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Hidden face of Parkinson's disease: Is it a new autoimmune disease?

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From the Contents

Abstract

Parkinson's disease is a neurodegenerative disorder marked by the degeneration of dopaminergic neurons and clinical symptoms such as tremors, rigidity, and slowed movements. A key feature of Parkinson's disease is the accumulation of misfolded α-synuclein, forming insoluble Lewy bodies in the substantia nigra pars compacta, which contributes to neurodegeneration. These α-synuclein aggregates may act as autoantigens, leading to T-cell-mediated neuroinflammation and contributing to dopaminergic cell death. Our perspective explores the hypothesis that Parkinson's disease may have an autoimmune component, highlighting research that connects peripheral immune responses with neurodegeneration. T cells derived from Parkinson's disease patients appear to have the potential to initiate an autoimmune response against α-synuclein and its modified peptides, possibly leading to the formation of neo-epitopes. Recent evidence associates Parkinson's disease with abnormal immune responses, as indicated by increased levels of immune cells, such as $CD4^+$ and $CD8^+$ T cells, observed in both patients and mouse models. The convergence of T cells filtration increasing major histocompatibility complex molecules, and the susceptibility of dopaminergic neurons supports the hypothesis that Parkinson's disease may exhibit autoimmune characteristics. Understanding the immune mechanisms involved in Parkinson's disease will be crucial for developing therapeutic strategies that target the autoimmune aspects of the disease. Novel approaches, including precision medicine based on major histocompatibility complex/human leukocyte antigen typing and early biomarker identification, could pave the way for immune-based treatments aimed at slowing or halting disease progression. This perspective explores the relationship between autoimmunity and Parkinson's disease, suggesting that further research could deepen understanding and offer new therapeutic avenues. In this paper, it is organized to provide a comprehensive perspective on the autoimmune aspects of Parkinson's disease. It investigates critical areas such as the autoimmune response observed in Parkinson's disease patients and the role of autoimmune mechanisms targeting α-synuclein in Parkinson's disease. The paper also examines the impact of $CD4^+$ T cells, specifically Th1 and Th17, on neurons through *in vitro* and *ex vivo* studies. Additionally, it explores how α-synuclein influences glia-induced neuroinflammation in Parkinson's disease. The discussion extends to the clinical implications and therapeutic landscape, offering insights into potential treatments. Consequently, we aim to provide a comprehensive perspective on the autoimmune aspects of Parkinson's disease, incorporating both supportive and opposing views on its classification as an autoimmune disorder and exploring implications for clinical applications.

Key Words: astrocyte; autoimmune response; biomarkers; clinical implication; major histocompatibility complex/human leukocyte antigen; microglia; neurodegenerative disease; neuroinflammation; Parkinson's disease; T cells; α-synuclein

Introduction

Parkinson's disease (PD) is a neurodegenerative disorder characterized by the loss of dopaminergic neurons in the brain, leading to clinical manifestations such as resting tremor, muscle rigidity, and bradykinesia (Bloem et al., 2021).

Misfolded α-synuclein (α-syn) aggregates form insoluble intracellular inclusions known as Lewy bodies within neuronal cell bodies. The accumulation of α-syn aggregates as misfolded α-syn became insoluble is a hallmark of PD, closely linked to the degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNpc) of the midbrain (Michel et al., 2016). It is thought to play a critical role in the onset and progression of PD-like neurodegeneration, as it can induce neurotoxicity through various pathways, including neuroinflammation and oxidative stress (Jiang et al., 2016). Although genetic or environmental factors have been associated with PD, its etiology remains largely unknown in most cases, highlighting the need for further research (Tansey et al., 2022).

Neuroinflammation, which has been connected to changes in peripheral adaptive immunity, is often linked to the progression of neurodegenerative diseases. $CD4^+$ T cells are essential for adaptive immunity, thus, any functional impairment in these cells may contribute to the inflammatory profile observed in PD (Zhu et al., 2010). Recent studies have observed abnormal changes in immune cells, including $CD4^+$ and $CD8^+$ T cells, B cells, and their subsets in both the SNpc of preclinical mouse model and PD patients (Brochard et al., 2009; Sulzer et al., 2017; Karikari et al., 2022). Additionally, evidence from various studies implicates autoimmune diseases, such as inflammatory bowel disease and rheumatoid arthritis (RA), and adaptive immune systems in the pathogenesis of PD.

Similar to the increased T cell levels found in the brains of multiple sclerosis (MS) patients, where T cells target oligodendrocytes, PD patients also show elevated T cell levels in the midbrain compared to age-matched healthy controls. Furthermore, autoreactive T lymphocytes and glia-mediated inflammation have been observed in

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PD patients and animal models (Brochard et al., 2009). In a previous study, α-syn-specific T cells in PD patients, combined with α-syn pathology, provided the hypothesis that PD might exhibit characteristics of an autoimmune disorder (Garretti et al., 2019). As a result, these findings imply a potential link between autoimmune responses and PD pathogenesis. This perspective aims to elucidate the relationship between autoimmune responses and PD and to propose future directions for clinical and basic research in this field.

Search Strategy

We conductced an extensive search of the PubMed databases using targeted keywords, including "Parkinson's disease," "Parkinson's disease patients," "autoimmune response," "Parkinson's disease mouse model," "α-synuclein-specific T cell response," "Parkinson's disease therapeutics." This approach allowed for a thorough review of recent research in these areas. To ensure a comprehensive understanding, we focused on publications from 1988 to 2024, incorporating key studies to provide a well-rounded perspective in our review.

An Autoimmune Response in Patients With Parkinson's Disease

An epidemiological study has revealed a link between PD and several organ-specific and multi-organ autoimmune disorders. Patients diagnosed with MS or polymyalgia rheumatica have a 33% higher risk of developing PD and this risk is exacerbated after hospitalization for an autoimmune disorder (Kang et al., 2023). A recent genome-wide association study revealed 17 shared genetic loci between PD and seven autoimmune diseases, including RA, MS, and type 1 diabetes (Witoelar et al., 2017).

The central nervous system (CNS) was thought to be an immune-privileged site, primarily because the blood–brain barrier (BBB) prevents blood protein, antibodies, immune cells, and drugs from penetrating the brain (Biswas et al., 2020). Pro-inflammatory cytokines, such as interleukin (IL)-2, IL-6, IL-8, RANTES, tumor necrosis factor alpha (TNFα), and interferon gamma (IFNγ), are elevated in the blood of PD patients (Reale et al., 2009). The levels of these cytokines and chemokines are linked to the clinical stages of PD, suggesting that peripheral inflammation contributes to disease progression. Peripheral inflammation, alterations in lymphocyte subtypes, and the breakdown of the BBB may contribute to T cell infiltration into affected brain regions in PD (**Figure 1-(1)**). $CD3^+$ T cells, representing total T cell makers, were identified in the brains of PD patients for the first time (McGeer et al., 1988a, b). Previous studies have observed a general decline in total helper T cells (Th cells) and $CD8^+$ cytotoxic T cells (Tc cells), while others have shown no change in regulatory T cells (Treg cells), but an increase in Th1 cells, particularly the Th17 cells in PD patients (Baba et al., 2005; Brochard et al., 2009). Recent studies also found notable abnormalities increasing innate immune factors in the peripheral blood and cerebrospinal fluid of PD patients (Chen et al., 2017; Gate et al., 2021). These observations imply that peripheral inflammation and immune cell alterations with the pathogenesis of PD. Nevertheless, the underlying cause of this immune response remains unclear.

A previous study demonstrated that T cells isolated from PD patients exhibited toxicity towards induced pluripotent stem cell-derived neurons (Sommer et al., 2018). While these findings are intriguing, additional validation is required to determine whether the identified α-syn peptides can provoke *in-vivo* T-cell responses and contribute to neurodegenerative processes in PD, such as neurotoxicity and neuroinflammation. Previous studies have identified multiple antigenic regions, including α-syn 61–75, α-syn 92–100, α-syn 100–114, α-syn 121–128, and α-syn 120–134 as potential T-cell epitopes (Lindestam Arlehamn et al., 2020; Karikari et al., 2022).

Nevertheless, counterarguments are challenging the autoimmune hypothesis in PD. Although evidence increasingly supports immune system involvement in PD, the degree to which autoimmunity drives disease progression remains a topic of debate. In a recent clinical study, total $CD3^+$ T cells were decreased in PD patients, which was associated with disease severity. They then explored whether the reduction in $CD3^+$ T cells in PD patients was due to changes in the proportions of $CD3^+CD4^+$ or $CD3^+CD8^+$ T-cell subpopulations. The findings indicated a significant decrease in both $CD3^+CD4^+$ and $CD3^+CD8^+$ T cells in PD patients (Bhatia et al., 2021). Another clinical study evaluated changes in circulating leukocyte populations in PD patients compared to controls and addressed discrepancies in the literature by examining the potential influence of clinical variables on these data. The study confirmed a reduction in $CD4^+$ T helper and B cells in individuals with PD (Stevens et al., 2012). The primary limitation of these studies is the relatively small cohort size, which reduces statistical power and limits confidence in ruling out correlations with other clinical parameters. Moreover, these findings indicate that clinical variability may explain discrepancies observed among previous studies, underscoring the need for future studies to account for these factors.

Role of Autoimmune Response Targeting α-Synuclein in Parkinson's Disease

Intracellular degradation of self- and foreign proteins results in the generation of peptides that are presented on the major histocompatibility complex (MHC) molecules. These epitopes are presented to T cells, which can recognize the complex formed between MHC molecules and peptide epitopes (**Figure 1-(2)**). The excessive accumulation of α-syn can cause it to be recognized as an autoantigen by the immune system (**Figure 1-(2)**). The hypothesis α-syn plays a role in the autoimmune processes underlying PD has been widely discussed and debated. MHC molecules are expressed on dopaminergic neurons, and when the appropriate antigen and $CD8^+$ T cells are present, these MHC I-expressing neurons are more susceptible to destruction. It suggests that antigenic epitopes may activate $CD8^+$ T cells, contributing to autoimmune responses and dopaminergic neuronal cell death (**Figure 1-(3)**) (Cebrian et al., 2014). Notably, recent groundbreaking studies have shown an increase in α-syn-specific T cells in PD patients, likely to certain human leukocyte antigen (HLA) risk haplotypes, indicating a potential autoimmune role of T cells in PD (Sulzer et al., 2017; Lindestam Arlehamn et al., 2020). Sulzer et al. (2017) focused on the properties of α-syn, investigating its potential role as a self-antigen target for T cells. They demonstrated the immune responses of peripheral blood mononuclear cells from both PD patients and healthy controls when exposed to various α-syn-derived peptides (Sulzer et al., 2017). This study has shown that α-syn-derived peptides around the Y39 and S129 phosphorylation sites can trigger the T cell response. Additionally, the T cell subsets responding to these α-syn epitopes are primarily $CD4^+$ T cells, with a smaller proportion of $CD8^+$ T cells (Sulzer et al., 2017).

A prior study demonstrated that α-syn in hematopoietic cells is associated with aberrant activation of the adaptive immune response in PD. Furthermore, α-syn can be presented by microglia, which act as antigen-presenting cells (APCs) to stimulate T-cell mediated responses. Several studies on PD have reported dysregulation of $CD4^+$ T cell subpopulations. In animal models based on α-syn, such as Thy1-α-syn, AAV2-α-syn overexpression, and preformed fibril-injected models, enhanced infiltration of $CD4^+$ or $CD8^+$ T cells into the midbrain has been observed (**Figure 1-(3)**). In postmortem brain samples from PD patients, as well as in a 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine mouse model, both $CD4^+$ and $CD8^+$ T cells were found to have invaded the SNpc (Brochard et al., 2009). This study highlighted that $CD4^+$ T cells, but not $CD8^+$ T cells, exhibited deleterious effects, indicating a possible role of the adaptive immune system in the progression of PD (Brochard et al., 2009). In the AAV2-SYN mouse model, CNS myeloid cells showed increased MHC II protein expression, and $CD4^+$ and $CD8^+$ T cells infiltrated the CNS. Furthermore, in $CD4^{-/-}$ and $CD8^{-/-}$ knockout mice, CD4-deficient mice were found to be protected from dopaminergic cell loss caused by α-syn overexpression (Williams et al., 2021). Additionally, nitrated α-syn triggered an abundance of Th17 cells and Treg cell dysfunction (Benner et al., 2008). In our previous study, we demonstrated that α-syn monomers, preformed fibrils, and α-syn peptide-induced T-cell response, an increase in Th1 and Th17 cells, and an imbalance in Treg cells after experimental immunization of mice and *ex vivo* α-syn peptide recall response. Hence, the α-syn peptide-induced autoimmune T-cell response, particularly involving Th1 and Th17 cells, contributes to neuronal cell death (Choe et al., 2024). Furthermore, α-syn peptides elicited specific $CD4^+$ or $CD8^+$ T-cell responses in the AAV-A53T-α-syn PD mouse model (Karikari et al., 2022).

Effect of $CD4^+$ (Th1 and Th17) T Cells on Neurons *In Vitro* and *Ex Vivo* Studies

A previous study has reported a higher proportion of Th1 cells in the peripheral blood of individuals

with PD (Sulzer et al., 2017). T cell population change can also influence the levels of circulating cytokines, with Th1 and Th17 cells leading to elevated levels of TNFα, IFNγ, and IL-17 (**Figure 1-(4)**) (Kustrimovic et al., 2018; Sommer et al., 2018). Cytokines such as TNFα and IFNγ, secreted by activated Th1 cells, may have a detrimental effect on neurons (**Figure 1-(4)**). Th1 cells exacerbate inflammation by stimulating cytokine secretion (**Figure 1-(4)**). However, the precise mechanisms underlying the involvement of Th1 cells in PD pathogenesis remain uncertain.

Elevated levels of circulating Th17 cells were observed in the early stages of PD (Sommer et al., 2018). Pro-inflammatory Th17 cells are known to contribute to PD pathology by upregulating cytokines like IL-17A, IL-6, IL-23, and IL-1β (**Figure 1-(4)**). Th17 cells can directly induce the death of dopaminergic neurons by binding to specific proteins on the cell membrane, including leukocyte function-associated antigen-1 and intracellular adhesion molecule-1 (Sommer et al., 2018). This interaction activates signaling pathways that lead to dopaminergic neuronal cell death. Midbrain neurons derived from PD-induced pluripotent stem cells exhibit a pathogenic mechanism distinct from healthy normal cells. This pathogenic mechanism is characterized by increased IL-17A signaling and nuclear factor-κB expression, associated with the activation of Th17 cells. This study suggests that PD-derived T cells can directly target dopaminergic neurons; however, the lack of antigenicity, neuronal specificity, and APC leaves out several key *in vivo* factors crucial to understanding PD progression. Th17 cells are central to MS, a well-studied autoimmune neurological disorder. Notably, a study investigating the function of Th17 cells in experimental autoimmune encephalomyelitis, as a well-known MS mouse model, has not focused on IL17R-mediated neurotoxicity (Siffrin et al., 2010). This point could serve as a basis for similar studies in PD mouse models, providing insights into the role and mechanisms of Th17 lymphocytes in PD pathogenesis.

Effect of α-Synuclein on Glia-Induced Neuroinflammation in Parkinson's Disease Studies

Autoimmune diseases are characterized by chronic activation of the peripheral immune system, leading to the production of inflammatory mediators that can potentially stimulate neuroinflammation and contribute to the development of PD. Neuroinflammation encompasses the activation of microglia and astrocytes, resulting in the release of proinflammatory cytokines and chemokines, as well as the infiltration of peripheral immune cells into the CNS (Fornari Laurindo et al., 2023).

The interaction between microglia and α-syn plays a critical role in the development of PD. During PD progression, abnormally accumulated α-syn can lead to BBB leakage, and recruitment of T- and B-cells into the SNpc (**Figure 1-(1)**) (Theodore et al., 2008). It may also become an autoantigen that binds to Toll-like receptors, activating microglia and causing them to differentiate into the microglia type-1 (M1) subtype (**Figure 1-(5)**). These activated microglia stimulate intracellular inflammatory pathways, induce the release of pro-inflammatory cytokines, and promote the differentiation of $CD4^+$ T cells into Th1 and Th17 cells, thus contributing to neuronal damage. The upregulation of MHC II allowed microglia to present self-antigens to auto-reactive T cells (Thompson and Tsirka, 2017). In the PD mouse model, activation of microglia by classical inflammatory mediators can convert into neurotoxic A1-phenotype astrocytes (Liddelow et al., 2017; Yun et al., 2018). Considering the correlative presence, our previous *ex vivo* study demonstrated that various factors secreted by splenocytes immunized with α-syn peptides induce neuroinflammation by activating glial cells. In primary microglia, α-syn peptide immunization increased several cytokines, including *Tnf-α*, *Il-6*, *Il-1α*, and *Ifn-γ*, which are markers of M1-type microglia (**Figure 1-(6)**). In primary astrocytes, α-syn peptide immunization resulted in the preferential upregulation of general astrocyte reactive and neurotoxic form of A1-specific transcripts, but not the neuroprotective A2-specific transcripts (**Figure 1-(6)**) (Choe et al., 2024). Therefore, activated M1-microglia and A1-astrocytes can release proinflammatory cytokines, such as TNFα and IL-1β, which contribute to neuronal cell death (**Figure 1-(7)**) (Gao et al., 2023).

Following previous *ex vivo* findings, our research team is developing an *in vivo* mouse model in mimetic PD with autoimmune response-like features, using α-syn peptides (α-syn 31–45, α-syn 32–46, α-syn 60–95, α-syn 121–135, and α-syn 126–140 as potential T cell epitopes) immunization as outlined in our prior study. In α-syn peptide immunized mouse model, it may suggest which α-syn causes T cell-specific autoimmune responses and whether α-syn-specific T cells cause dopaminergic neuronal cell death.

Clinical Implications and Therapeutic Landscape

The immune system is gradually recognized as playing a more substantial role in the progression of PD, making it a promising avenue for therapeutic intervention. Clarifying the extent of the immune response's contribution to PD pathogenesis could open new avenues for diagnosis and treatment. As observed in other neurodegenerative diseases, the efficacy of anti-inflammatory drug trials in PD has been notably underwhelming, suggesting a need for a revised approach to these trials.

Inflammation can stimulate the recruitment of immune cells, activating the JAK/STAT pathway, which is vital for initiating innate immune response, coordinating adaptive immune response, and ultimately regulating both inflammatory and immune reactions. Dysregulated activation of the JAK/STAT pathway is associated with various autoimmune and neuroinflammatory diseases. Blocking the JAK/STAT pathway has shown protective effects against α-syn-induced neuroinflammation and dopaminergic neurodegeneration by reducing microglial activation, preventing the infiltration of macrophages and $CD4^+$ T cells, and decreasing the production of proinflammatory cytokines (Qin et al., 2016). Several JAK inhibitors, such as tofacitinib, baricitinib, upadacitinib, and filgotinib, have been evaluated in randomized trials for RA, a chronic autoimmune disease affecting the joints and leading to progressive articular damage (McLornan et al., 2021). Tofacitinib was the first JAK inhibitor to receive FDA and EMA approval for patients with moderate to severe RA who had not responded adequately to conventional synthetic disease-modifying anti-rheumatic drugs (Fleischmann et al., 2017). Baricitinib, a JAK1/JAK2 inhibitor, has also been approved by both agencies for the treatment of RA (Taylor et al., 2017). To overcome the limitation of current PD treatments, drug repositioning related to autoimmune disease offers a promising alternative to traditional drug discovery, which is often costly and time-consuming. This strategy enables the development of new PD therapies more quickly and with lower risk, providing a faster and more economical path compared to de novo drug discovery.

A previous study has demonstrated a significant increase in the density of $CD4^+$ and $CD8^+$ T cells within the SNpc of the brain in PD postmortem (Brochard et al., 2009). Additionally, Th17 cells and myeloid-derived suppressor cells were increased in the peripheral blood of individuals with PD (Chen et al., 2017). Different types of T cells have been implicated in PD pathogenesis and could potentially serve as therapeutic targets. Th17 cells have been shown to induce dopaminergic neuronal cell death either through direct interactions between leukocyte function-associated antigen-1 on Th17 cells and intracellular adhesion molecule-1 on neurons or through the release of IL-17A. These findings provide compelling evidence that autoimmune-associated immune cells contribute to the pathogenesis and progression of PD. In this regard, identifying individuals with MHC (known as HLA in humans) alleles associated with an increased risk of developing α-syn-specific T cells could facilitate early diagnosis and treatment of PD. In light of these insights, α-syn-specific T cells could serve as early biomarkers, enabling the detection of autoimmunity against self-proteins before motor symptoms appear, and improving clinical diagnosis and treatment by recognizing individuals at risk or in the early phases of PD. Furthermore, approaches focused on suppressing the immune response or elevating the threshold for recognizing self-antigens may represent promising therapeutic targets for the management of PD. T-cell counts and phenotyping offer an accessible, automatable, and cost-effective approach to disease progression. Nevertheless, the specificity of the T-cell characteristics remains limited, underscoring the need to account for common confounding factors and pair this approach with additional, more specific biomarkers. Evidence suggests that autoimmune T-cell responses to α-syn are present before the onset of motor symptoms and PD diagnosis, with the strongest responses occurring in the earliest stages of the disease but largely diminishing by about 10 years post-diagnosis (Lindestam Arlehamn et al., 2020). These findings indicate that α-syn-specific T cells are circulating prior to disease onset, potentially playing an early role in PD pathogenesis. Given the potential impact of peripheral inflammation, leakage of BBB, and α-syn-specific T cells on neuronal death, early intervention in PD patients—

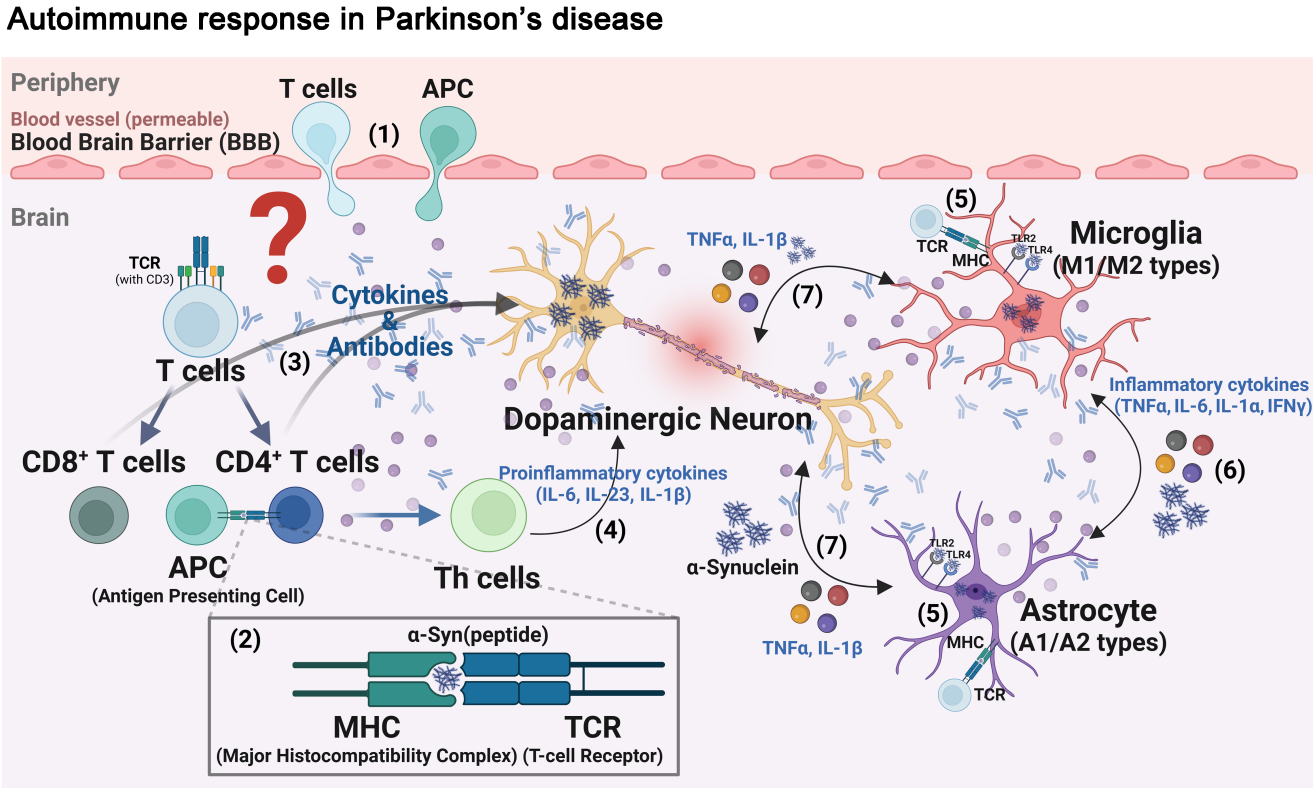

Figure 1 | **Dopaminergic neuronal cell death induced by glial cell activation via α-syn, and the relationship between α-syn and T cell-mediated autoimmune response.**
A schematic diagram illustrates the relationship between autoimmune response and Parkinson's disease pathology. (1) Peripheral inflammation, shifts in lymphocyte subtypes, and disruption of the BBB may facilitate T cell and APC infiltration into affected brain regions in PD. (2) These epitopes are displayed to T cells, allowing them to recognize the complex formed between MHC molecules and α-syn peptide epitopes. This may lead the immune system to identify as an autoantigen. (3) $CD4^+$ and $CD8^+$ T cells can directly or indirectly release several cytokines that promote neuronal cell death. (4) Changes in T cell populations can affect circulating pro-inflammatory cytokine levels. These cytokines may have a detrimental effect on neurons. (5) α-Syn can be transmitted from neuron to neuron or from neuron to glia. Glia cells and APCs can present α-syn to T cells. α-Syn can be presented by microglia or APCs via MHC to stimulate T cell-mediated responses. (6) Activated microglia led to increased levels of cytokines such as TNFα, IL-6, IL-1α, and IFNγ. It can induce an upregulation of reactive astrocyte and neurotoxic A1-specific transcripts. (7) The accumulation of α-syn released from neurons can induce a pro-inflammatory cascade. Pro-inflammatory cytokines released from glia can contribute to neuronal cell death. Created with BioRender.com. APC: Antigen-presenting cell; BBB: blood–brain barrier; IFN: interferon; IL: interleukin; MHC: major histocompatibility complex; PD: Parkinson's disease; TCR: T-cell receptor; Th cell: T-helper cell; TNF: tumor necrosis factor; α-syn: α-synuclein.

before the autoimmune response is triggered—is essential; α-syn-specific T cells could provide early biomarkers, identifying autoimmunity before motor symptoms appear, especially in individuals with HLA alleles linked to PD. A promising approach for treating PD may involve immunomodulatory therapy, particularly when administered early in the disease progression, before the loss of α-syn tolerance and the targeting of dopaminergic cells by immune cells. When abnormal α-syn processing generates atypical cleavage products, the immune system may mistakenly identify these as "non-self" proteins, initiating autoimmune responses. Consequently, these post-translational modifications could create neoantigens that trigger autoimmune responses. The development of biomarkers to identify α-syn-specific T cells in the early stage could extend the period available for starting immunomodulatory treatments, potentially slowing the disease progression of PD. Vaccines may generate anti-drug antibodies that, while unable to cross the BBB, can bind to the drug and inhibit its transport to the brain without impacting brain function (Schijns et al., 2020). In the approach of an Alzheimer's disease therapeutic vaccine, several redesigned vaccines targeting various forms of soluble and aggregated amyloid-beta and tau proteins, formulated with immune-modulating adjuvants, are currently being assessed in early-stage clinical trials (Herline et al., 2018). Likewise, active immunotherapy has demonstrated potential in clinical trials as a strategy to alter the progression of the widely prevalent PD. In developing a therapeutic vaccine for PD, the antigen includes a sequence of ten residues from the negatively charged C-terminus of α-syn, a key region that enables the uptake of aggregated into healthy neurons and microglia (Gonzalez-Artero et al., 2024). The UB-312 vaccine reduced levels of aggregated α-syn, and PD patients with detectable antibodies in cerebrospinal fluid showed improvements in motor function in a Phase 1 clinical trial (Eijsvogel et al., 2024). The PD01A and PD03A vaccines incorporate structural constraints to selectively target toxic misfolded species (Mandler et al., 2014). They use mimotopes that mimic a structural epitope in α-syn oligomers without duplicating the natural sequence, thereby minimizing cross-reaction with the native protein. A Phase 1 clinical study demonstrated that these vaccines were well tolerated and effectively induced a humoral immune response. A Phase 2 study is currently in progress for the patients with early-stage PD. However, these processes could be invasive, costly, and carry certain risks. Therefore, it should be needed to develop and validate blood-based biomarker tests that can enable ongoing assessment of the disease-modifying effects of immunotherapies. It will be precious for the preventive application of vaccines in neurodegenerative disease, facilitating therapeutic interventions at the onset of the disease.

Conclusions and Future Directions

The infiltration of T cells, increased MHC expression, and the susceptibility of dopaminergic neurons to neuroinflammation collectively support the hypothesis that PD may have features of an autoimmune disorder. T cells from PD patients can drive an autoimmune response to α-syn and its peptides. It is subject to post-translational modifications in an environment where protein processing is disrupted, potentially resulting in the formation of neo-epitopes, self-peptides that the host immune system may not identify as non-foreign. To determine whether the α-syn sequence can elicit a $CD4^+$ T-cell response, it should be assessed whether the candidates of the α-syn sequence can present to the MHC II *in vivo* mouse model.

Future studies should aim to elucidate that α-syn aggregation, glia-mediated neuroinflammation, and antigen presentation within the CNS contribute to the recruitment and attraction of α-syn-specific T cells. Additionally, it is necessary to demonstrate that α-syn-mediated $CD4^+$ and $CD8^+$ T cells detected in PD patients can recognize specific peptides presented by MHC II and MHC I on dopaminergic neurons. The observation of these phenomena in PD patients suggests their potential importance. Future research should aim

to establish their critical role in reproducing the disease in animal models. Also, studies should integrate the α-syn specificity and HLA associations detected in PD patients to thoroughly replicate the processes occurring in the CNS throughout the disease. Such insights could advance the development of biomarkers, diagnostic tools, and treatments to identify and target autoimmune cells in patients.

Another future study should confirm that α-syn (or peptide) can induce M1-type microglia activation caused by the T cell-mediated autoimmune response, which may then convert astrocytes into the toxic A1-type form in the *in vivo* mouse model.

Despite advancements in therapeutic strategies, PD continues to be an incurable condition. Therapeutic vaccine, as a promising treatment candidate for PD, has the potential to translate the positive outcomes of active immunotherapy into meaningful benefits by strategically combining structure-based epitope selection. Understanding the relationship between α-syn and the autoimmune system is predicted to be key for developing future treatments for PD. Further research into the autoimmune mechanisms related to α-syn could lead to the development of novel treatments aimed at slowing or preventing the progression of PD. These findings indicate that targeting T cells and reducing the incidence or disease severity of CNS autoimmune diseases could be beneficial in managing PD.

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