New Perspectives on Immune Involvement in Parkinson’s Disease Pathogenesis

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Abstract. Accumulating evidence implicates immune dysfunction in the etiology of Parkinson’s disease (PD). For instance, impaired cellular and humoral immune responses are emerging as established pathological hallmarks in PD. Further, in experimental models of PD, inflammatory cell activation and immune dysregulation are evident. Genetic and epidemiologic studies have drawn associations between autoimmunity disease and PD. Distillation of these various lines of evidence indicates dysregulated immunogenetics as a primary risk factor for PD. This article will present novel perspectives on the association between genetic risk factors and immune processes in PD. The objective of this work is to synthesize the data surrounding the role of immunogenetics in PD to maximize the potential of targeting the immune system as a therapeutic modality.

Keywords: Parkinson’s disease, immune, T cells, adaptive immunity, immunogenetics

INTRODUCTION

Parkinson’s disease (PD) is a progressive, debilitating neurodegenerative disorder that presents with a range of clinical manifestations. PD varies in the onset, symptoms, and progression of the disorder, suggestive of a complex interplay between genetics and environment. Much attention has been lent towards understanding the pathological features underpinning PD; loss of nigral dopaminergic neurons and accumulation of toxic α-synuclein in the form of Lewy bodies and Lewy neurites [1]. Neuroinflammation is an additional hallmark of PD, underscored by reactive gliosis [2] and an upregulation of major histocompatibility class II (MHCII) molecules [3, 4]. Yet, inflammatory activation in PD is not only confined to the brain. Accumulating evidence implicates peripheral immune activation in PD pathogenesis, including increased expression of inflammatory molecules in the central [5] and peripheral nervous systems [6]. Moreover, several recent reports implicate adaptive immune T cells in the neurodegenerative process of PD [7–10]. This review will synthesize the key concepts surrounding peripheral immune involvement in PD and the role of immunogenetics in PD risk. This work posits that targeting the peripheral immune system is a potential therapeutic modality for PD.

THE ROLE OF IMMUNOGENETICS IN PD ETIOPATHOLOGY

Immunogenetics, the study of the genetic basis of the immune response, includes the investigation of normal immunologic pathways and the identification of genetic variations that cause immune defects. The premise of immunogenetics is the identification of new therapeutic targets for diseases with immunologic underpinnings. Immunogenetics gained prominence following the awarding of the 1980 Nobel Prize in Physiology or Medicine to Baruj Benacerraf, Jean Dausset, and George D. Snell for...
their discoveries concerning genetically determined structures on the cell surface that regulate immunological reactions [11]. These researchers elegantly showed that certain MHC molecules found on the cell membrane predispose certain individuals to certain diseases. Their work showed how genetic variants contribute to inter-individual variation in immune response and risk of disease. Notably, many of the genetic variants linked to PD play a role in modulating the immune response. In fact, numerous studies have reported that subtle mutations in the genetic components of MHC, or human leukocyte antigen (HLA), are associated with PD risk [12–18]. HLA is a highly polymorphic region of the human genome. HLA encodes both MHCI and MHCII molecules that present antigens to adaptive immune CD8 and CD4 T cells, respectively. Several studies have found associations between single nucleotide polymorphisms and alleles in HLA class II and PD [12–18]. Cumulatively, these studies have provided functional insight into the observed increased expression of MHCII molecules in PD brains. However, the manner in which HLA allelic variability affects the interaction between antigen-presenting cells and T cells is an area of active investigation.

In addition to HLA alleles, other genes associated with monogenic PD have immunogenetic components, too. Mutations in Leucine Rich Repeat Kinase 2 (LRRK2) account for approximately 1–2% of PD cases [19, 20]. LRRK2 encodes a large protein with multiple functions in immune cells. High levels of LRRK2 disrupt immune function in PD patients [21]. Interestingly, the LRRK2 G2019S variant associated with PD may help protect against infection by enhancing the immune response to peripheral infection [22]. However, in the brains of mice expressing the LRRK2 G2019S variant, this enhanced response to infection may backfire, as immune cells release reactive oxygen species that exacerbate neurodegeneration [22]. Notably, mice expressing the LRRK2 G2019S variant have increased amounts α-synuclein deposits when harboring peripheral infections. Taken together, these data raise the possibility that the combination of the LRRK2 G2019S variant and an environmental trigger, such as systemic inflammation, might be involved in PD etiopathology. In fact, recent evidence suggests that independent of mutations, wild-type LRRK2 plays a role in idiopathic PD via endolysosomal and autophagic functions [21, 23, 24]. LRRK2 kinase inhibitors, which improve endosomal maturation and lysosomal function [23, 24], may therefore be useful for limiting systemic inflammation in idiopathic PD patients who do not harbor LRRK2 mutations.

Parkin (PRKN) and PTEN Induced Kinase 1 (PINK1) are additional PD-associated genes involved in immune modulation. Both genes target damaged mitochondria for elimination by mitophagy [25]. Recently, these genes were shown to link the mitochondrial dysfunction and T cell autoimmunity tenets implicated in PD pathogenesis [26]. In familial forms of PD, mitochondrial proteins are processed for recognition by CD8 T cells [26]. This finding provides a mechanism by which selected proteins from damaged mitochondria are presented by MHC molecules to T cells. This pathway is antagonized by PINK1 and Parkin, indicating that mitochondrial antigen presentation could influence PD pathogenesis. Notably, in mice, expression of Prkn and Pink1, suppresses antigen presentation by MHC class I molecules in immune cells [26]. Thus, mutations in these genes could block the inhibitory effects and increased immune responses mediated by cytotoxic CD8 T cells, ultimately leading to dopaminergic neuronal death [26, 27].

Mutations and copy number variations in the Synuclein Alpha (SNCA) gene are also linked to dominantly inherited monogenic PD [28, 29]. Further, genome-wide association studies (GWAS) have identified numerous single nucleotide polymorphisms in the SNCA gene associated with idiopathic PD risk [30]. Notably, the protein product of SCNA, α-synuclein, inhibits viral infection in the central nervous system [31], indicating a functional role for the native expression of α-synuclein. Several recent reports indicate that T cells can be activated upon recognition of α-synuclein epitopes presented on MHC molecules [7–10]. Further, α-synuclein-specific T cells contribute to neurodegeneration in mouse models of PD [32] and in PD dementia [7]. Most recently, α-synuclein was shown to be required for normal immune function in mice [33]. Cumulatively, these data raise the hypothesis that α-synuclein accumulates within the nervous system of PD individuals due to an inflammatory/immune response. This response may, in turn, spur a feed-forward mechanism of immune activation given that α-synuclein itself can serve as an immunostimulatory antigen.

**IS PD AN AUTOIMMUNE DISORDER?**

Autoimmunity occurs when immune responses of an organism are mounted against its own healthy
cells, tissues and other normal body constituents. Notably, autoimmune diseases and PD share common genetic pathways [34, 35]. Dozens of loci have been found to be shared between PD and autoimmune disorders by GWAS, including type 1 diabetes, Crohn’s disease, ulcerative colitis, rheumatoid arthritis, celiac disease, psoriasis, and multiple sclerosis [34]. In fact, PD-associated variants in LRRK2 partially overlap with LRRK2 variants associated with inflammatory diseases, including Crohn’s disease, an inflammatory bowel disorder that causes chronic inflammation of the gastrointestinal tract [36]. It is estimated that patients with an autoimmune disease have a 33% excess risk of developing PD [37]. The identification of common genetic pathways for PD and autoimmune disorders further strengthens the importance of immunogenetics and immune therapy in PD.

What could be driving the association between PD and autoimmune diseases? Secondary parkinsonism is a symptom of some autoimmune disorders and a confounding factor in interpreting the association between PD and autoimmunity. Additional cofactors that may alter inflammation and immunity in PD include stress and depression, which are symptoms in PD that also commonly exacerbate autoimmune diseases. Yet, the association between autoimmunity and PD might be explained by immunogenetic aberrations that are shared between these conditions and that affect immune function. In support of this hypothesis, expression quantitative trait locus analysis has shown that protein expression profiles of CD4 T cells and monocytes are associated with genetic variants that underlie some of the heritable risk for PD [27, 38]. Notably, abnormal expression patterns of α-synuclein and LRRK2 in monocytes were associated with autoimmune diseases [38]. Thus, protein expression profiles could partly explain the observed clinical associations between autoimmune diseases and PD [27, 38]. Yet, aside from genetic overlap with autoimmunity, it remains unclear which immune stimuli dictate the propensity for one to develop the region-specific brain pathology observed in PD.

One potential mechanism underlying the association between PD and autoimmunity could be molecular mimicry, whereby the structure of α-synuclein resembles that of a viral protein [39]. In this regard, influenza and herpes simplex virus infections have been loosely associated with increased risk of subsequent PD [40], but further delineation of molecular mimicry mechanisms is warranted.

**IMMUNE CELL ACCESS TO THE SUBSTANTIA NIGRA IN PD**

It has been postulated that PD is an inflammatory disorder that arises from the combination of immunogenetic risk factors and an environmental trigger such as infection. In fact, Braak and Del Tredici first postulated that PD originates in the enteric nervous system and olfactory bulb, due to the proximity of these brain structures to the environment [41]. Others have suggested that idiopathic PD is caused by interactions between genetic susceptibility, infection history, sex and age [42]. But, how might immune cells inflict region-specific damage to the substantia nigra in PD? The brain has historically been regarded as an immune privileged organ owing to the existence of the blood–brain barrier. However, the identification of meningeal lymphatic vasculature has challenged the notion that the peripheral immune system does not directly interact with the brain [43, 44]. Now, it is understood that brain-derived antigens in the cerebrospinal fluid (CSF) accumulate around the dural sinuses, are captured by local antigen-presenting cells, and are presented to patrolling T cells [45]. The CSF, after circulating through the ventricular system and subarachnoid space of the cortex and spinal cord, penetrates perivascular spaces [46]. Perivascular spaces are fluid-filled spaces that surround small arterioles, capillaries and venules in the brain. Notably, enlarged perivascular spaces are associated with PD [47, 48], raising the possibility that T cells have enhanced access to PD-associated antigens.

What is the mechanism by which T cells home to the substantia nigra in PD? Recent evidence suggests that increased expression of C-X-C motif chemokine receptor 4 (CXCR4) in CD4 T cells mediates their homing to the PD substantia nigra [7]. CD4 T cells are likely drawn to the brain via increased CSF protein levels of the CXCR4 ligand, C-X-C motif chemokine ligand 12 (CXCL12), since levels of CXCL12 are associated with neuroaxonal damage [7]. Interestingly, a variant of CXCR4 is associated with increased PD risk [49]. Further research is required to determine the impact of this CXCR4 variant on T cell trafficking in PD. Given that enhanced MHCI expression is a component of PD, the CXCR4-CXCL12 signaling axis may represent a mechanistic target for inhibiting pathological CD4 T cell trafficking in PD.
CONCLUSION

In conclusion, it is likely that a complicated mix of immunogenetics and environment, such as infection history, play a role in PD. There are several PD-associated risk factors that modulate the immune system, including the aforementioned LRRK2, SCNA, PINK1, and PRKN genes. Genetic alterations to HLA genes, which are critical for antigen-specific immune responses, are also implicated in PD. Importantly, to fully delineate the role of immunogenetics in PD, it will be critical to thoroughly document patient history of infections and to stratify patients by HLA haplotypes. The HLA region is highly polymorphic, so epigenetic effects of ethnicity and environmental factors in addition to viral infections need to be taken into account before a pathogenic link between HLA genes and PD can be solidified [50]. Furthermore, associations of non-coding single-nucleotide polymorphisms with PD have been found even without the classic HLA risk alleles [18]. So, the association with non-coding single-nucleotide polymorphisms in the HLA region is not necessarily dependent on structural genetic variants in HLA genes. With advancements in vaccine technology, underscored by improvements in mRNA vaccines [51], controlled studies may identify virus-PD associations that decline in vaccinated populations harboring PD HLA risk alleles.

Reports on α-synuclein immunoreactivity have shown that patients with advanced PD have lower levels of α-synuclein reactive antibodies than patients with early PD [52, 53]. Further, autoantibodies to α-synuclein are consistently observed to be higher in early-stage PD in a meta-analysis [54]. In addition to the humoral immune response, T cell responses to α-synuclein have also been shown to occur early in PD disease course [9, 10]. These results imply that adaptive immunity plays an early role in PD etiopathology. However, discordance exists in the type of T cell response involved in PD. While some studies implicate CD4 T helper 1 (Th1) or Th2 class II T cells [9, 10], others implicate CD4 interleukin-17 (IL-17)-producing (Th17) cells [7, 55, 56]. Thus, the function and phenotype of CD4 T cells and their pathobiological role in synucleinopathies is unclear. Yet, it is likely that a complicated mix of immunogenetics, including HLA haplotype, and disease state influence the T cell response in PD. Adding to this complexity are recent findings on the role of intestinal inflammation in PD (reviewed in [57]). Epidemiologic and genetic studies have underscored the similarities between gastrointestinal disorders and PD. As mentioned, LRRK2 is also a common susceptibility locus for Chron’s disease [58]. Yet, the mechanism by which LRRK2 mutations might synergize with intestinal inflammation to promote neuroinflammation in PD remains an outstanding question. Thus, investigating the role of LRRK2 in the gut–brain axis in PD is highly warranted.

To summarize, aberrant immune function is an established component of susceptibility to and progression of PD. This emergent field provides opportunities to identify novel therapeutic targets and strategies to slow or reverse PD [27, 59, 60]. While immunological changes have been difficult to interpret, immune system involvement in PD is supported by several independent lines of clinical and preclinical evidence [27]. Importantly, T cell responses associated with α-synuclein pathology have been detected in adeno-associated viral models which overexpress α-synuclein in the substantia nigra [32, 61]. These models will serve as a critical tool assess future pre-clinical immunotherapeutic strategies. The CXCR4-CXCL12 signaling axis is a potential pre-clinical therapeutic target to inhibit CD4 T cell trafficking to the PD brain. To this end, longitudinal studies are needed to identify PD patients who are most suitable for immunotherapy. Of course, clinical trial studies will need to determine the long-term efficacy, outcome and viability of immunotherapeutic treatments.

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CONFLICT OF INTEREST

The author has no conflict of interest to report.

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