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Review

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 autoimmune 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

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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 exasperate 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 MHCII 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 mouse 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.

REFERENCES

[1] Spillantini MG, Crowther RA, Jakes R, Hasegawa M, Goedert M (1998) alpha-Synuclein in filamentous inclusions of Lewy bodies from Parkinson's disease and dementia with lewy bodies. *Proc Natl Acad Sci U S A* **95**, 6469-6473.

[2] Gerhard A, Pavese N, Hotton G, Turkheimer F, Es M, Hammers A, Eggert K, Oertel W, Banati RB, Brooks DJ (2006)

In vivo imaging of microglial activation with [11C](R)-PK11195 PET in idiopathic Parkinson's disease. *Neurobiol Dis* **21**, 404-412.

[3] McGeer PL, Itagaki S, Boyes BE, McGeer EG (1988) Reactive microglia are positive for HLA-DR in the substantia nigra of Parkinson's and Alzheimer's disease brains. *Neurology* **38**, 1285-1291.

[4] Harms AS, Cao S, Rowse AL, Thome AD, Li X, Mangieri LR, Cron RQ, Shacka JJ, Raman C, Standaert DG (2013) MHCII is required for alpha-synuclein-induced activation of microglia, CD4 T cell proliferation, and dopaminergic neurodegeneration. *J Neurosci* **33**, 9592-9600.

[5] Mogi M, Harada M, Kondo T, Riederer P, Inagaki H, Minami M, Nagatsu T (1994) Interleukin-1 beta, interleukin-6, epidermal growth factor and transforming growth factor-alpha are elevated in the brain from parkinsonian patients. *Neurosci Lett* **180**, 147-150.

[6] Qin XY, Zhang SP, Cao C, Loh YP, Cheng Y (2016) Aberrations in peripheral inflammatory cytokine levels in Parkinson disease: A systematic review and meta-analysis. *JAMA Neurol* **73**, 1316-1324.

[7] Gate D, Tapp E, Leventhal O, Shahid M, Nonninger TJ, Yang AC, Strempfl K, Unger MS, Fehlmann T, Oh H, Channappa D, Henderson VW, Keller A, Aigner L, Galasko DR, Davis MM, Poston KL, Wyss-Coray T (2021) CD4(+) T cells contribute to neurodegeneration in Lewy body dementia. *Science* **374**, 868-874.

[8] Singhania A, Pham J, Dhanwani R, Frazier A, Rezende Dutra J, Marder KS, Phillips E, Mallal S, Amara AW, Standaert DG, Sulzer D, Peters B, Sette A, Lindestam Arlehamn CS (2021) The TCR repertoire of alpha-synuclein-specific T cells in Parkinson's disease is surprisingly diverse. *Sci Rep* **11**, 302.

[9] Lindestam Arlehamn CS, Dhanwani R, Pham J, Kuan R, Frazier A, Rezende Dutra J, Phillips E, Mallal S, Roederer M, Marder KS, Amara AW, Standaert DG, Goldman JG, Litvan I, Peters B, Sulzer D, Sette A (2020) alpha-Synuclein-specific T cell reactivity is associated with preclinical and early Parkinson's disease. *Nat Commun* **11**, 1875.

[10] Sulzer D, Alcalay RN, Garretti F, Cote L, Kanter E, Agin-Liebes J, Liong C, McMurtrey C, Hildebrand WH, Mao X, Dawson VL, Dawson TM, Oseroff C, Pham J, Sidney J, Dillon MB, Carpenter C, Weiskopf D, Phillips E, Mallal S, Peters B, Frazier A, Lindestam Arlehamn CS, Sette A (2017) T cells from patients with Parkinson's disease recognize alpha-synuclein peptides. *Nature* **546**, 656-661.

[11] Marx JL (1980) 1980 Nobel Prize in Physiology or Medicine. *Science* **210**, 621-623.

[12] Hollenbach JA, Norman PJ, Creary LE, Damotte V, Montero-Martin G, Caillier S, Anderson KM, Misra MK, Nemat-Gorgani N, Osoegawa K, Santaniello A, Renschen A, Marin WM, Dandekar R, Parham P, Tanner CM, Hauser SL, Fernandez-Vina M, Oksenberg JR (2019) 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* **116**, 7419-7424.

[13] Hamza TH, Zabetian CP, Tenesa A, Laederach A, Montimurro J, Yearout D, Kay DM, Doheny KF, Paschall J, Pugh E, Kusel VI, Collura R, Roberts J, Griffith A, Samii A, Scott WK, Nutt J, Factor SA, Payami H (2010) Common genetic variation in the HLA region is associated with late-onset sporadic Parkinson's disease. *Nat Genet* **42**, 781-785.

[14] International Parkinson Disease Genomics C, Nalls MA, Plagnol V, Hernandez DG, Sharma M, Sheerin UM, Saad M, Simon-Sanchez J, Schulte C, Lesage S, Sveinbjornsdottir S, Stefansson K, Martinez M, Hardy J, Heutink P, Brice A, Gasser T, Singleton AB, Wood NW (2011) Imputation of sequence variants for identification of genetic risks for Parkinson's disease: A meta-analysis of genome-wide association studies. *Lancet* **377**, 641-649.

[15] Hill-Burns EM, Factor SA, Zabetian CP, Thomson G, Payami H (2011) Evidence for more than one Parkinson's disease-associated variant within the HLA region. *PLoS One* **6**, e27109.

[16] Ahmed I, Tamouza R, Delord M, Krishnamoorthy R, Tzourio C, Mulot C, Nacfer M, Lambert JC, Beaune P, Laurent-Puig P, Loriot MA, Charron D, Elbaz A (2012) Association between Parkinson's disease and the HLA-DRB1 locus. *Mov Disord* **27**, 1104-1110.

[17] Simon-Sanchez J, van Hilten JJ, van de Warrenburg B, Post B, Berendse HW, Arepalli S, Hernandez DG, de Bie RM, Velseboer D, Scheffer H, Bloem B, van Dijk KD, Rivadeneira F, Hofman A, Uitterlinden AG, Rizzu P, Bochdanovits Z, Singleton AB, Heutink P (2011) Genome-wide association study confirms extant PD risk loci among the Dutch. *Eur J Hum Genet* **19**, 655-661.

[18] Wissemann WT, Hill-Burns EM, Zabetian CP, Factor SA, Patsopoulos N, Hoglund B, Holcomb C, Donahue RJ, Thomson G, Erlich H, Payami H (2013) Association of Parkinson disease with structural and regulatory variants in the HLA region. *Am J Hum Genet* **93**, 984-993.

[19] Zimprich A, Biskup S, Leitner P, Lichtner P, Farrer M, Lincoln S, Kachergus J, Hulihan M, Uitti RJ, Calne DB, Stoessl AJ, Pfeiffer RF, Patenge N, Carbajal IC, Vieregge P, Asmus F, Muller-Myhsok B, Dickson DW, Meitinger T, Strom TM, Wszolek ZK, Gasser T (2004) Mutations in LRRK2 cause autosomal-dominant parkinsonism with pleomorphic pathology. *Neuron* **44**, 601-607.

[20] Paisan-Ruiz C, Jain S, Evans EW, Gilks WP, Simon J, van der Brug M, Lopez de Munain A, Aparicio S, Gil AM, Khan N, Johnson J, Martinez JR, Nicholl D, Marti Carrera I, Pena AS, de Silva R, Lees A, Marti-Masso JF, Perez-Tur J, Wood NW, Singleton AB (2004) Cloning of the gene containing mutations that cause PARK8-linked Parkinson's disease. *Neuron* **44**, 595-600.

[21] Cook DA, Kannarkat GT, Cintron AF, Butkovich LM, Fraser KB, Chang J, Grigoryan N, Factor SA, West AB, Boss JM, Tansey MG (2017) LRRK2 levels in immune cells are increased in Parkinson's disease. *NPJ Parkinsons Dis* **3**, 11.

[22] Shutinoski B, Hakimi M, Harmsen IE, Lunn M, Rocha J, Lengacher N, Zhou YY, Khan J, Nguyen A, Hake-Volling Q, El-Kodsi D, Li J, Alikashani A, Beauchamp C, Majithia J, Coombs K, Shimshek D, Marcogliese PC, Park DS, Rioux JD, Philpott DJ, Woulfe JM, Hayley S, Sad S, Tomlinson JJ, Brown EG, Schlossmacher MG (2019) Lrrk2 alleles modulate inflammation during microbial infection of mice in a sex-dependent manner. *Sci Transl Med* **11**, eaas9292.

[23] Rocha EM, De Miranda BR, Castro S, Drolet R, Hatcher NG, Yao L, Smith SM, Keeney MT, Di Maio R, Kofler J, Hastings TG, Greenamyre JT (2020) LRRK2 inhibition prevents endolysosomal deficits seen in human Parkinson's disease. *Neurobiol Dis* **134**, 104626.

[24] Di Maio R, Hoffman EK, Rocha EM, Keeney MT, Sanders LH, De Miranda BR, Zharikov A, Van Laar A, Stepan AF, Lanz TA, Kofler JK, Burton EA, Alessi DR, Hastings TG, Greenamyre JT (2018) LRRK2 activation in idiopathic Parkinson's disease. *Sci Transl Med* **10**, eaar5429.

[25] Pickrell AM, Youle RJ (2015) The roles of PINK1, parkin, and mitochondrial fidelity in Parkinson's disease. *Neuron* **85**, 257-273.

[26] Matheoud D, Sugiura A, Bellemare-Pelletier A, Laplante A, Rondeau C, Chemali M, Fazel A, Bergeron JJ, Trudeau LE, Burelle Y, Gagnon E, McBride HM, Desjardins M (2016) Parkinson's disease-related proteins PINK1 and Parkin repress mitochondrial antigen presentation. *Cell* **166**, 314-327.

[27] Tan EK, Chao YX, West A, Chan LL, Poewe W, Jankovic J (2020) Parkinson disease and the immune system - associations, mechanisms and therapeutics. *Nat Rev Neurol* **16**, 303-318.

[28] Polymeropoulos MH, Lavedan C, Leroy E, Ide SE, Dehejia A, Dutra A, Pike B, Root H, Rubenstein J, Boyer R, Stenroos ES, Chandrasekharappa S, Athanassiadou A, Papapetropoulos T, Johnson WG, Lazzarini AM, Duvoisin RC, Di Iorio G, Golbe LI, Nussbaum RL (1997) Mutation in the alpha-synuclein gene identified in families with Parkinson's disease. *Science* **276**, 2045-2047.

[29] Singleton AB, Farrer M, Johnson J, Singleton A, Hague S, Kachergus J, Hulihan M, Peuralinna T, Dutra A, Nussbaum R, Lincoln S, Crawley A, Hanson M, Maraganore D, Adler C, Cookson MR, Muenter M, Baptista M, Miller D, Blancato J, Hardy J, Gwinn-Hardy K (2003) alpha-Synuclein locus triplication causes Parkinson's disease. *Science* **302**, 841.

[30] Nalls MA, Pankratz N, Lill CM, Do CB, Hernandez DG, Saad M, DeStefano AL, Kara E, Bras J, Sharma M, Schulte C, Keller MF, Arepalli S, Letson C, Edsall C, Stefansson H, Liu X, Pliner H, Lee JH, Cheng R, International Parkinson's Disease Genomics C, Parkinson's Study Group Parkinson's Research: The Organized GI, andMe, GenePd, NeuroGenetics Research C, Hussman Institute of Human G, Ashkenazi Jewish Dataset I, Cohorts for H, Aging Research in Genetic E, North American Brain Expression C, United Kingdom Brain Expression C, Greek Parkinson's Disease C, Alzheimer Genetic Analysis G, Ikram MA, Ioannidis JP, Hadjigeorgiou GM, Bis JC, Martinez M, Perlmutter JS, Goate A, Marder K, Fiske B, Sutherland M, Xiromerisiou G, Myers RH, Clark LN, Stefansson K, Hardy JA, Heutink P, Chen H, Wood NW, Houlden H, Payami H, Brice A, Scott WK, Gasser T, Bertram L, Eriksson N, Foroud T, Singleton AB (2014) Large-scale meta-analysis of genome-wide association data identifies six new risk loci for Parkinson's disease. *Nat Genet* **46**, 989-993.

[31] Beatman EL, Massey A, Shives KD, Burrack KS, Chamanian M, Morrison TE, Beckham JD (2015) Alpha-synuclein expression restricts RNA viral infections in the brain. *J Virol* **90**, 2767-2782.

[32] Karikari AA, McFleder RL, Ribechini E, Blum R, Bruttel V, Knorr S, Gehmeyr M, Volkmann J, Brotchie JM, Ahsan F, Haack B, Monoranu CM, Keber U, Yeghiazaryan R, Pagenstecher A, Heckel T, Bischler T, Wischhusen J, Koprich JB, Lutz MB, Ip CW (2022) Neurodegeneration by alpha-synuclein-specific T cells in AAV-A53T-alpha-synuclein Parkinson's disease mice. *Brain Behav Immun* **101**, 194-210.

[33] Alam MM, Yang, Li XQ, Liu J, Back TC, Trivett A, Karim B, Barbut D, Zasloff M, Oppenheim JJ (2022) Alpha synuclein, the culprit in Parkinson disease, is required for normal immune function. *Cell Rep* **38**, 110090.

[34] Witoelar A, Jansen IE, Wang Y, Desikan RS, Gibbs JR, Blauwendraat C, Thompson WK, Hernandez DG, Djurovic S, Schork AJ, Bettella F, Ellinghaus D, Franke A, Lie BA, McEvoy LK, Karlsen TH, Lesage S, Morris HR, Brice A, Wood NW, Heutink P, Hardy J, Singleton AB, Dale AM, Gasser T, Andreassen OA, Sharma M; International Parkinson's Disease Genomics Consortium (IPDGC), North American Brain Expression Consortium (NABEC), and United Kingdom Brain Expression Consortium (UKBEC) Investigators. (2017) Genome-wide pleiotropy between Parkinson disease and autoimmune diseases. *JAMA Neurol* **74**, 780-792.

[35] Holmans P, Moskvina V, Jones L, Sharma M, International Parkinson's Disease Genomics C, Vedernikov A, Buchel F, Saad M, Bras JM, Bettella F, Nicolaou N, Simon-Sanchez J, Mittag F, Gibbs JR, Schulte C, Durr A, Guerreiro R, Hernandez D, Brice A, Stefansson H, Majamaa K, Gasser T, Heutink P, Wood NW, Martinez M, Singleton AB, Nalls MA, Hardy J, Morris HR, Williams NM (2013) A pathway-based analysis provides additional support for an immune-related genetic susceptibility to Parkinson's disease. *Hum Mol Genet* **22**, 1039-1049.

[36] Rivas MA, Avila BE, Koskela J, Huang H, Stevens C, Pirinen M, Haritunians T, Neale BM, Kurki M, Ganna A, Graham D, Glaser B, Peter I, Atzmon G, Barzilai N, Levine AP, Schiff E, Pontikos N, Weisburd B, Lek M, Karczewski KJ, Bloom J, Minikel EV, Petersen BS, Beaugerie L, Seksik P, Cosnes J, Schreiber S, Bokemeyer B, Bethge J; International IBD Genetics Consortium; NIDDK IBD Genetics Consortium; T2D-GENES Consortium, Heap G, Ahmad T, Plagnol V, Segal AW, Targan S, Turner D, Saavalainen P, Farkkila M, Kontula K, Palotie A, Brant SR, Duerr RH, Silverberg MS, Rioux JD, Weersma RK, Franke A, Jostins L, Anderson CA, Barrett JC, MacArthur DG, Jalas C, Sokol H, Xavier RJ, Pulver A, Cho JH, McGovern DPB, Daly MJ. (2018) Insights into the genetic epidemiology of Crohn's and rare diseases in the Ashkenazi Jewish population. *PLoS Genet* **14**, e1007329.

[37] Li X, Sundquist J, Sundquist K (2012) Subsequent risks of Parkinson disease in patients with autoimmune and related disorders: A nationwide epidemiological study from Sweden. *Neurodegener Dis* **10**, 277-284.

[38] Raj T, Rothamel K, Mostafavi S, Ye C, Lee MN, Replogle JM, Feng T, Lee M, Asinovski N, Frohlich I, Imboywa S, Von Korff A, Okada Y, Patsopoulos NA, Davis S, McCabe C, Paik HI, Srivastava GP, Raychaudhuri S, Hafler DA, Koller D, Regev A, Hacohen N, Mathis D, Benoist C, Stranger BE, De Jager PL (2014) Polarization of the effects of autoimmune and neurodegenerative risk alleles in leukocytes. *Science* **344**, 519-523.

[39] Limphaibool N, Iwanowski P, Holstad MJV, Kobylarek D, Kozubski W (2019) Infectious etiologies of parkinsonism: Pathomechanisms and clinical implications. *Front Neurol* **10**, 652.

[40] Lai SW, Lin CH, Lin HF, Lin CL, Lin CC, Liao KF (2017) Herpes zoster correlates with increased risk of Parkinson's disease in older people: A population-based cohort study in Taiwan. *Medicine (Baltimore)* **96**, e6075.

[41] Braak H, Del Tredici K (2008) Invited Article: Nervous system pathology in sporadic Parkinson disease. *Neurology* **70**, 1916-1925.

[42] Schlossmacher MG, Tomlinson JJ, Santos G, Shutinoski B, Brown EG, Manuel D, Mestre T (2017) Modelling idiopathic Parkinson disease as a complex illness can inform incidence rate in healthy adults: The PR EDIGT score. *Eur J Neurosci* **45**, 175-191.

[43] Louveau A, Smirnov I, Keyes TJ, Eccles JD, Rouhani SJ, Peske JD, Derecki NC, Castle D, Mandell JW, Lee KS,

Harris TH, Kipnis J (2015) Structural and functional features of central nervous system lymphatic vessels. *Nature* **523**, 337-341.

[44] Aspelund A, Antila S, Proulx ST, Karlsen TV, Karaman S, Detmar M, Wiig H, Alitalo K (2015) A dural lymphatic vascular system that drains brain interstitial fluid and macromolecules. *J Exp Med* **212**, 991-999.

[45] Rustenhoven J, Drieu A, Mamuladze T, de Lima KA, Dykstra T, Wall M, Papadopoulos Z, Kanamori M, Salvador AF, Baker W, Lemieux M, Da Mesquita S, Cugurra A, Fitzpatrick J, Sviben S, Kossina R, Bayguinov P, Townsend RR, Zhang Q, Erdmann-Gilmore P, Smirnov I, Lopes MB, Herz J, Kipnis J (2021) Functional characterization of the dural sinuses as a neuroimmune interface. *Cell* **184**, 1000-1016 e1027.

[46] Iliff JJ, Wang M, Liao Y, Plogg BA, Peng W, Gundersen GA, Benveniste H, Vates GE, Deane R, Goldman SA, Nagelhus EA, Nedergaard M (2012) A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid beta. *Sci Transl Med* **4**, 147ra111.

[47] Laitinen LV, Chudy D, Tengvar M, Hariz MI, Bergenheim AT (2000) Dilated perivascular spaces in the putamen and pallidum in patients with Parkinson's disease scheduled for pallidotomy: A comparison between MRI findings and clinical symptoms and signs. *Mov Disord* **15**, 1139-1144.

[48] Lee D, Hong IK, Ahn TB (2015) Dilated Virchow-Robin space and dopamine transporter imaging in the striatum of patients with parkinsonism. *Can J Neurol Sci* **42**, 248-254.

[49] Bonham LW, Karch CM, Fan CC, Tan C, Geier EG, Wang Y, Wen N, Broce IJ, Li Y, Barkovich MJ, Ferrari R, Hardy J, Momeni P, Höglinger G, Müller U, Hess CP, Sugrue LP, Dillon WP, Schellenberg GD, Miller BL, Andreassen OA, Dale AM, Barkovich AJ, Yokoyama JS, Desikan RS; International FTD-Genomics Consortium (IFGC); International Parkinson's Disease Genetics Consortium (IPDGC); International Genomics of Alzheimer's Project (IGAP) (2018) CXCR4 involvement in neurodegenerative diseases. *Transl Psychiatry* **8**, 73.

[50] Zhao Y, Gopalai AA, Ahmad-Annuar A, Teng EW, Prakash KM, Tan LC, Au WL, Li HH, Lim SY, Lim SK, Chong YB, Tan LP, Ibrahim NM, Tan EK (2013) Association of HLA locus variant in Parkinson's disease. *Clin Genet* **84**, 501-504.

[51] Pardi N, Hogan MJ, Porter FW, Weissman D (2018) mRNA vaccines - a new era in vaccinology. *Nat Rev Drug Discov* **17**, 261-279.

[52] Yanamandra K, Gruden MA, Casaite V, Meskys R, Forsgren L, Morozova-Roche LA (2011) alpha-synuclein reactive antibodies as diagnostic biomarkers in blood sera of Parkinson's disease patients. *PLoS One* **6**, e18513.

[53] Horvath I, Iashchishyn IA, Forsgren L, Morozova-Roche LA (2017) Immunochemical detection of alpha-synuclein autoantibodies in Parkinson's disease: Correlation between plasma and cerebrospinal fluid levels. *ACS Chem Neurosci* **8**, 1170-1176.

[54] Scott KM, Kouli A, Yeoh SL, Clatworthy MR, Williams-Gray CH (2018) A systematic review and meta-analysis of alpha synuclein auto-antibodies in Parkinson's disease. *Front Neurol* **9**, 815.

[55] Sommer A, Marxreiter F, Krach F, Fadler T, Grosch J, Maroni M, Graef D, Eberhardt E, Riemenschneider MJ, Yeo GW, Kohl Z, Xiang W, Gage FH, Winkler J, Prots I, Winner B (2018) Th17 lymphocytes induce neuronal cell death in a human iPSC-based model of Parkinson's disease. *Cell Stem Cell* **23**, 123-131 e126.

[56] Liu Z, Huang Y, Cao BB, Qiu YH, Peng YP (2017) Th17 cells induce dopaminergic neuronal death via LFA-1/ICAM-1 interaction in a mouse model of Parkinson's disease. *Mol Neurobiol* **54**, 7762-7776.

[57] Herrick MK, Tansey MG (2021) Is LRRK2 the missing link between inflammatory bowel disease and Parkinson's disease? *NPJ Parkinsons Dis* **7**, 26.

[58] Hui KY, Fernandez-Hernandez H, Hu J, Schaffner A, Pankratz N, Hsu NY, Chuang LS, Carmi S, Villaverde N, Li X, Rivas M, Levine AP, Bao X, Labrias PR, Haritunians T, Ruane D, Gettler K, Chen E, Li D, Schiff ER, Pontikos N, Barzilai N, Brant SR, Bressman S, Cheifetz AS, Clark LN, Daly MJ, Desnick RJ, Duerr RH, Katz S, Lencz T, Myers RH, Ostrer H, Ozelius L, Payami H, Peter Y, Rioux JD, Segal AW, Scott WK, Silverberg MS, Vance JM, Ubarretxena-Belandia I, Foroud T, Atzmon G, Pe'er I, Ioannou Y, McGovern DPB, Yue Z, Schadt EE, Cho JH, Peter I (2018) Functional variants in the LRRK2 gene confer shared effects on risk for Crohn's disease and Parkinson's disease. *Sci Transl Med* **10**, eaai7795.

[59] Jankovic J (2019) Pathogenesis-targeted therapeutic strategies in Parkinson's disease. *Mov Disord* **34**, 41-44.

[60] Chao Y, Wong SC, Tan EK (2014) Evidence of inflammatory system involvement in Parkinson's disease. *Biomed Res Int* **2014**, 308654.

[61] Williams GP, Schonhoff AM, Jurkuvenaite A, Gallups NJ, Standaert DG, Harms AS (2021) CD4 T cells mediate brain inflammation and neurodegeneration in a mouse model of Parkinson's disease. *Brain* **144**, 2047-2059.