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Parkinson's disease is an autoimmune disease: a reappraisal

Srinivasa Reddy Bonam^{a,b*} and Sylviane Muller^{a,b,c,d,*}

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

^b Institut national de la santé et de la recherche médicale, Centre de Recherche des Cordeliers, Sorbonne Université, Université de Paris, Paris, France

^c Fédération Hospitalo-Universitaire OMICARE, Fédération de Médecine Translationnelle de Strasbourg, Strasbourg University, Strasbourg, France

^d University of Strasbourg Institute for Advanced Study, Strasbourg, France

*Corresponding authors: Srinivasa R. Bonam bsrpharmacy90@gmail.com; Sylviane Muller sylviane.muller@unistra.fr

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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 α -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, α -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⁺ 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⁺ 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].

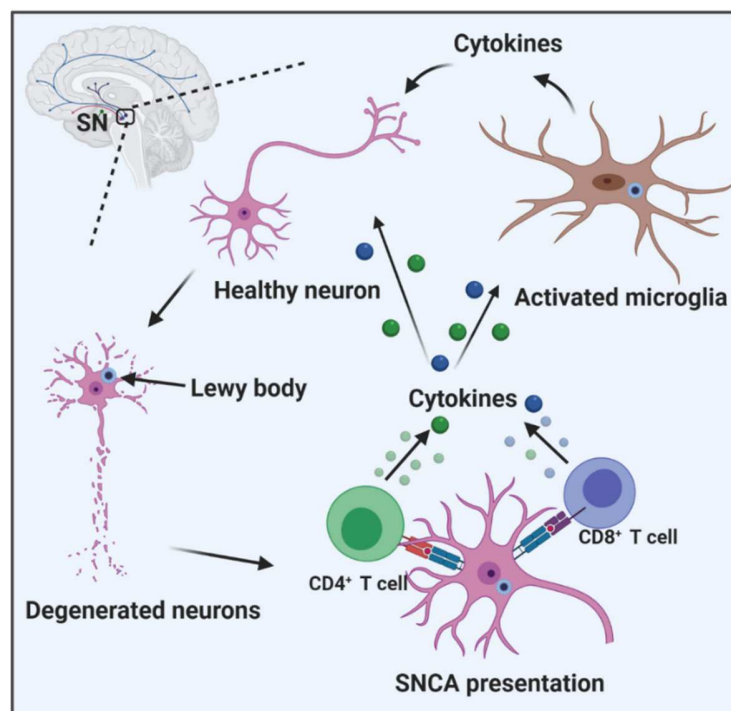


Fig. 1. SNCA, a central component of the immune and autoinflammatory damages in PD. Aging, mitochondrial dysfunction, cellular oxidative stress, particularly in dopaminergic neurons in the *substantia nigra*, environmental exposure to heavy metals and pesticides, autophagic alterations and proteins aggregation 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⁺ T and CD8⁺ 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 |
|---|---|------------|
| α -synuclein/SNCA | <ul style="list-style-type: none"> Increased serum levels of SNCA-reacting Abs were observed | [29-33] |
| GM1-ganglioside | <ul style="list-style-type: none"> Increase serum levels of GM1-ganglioside-reacting Abs within the tremor-dominant form were observed | [34] |
| Unknown, present in dopaminergic neurons in the <i>substantia nigra</i> | <ul style="list-style-type: none"> 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. | [35] |
| Neuronal antigens (aldolase C, neuron-specific enolase, and pyruvate kinase M1) | <ul style="list-style-type: none"> Significantly different anti-neuronal Abs levels were observed in the sera of PD patients compared to healthy controls | [36] |
| Neuronal cells | <ul style="list-style-type: none"> Increased levels of autoAbs reactive to neuronal cells, brain lysate, and dsDNA were found 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 | [37] |
| Brain lysate | | |
| dsDNA | | |
| ICAM4 (Landsteiner-Wiener blood group), transcript variant 1 | <ul style="list-style-type: none"> Identified by microarray analysis | [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⁺ (Th1 [IFN- γ] and Th2 [IL-5]) and CD8⁺ T cells (IFN- γ) 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 ⁶¹EQVTNVGGAVVTGVT⁷⁵ and evaluated for the CD4⁺, CD8⁺, and Tregs responses; SNCA-reactive CD4⁺ T responses (IL-4 and IFN- γ) 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- γ , IL-4, and IL-10 were secreted by CD4⁺ and IL-10 was secreted by CD8⁺ 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.

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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

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