



**HAL**  
open science

# **Parkinson's disease is an autoimmune disease: A reappraisal**

Srinivasa Reddy Bonam, Sylviane Muller

► **To cite this version:**

Srinivasa Reddy Bonam, Sylviane Muller. Parkinson's disease is an autoimmune disease: A reappraisal. *Autoimmunity Reviews*, 2020, 19, pp.102684 -. <10.1016/j.autrev.2020.102684>. <hal-03493431>

**HAL Id: hal-03493431**

**<https://hal.science/hal-03493431v1>**

Submitted on 15 Dec 2022

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons CC BY-NC 4.0 - Attribution - Non-commercial use - International License

## **Parkinson's disease is an autoimmune disease: a reappraisal**

Srinivasa Reddy Bonam<sup>a,b\*</sup> and Sylviane Muller<sup>a,b,c,d,\*</sup>

<sup>a</sup> CNRS, Biotechnology and Cell Signaling, Ecole Supérieure de Biotechnologie de Strasbourg, Strasbourg University/Laboratory of Excellence Medalis, Strasbourg, France

<sup>b</sup> Institut national de la santé et de la recherche médicale, Centre de Recherche des Cordeliers, Sorbonne Université, Université de Paris, Paris, France

<sup>c</sup> Fédération Hospitalo-Universitaire OMICARE, Fédération de Médecine Translationnelle de Strasbourg, Strasbourg University, Strasbourg, France

<sup>d</sup> University of Strasbourg Institute for Advanced Study, Strasbourg, France

\*Corresponding authors: Srinivasa R. Bonam [bsrpharmacy90@gmail.com](mailto:bsrpharmacy90@gmail.com); Sylviane Muller [sylviane.muller@unistra.fr](mailto:sylviane.muller@unistra.fr)

**Keywords:** Parkinson's disease; autoimmunity; autophagy;  $\alpha$ -synuclein/SNCA; therapy

## **Abstract**

Parkinson's disease (PD) is a common, age-related, neurodegenerative disorder characterized by motor deficits and a cognitive decline. In the large majority of cases, it is associated with cytoplasmic aggregation of  $\alpha$ -synuclein/SNCA and the formation of Lewy bodies in the dopamine neurons in the *substantia nigra pars compacta*. The etiopathogenesis of PD remains poorly understood. The disease results from an interplay of genetic and environmental factors, including pharmacological molecules, which destroy dopaminergic neurons. Recently, several notable data have highlighted various immune alterations underlying that PD is associated to autoimmune features and could be considered as an autoimmune disease. In this short article, we briefly review key elements participating to this emerging viewpoint.

## 1. Introduction

Parkinson's disease (PD) is the second most common progressive neurodegenerative disorder after Alzheimer's disease (AD). It affects about 3% of the population by the age of 65 and up to 5% of individuals over 85 years of age. The risk of developing PD is one-and-a-half times higher in men than in women, possibly due to estrogens [1]. Patients display a variable and broad range of clinical phenotypes in terms of severity and response to therapies. They show motor symptoms, including bradykinesia, rigidity, tremor, postural imbalance, and nonmotor symptoms, such as anosmia, sleep disturbances, anxiety, depression, and gastrointestinal dysfunctions. The etiopathology of PD remains poorly understood but implicates several interplaying risk factors, such as genetics, environment and age. Here, we will focus our attention on the immunological front that recently emerged as an important component of PD.

At the cellular level, PD is characterized by the degeneration of mesencephalic dopamine neurons located in the *substantia nigra pars compacta*. Most of the neurodegenerative process in PD is thought to be due to the pathological aggregation and accumulation of a presynaptic neuronal protein,  $\alpha$ -synuclein/SNCA, in Lewy bodies and Lewy neurites [2,3]. SNCA aggregates are found in the CNS and various peripheral tissues, including those of the gastrointestinal tract [3-5]. Although SNCA is associated to other neurodegenerative diseases grouped under the name of synucleinopathies [6,7], it is often presented as a good biomarker, especially when SNCA with post-translational modifications are considered [8] or when neuronal exosomal SNCA is sought in the blood plasma of patients [9]. Besides its interest as a possible marker used in the diagnostic of PD, SNCA also emerged with other genes in genetic studies performed in familial forms of the disease [10].

Aside from genetic and environmental factors, which destroy dopaminergic neurons, immune and autoimmune mechanisms play an important role in PD. Elements of both innate and adaptive immune system are involved in this process in which SNCA is central.

## 2. Innate and adaptive immunity in PD

Several genes implicated in familial forms of PD (5-10% of all PD cases) are associated with mechanisms linked to immunity. They are involved in immune responses, endocytosis, lysosomal functions, autophagy, and mitochondrial biology. Some of them, such as *LRRK2* (DARDARIN; leucine-rich repeat kinase 2/PARK8), *PRKN* (PARKIN/E3 ubiquitin

ligase/PARK2), *PINK1* (PTEN-induced putative kinase/PARK6), and *DJ-1* (DJ1 protein/PARK7) have been particularly investigated in addition to *SNCA*. Several specific knockout mouse models have been generated to study the effect of these PARK genes in the autophagy context. Autophagy plays a major role in the presentation of antigenic peptides to the receptor of CD4<sup>+</sup> T cells in the context of antigen-presenting cells (APCs) and major histocompatibility complex (MHC) class II. It is also central in lymphocytes ontogenesis and differentiation and the inflammasome regulation. This may explain why any defect in autophagy processes have major implications in the overall immune pathway network. In PD patients, significant alterations are found in different autophagy processes including mitophagy and chaperone-mediated autophagy (CMA), with a decreased expression level of two CMA makers, LAMP2A and HSPA8, in amygdala and *substantia nigra* where *SNCA* aggregates [11,12], leading to dysregulated innate and adaptive immune responses.

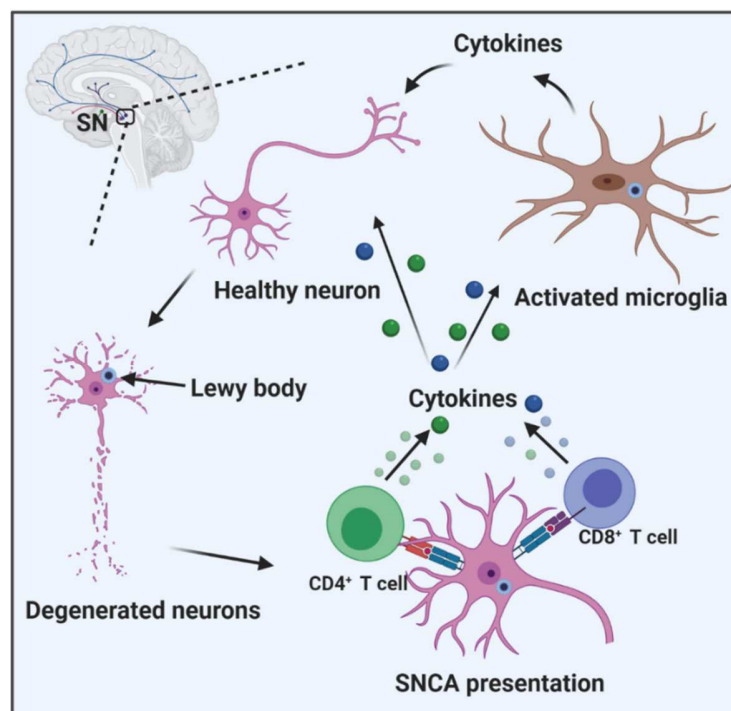
Other immune predisposition features have been identified in PD. Thus, the class II HLA-DR antigens encoded by the *HLA-DRB6* locus has been described in the CD4<sup>+</sup> T cell function [13,14]. Other studies associating *HLA-DR* loci and PD have been documented ([15]; reviewed in [16]). Below a focus is more especially given to autoimmune responses that develop in PD.

### **3. Autoimmunity in PD**

Autoimmune diseases (AD) are defined as ailments in which an immune response occurs in the host body against autologous tissues and provokes a pathological state of the host tissue due to damages. Patients affected with ADs have autoantibodies or autoreactive antigen-specific T cells driving the disease process. In general, and in contrast to anti-inflammatory states, a distinct MHC class II-associated haplotype susceptibility is associated with ADs [17]. Most generally, ADs are polygenic diseases, and a few only (autoimmune polyendocrinopathy syndrome type 1, immunodysregulation polyendocrinopathy enteropathy X-linked syndrome, autoimmune lymphoproliferative syndrome, and C1q deficiency) are monogenic. In general, also, they are polymorphic and multisystemic, but some of them are organ-specific, such as Addison's disease, in which autoantibodies attack the adrenal cortex, and myasthenia gravis, in which specific autoantibodies attack neuromuscular junctions.

Several studies have documented that dysregulated innate and adaptive immune responses are associated with PD [3]. At the center of the autoimmune response that occurs in PD is SNCA (**Fig. 1**). Investigations centered on this protein have shown that aggregates, which escape from both proteasomal and autophagosomal degradation [18], can trigger the activation of microglia [18], a specialized population of macrophages, which account for 10–15% of all cells in the brain. This condition critically alters the neurotransmitter pathways. Common immunopathological features at the *substantia nigra*, in PD, include activated microglia, the expression of MHC-I and MHC-II alleles [13,14,18-21], altered antigen presentation, and an amplified pro-inflammatory cytokine profile, contributing all to dysregulated innate and adaptive immune system activity and to typical self-tissue damages [12,22-24].

SNCA occurs at high levels in healthy appendix tissues, which is enriched in lymphoid tissues and immune cells, especially in mucosal macrophages [5,25]. It has been suggested that pathogenic SNCA could be generated under the influence of gut microbiome, linking, therefore, the immune system, the nervous system and the intestinal microbiota to PD (reviewed in [5]). Future investigations are, however, required to consolidate this link, which is still subjected to conflicting viewpoints [5].



**Fig. 1.** SNCA, a central component of the immune and autoinflammatory damages in PD. Aging, mitochondrial dysfunction, cellular oxidative stress, particularly in dopaminergic neurons in the *substantia nigra*, environmental exposure to heavy metals and pesticides, autophagic alterations and proteins aggregation have been proposed as crucial processes in the pathogenesis of PD. In this complex picture, SNCA plays a pivotal role. This simplified scheme highlights how SNCA epitopes presented in the context of APCs and MHC molecules activate CD4<sup>+</sup> T and CD8<sup>+</sup> T cells, which produce cytokines that especially induce activation of microglia and alter neurons. The figure was created by using BioRender.com

Autoantibodies have been detected in the serum from PD patients (**Table 1**). As it is generally the case with most of the autoantibodies identified in ADs, their origin and against which native structure (proteins, nucleic acids, sugars, lipids and/or assembly of these membrane or cellular elements) they have originally been generated remain totally unknown. What we know is that they cross-react with neuronal structures, such as SNCA and other neuronal antigens, and with neuronal cells (**Table 1**). To the best of our knowledge, autoantibodies to PARKIN, LRRK2, and PRKN have not been described. Well-described autoantibodies to N-methyl-D-aspartate-type glutamate receptors do not play any significant role in the pathogenesis or progression of PD, nor, for example, in PD with dementia [26]. A strict link with PD of much of the antibodies listed in **Table 1** has not been found, and therefore, they are not considered as proper marker of the disease. Although not tested in routine, serum antibodies reactive with SNCA (monomer or aggregates) are, however, occasionally regarded as a “biomarker” for different stages of PD [18-22]. Concerning their potential intrinsic pathogenicity, some subsets of autoantibodies listed in **Table 1** have been shown to induce dopaminergic neuronal cell death (e.g. apoptosis), enhanced complement function, and microglia cell injury. Experiments in animal models have shown that IgG antibodies purified from the serum of PD patients could induce a PD-like pathology [23]. It should be determined, however, if the pathogenic effects directly result from autoantibodies. In line, it may be noted that the cerebrospinal fluid (CSF) from PD patients was also seen to exhibit some toxicity on dopamine neurons [12]. Altogether, these experimental studies argue for an autoimmune component in PD. Additional investigations have however, to be undertaken to reinforce this assumption. Especially, it would be central to better identify the specificity and fine characteristics of the autoantibodies, which seem to be pathogenic in PD. Another aspect that remains elusive is to explain how these antibodies reach their target and determine if they act as trigger elements (at the emergence of the disease) or as a consequence when the clinical signs are present and the blood-brain barrier integrity is already

affected. It has also been argued that in fact, some naturally-occurring autoantibodies, especially to SNCA that circulate in the blood and CSF of PD patients, are protective. Their level appears to be lower in the blood and CSF of PD patients, which might diminish the neuroprotection they display [27,28]. This aspect requires further investigation.

**Table 1: Autoantibodies identified in the serum of PD patients**

Autoantibodies to	Comments	References
$\alpha$ -synuclein/SNCA	<ul style="list-style-type: none"> <li>Increased serum levels of SNCA-reacting Abs were observed</li> </ul>	[29-33]
GM1-ganglioside	<ul style="list-style-type: none"> <li>Increase serum levels of GM1-ganglioside-reacting Abs within the tremor-dominant form were observed</li> </ul>	[34]
Unknown, present in dopaminergic neurons in the <i>substantia nigra</i>	<ul style="list-style-type: none"> <li>Identified by immunocytochemistry. Discovered in 78% of the CSF samples taken from patients with clinical PD versus 3% only in the CFS of control patients or patients with neurological symptoms other than PD. Their fine specificity remained unknown.</li> </ul>	[35]
Neuronal antigens (aldolase C, neuron-specific enolase, and pyruvate kinase M1)	<ul style="list-style-type: none"> <li>Significantly different anti-neuronal Abs levels were observed in the sera of PD patients compared to healthy controls</li> </ul>	[36]
Neuronal cells	<ul style="list-style-type: none"> <li>Increased levels of autoAbs reactive to neuronal cells, brain lysate, and dsDNA were found</li> <li>The presence of these Abs has been associated to dyskinesia and depression observed in PD patients. The possible link between these autoAbs and clinical symptoms remains elusive</li> </ul>	[37]
Brain lysate		
dsDNA		
ICAM4 (Landsteiner-Wiener blood group), transcript variant 1	<ul style="list-style-type: none"> <li>Identified by microarray analysis</li> </ul>	[38]
PTCD2		

Abbreviations: Abs, antibodies; CSF, cerebrospinal fluid; dsDNA, double-stranded DNA; ICAM4, intercellular adhesion molecule 4; PD, Parkinson's disease; PTCD2, pentatricopeptide repeat domain 2.

T cell responses to PD-related antigens have been described. These antigens notably include DJ-1 that has been reported to affect the development of natural regulatory T cell (Tregs) and induced Tregs (previously known as suppressor T cells), and SNCA [5,39-43]. SNCA epitopes recognized by helper and cytotoxic T cells have been identified [44]. They were

identified in studying peripheral blood mononuclear cells (PBMCs) from PD patients primed with 9-10-mer (MHC-I) and 15-mer (MHC-II) SNCA peptides, and analyzed for CD4<sup>+</sup> (Th1 [IFN- $\gamma$ ] and Th2 [IL-5]) and CD8<sup>+</sup> T cells (IFN- $\gamma$ ) responses [44]. Most interestingly, the cryopreserved PBMCs of one PD patient used in a one-case study, responded similarly to a SNCA peptide [45]. PBMCs collected from this patient were stimulated with the SNCA peptide <sup>61</sup>EQVTNVGGAVVTGVT<sup>75</sup> and evaluated for the CD4<sup>+</sup>, CD8<sup>+</sup>, and Tregs responses; SNCA-reactive CD4<sup>+</sup> T responses (IL-4 and IFN- $\gamma$ ) were significantly maintained. In fact, this response was detectable in a blood sample of this patient collected 10 years before the onset of his PD clinical signs and was found low during the evolution of the disease [46]. This result was confirmed using a larger series of 11 different SNCA peptides tested with the PBMCs from PD and AD patients and healthy controls, indicating that SNCA-reactive T cell responses are associated with the onset of motor signs. Further, the cellular cytokine secretion immunophenotype study revealed that IFN- $\gamma$ , IL-4, and IL-10 were secreted by CD4<sup>+</sup> and IL-10 was secreted by CD8<sup>+</sup> T cells. Together, these results suggest that identifying SNCA-reactive T cells might have a prognostic interest if tested and detected at the onset (suspicion) of the disease, but is not appropriate for the diagnosis, as there is no significant correlation between the T cell responses and clinical symptoms. These results, however, are of prime importance in terms of therapeutic implication for developing potent immunomodulating approaches.

#### **4. Conclusion**

There is a growing body of evidence suggesting that PD could be considered as an autoimmune disease. In addition to T cell responses, an abundant literature has been documented on the B cells producing autoantibodies against SNCA antigen, neo-antigens, GM1-gangliosides, catecholamine-based melanins, and others [3,22,37,47,48]. Therefore, although more work is required to sustain the concept, the involvement of both autoreactive T cells (especially but not only SNCA-reactive responses) and B cells (autoantibody production) in the pathogenesis of PD support this assumption [49].

As mentioned above, SNCA aggregates/toxic oligomers escape from the intracellular degradation systems, either proteasomal or autophagosomal. Since in addition, PARKIN and PINK1, mutations in which were convincingly associated to PD [50], are key elements of mitophagy, the latter process is currently actively investigated in relation to PD [11,12,51].

Furthermore, possible disturbances of CMA are also under study in PD and may lead to decisive results with valuable therapeutic implications [52]. Thus, in addition to classical drugs that act on autoimmune diseases, and the ones used to treat PD symptoms, the rational introduction of specific agents aimed at modulating mitophagy and/or other forms of autophagy, such as CMA, might prove promising in PD.

### **Acknowledgements**

We thank Prof. Alessandro Sette (La Jolla) and Prof. Christine Tranchant (Strasbourg) for critical reading the manuscript and for their valuable advises. This research was funded by the French Centre National de la Recherche Scientifique, Région Grand-Est and the FHU ARRIMAGE, the Laboratory of Excellence Medalis (ANR-10-LABX-0034), Initiative of Excellence (IdEx), Strasbourg University, the University of Strasbourg Institute for Advanced Study (USIAS). SM acknowledges the support of the TRANSAUTOPHAGY COST Action (CA15138), the Club francophone de l'autophagie (CFATG) and the European Regional Development Fund of the European Union in the framework of the INTERREG V Upper Rhine program.

### **Author Contributions**

Both authors wrote the manuscript.

### **Researcher IDs**

Srinivasa Reddy Bonam: 0000-0002-2888-2418

Sylviane Muller: 0000-0002-0481-0620

### **Competing interests**

No conflict of interest

### **References**

- [1] Cerri S, Mus L, Blandini F. Parkinson's disease in women and men: what's the difference? *J Parkinsons Dis* 2019;9:501-515.
- [2] Stefanis L.  $\alpha$ -Synuclein in Parkinson's disease. *Cold Spring Harb Perspect Med* 2012;2:a009399.
- [3] Tan E-K, Chao Y-X, West A, Chan L-L, Poewe W, Jankovic J. Parkinson disease and the immune system — associations, mechanisms and therapeutics. *Nat Rev Neurol* 2020;16:303-318.
- [4] Challis C, Hori A, Sampson TR, Yoo BB, Challis RC, Hamilton AM, et al. Gut-seeded  $\alpha$ -synuclein fibrils promote gut dysfunction and brain pathology specifically in aged mice. *Nat Neurosci* 2020;23:327-336.
- [5] Cosentino M, Comi C, Marino F. The vermiform appendix in Parkinson's disease: At the crossroad of peripheral immunity, the nervous system and the intestinal microbiome. *Autoimmun Rev* 2019;18:102357.
- [6] Atik A, Stewart T, Zhang J. Alpha-synuclein as a biomarker for Parkinson's disease. *Brain Pathol* 2016;26:410-418.

- [7] Shahnawaz M, Mukherjee A, Pritzkow S, Mendez N, Rabadia P, Liu X, et al. Discriminating  $\alpha$ -synuclein strains in Parkinson's disease and multiple system atrophy. *Nature* 2020;578:273-277.
- [8] Ashton NJ, Hye A, Rajkumar AP, Leuzy A, Snowden S, Suárez-Calvet M, et al. An update on blood-based biomarkers for non-Alzheimer neurodegenerative disorders. *Nat Rev Neurol* 2020;16:265-284.
- [9] Niu M, Li Y, Li G, Zhou L, Luo N, Yao M, et al. A longitudinal study on  $\alpha$ -synuclein in plasma neuronal exosomes as a biomarker for Parkinson's disease development and progression. *Eur J Neurol*.
- [10] Polymeropoulos MH, Lavedan C, Leroy E, Ide SE, Dehejia A, Dutra A, et al. Mutation in the  $\alpha$ -synuclein gene identified in families with Parkinson's disease. *Science* 1997;276:2045-2047.
- [11] Menzies FM, Fleming A, Caricasole A, Bento CF, Andrews SP, Ashkenazi A, et al. Autophagy and neurodegeneration: pathogenic mechanisms and therapeutic opportunities. *Neuron* 2017;93:1015-1034.
- [12] Bonam SR, Wang F, Muller S. Lysosomes as a therapeutic target. *Nat Rev Drug Discov* 2019;18:923-948.
- [13] Chang D, Nalls MA, Hallgrímsdóttir IB, Hunkapiller J, van der Brug M, Cai F, et al. A meta-analysis of genome-wide association studies identifies 17 new Parkinson's disease risk loci. *Nat Genet* 2017;49:1511-1516.
- [14] Hammond TR, Marsh SE, Stevens B. Immune signaling in neurodegeneration. *Immunity* 2019;50:955-974.
- [15] Hollenbach JA, Norman PJ, Creary LE, Damotte V, Montero-Martin G, Caillier S, et al. A specific amino acid motif of HLA-DRB1 mediates risk and interacts with smoking history in Parkinson's disease. *Proc Natl Acad Sci U S A* 2019;116:7419-7424.
- [16] Scheiblich H, Trombly M, Ramirez A, Heneka MT. Neuroimmune connections in aging and neurodegenerative diseases. *Trends Immunol* 2020;41:300-312.
- [17] Doria A, Zen M, Bettio S, Gatto M, Bassi N, Nalotto L, et al. Autoinflammation and autoimmunity: Bridging the divide. *Autoimmun Rev* 2012;12:22-30.
- [18] Theodore S, Cao S, McLean PJ, Standaert DG. Targeted overexpression of human alpha-synuclein triggers microglial activation and an adaptive immune response in a mouse model of Parkinson disease. *J Neuropathol Exp Neurol* 2008;67:1149-1158.
- [19] Lampe JB, Gossrau G, Herting B, Kempe A, Sommer U, Füssel M, et al. HLA typing and Parkinson's disease. *Eur Neurol* 2003;50:64-68.
- [20] Hamza TH, Zabetian CP, Tenesa A, Laederach A, Montimurro J, Yearout D, et al. Common genetic variation in the HLA region is associated with late-onset sporadic Parkinson's disease. *Nat Genet* 2010;42:781-785.
- [21] Cebrián C, Zucca FA, Mauri P, Steinbeck JA, Studer L, Scherzer CR, et al. MHC-I expression renders catecholaminergic neurons susceptible to T-cell-mediated degeneration. *Nat Commun* 2014;5:3633.
- [22] De Virgilio A, Greco A, Fabbrini G, Inghilleri M, Rizzo MI, Gallo A, et al. Parkinson's disease: autoimmunity and neuroinflammation. *Autoimmun Rev* 2016;15:1005-1011.
- [23] Poewe W, Seppi K, Tanner CM, Halliday GM, Brundin P, Volkman J, et al. Parkinson disease. *Nat Rev Dis Primers* 2017;3:17013.
- [24] Muller S, Brun S, Rene F, de Seze J, Loeffler JP, Jeltsch-David H. Autophagy in neuroinflammatory diseases. *Autoimmun Rev* 2017;16:856-874.
- [25] Killinger BA, Madaj Z, Sikora JW, Rey N, Haas AJ, Vepa Y, et al. The vermiform appendix impacts the risk of developing Parkinson's disease. *Sci Transl Med* 2018;10:eaar5280.

- [26] Hopfner F, Müller SH, Steppat D, Miller J, Schmidt N, Wandinger K-P, et al. No association between Parkinson disease and autoantibodies against NMDA-type glutamate receptors. *Transl Neurodegener* 2019;8:11-11.
- [27] Brudek T, Winge K, Folke J, Christensen S, Fog K, Pakkenberg B, et al. Autoimmune antibody decline in Parkinson's disease and Multiple System Atrophy; a step towards immunotherapeutic strategies. *Mol Neurodegener* 2017;12:44.
- [28] Rabenstein M, Besong Agbo D, Wolf E, Dams J, Nicolai M, Roeder A, et al. Effect of naturally occurring  $\alpha$ -synuclein-antibodies on toxic  $\alpha$ -synuclein-fragments. *Neurosci Lett* 2019;704:181-188.
- [29] Papachroni KK, Ninkina N, Papapanagiotou A, Hadjigeorgiou GM, Xiromerisiou G, Papadimitriou A, et al. Autoantibodies to alpha-synuclein in inherited Parkinson's disease. *J Neurochem* 2007;101:749-756.
- [30] Yanamandra K, Gruden MA, Casaita V, Meskys R, Forsgren L, Morozova-Roche LA.  $\alpha$ -Synuclein reactive antibodies as diagnostic biomarkers in blood sera of Parkinson's disease patients. *PLoS One* 2011;6:e18513.
- [31] Henschcliffe C. Blood and cerebrospinal fluid markers in Parkinson's disease: current biomarker findings. *Curr Biomark Find* 2015;5:1-11.
- [32] Shalash A, Salama M, Makar M, Roushdy T, Elrassas HH, Mohamed W, et al. Elevated serum  $\alpha$ -synuclein autoantibodies in patients with Parkinson's disease relative to Alzheimer's disease and controls. *Front Neurol* 2017;8:720-720.
- [33] Scott KM, Kouli A, Yeoh SL, Clatworthy MR, Williams-Gray CH. A systematic review and meta-analysis of alpha synuclein auto-antibodies in Parkinson's Disease. *Front Neurol* 2018;9.
- [34] Zappia M, Crescibene L, Bosco D, Arabia G, Nicoletti G, Bagalà A, et al. Anti-GM1 ganglioside antibodies in Parkinson's disease. *Acta Neurol Scand* 2002;106:54-57.
- [35] Carvey PM, McRae A, Lint TF, Ptak LR, Lo ES, Goetz CG, et al. The potential use of a dopamine neuron antibody and a striatal-derived neurotrophic factor as diagnostic markers in Parkinson's disease. *Neurology* 1991;41:53-58.
- [36] van de Warrenburg BPC, Church AJ, Martino D, Candler PM, Bhatia KP, Giovannoni G, et al. Antineuronal antibodies in Parkinson's disease. *Mov Disord* 2008;23:958-963.
- [37] Benkler M, Agmon-Levin N, Hassin-Baer S, Cohen OS, Ortega-Hernandez O-D, Levy A, et al. Immunology, autoimmunity, and autoantibodies in Parkinson's Disease. *Clin Rev Allergy Immunol* 2012;42:164-171.
- [38] Han M, Nagele E, DeMarshall C, Acharya N, Nagele R. Diagnosis of Parkinson's disease based on disease-specific autoantibody profiles in human sera. *PLoS One* 2012;7:e32383.
- [39] Brochard V, Combadière B, Prigent A, Laouar Y, Perrin A, Beray-Berthet V, et al. Infiltration of CD4+ lymphocytes into the brain contributes to neurodegeneration in a mouse model of Parkinson disease. *J Clin Invest* 2009;119:182-192.
- [40] Chen Z, Chen S, Liu J. The role of T cells in the pathogenesis of Parkinson's disease. *Prog Neurobiol* 2018;169:1-23.
- [41] Jiang T, Li G, Xu J, Gao S, Chen X. The challenge of the pathogenesis of Parkinson's disease: is autoimmunity the culprit? *Front Immunol* 2018;9.
- [42] Campos-Acuña J, Elgueta D, Pacheco R. T-cell-driven inflammation as a mediator of the gut-brain axis involved in Parkinson's disease. *Front Immunol* 2019;10.
- [43] Garretti F, Agalliu D, Lindestam Arlehamn CS, Sette A, Sulzer D. Autoimmunity in Parkinson's disease: the role of  $\alpha$ -synuclein-specific T cells. *Front Immunol* 2019;10.
- [44] Sulzer D, Alcalay RN, Garretti F, Cote L, Kanter E, Agin-Lieb J, et al. T cells from patients with Parkinson's disease recognize  $\alpha$ -synuclein peptides. *Nature* 2017;546:656-661.

- [45] Reynolds AD, Stone DK, Hutter JAL, Benner EJ, Mosley RL, Gendelman HE. Regulatory T Cells attenuate Th17 cell-mediated nigrostriatal dopaminergic neurodegeneration in a model of Parkinson's disease. *J Immunol* 2010;184:2261-2271.
- [46] Lindestam Arlehamn CS, Dhanwani R, Pham J, Kuan R, Frazier A, Rezende Dutra J, et al.  $\alpha$ -Synuclein-specific T cell reactivity is associated with preclinical and early Parkinson's disease. *Nat Commun* 2020;11:1875.
- [47] Kunas RC, McRae A, Kesselring J, Villiger PM. Antidopaminergic antibodies in a patient with a complex autoimmune disorder and rapidly progressing Parkinson's disease. *J Allergy Clin Immunol* 1995;96:688-690.
- [48] Benkler M, Agmon-Levin N, Shoenfeld Y. Parkinson's disease, autoimmunity, and olfaction. *Int J Neurosci* 2009;119:2133-2143.
- [49] Sabatino JJ, Pröbstel A-K, Zamvil SS. B cells in autoimmune and neurodegenerative central nervous system diseases. *Nat Rev Neurosci* 2019;20:728-745.
- [50] Narendra D, Walker JE, Youle R. Mitochondrial quality control mediated by PINK1 and Parkin: links to parkinsonism. *Cold Spring Harb Perspect Biol* 2012;4:a011338.
- [51] Narendra D, Tanaka A, Suen D-F, Youle RJ. Parkin is recruited selectively to impaired mitochondria and promotes their autophagy. *J Cell Biol* 2008;183:795-803.
- [52] Orenstein SJ, Kuo S-H, Tasset I, Arias E, Koga H, Fernandez-Carasa I, et al. Interplay of LRRK2 with chaperone-mediated autophagy. *Nat Neurosci* 2013;16:394-406.