Evidence of Inflammation in Parkinson's Disease and Its Contribution to Synucleinopathy

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ABSTRACT

Accumulation of alpha-synuclein (αSyn) protein in neurons is a renowned pathological hallmark of Parkinson's disease (PD). In addition, accumulating evidence indicates that activated inflammatory responses are involved in the pathogenesis of PD. Thus, achieving a better understanding of the interaction between inflammation and synucleinopathy in relation to the PD process will facilitate the development of promising disease-modifying therapies. In this review, the evidence of inflammation in PD is discussed, and human, animal, and laboratory studies relevant to the relationship between inflammation and αSyn are explored as well as new therapeutic targets associated with this relationship.

Keywords Alpha-synuclein; Astrocyte; Inflammation; Lymphocyte; Microglia; Parkinson's disease.

INTRODUCTION

The pathological hallmarks of Parkinson's disease (PD), the second most common neurodegenerative disorder, include Lewy bodies, aggregated alpha-synuclein (αSyn) protein accumulation in neurons, and dopaminergic neuron degeneration. The pathology of αSyn-stained Lewy bodies has a spatial progression pattern associated with the disease course, which was proposed by Braak et al.1 Furthermore, mutations in the SNCA gene, which encodes the αSyn protein, especially copy number variation or aggregation-prone mutations, cause the familial form of PD.2-3 Furthermore, misfolding and cell-to-cell transmission of αSyn protein have been evidenced using a fibrillar αSyn-injected animal model and by the emergence of Lewy body pathology in fetal nigral cells grafted into the striatum of PD patients.4-9 Accordingly, the hypothesis that αSyn misfolding and propagation cause PD has become a popular theory by which to explain the pathophysiology of the disease.

Various mechanisms, including autophagy–lysosomal pathway dysfunction or mitochondrial dysfunction and oxidative stress, are known to be involved in PD pathogenesis.10 In addition, evidence that neuroinflammation is an important contributor to PD pathogenesis has emerged.11,12 Epidemiological studies have found that various autoimmune diseases, such as type 1 diabetes, rheumatic disease, Crohn's disease, and ulcerative colitis, are associated with an increased risk of PD development. Conversely, anti-inflammatory drugs, such as nonsteroidal anti-inflammatory drugs or corticosteroids, can delay or prevent PD onset.13,14 In a genome-wide association study, pleiotropy was observed between autoimmune disease and PD.15 Moreover, in genetic studies, more than 90 loci of human leukocyte antigen (HLA) genes encoded by major histocompatibility complex class II (MHC-II) have been identified. These genes participate in antigen presentation during the immune response and are associated with sporadic PD.16 Thus, there is evidence that the immune response may be involved in the PD process. Although the precise role of inflammation in synucleinopathy is currently unclear, recent research demonstrates that inflammation is not only the result of the PD...
process but also an important contributor to the disease.\textsuperscript{11,12,17-19} Therefore, the interaction between the immune response and synucleinopathy may be an important pathomechanism of PD and a possible target for future disease-modifying therapy.

In this review, evidence of activated inflammation in PD is highlighted from autopsy data, in vivo imaging, and laboratory findings. In addition, the temporal and molecular relationship between inflammation and synucleinopathy is evaluated in relation to various aspects of disease progression.

**EVIDENCE OF INFLAMMATION IN PD**

Epidemiological and genetic studies have demonstrated that inflammation may be associated with PD.\textsuperscript{13,16} In addition, recent studies have reported that an altered gut microbiome in PD and its relevant gut inflammation may contribute to PD pathogenesis.\textsuperscript{20} Evidence of inflammation in PD can be concretized by autopsy and in vivo studies. The immune response in the central nervous system (CNS) is distinct from that in the peripheral system in terms of the blood–brain barrier (BBB), resident glial cells (microglia and astrocytes), and absence of an adaptive immune response in itself.\textsuperscript{21} However, because αSyn pathology in PD has been observed from the periphery, such as the enteric nervous system, to the central nervous system, immune responses should be evaluated inside and outside of the CNS in PD. This can be addressed by autopsy studies, in vivo imaging of inflammation, and laboratory analysis of the blood and cerebrospinal fluid (CSF) of patients (Table 1).

**An activated innate immune response was found in the postmortem PD brain**

Early studies demonstrated that innate immune cells were found in the postmortem PD brain. Both microglial and astrocytic activation was observed, with consistent microglial activation. Microglia constitute approximately 5%–12% of CNS cells and are capable of self-renewal independent of hematopoietic stem cells.\textsuperscript{22} In the CNS, microglia present as major immune mediators; in particular, they perform the functions necessary for the recruitment of the immune system.\textsuperscript{22} In PD postmortem studies, microglial activation was observed to varying degrees in different brain regions. Mirza et al.\textsuperscript{23} described the activation of microglia labeled with CR3/43 and ferritin in the substantia nigra (SN) but not in the putamen of the PD brain. Moreover, MHC-II-expressing microglia are found at significantly higher levels in the SN, putamen, hippocampus, transentorhinal cortex, cingulate cortex, and temporal cortex as well as in the lymphatic system in PD than in the brain regions of normal controls.\textsuperscript{24} Doorn et al.\textsuperscript{25} showed differential microglial expression patterns in the PD brain and age-matched control brain: CD68-stained amoeboid microglia were identified in the SN and hippocampus, especially in the hippocampal CA2 region, whereas Iba1-stained microglia were significantly increased in the SN of the PD brain. However, such microglia were not found in the subregions of the hippocampus in age-matched control brains.\textsuperscript{25} In another study, Kouli et al.\textsuperscript{26} characterized microglial responses in various brain regions by human leukocyte antigen–DR isotype (HLA-DR) and Iba1 staining. They found significantly higher microglial activation in the amygdala of demented PD patients than in age-matched controls.\textsuperscript{25} Consequently, although microglia exhibited different activation patterns in terms of microglial phenotypic markers and PD brain regions, microglial activation was consistently observed in the postmortem PD brain.

In addition to microglia, astrocytes are the most abundant CNS cell type. They demonstrate diverse morphological and functional characteristics dependent on specific brain areas.\textsuperscript{27} Astrocytes are known to contribute to various physiological functions, including maintenance of neurons, formation of the BBB, and regulation of synapse functions.\textsuperscript{28} Astrocytic activation in postmortem PD brains was thought not to exist because the differences in the distribution and cellular density of astrocytes stained for glial fibrillary acidic protein (GFAP) or metallothioneins I and II were not observed in the SN and putamen of PD patients.\textsuperscript{23} However, astrocytes containing aggregated αSyn have been found in the PD brain, suggesting that astrocytes play a role in taking up abnormal αSyn.\textsuperscript{29,30} Recently, reported data show that GFAP-positive astrocytes are significantly increased in the SN but are not found in other brain regions of PD subjects relative to age-matched controls.\textsuperscript{31} Therefore, human autopsy studies demonstrate that microglial and astrocytic activation is involved in the PD process. However, the data obtained from postmortem brains might reflect the findings of advanced disease status or confounding terminal status affecting inflammation at death. Consequently, the in vivo status of PD must also be investigated.

**In vivo evidence of inflammation in PD patients**

In vivo evaluation can reflect the various stages of PD, and compared with autopsy data, it can better exclude the confounding factors affecting inflammation. Positron emission tomography (PET) imaging using ligands targeting microglial or astroglial activation has provided some insights into this respect.

Activated microglia largely exist in two polarized states, namely, the M1 phenotype and the M2 phenotype.\textsuperscript{31} The M1 phenotype is associated with the release of proinflammatory cytokines, whereas the M2 phenotype is accompanied by the production of anti-inflammatory molecules.\textsuperscript{31} Current PET imaging using 18 kDa translocator protein (TSPO), which is the main target for the development of ligands, can detect activated microglial status because this protein is expressed increasingly when microg-
### Table 1. Postmortem and in vivo evidence of inflammation in PD

| Type of inflammation | Markers for inflammation | Sources | Regions | PD vs. healthy control |
|----------------------|---------------------------|---------|---------|------------------------|
| Microglia | Iba1 | Postmortem brain | SN | Increase<sup>25</sup> |
|  |  |  | SN, HIP, ERC, PFC, OTC, PPC, Mesencephalon | No difference<sup>23,26,41</sup> |
| HLA-DR |  | Amygdala | SN | Increase<sup>26</sup> |
| CR3/43 |  | SN | Putamen | No difference<sup>23</sup> |
| CD68 |  | SN, HIP |  | Increase<sup>23</sup> |
| TMEM119 |  | Putamen |  | Increase<sup>13</sup> |
| ¹⁸⁰-PK11195 | PET imaging | Temporal cortex, occipital cortex, SN, putamen |  | Increase<sup>33-35</sup> |
| ¹¹⁰-DPA713 |  | Temporal cortex, occipital cortex, parietal cortex |  | No difference<sup>38</sup> |
| ¹⁸⁰-F-FEPPA |  | Thalamus, caudate, putamen, HIP |  | Increase<sup>37</sup> |
| ¹⁸⁰-F-DPA714 |  | Midbrain, frontal cortex, putamen |  | Increase<sup>38</sup> |
| Astrocyte | GFAP | Postmortem brain | SN | Increase<sup>26</sup> |
|  |  | Amygdala, HIP, ERC, PFC, OTC, PPC, Mesencephalon |  | No difference<sup>23,33</sup> |
| GLAST |  | Mesencephalon |  | No difference<sup>23</sup> |
| Metallothioneins I and II |  | SN, putamen |  | No difference<sup>23</sup> |
| MHC-II |  | SN, putamen, HIP, transentorhinal cortex, cingulate cortex, temporal cortex, lymphatic system, mesencephalon |  | Increase<sup>24,41</sup> |
| ¹⁰⁰-BU9908 | PET imaging | Cortex, brain stem |  | Increase<sup>39</sup> |
| Lymphocyte | CD4+ | Postmortem brain | SN, amygdala | Increase<sup>24,41,45</sup> |
|  |  | Blood | PBMC | Increase<sup>42</sup> |
| CD8+ |  | Postmortem brain | SN | Increase<sup>44</sup> |
|  |  | Peripheral blood lymphocytes |  | Lower<sup>46</sup> |
|  |  | SN, perivascular, amygdala |  | No difference<sup>26,44,45</sup> |
| CD45 |  | Blood | PBMC | No difference<sup>42</sup> |
| B cells | CD79a+ | Postmortem brain | SN | No difference<sup>45</sup> |
| CD20+ |  |  |  |  |
| NK cells | CD57+ | Postmortem brain | SN | No difference<sup>45</sup> |
| CD56+ |  | Blood | PBMC | Increase<sup>47,49,50</sup> |
| Monocytes | CD14+ | Blood | Peripheral blood | Increase<sup>46</sup> |
|  |  | CD16+ | Peripheral blood | Increase<sup>46</sup> |
|  |  | CD14+/CD16- | CSF | No difference<sup>51</sup> |
|  |  | CD14+/CD16+ | CSF | Lower<sup>52</sup> |
| Inflammasome | NLRP3 | Blood | PBMC, plasma | Increase<sup>54,56</sup> |
|  |  |  | PBMC | No difference<sup>51</sup> |
|  | NLRP1 |  | PBMC | No difference<sup>54</sup> |
|  | NLRP4 |  |  |  |
| Cytokines | IL-1β | Postmortem brain | SN, frontal cortex | Increase<sup>36</sup> |
|  |  | Blood | Plasma, serum | Increase<sup>103</sup> |
|  | IFNγ | Blood | PBMC | No difference<sup>54</sup> |
|  |  | Serum |  | Lower<sup>26</sup> |
| TNFα |  | Postmortem brain | SN, HIP, amygdala, frontal cortex | No difference<sup>26</sup> |
|  |  | Blood | Serum | Lower<sup>26</sup> |
|  |  |  | Plasma | Increase<sup>16</sup> |
Increased microglial activation is also shown in the SN and putamen which further demonstrates the immune association in PD.36,40-44 Increased CD4 and CD8+ T cells but not B cells or natural killer (NK) cells have been observed in the SN of the post-mortem PD brain.41 In a recent study, CD4+ T cell infiltration was identified in post-mortem brain sections, especially in the perivascular space and vessel wall directly in contact with astrocytes expressing MHC-II.41 This suggested that astrocytes were capable of expressing the factors required for T cell infiltration and activation during PD progression.41 In another study, a significant increase in CD4+ T lymphocytes in the SN was reported in demitted PD patients, whereas a correlation existed between the number of CD4+ T cells and activated microglia in the amygdala.26 In another study, a significant increase in CD8+ T cells but not CD4+ T cells was observed in the SN of PD patients compared with that in the SN of the control group, according to Lewy body staging.44 The presence of infiltrating lymphocytes in specific brain regions affected by PD, such as the SN and amygdala, suggests that they reach these locations through targeted extravasation rather than through a random event.

In addition, the peripheral blood of PD patients presents altered lymphocytic patterns.45-48 Increased monocyte48 or NK cell activation has also been reported in the blood of PD patients.47-50 Furthermore, Niwa et al.49 reported an increase in NK cells but not regulatory T cells and type 17 helper T cells in the blood of PD patients. Similarly, a significantly high percentage of NK cells with a lower percentage of CD3+ T cells and CD4+ T cells was identified in PD patients with clinical features relative to healthy controls.49

In addition to the blood, the CSF of PD patients has been shown to have higher activation of immune cells, such as T lymphocytes and monocytes, than that of control subjects.51 Additional evidence of the increased number of monocytes in the CSF of PD patients was recently reported by Pillen et al.52 These findings indicate that peripheral inflammatory cell activation occurs in the blood and CNS of PD patients and that peripheral immune cell activation may be involved in PD pathogenesis.

However, it is less known how inflammation contributes to selective neuronal vulnerability in PD, but it is postulated that genetic predisposition combined with environmental factors may

### Table 1. Postmortem and in vivo evidence of inflammation in PD (continued)

| Type of inflammation | Markers for inflammation | Sources | Regions | PD vs. healthy control |
|----------------------|--------------------------|---------|---------|------------------------|
| IL-2                 | Postmortem brain         | Frontal cortex | Increase³⁷ |
| IL-13                |                          | Frontal cortex | Lower²⁷ |
| IL-10                | Blood                    | PBMC, plasma | Increase²⁷,²⁸ |
| IL-5                 | PBMC                     | No difference⁵² |
| IL-6                 | Plasma                   | Increase⁵⁰ |

**Sources**
- PD, Parkinson’s disease; SN, substantia nigra; HIP, hippocampus; ERC, entorhinal cortex; PFC, prefrontal cortex; OTC, occipito-temporal cortex; PPC, posterior parietal cortex; HLA-DR, human leukocyte antigen DR isotype; PET, positron emission tomography; GFAP, glial fibrillary acidic protein; GLAST, glutamate aspartate transporter; MHC-II, major histocompatibility complex class II; PBMC, peripheral blood mononuclear cell; NK cells, natural killer cells; CSF, cerebrospinal fluid.

**Markers for inflammation**
- IL-2: Interleukin-2, a cytokine involved in immune responses.
- IL-13: Interleukin-13, involved in inflammatory processes and tissue repair.
- IL-10: Interleukin-10, an anti-inflammatory cytokine.
- IL-5: Interleukin-5, involved in regulating immune responses.
- IL-6: Interleukin-6, a pro-inflammatory cytokine.

**Regions**
- Frontal cortex: The frontal lobes of the brain, responsible for executive functions, decision making, and motor control.
- PBMC: Peripheral blood mononuclear cells, a type of immune cell.
- Plasma: Blood plasma, which is fluid containing proteins and nutrients.

**PD vs. healthy control**
- Increase: Indicates a significant increase in the PD group compared to the healthy control group.
- Lower: Indicates a significant decrease in the PD group compared to the healthy control group.
- No difference: Indicates no significant difference between the PD and healthy control groups.

**Notes**
-增加microglial activation was demonstrated in the pons, basal ganglia, frontal cortex, and temporal cortex in PD.32 With the same ligand, microglial activation in the temporal and occipital regions of PD patients was demonstrated to be increased by 25%-30% compared with activation in the temporal and occipital regions of PD patients.

From another perspective, increased astrocytic activation in the blood, the CSF of PD patients has been shown to have higher activation of immune cells, such as T lymphocytes and monocytes, than that of control subjects.51 Additional evidence of the increased number of monocytes in the CSF of PD patients was recently reported by Pillen et al.52 These findings indicate that peripheral inflammatory cell activation occurs in the blood and CNS of PD patients and that peripheral immune cell activation may be involved in PD pathogenesis.

However, it is less known how inflammation contributes to selective neuronal vulnerability in PD, but it is postulated that genetic predisposition combined with environmental factors may
increase selective nigral dopaminergic degeneration during chronic inflammation.53

Changes in inflammatory mediators in PD

In addition to the activation of innate CNS immune cells and peripheral immune cells, the levels of various inflammatory cytokines, which are produced by activated immune cells, have been investigated in PD.44,54-56 The released cytokines may cause endogenous αSyn to misfold and aggregate. Aggregated αSyn can induce an inflammatory cell response that continues to release cytokines, which accounts for the continued presence of inflammation and progressive αSyn pathology.43

Altered cytokine expression has been detected in the postmortem PD brain;26,46,57 cytokine expression was altered in the frontal cortex, with IL-2 levels significantly higher and IL-13 and IL-8 levels lower in PD brains than in controls.57 In another study, a significant increase in the expression of proinflammatory IL-1β cytokine was observed in the SN and frontal cortex, whereas cytokine levels in other brain regions did not differ in PD patients and healthy controls.26

With regard to the inflammatory response in the peripheral system, Eidson et al.49 found that the levels of two proinflammatory cytokines, namely, TNFα and IFNγ, were decreased in the serum of PD patients compared with that in the serum of control subjects. Recently, a significant increase in plasma proinflammatory cytokines, i.e., TNFα, IL-6, and IL-1β, was also found in PD patients.54,58,59 However, variation in serum cytokine levels over time between T cell activity in PBMCs and the time of PD diagnosis in longitudinal observation demonstrated that αSyn-specific T cell reactivity was significantly increased in all periods of PD but was especially highest close to the onset of PD.61 Overall, these findings indicate the possibility that inflammation can start from an early disease state and possibly precede αSyn pathology. Therefore, in this section of the review, the association between inflammation and αSyn pathological progression has been described in three parts: whether 1) αSyn triggers inflammation, 2) inflammation participates in αSyn removal, or 3) inflammation contributes to αSyn propagation (Figure 1).

Pathological αSyn triggers inflammation

PD animal models can provide evidence of immune cell activation during pathological αSyn introduction and its propagation.62-67 After fibrillar αSyn injection into the brains of mice, thriving microglial and astrocytic activation was observed with αSyn propagation in these brains (Figure 2).63,64,66 Moreover, Lee et al.70 reported that αSyn accumulation in glial cells produces proinflammatory cytokines and chemokines. In addition, fibrillar αSyn has been shown to induce an inflammatory response through synthesis of IL-1β through toll-like receptor (TLR) 2 interactions, which thereby leads to the activation of the NLRP3 inflammasome, followed by increased reactive oxygen species production in human monocytes.71 This suggests that fibrillar αSyn encountering the TLR2 receptor on the surface of immune cells and triggers a downstream signaling pathway with the subsequent pro-
The inflammatory response is closely related to pathological αSyn accumulation and transmission. Various immune receptors and proteins are involved in the internalization of pathological αSyn or its intracellular signaling, and consequently, the cytoplasmic autophagosome and inflammasome cascade will be activated in immune cells. Responding to pathological αSyn stimuli, microglia changed their morphology to a proinflammatory phenotype, which enabled the phenotypic conversion of astrocytes to an A1 neurotoxic phenotype. Antigen presentation of processed αSyn by immune cells can recruit peripheral lymphocytes, and peripheral immune cells can infiltrate the CNS with targeted extravasation. Immune cells can contribute pathological αSyn to transfer to other immune cells or neurons in various ways, such as direct contact, exosomal transfer, and nanotubules. αSyn, alpha-synuclein; CNS, central nervous system; LAG3, lymphocyte activation gene 3 protein; CR4, complement receptor 4; TLR, toll-like receptor; MHC, major histocompatibility complex; IL, interleukin; TNF, tumor necrosis factor; BBB, blood–brain barrier; NK cells, natural killer cells.

Figure 1. The inflammatory response is closely related to pathological αSyn accumulation and transmission. Various immune receptors and proteins are involved in the internalization of pathological αSyn or its intracellular signaling, and consequently, the cytoplasmic autophagosome and inflammasome cascade will be activated in immune cells. Responding to pathological αSyn stimuli, microglia changed their morphology to a proinflammatory phenotype, which enabled the phenotypic conversion of astrocytes to an A1 neurotoxic phenotype. Antigen presentation of processed αSyn by immune cells can recruit peripheral lymphocytes, and peripheral immune cells can infiltrate the CNS with targeted extravasation. Immune cells can contribute pathological αSyn to transfer to other immune cells or neurons in various ways, such as direct contact, exosomal transfer, and nanotubules. αSyn, alpha-synuclein; CNS, central nervous system; LAG3, lymphocyte activation gene 3 protein; CR4, complement receptor 4; TLR, toll-like receptor; MHC, major histocompatibility complex; IL, interleukin; TNF, tumor necrosis factor; BBB, blood–brain barrier; NK cells, natural killer cells.

In addition to the inflammatory response through glial cells, the adaptive immune response through lymphocytes may be affected by αSyn. Following fibrillar αSyn injection into the CNS parenchyma, a significant increase in peripheral immune cell infiltration, such as B lymphocyte (CD19+), T helper lymphocyte (CD4+), T cytotoxic lymphocyte (CD8+), activated myeloid cell (CD11+), and NK cell infiltration, was observed in the CNS compared with the effects in a monomer-injected mouse model. Likewise, an alteration of peripheral immune cells was identified in the blood and peripheral organs, including the spleen and lymph nodes, following fibrillar αSyn injection into the brain. These data suggest that pathological αSyn triggers immune cell infiltration and activation in the brain as well as in the peripheral system. Moreover, Harms et al. reported that αSyn overexpression induced MHC-II-mediated antigen presentation on microglia to CD4+ T cell expression; thus, the interaction between microglia and CD4+ T cells led to potent cytokine production. In agreement with this, a recent study demonstrated that αSyn triggers incremental MHC-II expression associated with an accompanying T cell response; therapeutic targeting of T cell disruption in animal models was found to reduce MHC-II expres-
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sion as well as CNS myeloid cells in relation to αSyn expression.82

To understand the differential contribution of various peripheral immune cells in synucleinopathy, Iba et al.83 evaluated T lymphocyte populations in 10–11-month-old transgenic mice overexpressing human αSyn, which demonstrated considerable accumulation of αSyn in the cortical and subcortical regions. The authors found an increase in the number of CD3 and CD4+ T cells in mouse brains, and CD3+ T cells were detected in close proximity to glial cells (Iba1 and GFAP) and human αSyn (SYN211)-positive neurons in the neocortex, hippocampus, and striatum, which supports previous observations in the human brain.40,41 Furthermore, an accompanying increase in IFNγ and CD1d-restricted NK T cells was identified in this animal model.83 In another study, when αSyn oligomer was increased using an injection of adeno-associated virus coding αSyn in the T cell-competent rat brain, the presence of CD4+ and CD8+ T cell infiltration was correlated with the upregulation of MHC-II-expressing microglia. However, this correlation was not observed in T cell-deficient rats.89 Taken together, these studies imply that pathological αSyn contributes to the recruitment of lymphocytes as well as the activation of innate immune cells.

Inflammation opposes αSyn toxicity

One of the primary roles of microglia and astrocytes is their macrophage-like function.84,85 Lee et al.86 explored the efficiency of clearing extracellular αSyn in different brain cell types, including neurons, astrocytes, and microglia, and found that microglia exhibited the highest rate of αSyn clearance. Supporting evidence by Loria et al.87 also indicated that astrocytes were able to efficiently clear fibrillar αSyn more efficiently than neurons. A recent study by Tsunemi et al.88 also emphasized the importance of lysosomal function in astrocytes for αSyn degradation during the pathogenesis of the disease. Although neurons and astrocytes can clear αSyn, microglia are the major immune cells that quickly engulf and degrade αSyn to maintain brain health by changing their morphological state to M1 (the proinflammatory phenotype) or M2 (the antiinflammatory phenotype).89 Choi et al.74 suggested that the neuroprotective function of microglia occurs through ingestion and degradation of neuron-released αSyn through a selective autophagy mechanism. Therefore, a better understanding of microglial function in relation to αSyn will likely contribute to the identification of therapeutic targets for inflammation in synucleinopathies.

Figure 2. Fibrillar αSyn injection induced inflammation in the mouse brain. Iba1-positive microglia and GFAP-positive astrocyte immunoreactivity were significantly increased in the striatum of fibrillar αSyn-injected mice compared to monomeric αSyn-injected and PBS-injected mice at 7 days after injection. DAB staining immunohistochemistry. Scale bar: 100 μm. αSyn, alpha-synuclein; GFAP, glial fibrillary acidic protein; PBS, phosphate buffered saline; DAB, 3,3'-diaminobenzidine.
In studies of the cellular mechanism underlying αSyn clearance, in vitro research has identified that αSyn alters microglial function through interactions with TLR. Stefanova et al. demonstrated that TLR4 deficiency in αSyn-overexpressing transgenic mice led to significantly increased levels of αSyn in the midbrain and forebrain compared with αSyn-overexpressing transgenic mice with intact TLR4 expression, indicating that impairment of TLR4 influences extracellular αSyn clearance through microglia. In accordance with this study, Fellner et al. indicated that TLR4 is required for the αSyn-dependent activation of glial cells. In addition, TLR4 was recently linked to selective autophagic degradation of αSyn in synucleinopathy, whereas oligomeric αSyn interacts with TLR2 to induce microglial activation. Therefore, the modulation of the TLR response to αSyn can be a possible treatment target for the improvement of αSyn propagation.

Disruption of the BBB in synucleinopathy has been observed in a PD animal model; this process may allow the entrance of peripheral immune cells into the brain for pathological αSyn clearance. A recent study demonstrated the protective role of NK cells (granular lymphocytes of the innate immune system) in efficiently internalizing and degrading extracellular αSyn; the systemic depletion of NK cells in a PD mouse model exacerbated motor abnormalities and αSyn propagation compared with the effects in a control group. In another study, reconstitution of T cell populations reduced αSyn accumulation and resulted in persistent microgliosis in the striatum of mice with an immune system impaired by αSyn preformed fibril injection. These data support that NK cells, T lymphocytes, microglia, and astrocytes can play protective roles in the αSyn pathology of PD.

**Inflammation contributes to αSyn propagation**

Accumulating evidence now supports the case that glial activation contributes to αSyn propagation. Microglial exosomes also contribute to the progression of αSyn pathology through exosomal transfer of αSyn from cell to cell. In addition, reactive microglia enhance the transmission of exosomal αSyn through TLR2. Recently, Izco et al. investigated the temporal relationship between αSyn and inflammation in a mouse model of PD. They found that the peak expression of Iba1-positive microglia, GFAP-positive astrocytes, and IL-1β occurred before αSyn accumulation. Furthermore, several researchers have been able to block or suppress microglial activation using pharmacological drugs and thereby have identified decreases in αSyn pathology in a mouse model.

There is also evidence that astrocytes actively transfer aggregated αSyn to healthy astrocytes through direct contact or tunneling nanotubes. Ngolab et al. demonstrated that DLB brain-derived exosomes trigger αSyn accumulation in astrocytes in the mouse brain, suggesting the participation of astrocytes in αSyn transmission. In addition, activated microglia have been shown

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**Figure 3.** Ongoing therapeutic option targeting the interaction of inflammation and αSyn. Therapeutic targets currently under evaluation are described in the figure, but all are in the early stages. Efforts to explore new therapeutic targets based on this mechanism will be required. αSyn, alpha-synuclein; PAP, papaverine; LAG3, lymphocyte activation gene 3 protein; CR4, complement receptor 4; TLR, toll-like receptor; IL, interleukin; TNF, tumor necrosis factor; GLP-1R, glucagon-like peptide-1 receptor; SGK1, serum and glucocorticoid-regulated kinase 1 inhibitor; CSF, cerebrospinal fluid.
| Status | Category | Compound | Description | Findings |
|--------|----------|----------|-------------|----------|
| Preclinical | Microglia | CSF1R inhibitor (PPLX3397- Pexidartinib) | Inhibits microglia/macrophage Depletion of microglia suppressed α-Syn aggregation and transmission in mice17,94 Preclinical | Preclinical |
| | | Minocycline (Mino) | Reduces the proliferation/activation of resting microglia Prevention of the dopaminergic neurons loss, increased the dopamine level, decreased the Lewy body pathology in mice104 | Phase 2 NINDS NET-PD |
| | | Fingolimod | Blocks T cell egress from lymph nodes (prevents T-cell entry to the brain) Decreased α-Syn pathology in enteric nervous system of A53T transgenic mice105 Preclinical | Preclinical |
| | | Rosiglitazone | PPARγ, inhibits microglial release of TNFα Reduced α-Syn pathology and prevented loss of dopaminergic neurons106 Preclinical | Preclinical |
| | | Pioglitazone | PPARγ agonists, inhibits microglia activation Modifies progression in early PD107 Phase 2 | Preclinical |
| | Astrocyte | NLY01 (GLP-1R agonist) | Blocks A1 neurotoxic astrocyte generation by microglia Reduced α-Syn pathology in A53T transgenic mice99 Preclinical Phase 1, the drug was found to be safe and well-tolerated Phase 2 NCT03672604 | Preclinical |
| | | SGK1 inhibitor | SGK1 is negatively regulated by Nurr and Fox2 in glial cells Ameliorated neuronal α-Syn aggregation and protected dopaminergic neuron loss108 Preclinical | Preclinical |
| | | TLR2 T2.5 antibodies | Blocks TLR2 Decreased α-Syn pathology and inflammation in mice109 Preclinical | Preclinical |
| | | LAG3 receptor | LAG3 antibodies (C9B7W and 410C9) Blocks LAG3 receptor Reduced α-Syn transmission77 Preclinical | Preclinical |
| | | T lymphocytes | GA Attenuates the activation of CD4+ T cells and the pro-inflammatory response Improved the motor function and restored the α-Syn level in the midbrain and striatum of MPTP-treated mice110 Preclinical | Preclinical |
| | | Sargramostim (Leukine) | Human recombinant granulocyte-macrophage colony-stimulating factor affects myeloid recovery Sargramostim treatment in PD is well-tolerated111 Phase 1 | Phase 1 NCT010882100 |
| | | Inflammasome | MCC950 Blocks ATP and nigericin dependent NLRP3 activation Prevented inflammasome activation by fibrillar α-Syn, and led to less neuron loss and better dopaminergic signaling112 Preclinical | Preclinical |
| | | PAP | Selective inhibitor of phosphodiesterase 10A activity Inhibited α-Syn aggregation and neuronal cell death results from MPTP/P mice model113 Preclinical | Preclinical |
| | | VX-765 (caspase-1 inhibitor) | Inhibits proteolytic processing of IL-1β and IL-18 to secreted forms Inhibition of caspase-1 rescued BE(2)-M17 human dopaminergic neuroblastoma cells from the toxic effects of α-Syn114 Reduced α-Syn pathology in transgenic mouse model of MSA115 Preclinical | Preclinical |
| | | Inzomelid (IZD174) (NLRP3 inhibitor) | Inhibitor of inflammasomes containing NLRP3, or nod-like receptor family, pyrin domain-containing protein 3 The treatment was well tolerated in double-blind evaluations in healthy volunteers | Phase 1 NCT04389697 |
| | | Cytokines | XPro1595 (TNF inhibitor) Targeted soluble TNF Reduced the α-Syn protein level Neuroprotective effects in rat model117 Preclinical | Preclinical |

α-Syn, alpha-synuclein; PD, Parkinson’s disease; NINDS NET-PD, National Institute of Neurological Disorders and Stroke Neuroprotection Exploratory Trials in Parkinson’s Disease; PPARγ, peroxisome proliferator activated receptor gamma; GLP-1R, glucagon-like peptide-1 receptor; SGK1, serum and glucocorticoid-regulated kinase 1 inhibitor; TLR, toll-like receptor; GA, glatiramer acetate; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; ATP, adenosine triphosphate; PAP, papaverine; IL, interleukin; MSA, multiple system atrophy; TNF, tumor necrosis factor.
to induce neurotoxic A1 astrocytes by secreting IL-1α, TNFα, and C1q complements.98 Thus, Yun et al.99 demonstrated that microglia-induced inhibition of A1 astrocytes led to a decrease in pathological αSyn in an animal model.

A recent study using intranasal infusion of endotoxin–lipopolysaccharide (LPS) to induce olfactory bulb (OB) inflammation in mice found that LPS triggered microglial activation, inflammatory cytokine expression, and phosphorylated αSyn accumulation in the OB and SN through IL-1β/IL-1 receptor 1-dependent signaling.100 This finding suggests that inflammation, particularly IL-1, plays a role in mediating the initiation and propagation of αSyn pathology from the OB.100

In relation to systemic inflammation, La Vitola et al.101 developed a PD mouse model through systemic administration of LPS followed by intracerebroventricular injection of an αSyn oligomer as well as an αSyn-overexpression transgenic mouse administered LPS. The authors demonstrated that peripherally induced neuroinflammation influences the action of αSyn oligomers to potentiate a detrimental effect.102 By crossing human αSyn-overexpressing transgenic mice and lymphocyte-lacking mice, Sommer et al.102 determined that the presence of T lymphocytes modulated toward a proinflammatory M1 phenotype was associated with an increased number of αSyn aggregates in the SN and striatum. Their findings indicate that the inflammatory response contributes to αSyn transmission through various pathways.

Therapeutic strategies targeting the interaction between inflammation and αSyn in PD

As discussed above, extensive evidence suggests that inflammation plays a critical role in αSyn-associated PD pathogenesis (Figure 1). Therefore, researchers have explored treatment targets by modulating the immune response to ameliorate αSyn-associated PD pathology (Figure 3). This has led to numerous preclinical and clinical trials, as presented in Table 2.103–117

CONCLUSION

In conclusion, inflammation plays important roles in αSyn-related pathological processes and vice versa. Based on the current understanding, CNS innate immune cells, i.e., microglia and astrocytes, are activated in response to pathological αSyn, promote the propagation of αSyn, and clear abnormal αSyn. In addition, peripheral immune cells, such as lymphocytes and NK cells, interact with CNS innate immune cells responding to abnormal αSyn and contribute to αSyn propagation (Figure 4). A vicious cycle is thereby created through the interaction between activated inflammation and αSyn propagation, which may support prolonged PD progression. Thus, blocking this cycle using anti-inflammatory methods could represent a promising option for future therapy.

Conflicts of Interest

The authors have no financial conflicts of interest.

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