Additionally, a recent study using an animal model to overexpress α-synuclein in the substantia nigra pars compacta of mice demonstrated that such overexpression leads to the infiltration of CD8 and CD4 T-cells into the CNS. In this scenario, CD4 T-cells were particularly crucial in driving the myeloid inflammation and neurodegeneration triggered by α-synuclein. Further animal studies have shown abnormalities in the CD8 T-cell compartment, such as in PARKIN and PINK1 knockout mice, where exposure to peripheral inflammation from conditions like EAE or Gram-negative bacterial infection resulted in a marked increase in peripheral CD8 T-cell numbers compared to controls [36,37]. A comprehensive study analyzing over 700 immune features found an enhanced cytotoxic immune profile in females with early-to-mid-stage idiopathic PD, characterized by an increase in terminally differentiated effector memory CD8 T-cells, CD8 NKT cells, and circulating cytotoxic molecules, with a notable increase in the co-expression of cytotoxic molecules in CD8 TEMRA and effector memory cells [38]. Regarding CNS immune responses, activated microglia have been identified in post-mortem brain tissues of PD patients, and brain PET imaging studies have shown activated microglia in the midbrain, especially on the side most affected by the disease. In neurodegenerative conditions, microglia, the CNS's resident macrophages, quickly respond to brain homeostasis disruptions by migrating to the injury site and releasing pro-inflammatory and anti-inflammatory factors, also playing a key role in activating astrocytes. In vitro experiments have demonstrated that microglia can phagocytose oligomeric α-synuclein, leading to a pro-inflammatory state in these cells, with α-synuclein influencing microglial activation through TLRs and proteins like integrin CD11b [39,40].

Recent studies employing a model that introduces α-synuclein preformed fibrils directly into the mouse brain have highlighted the critical involvement of microglia in PD development. These studies reveal that the degeneration of neurons and the activation of microglia can happen even without the accumulation of α-syn aggregates. It seems that in the initial phases of PD, the disease progression is primarily driven by the activation of microglia in response to oligomeric α-synuclein. In experiments using PARKIN-deficient mice, neuroinflammation triggered by active experimental autoimmune encephalomyelitis (EAE) resulted in a significant increase in the activation of M1 microglia in these mice compared to their normal counterparts [41-43]. This is particularly interesting because the autosomal recessive form of PD, which lacks Lewy bodies, indicates that mitochondrial dysfunction can also initiate an inflammatory response from microglia. Additionally, in this genetic model, a higher presence of CD8 T-cells was observed in the brains of the PARKIN-deficient mice than in the controls. In the context of PD, there's an elevated number of CD8 T-cells in brain regions affected by the disease. Moreover, there's a significant increase in the variety of clonally distinct terminal effector CD8 T-cells found in the cerebrospinal fluid (CSF) of PD patients [44,45].

3. AUTOIMMUNITY AND PD

Some autoimmune disorders have been linked to a higher risk of PD, indicating that autoimmunity may contribute to PD's development. A significant study in Sweden, involving over 310,000 patients with 33 different autoimmune disorders, found that conditions such as multiple sclerosis, amyotrophic lateral sclerosis, pernicious anemia, Hashimoto's disease, polymyalgia rheumatica, and Graves' disease were linked to a higher risk of PD [46,47]. On average, individuals with an autoimmune disease were found to have a 33% higher risk of developing PD. Research on the ethnic Chinese population in Taiwan also showed that Sjögren's syndrome was linked to an increased PD risk, and autoimmune rheumatic diseases were associated with a 23% higher risk of PD compared to age and sex-matched controls without these conditions [48,49].

However, the connection between autoimmune disorders and PD is not always consistent. For instance, one study found that the risk of PD was 0.83% lower in patients with systemic lupus erythematosus compared to controls without the condition. The reliability of such association studies may be affected by factors like unverified diagnoses, the use of various medications, and numerous environmental and genetic factors. Additionally, secondary parkinsonism, which can occur as a feature of some autoimmune disorders, may complicate the interpretation of these findings [50,51].

The link between PD and autoimmune diseases might be partially due to shared genetic mutations that impact immune system functioning. Supporting this theory, studies using expression quantitative trait locus analysis have shown that the protein expression in CD4+ T cells and monocytes (indicators of an immune response) is linked to genetic variations that

contribute to the inherited risk of neurodegenerative diseases like PD and Alzheimer's disease [52,53]. For instance, unusual expression levels of proteins linked to PD, such as α-synuclein, LRRK2, and Rab29 in monocytes, have been found in connection with autoimmune diseases. These findings could help explain the clinical links observed between autoimmune diseases and PD. Additionally, certain genetic variations in LRRK2 associated with PD also coincide with variations linked to inflammatory conditions like Crohn's disease. Further research into gene networks and ontologies indicates that genes regulating white blood cell activity and cytokine signaling are tied to PD risk [54,55].

Infections from influenza and herpes simplex virus have also been seen to heighten the risk of developing PD later on. This increased risk is thought to be due to the infections initiating autoimmunity, potentially through molecular mimicry. This occurs when the structure of a viral protein closely resembles that of human α-syn, possibly triggering an autoimmune response [56,57].

Numerous research efforts have identified the presence of autoantibodies against α-synuclein in both the serum and CSF of PD patients. However, the findings regarding these autoantibodies have been mixed. While some research indicates that PD patients exhibit elevated levels of these antibodies, other studies report lower levels. Some research suggests a negative correlation between serum autoantibody levels to α-synuclein and PD progression, with lower immunoreactivity observed in advanced PD stages compared to early stages, and higher autoantibody levels typically seen in the early phase of the disease [58,59]. Conversely, another study associates the presence of these autoantibodies in the blood with more severe PD cases. When comparing antibody levels in serum and CSF, one analysis found no difference in serum levels between PD patients and healthy controls, but did find elevated levels in the CSF of PD patients [60].

These inconsistent results complicate the understanding of whether α-synuclein autoantibodies are harmful or protective. However, analyzing antibody titers in the CSF revealed higher titers in mild PD cases compared to moderate cases and healthy individuals. This suggests that the autoantibodies may aid in clearing α-synuclein, and that a failure in this antibody-mediated clearance mechanism could lead to α-synuclein accumulation as the disease advances. Furthermore, identifying the most reactive antigenic sites within α-synuclein that trigger responses from T helper cells and cytotoxic T cells has highlighted a subset of PD characterized by cytotoxic T cell reactions to these sites. This indicates that in some patients, an adaptive immune response to α-synuclein occurs early in the disease [61,62].

4. NSAIDS AND PD

Considering that NSAIDs have been shown to lower the risk of various neurodegenerative diseases, it's not surprising to find a similar link with PD. Early studies revealed that ibuprofen, acetaminophen, and aspirin could protect dopaminergic neurons in laboratory settings, thereby preserving the health of these neurons. Additionally, NSAIDs such as sodium salicylate, aspirin, and meloxicam have been found to guard against MPTP-induced damage to dopaminergic neurons in animal studies [63,64]. Subsequent to these findings, an epidemiological study indicated that individuals who regularly consumed non-aspirin NSAIDs (at least two tablets daily) exhibited a reduced risk of developing PD compared to those who did not use these NSAIDs regularly. This observation was further supported by another study which found that ibuprofen users, but not those using acetaminophen or aspirin, had a 35% decreased risk of PD compared to non-users [65,66]. A particular study highlighted that while NSAIDs as a group did not alter PD risk, ibuprofen specifically showed a modest protective effect, suggesting that certain NSAIDs might offer protective benefits. This protective mechanism is likely due to NSAIDs' ability to block cyclooxygenase 1 (COX1) and COX2, reducing the production of nitric oxide radicals and oxidative stress, which are particularly harmful to dopaminergic neurons [67,68]. In 2006, research showed that non-aspirin NSAIDs reduced PD risk by 20% in men, but interestingly, increased the risk by 20% in women, marking one of the first studies to report gender differences in NSAID use and PD risk. While some studies have not replicated the association between NSAID use and PD incidence, they have noted that PD patients often have a higher prevalence of immediate-type hypersensitivity (such as asthma, hay fever, or allergic rhinitis), suggesting an inflammatory component in PD's development and highlighting the importance of evaluating NSAID use's impact before PD onset [69].

5. GUT DYSBIOSIS AND INFLAMMATORY BOWEL DISEASE

In 2003, it was proposed that the origins of PD could be traced back to the gut, with gastrointestinal issues such as constipation appearing long before the motor symptoms and clinical diagnosis of PD. This theory has since evolved to include the role of gut microbiota and intestinal inflammation in driving the disease. Studies have consistently shown differences in the gut bacteria of PD patients compared to healthy individuals, highlighting the impact of the gastrointestinal milieu and its microbial residents on PD [70,71]. Although research has identified shifts in the abundance of specific bacteria like Prevotellaceae, Bifidobacterium, Akkermansia, and Lactobacillus in PD patients, findings vary due to differences in research design, patient groups, and control selections. The exact contribution of specific gut bacteria to the onset or progression of PD is still unclear, but there is evidence linking the presence of certain bacterial families in fecal samples to motor symptoms, disease progression, and early non-motor stages of PD. Additionally, a connection between changes in gut bacteria and intestinal inflammation in PD has been observed [72,73]. PD patients' stool samples have shown higher levels of inflammatory markers compared to healthy controls, and the presence of these markers inversely correlates

with the age at which PD symptoms begin. This suggests a potential role in disease development. Correlations between levels of Bacteroides and Verrucomicrobia with plasma levels of TNF and IFNγ, respectively, support the idea that gut dysbiosis and inflammation might initiate PD pathology. Research into how targeting the gut microbiome could potentially slow or alter the course of PD is ongoing and represents a promising field of study [74-76].

Numerous studies in the field of epidemiology have linked the risk of PD with the presence of inflammatory bowel disease (IBD). A meta-analysis has indicated that individuals with IBD are at a 28–30% higher risk of developing PD. Furthermore, a systematic review and meta-analysis revealed that IBD patients undergoing long-term anti-inflammatory treatment with anti-TNF biologics exhibit a 78% reduced likelihood of developing PD compared to those not treated with anti-TNF medications. This supports the theory that ongoing inflammation plays a role in the development of PD [77-79]. Further studies are necessary to determine the optimal timing, duration, and whether therapy should be preventative or initiated prior to the appearance of clinical (motor) symptoms. Importantly, the anti-TNF biologics currently approved by the FDA may not be ideal for prolonged use due to their immunosuppressive nature, stemming from their ability to inhibit both the membrane-bound and soluble forms of TNF, and their limited ability to penetrate the brain [80,81]. Pegipanermin, a second-generation biologic with a unique dominant-negative mechanism that selectively targets soluble TNF without causing immunosuppression, is capable of crossing the blood-brain barrier and has demonstrated neuroprotective effects in various preclinical studies on aging, neuronal dysfunction, and neurodegeneration [82,83]. This drug, currently being tested in clinical trials for treating pulmonary complications in COVID-19 under the name QUELLOR (ClinicalTrials.gov identifier NCT04370236), could potentially be beneficial in treating PD and other chronic neuroinflammatory disorders of the brain.

6. IMMUNE-BASED THERAPEUTIC APPROACHES

Several immunotherapy strategies show promise for PD. These strategies encompass the use of anti-inflammatory medications and immunosuppressive agents early on to reduce risk; employing antibodies to neutralize extracellular α-synuclein clumps; enhancing lysosome function to speed up the removal of α-synuclein; using immunosuppressants to block the release of proinflammatory cytokines; preventing the migration of immune cells and the presentation of MHC antigens to T cells; adjusting the activity of CD4+ and CD8+ T cells; promoting immune tolerance through the regulation of regulatory T cells' activity; and altering the expression of genes associated with PD risk [84]. The most promising among these strategies are examined thoroughly in the further sections.

7. PREVENTIVE STRATEGIES

PD is a complex, age-related condition, with studies in both animals and humans highlighting the role of ongoing inflammatory processes and immune system responses. Research has explored the potential of non-steroidal anti-inflammatory drugs (NSAIDs) to lower PD risk when used before the disease develops. Early studies hinted at NSAIDs offering protection against PD, but later research failed to confirm these results. Comprehensive reviews in 2018 and 2019, which combined data from all available studies, including over two million people and 14,000 PD patients, found no significant link between NSAID use and PD risk [85-87]. However, one analysis suggested a minor protective effect from non-aspirin NSAIDs (relative risk 0.91), but inconsistencies in examining or standardizing potential confounding factors across studies mean an association in certain groups cannot be entirely ruled out [88,89].

A 2018 study in the USA analyzing prescription data revealed that corticosteroids and inosine monophosphate dehydrogenase inhibitors, both widely used immunosuppressants, might lower PD risk. Corticosteroids affect various inflammatory pathways, while inosine monophosphate dehydrogenase inhibitors dampen T cell activity. Nonetheless, these findings could be skewed by missing information on long-term medication adherence and the influence of other variables, such as smoking habits [90,91].

8. IMMUNOTHERAPY TARGETING A-SYN

The discovery that the accumulation of α-synuclein is a key pathological feature of PD has highlighted it as a critical target for immunotherapy. Beyond its toxic impact on dopaminergic neurons, α-synuclein can also trigger various immune responses. Consequently, strategies to mitigate or halt its buildup within cells and prevent its spread from one cell to another have become central to efforts aimed at altering the disease's progression. Strategies being explored include decreasing the production of α-synuclein, promoting its breakdown within cells, preventing the formation of α-synuclein clusters outside cells, inhibiting its oligomerization, fibrillization, and aggregation, and stopping its transmission between cells. Presently, immunotherapy trials are concentrating on the latter three strategies [92,93].

The aggregation of α-synuclein is believed to stem from a failure in its removal. Studies conducted in both test tubes and living organisms have demonstrated that a naturally occurring antibody against α-synuclein aids in its removal, diminishes its aggregation, and lessens neuronal damage. However, individuals with PD typically have lower levels of this antibody in their plasma, indicating a deficiency in the clearance or neutralization of α-synuclein. As a result, numerous clinical trials are either underway or have been completed, focusing on targeting α-synuclein through active or passive

immunization. These efforts have been the subject of extensive reviews in the scientific literature [94,95].

9. TARGETING IMMUNE MEDIATORS

An unconventional strategy to directly target α-synuclein involves the regulation of immune responses that contribute to the deterioration of dopaminergic neurons. Various compounds that can modulate these responses have been explored in animal models of PD. A key target in this approach is the microglial NACHT, LRR, and PYD domains-containing protein 3 (NLRP3) inflammasome, which plays a significant role in chronic neuroinflammation leading to the progressive loss of dopaminergic neurons [96,97]. In PD animal models, the NLRP3 inhibitor MCC950 effectively prevented the activation of microglial inflammasomes, protected dopaminergic neurons in the substantia nigra, and improved motor symptoms. Additionally, antidiabetic medications like pioglitazone and rosiglitazone have been shown to reduce inflammation and safeguard dopaminergic neurons in animal studies, though their effectiveness in human PD patients remains to be verified. Similarly, the immunosuppressants cyclosporine and FK506 have demonstrated neuroprotective effects in PD animal models, suggesting their potential utility in treating PD in humans [98,99].

10. POTENTIAL IMMUNE TARGETS

In addition to the inflammation caused by microglia within the brain, elements of the body's cellular and antibody-based immune responses can enter the brain tissue, intensifying inflammation and accelerating the damage to dopamine-producing neurons. Thus, targeting these immune components and their entry into the brain could represent alternative therapeutic strategies in PD [100,101].

The use of immune checkpoint inhibitors, which enhance the body's adaptive immune response and have transformed cancer treatment, can also induce neuroinflammation and cognitive impairment in animal models of cancer. This indicates that increased neuroinflammation plays a role in neurodegenerative diseases, suggesting that treatments which suppress the immune system, targeting mechanisms activated by immune checkpoint inhibitors, might offer a new treatment pathway [102,103].

Different T cell types have been linked to the development of PD and could serve as targets for treatment. TH17 cells, for example, are known to destroy dopamine-producing neurons either by direct contact between the TH17 cell's LFA1 and the neuron's ICAM1 or by releasing IL-17. Strategies to inhibit TH17 cell development or block the interactions between LFA1 and ICAM1 or between IL-17 and its receptor could therefore be potential treatments for PD [104,105]. TH1 cells and cytotoxic T cells have also been associated with PD, suggesting that broad-spectrum T cell inhibitors, which prevent T cell proliferation or promote immune tolerance through regulatory T cells, could be beneficial. One method might involve using CTLA4, which inhibits T cell activation by competing with CD28 for B7 binding on antigen-presenting cells. CTLA4 fusion proteins with antibodies, such as abatacept and belatacept, represent possible treatments, although they require more research [106,107].

11. CONCLUSION

The growing body of evidence underscores that Parkinson's disease is not solely a neurodegenerative disorder confined to the central nervous system but a systemic condition with significant immune involvement. Both innate and adaptive immune responses participate in the disease's pathogenesis through chronic neuroinflammation, aberrant microglial activation, and maladaptive T-cell responses against α-synuclein. Peripheral immune alterations, autoimmune associations, and gut inflammation further reinforce the concept of PD as a disorder at the intersection of neurology and immunology.

While traditional therapies target dopaminergic symptoms, they fail to halt disease progression. Immunomodulatory and anti-inflammatory approaches—ranging from monoclonal antibodies against α-synuclein to inhibitors of the NLRP3 inflammasome and TNF signaling—represent promising avenues to slow neurodegeneration. However, translating these experimental findings into effective clinical therapies requires further understanding of immune signaling pathways, patient stratification, and timing of intervention.

Ultimately, integrating immunological biomarkers into early PD diagnosis and developing personalized immune-targeted therapies may transform disease management, shifting the paradigm from symptomatic relief to disease modification.

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