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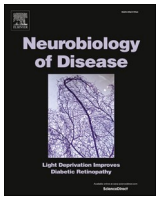

Convergence of signalling pathways in innate immune responses and genetic forms of Parkinson's disease

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ABSTRACT

In recent years progress in molecular biology and genetics have advanced our understanding of neurological disorders and highlighted synergistic relationships with inflammatory and age-related processes. Parkinson's disease (PD) is a common neurodegenerative disorder that is characterized by loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc). Increasing extensive evidence supports the contribution of genetic risk variants and inflammation in the pathobiology of this disease. Functional and genetic studies demonstrate an overlap between genes linked to increased risk for PD and autoimmune diseases. Variants identified in loci adjacent to LRRK2, GBA, and HLA establish a crosstalk between the pathobiologies of the two disease spectra. Furthermore, common signalling pathways associated with the pathogenesis of genetic PD are also relevant to inflammatory signaling include MAPK, NF-κB, Wnt and inflammasome signaling. Importantly, post-mortem analyses of brain and cerebrospinal fluid from PD patients show the accumulation of proinflammatory cytokines. In this review we will focus on the principal mechanisms of genetic, inflammatory and age-related risk that intersect in the pathogenesis of PD.

1. Introduction

Growing evidence from multidisciplinary studies suggest that Parkinson's disease (PD) is a multifactorial slow progressive condition that combines signalling changes caused by aging and genetic risk variants with environmental challenges including exposure to viruses, neurotoxins and allergens. The long-standing view of PD as the archetypal non-genetic disorder caused solely by environmental factors was abandoned with genetic studies discovering a heritable component of PD in several families where the disease was inherited in an autosomal dominant or recessive manner (Billingsley et al., 2018). Interestingly, family history of PD is found in approximately 15% of patients and 5–10% of PD patients follow a classical Mendelian inheritance pattern (Bandres-Ciga et al., 2020; Lesage and Brice, 2009). In addition, a recent meta-analysis of several datasets from PD genome-wide association studies (GWAS) has revealed many additional PD risk loci, explaining 16-36% of the heritable risk of PD and showing that a considerable genetic component of this disease remains unidentified (Nalls et al., 2019; Nalls et al., 2014). Furthermore, pathway analysis established enrichment of the nominated candidate genes in previously highlighted PD pathways including autophagy, endocytosis, mitochondrial biology, immune response, and lysosomal function (Billingsley et al., 2018). In this review we will focus on convergent signalling pathways between innate immune responses and genetic forms of PD.

Numerous genetic studies have linked mutations in immune-associated genes such as *BST1* (bone marrow stromal cell antigen 1) and *HLA* (human leukocyte antigen) with PD risk (Lampe et al., 2003; Nalls et al., 2014; Satake et al., 2009; Wissemann et al., 2013). Studies of human immune cells and epidemiological research have further supported the role of the immune system in PD. Pesticide exposure triggers an elevated immune response that contributes to PD in people with a genetic variation in *HLA* (Kannarkat et al., 2015; Kannarkat et al., 2013). Additionally, a critical role of inflammation in PD pathogenesis is supported by the presence of activated microglia and infiltrated lymphocytes in the areas of degeneration in postmortem PD brains and in mouse models (Brochard et al., 2009; Gelders et al., 2018; Krashia et al., 2019; Tansey and Goldberg, 2010).

There might be different triggers of the underlying observed brain

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inflammation in PD. These include head trauma, exposure to environmental toxins and microorganisms such as viruses and bacteria causing infections, as well as altered gut microbiota (Johnson et al., 2019; Smeyne et al., 2021; Tansey et al., 2022). Those triggers, although insufficient alone, might initiate the disease process in the brain and/or peripheral tissues and increase vulnerability to PD.

Overall, the consensus on PD pathogenesis has changed from an idiopathic disease, potentially caused by environmental toxins, to a multifactorial slow progressive condition, combining signalling changes caused by aging and genetic risk variants with environmental challenges giving rise to inflammation. Various genetic and environmental factors contribute to the changes in immune status of the brain toward a chronic pro-inflammatory state, synergistically interacting with genetic risk variants. In this light, the status of the immune system becomes an important factor in modulating adequate response and keeping the brain homeostasis to support neuronal survival. Understanding the complexity of the neuroimmune interaction with PD genetic predisposition will bring scientific insights, identify new targets for disease modifying treatments, and thereby give hope to patients that currently only have symptomatic treatment available.

2. Linking genetic forms of PD to immune responses

Functional and genetic studies have highlighted overlap between loci that increase risk to autoimmune diseases and PD. In a recent study, the biological correlation between top GWAS loci was investigated by analysing protein-protein association and gene expression alterations (Witoelar et al., 2017). Using a conjunction false discovery rate approach, the authors identified 17 novel loci with overlap between PD and autoimmune diseases. Among these, variants in *GAK, HLA-DRB5, LRRK2,* and *MAPT* were also associated with rheumatoid arthritis, ulcerative colitis and Crohn's disease. Furthermore, protein interaction networks map out functional relationships between the protein products of genes associated with autoimmune diseases and those of genes associated with PD. Among the novel genes discovered, *WNT3, KANSL1, CRHR1, BOLA2,* and *GUCY1A3* belong to a protein interaction network with known PD genes. Finally, a subset of novel loci was significantly associated with changes in methylation and expression levels of adjacent genes. These findings identify common genetic pathways between PD and autoimmune diseases and highlight the complexity in the way that individual genetic risk variants alter specific immune responses.

2.1. PD-linked genes and immune response

Since the mid 1990s, genetic studies have advanced our understanding of PD etiology. A number of autosomal dominant or recessive genes and an array of risk variants that associate with PD have been identified by genetic studies. PD genetics paint a picture of a polygenic complex disease while highlighting possible common cellular pathways that may be impaired in pathogenesis as well as provide functional bridges to inflammatory mechanisms. Mutations in *LRRK2* (encoding leucine-rich repeat kinase 2) and *SNCA* (encoding α-synuclein) have been linked to autosomal dominant PD, while risk variants for sporadic PD have also been identified around these genes. Furthermore, mutations that associate with early-onset recessive PD have been identified in genes encoding for Parkin, PINK1 and DJ-1. Here we will outline important genetic discoveries that link PD to immune response pathways.

2.2. LRRK2

The PARK8 locus was initially identified in 2002 by linkage analysis of a family with autosomal dominant PD (Funayama et al., 2002). Mutations in *LRRK2* were identified by two groups in 2004 as causative for PARK8 (Paisán-Ruíz et al., 2004; Zimprich et al., 2004). To date about 100 missense variants have been identified spanning the whole protein (Nuytemans et al., 2010) and seven are considered causative of inherited PD: N1437H, R1441C, R1441G, R1441H, Y1699C, G2019S and I2020T. *LRRK2* mutations are the most prevalent single genetic cause for PD, with mutation frequency varying between different ethnic groups. Furthermore, GWAS have identified common variation within the *LRRK2* locus that increases risk of sporadic PD. Interestingly, GWAS have identified different genetic variants in the *LRRK2* gene that confer risk of, or, protection from Crohn's disease (Hui et al., 2018), while also affecting the kinase activity of the protein. Several epidemiological studies have shown that the overall risk of PD in Crohn's disease and inflammatory bowel disease sufferers is increased, while these results were also validated in a recent meta-analysis (Zhu et al., 2019). LRRK2 has been linked to inflammatory pathways through a number of *in vivo* and *in vitro* studies. LRRK2 is highly expressed in immune cells and upregulation of expression at the mRNA and protein level have been reported in different systems in response to pro-inflammatory stimuli. LRRK2 activity has been suggested to attenuate immune response in microglia (Moehle et al., 2012), while LRRK2 levels are reportedly higher in T-cell subsets in PD patients (Cook et al., 2017). Furthermore, studies implicate LRRK2 in regulating inflammation and pathogen defense. A recent meta-analysis of human gene expression identified *LRRK2* as a highly significant differentially enriched gene in Mycobacterium tuberculosis infection (Wang et al., 2018). A recent study demonstrated that LRRK2 expression can alter immune cell chemotaxis *in vivo*, and highlighted an effect of LRRK2 in the course of microbial infections by modulating inflammation in a manner dependent on the genotype and sex of the host as well as the type of pathogen (Shutinoski et al., 2019). A case-control study reported that regular nonsteroidal anti-inflammatory drug use may be associated with reduced penetrance in LRRK2-associated PD (San Luciano et al., 2020). Finally, LRRK2 has been implicated in phagocytosis and phagosome maturation by regulating Rab GTPase signaling that orchestrates immune cell homeostasis (Kim et al., 2018; Lee et al., 2020; Maekawa et al., 2016).

2.3. SNCA

Mutations in *SNCA* were the first Mendelian trait identified in PD (Polymeropoulos et al., 1996). Since then, missense mutations as well as gene duplications and triplications have been identified in several families, with disease severity correlating to *SNCA* allele number in a dose-effect fashion. Aggregated and post-translationally modified α-synuclein is present in Lewy bodies in both familial and idiopathic PD, while several *in vivo* over-expression models have described synuclein accumulation, dopaminergic neuron degeneration and glial activation (Decressac et al., 2012; Sanchez-Guajardo et al., 2010). Several lines of evidence link synuclein to the innate immune system. Synuclein expression is upregulated in human macrophages and cultured human astrocytes following LPS or IL1β stimulation (Tanji et al., 2002), while extracellular synuclein released from neurons functions as an endogenous agonist for TLR2 (Kim et al., 2013). Furthermore, microglia from α-synuclein deficient mice exhibit an augmented reactive phenotype after stimulation in terms of cytokine release and phenotypic response (Austin et al., 2006). Recent studies suggest that α-synuclein peptides can drive helper and cytotoxic T lymphocyte cell responses in PD patients, highlighting an additional role in adaptive immunity (Sulzer et al., 2017).

The spread of α-synuclein pathology throughout interconnected brain regions is important for PD progression and might partially be mediated by neuronal receptors. In this context the lymphocyte activation gene 3 (LAG-3) has been investigated. LAG-3 is part of the immunoglobulin superfamily and preferentially expressed in peripheral immune cells including T cells. However, it was recently proposed as a selective receptor for the propagation of pathogenic forms of α-synuclein (Mao et al., 2016). Mao and colleagues further showed that animal models deficient of LAG-3 showed a delayed loss of dopaminergic

neurons as well as associated deficits when challenged with misfolded preformed α-synuclein fibrils. This work is important as it suggests specific LAG-3 inhibitors might slow the progression of PD in patients. Unfortunately, work trying to confirm LAG-3 as a therapeutic target for PD did not reproduce neuronal LAG-3 expression, showed only limited specificity of the described interaction of LAG-3 with pathogenic forms of α-synuclein and showed no correlation with the levels of LAG-3 expression and α-synuclein related pathology (Emmenegger et al., 2021). The opposing results are not easily reconciled by the differences in the used model systems or experimental designs and require further investigation to conclude with confidence if there is any role of LAG-3 in PD pathogenesis. However, the search for therapeutic targets affecting the propagation of α-synuclein is pivotal for finding disease modifying therapies that halt PD progression.

2.4. PINK1/Parkin

Mutations in PINK1 are found in up to 9% of patients with autosomal recessive early-onset PD and mutation frequency can vary between ethnic groups (Klein et al., 2005; Li et al., 2005; Rogaeva et al., 2004). More than 60 different missense and nonsense mutations have been identified in *PINK1* while exon deletions are less frequent (Camargos et al., 2009; Hatano et al., 2004). The most frequent mutation, Q456X, results in decreased transcript levels and loss of protein function (Siuda et al., 2014). L347P substitution decreases protein stability (Beilina et al., 2005) while C1366T promotes transcript degradation by nonsense-mediated decay (Grünewald et al., 2007). PINK1 is a serine/threonine kinase that can phosphorylate Parkin and ubiquitin (Kane et al., 2014), mediating mitochondria quality control (Buhlman et al., 2014; Clark et al., 2006; Park et al., 2006).

Parkin mutations were identified in families with cases of autosomal inherited young onset PD (Kitada et al., 1998; Matsumine et al., 1997). A large number of mutations are deletions or early termination mutations, suggesting that loss of function is the predominant mutation effect. Parkin is part of the E3 ubiquitin ligase complex, mediating protein degradation through the proteasome (Winklhofer, 2007). Under conditions of mitochondrial depolarization, Parkin is recruited to mitochondria where it mediates degradation of outer mitochondrial membrane proteins (Narendra et al., 2008). Mutations in Parkin impair its function in selective elimination of damaged mitochondria (Lee et al., 2010; Narendra et al., 2008; Rakovic et al., 2011). While mutations in PINK1 and Parkin have been linked to impairment in mitophagy and early onset PD, PINK1 and Parkin deficient mice do not exhibit PD-relevant phenotypes and mitophagy is not well understood in *in vivo* models. Recently, the role of mitophagy on innate immunity was highlighted by a study reporting an inflammatory phenotype in both Parkin and Pink1 deficient mice following exhaustive exercise as well as Parkin mutator mice, that express a proofreading-defective mtDNA polymerase (Sliter et al., 2018). Inflammation was rescued by concurrent loss of Stimulator of interferon genes (STING), which are important for protection against pathogens and central in stimulation of adaptive immunity (Barber, 2015). DA neuron loss in Parkin mutator mice was also rescued by STING loss. This study supports a role for Pink1 and Parkin mediated mitophagy in preventing inflammation and neurodegeneration and proposes a new model for how mitophagy may mitigate PD (Sliter et al., 2018).

2.5. HLA

HLA is one of the most polymorphic regions in the human genome and has been the focus of research studying neurodegenerative diseases for decades. *HLA* genes code for cell-surface glycoproteins that mediate immune response to foreign antigens. Class I *HLA* genes encode for MHCI molecules that present intracellular foreign antigen peptides to CD8+ T-lymphocytes. Class II *HLA* genes encode for MHCII molecules that present peptides to CD4 receptors promoting antibody production. *HLA* alleles are associated with numerous disorders, including autoimmune diabetes and rheumatoid arthritis. A recent study analyzed genetic risk variants conveying risk of both PD and autoimmune diseases to identify shared genetic variants and common biological pathways. This study investigated pleiotropy between PD and type 1 diabetes, Crohn disease, ulcerative colitis, rheumatoid arthritis, celiac disease, psoriasis, and multiple sclerosis and identified 17 shared loci (Witoelar et al., 2017) including a number of PD risk loci adjacent to *GAK, HLA-DRB5, LRRK2,* and *MAPT*. Fine mapping of the HLA locus in PD patients and controls of European origin identified specific HLA-DRB1 variants that are associated with reduced risk of PD (Yu et al., 2021). Finally, a shared HLA allelic profile has been identified between dementia and PD highlighting how common immunogenetic mechanisms can underlie manifestation of different neurodegenerative pathologies (James and Georgopoulos, 2020).

2.6. GBA

The *GBA* gene encodes for glucocerebrosidase (GCase), a lysosomal enzyme that cleaves the β-glucosidic linkage of glucocerebroside, a plasma membrane component intermediate in glycolipid metabolism. Mutations in *GBA* have been linked to autosomal recessive Gaucher's disease with more than 300 genetic variants associated with this disorder that can present with systemic and neurological manifestation. Furthermore, GWAS have confirmed mutations in *GBA* as a major risk factor for PD. Heterozygous mutations in *GBA* occur in between 8% to 12% of idiopathic PD patients. A number of studies highlight a link between GBA and inflammatory signaling in PD. Early studies identified increased plasma levels of inflammatory markers and cytokines, including IL-8 in GBA PD compared to idiopathic PD patients (Chahine et al., 2013). A recent study identified augmented neuroinflammation with microglial activation in brain regions susceptible to Lewy body pathology in *GBA* mutation carriers without PD (Mullin et al., 2021). Mouse models where GBA is deleted in hematopoietic cells exhibit impaired T-cell maturation and enhanced antigen presentation among other inflammatory phenotypes (Liu et al., 2012). Furthermore, macrophages from N370S homozygous Gaucher patients exhibit impaired lysosomal function and autophagy, and concomitant NLRP3 inflammasome hypersensitivity, pointing to a fundamental role for *GBA* in immune regulation (Aflaki et al., 2016). Lastly, synuclein turnover and release is altered in fibroblasts from PD patients carrying *GBA* mutations, highlighting cellular phenotypes not restricted to immune cells (Cerri et al., 2021).

2.7. Inflammatory triggers with importance for PD pathogenesis

The original hypothesis suggesting the initiation of PD pathology in the olfactory epithelium and intestines was proposed by Braak *et al.* (Braak et al., 2003), supported by the observation that olfactory impairment and chronic constipation often precede the onset of motor symptoms. Pathological aggregates of α-synuclein were detected in those tissues at prodromal stages of PD. The hypothesis proposes that axonal transport of α-synuclein from the olfactory bulb and peripheral nerves of the gastrointestinal tract to the central nervous system (CNS) forms part of the underlying pathogenesis.

Taking the above hypothesis further are observations of crosstalk between the gut and the brain with importance in modulating neurological disorders. Recent findings have shown that gut microbiota composition affect motor deficits and neuroinflammation in a mouse model of PD, suggesting that alterations in the human microbiome might represent a risk factor for PD (Sampson et al., 2016). This data is supported by recent findings of intestinal dysbiosis and gut inflammation in patients with PD that might contribute to PD pathology through release of higher levels of numerous inflammatory mediators (Tansey et al., 2022).

Various viral and bacterial infections functioning as environmental

stressors in combination with other factors such as aging, might also contribute to the increased risk of developing PD, although epidemiological evidence is not entirely consistent.

A recent epidemiological study tested the "multiple microbe" hypothesis and suggested that PD risk was increased compared to healthy controls in individuals who were seropositive for five or six of the pathogens studied (CMV, EBV, HSV-1, B. burgdorferi, C. pneumoniae, and H. pylori) but not less (Patrick et al., 2019). In addition, an association between prior diagnosis of Hepatitis C virus infection and an increased risk of subsequent PD has also been reported (Smeyne et al., 2021). However, the most common virus associated with encephalitis with parkinsonian features despite the lack of direct interaction with the CNS is the influenza virus. Influenza is able to induce significantly high levels of cytokines and chemokines, overwhelming the body's immune response and in some cases causing the induction of a so called "cytokine storm" (Ferrara et al., 1993, p. 1), that might also lead to an inflammatory cascade in the brain (Smeyne et al., 2021). Interestingly, similar observations were made during the recent global Covid-19 pandemic, where the SARS-CoV-2 coronavirus induces a significant "cytokine storm" with impaired IFN response and hyperinflammation in Covid-19 patients (Hadjadj et al., 2020; Lee and Shin, 2020). In addition, the central nervous system could also function as a SARS-CoV2 reservoir causing chronic inflammation and contributing to the development of neurodegenerative diseases (Gomez-Pinedo et al., 2020). This might suggest a potential risk for the development of neurological conditions within a genetically susceptible population, although epidemiological data are not yet available.

Johnson *et al.*, has suggested a three-step model in which triggers such as the microbial ones above first form the initial basis for the disease process in the brain or peripheral tissues. Additional "facilitators" such as peripheral inflammation are then required for PD pathology to develop further. During the third stage cellular changes including impaired autophagy and cell-to-cell propagation of α-synuclein pathology further spur neurodegeneration (Johnson et al., 2019). In general, a combination of initial inflammatory triggers with multiple risk factors, including aging and genetic predisposition, as well as immune status might contribute to the development of PD.

2.8. Common immune signalling pathways associated with the pathogenesis of genetic forms of PD

2.8.1. NF-κB signalling

The nuclear factor-kB (NF-κB) signalling pathway is one of the most studied mediators

of inflammatory responses. NF-κB regulates the expression of pro-inflammatory genes, including those encoding cytokines and chemokines, while also modulating inflammasome activity. In PD, NF-κB signaling has been linked to neuroinflammation in brain regions affected by PD pathology while a number of PD genes have been placed in NF-κB cellular pathways (Fig. 1). For example, in cultured microglia, LRRK2 deficiency or pharmacological inhibition results in increased phosphorylation of the NF-κB p50 inhibitory subunit downregulating NF-κB signaling (Russo et al., 2015). This is in accordance with previous studies placing LRRK2 upstream of PKA signaling (Parisiadou et al., 2014). Similarly, transcriptomic profiling of microglia isolated from LRRK2 deficient mice revealed an attenuated inflammatory response following stimulation by LPS and treatment with α-synuclein preformed fibrils compared to WT mice (Russo et al., 2019). In a separate study, LRRK2 was shown to increase pro-inflammatory cytokine secretion by modulating activation of NF-κB signalling components TAK1 complex and TRAF6 (Takagawa et al., 2018).

2.8.2. MAPK signaling

The *MAP* (mitogen-activated protein) kinase family is one of the most ubiquitously expressed and evolutionary conserved protein families involved in signaling cascades that mediate physiological and pathophysiological cell responses. In mammalian cells there are four main groups of MAPKs: ERK1/2, ERK5, JNKs and p38 MAPKs. MAPKs regulate several key functions of immune responses with the production of immunomodulatory cytokines, such as TNFα and interleukins downstream of p38 MAPK, JNK, and ERK activation. Many lines of evidence link PD to MAPK signaling. JNKs can be activated by a number of factors associated with PD including misfolded proteins and toxins (Brown et al., 2016). Furthermore, *in vivo* studies have demonstrated that JNKs are activated in neurotoxin or inflammation-based animal PD

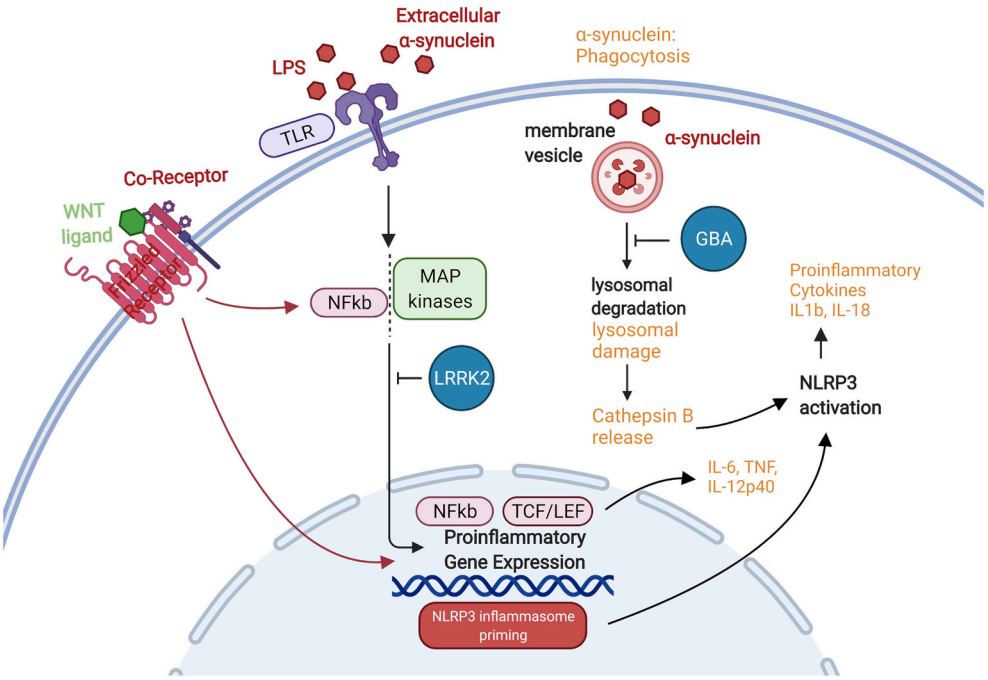

Fig. 1. Immune signalling in genetic forms of PD. Depicted are MAPK, Wnt, NF-kB and inflammasome pathways modulated by the PD proteins LRRK2, α-synuclein and GBA, resulting in downstream target gene transcription and expression of proinflammatory cytokines in a representative innate immune cell.

models while JNK inhibition can attenuate dopaminergic neuron damage (Kulich and Chu, 2001; Pan et al., 2010; Pan et al., 2009). LRRK2 can reportedly bind and phosphorylate MAPK kinases 3, 4, 6 and 7 with PD-linked mutations conferring increased kinase activity towards these targets (Gloeckner et al., 2009; Hsu et al., 2010). LRRK2 activates the MAP kinase 4 JNK pathway and induces degeneration of SNpc dopaminergic neurons in G2019S LRRK2 transgenic mice (Chen et al., 2012). Recently, it was demonstrated that Mn-induced production of ROS and TNF-α are attenuated in models of LRRK2 deficiency through modulation of p38 MAPK and ERK pathways in macrophages and microglia (Kim et al., 2019). Synuclein has also been implicated in MAPK pathways in cellular and *in vivo* models. Synuclein overexpression in cells reduces the amount of available MAPK regulating MAPK downstream signaling (Iwata et al., 2001). In transgenic models, expression of A53T synuclein induces p38 MAPK activation leading to Parkin phosphorylation and concomitant impairment of mitochondrial homeostasis (Chen et al., 2018).

2.8.3. *Wnt signalling*

Wnt signalling is less well studied in adult immune and CNS function than NF-κB and MAPK pathways. However, the importance of Wnt signalling pathways for CNS homeostasis, affecting transcriptional activity and cytoskeletal function in neurons and glia, has become increasingly clear. In addition, Wnt signaling was shown to be dysregulated by genetic PD mutations in *LRRK2* and *PRKN*, and *WNT3* encoding the canonical Wnt ligand Wnt3a was found in PD GWAS as a risk variant (Berwick et al., 2019; Berwick and Harvey, 2012; Harvey and Outeiro, 2019; Law et al., 2014; Salašová et al., 2017; Sancho et al., 2009; Witoelar et al., 2017; Yan and Liu, 2017). Together with the down-regulation of Wnt signaling during aging, all of these factors are highly relevant for its role in late-onset neurodegeneration. Despite this increasingly recognized importance of Wnt signaling in the above mechanisms, it is often still understudied, and we will therefore focus more closely on this for genetic PD relevant pathway.

Wnt signalling pathways are divided into canonical and non-canonical pathways. The canonical Wnt/β-catenin pathway is activated by binding of Wnt ligands to Frizzled receptors and LRP5/6 co-receptors. This induces signalling pathway activation via dishevelled (DVL) proteins and results in inhibition of kinases in the β-catenin destruction complex including GSK3β. Removal of the suppressive effect of GSK3β-mediated phosphorylation allows accumulation of β-catenin in the nucleus and thereby transcription of canonical Wnt target genes but also affects the phosphorylation of other GSK3β targets including tau (Berwick and Harvey, 2012; Law et al., 2014). The non-canonical/PCP and Wnt/Ca^{2+} pathways are, similar to the canonical signalling pathway, activated by binding of Wnt ligands to Frizzled receptors and transduced through DVL proteins. However, co-receptors and signalling cascades are different to the canonical Wnt signalling pathway. In fact, in most circumstances canonical and non-canonical Wnt signalling pathways act antagonistically to each other. Activation of one main non-canonical PCP pathway leads to cytoskeletal changes through the activation of small GTPases, whereas activation of the Wnt/Ca^{2+} pathway leads to an increase in intracellular Ca^{2+} levels and diacylglycerol resulting in the activation of NF-κB, NFAT and CREB-dependent transcription (Berwick and Harvey, 2012; Law et al., 2014).

Wnt signalling is important in the interplay between the immune system and neurons (L'Episcopo et al., 2018). Microglia and peripheral macrophages express Wnt receptors and their ligands. This allows for autocrine and paracrine Wnt signalling regulation of central and peripheral immune responses (Halleskog et al., 2012; Halleskog et al., 2011; Halleskog and Schulte, 2013; Halleskog and Schulte, 2013; Kilander et al., 2011; L'Episcopo et al., 2018; Neumann et al., 2010; Pereira et al., 2009; Staal et al., 2008). Even though Wnt ligands can induce a pro-inflammatory response, these ligands exert a dose-dependent decrease in inflammatory microglia responses, especially after LPS treatment (Halleskog et al., 2012; Halleskog and Schulte, 2013; Hooper et al., 2012; Neumann et al., 2010; Pereira et al., 2009). Importantly, the canonical Wnt3a ligand activates immune responses in microglia without leading to neuronal toxicity, promotes the anti-inflammatory M2 phenotype and reduces exacerbated TNF-α levels through autoregulatory activation of canonical Wnt signaling, for example in mycobacterium infected macrophages (Schaale et al., 2011). It is important to note that harmful M1-like microglia can promote canonical Wnt signalling in neurons and glia thereby alleviating neurotoxicity (L'Episcopo et al., 2018). Overall, Wnt signaling plays a critical role in pro- and anti-inflammatory responses, resulting in the fine regulation of immune responses that provides neuroprotection in dopaminergic neurons.

Canonical and non-canonical Wnt signalling pathways also play a role in peripheral macrophage responses for example though GSK3β and Wnt5a respectively. Non-canonical Wnt5a ligand and DVL3 mRNA expression were shown to be upregulated in primary human macrophages mediated by a NF-κB pathway following LPS and mycobacteria challenge though TLR-2 and TLR-4 respectively. These microbial-induced increases in Wnt5a expression further stimulated macrophage IL-12 expression inducing IFN-γ release from T lymphocytes (Blumenthal et al., 2006). GSK3β, a key negative regulator of canonical Wnt signalling has also been reported to play a critical part in TLR-2 mediated bacterial macrophage responses, inducing pro-inflammatory IL-6, IL-12p40 and TNF-α, and decreasing anti-inflammatory IL-10 through NF-κB and CREB signalling. In addition, IFN-γ was shown to induce GSK3β expression further. In line with these observations, inhibition of GSK3β with lithium increased survival of mice compared to an untreated infection group (Zhang et al., 2009).

The importance of Wnt signalling for mucosa repair in inflammatory bowel disease via M2 macrophages expressing Wnt ligands is also important to mention considering the relation between inflammatory bowel disease and PD. Results in an inflammatory bowel disease STAT6 knockout model demonstrated a STAT6 dependent M2 macrophage repair mechanism through activation of canonical Wnt signalling via Wnt2b, Wnt7b, and Wnt10a ligands, nuclear β-catenin, and Lgr5 and c-Myc Wnt target gene expression promoting mucosal repair and regeneration in inflammatory bowel disease (Cosín-Roger et al., 2016). In summary, the involvement of Wnt signalling in glia and macrophage biological functions is evident, and contributes to mediating inflammatory and immune response as well as tissue healing and regenerative processes in the CNS and periphery.

2.8.4. *Inflammasome*

Accumulating evidence has shown inflammasomes activation as a critical component of the innate immune system, playing an important role in the pathogenesis of various neuroinflammatory and neurological disorders including PD (Duan et al., 2020; Heneka et al., 2018). Inflammasomes are intracellular multiprotein complexes that assemble in response to pathogens and tissue damage through activation of different pattern recognition receptors (PRRs) that are expressed on innate immune cells. PRRs include TLRs, C-type lectine receptors, RIG-1 like receptors, and nucleotide-binding oligomerization domain-like receptors (NLRs). Assembled inflammasomes trigger maturation and secretion of pro-inflammatory cytokines such as IL-1β and IL-18 through caspase-1 activation. Currently, there are five members of PRRs confirmed to form inflammasomes (Duan et al., 2020; Tan et al., 2020). Specifically, the most studied activated microglial NLR family pyrin domain containing 3 (NLRP3) inflammasome serves as a source of sustained neuroinflammation that can contribute to progressive loss of dopaminergic neurons in animal models of PD (Tan et al., 2020). In human post-mortem brain from PD cases, NLRP3 expression is elevated in mesencephalic neurons (Holbrook et al., 2021). Activation of microglial inflammasome NLRP3 includes the priming signal that upregulates pro-IL-1β through the NF-kB mediated signaling pathway and a second stimuli such as ATP, pore-forming bacterial toxins and particulate matter (Duan et al., 2020). Results from genetic studies also

support the role of variants from NLRP3 inflammasome associated genes as susceptible candidates for different inflammatory diseases by influencing the balance of immune response (Holbrook et al., 2021). Analysis of exome sequencing data for genetic variation of *NLRP3* identified multiple single-nucleotide polymorphisms (SNPs) including rs7525979 that was associated with downregulation of NLRP3 activity and reduced risk of developing PD (von Herrmann et al., 2018). Q705K is a gain-of-function, low penetrant polymorphism of the *NLRP3* gene associated with several inflammatory diseases, leading to an overactive NLRP3 inflammasome and somewhat counterintuitively was found to confer a protective effect on AD, while several other genetic *NLRP3* variants were found to be associated with increased risk of late-onset AD (Paramel et al., 2015; Verma et al., 2021). Future genetic studies are needed to confirm and explore the role of *NLRP3* variants in the susceptibility of PD and other neurodegenerative disorders in more detail.

3. Signalling pathways dysregulated during aging

During aging several cell biological mechanisms important for neuronal maintenance and immune responses including autophagy and lysosomal, proteasomal and mitochondrial function are altered contributing to the pathogenesis of late onset neurodegeneration including PD. Cell signalling mechanisms are at the centre of these functions with overall immune response and associated signalling pathway function decreasing with age. However, lifelong immune challenge is likely to keep innate immune cells at an overall higher basal activation state. Some response mechanisms are increased often leading to a chronic low-grade inflammation with increased production of proinflammatory mediators including pro-inflammatory cytokines such as IL-6 (Bandaranayake and Shaw, 2016; Fortin et al., 2006; Fülöp et al., 2019; Larbi et al., 2008; Sauce et al., 2017). The underlying mechanisms of this 'immunosenescence' might result from a combination of age-related cellular and signalling changes together with continuous adaptation to pathogen exposure leading to so called 'inflammaging' (Chandran et al., 2019; Fortin et al., 2006; Franceschi et al., 2000). The number of upstream receptors in immune cells such as receptors for Fc and C3b, and TLRs, NLRPs, and RIG-like receptors (RLRs) might change during aging (Bailey et al., 2019; De Maeyer and Chambers, 2021; Shaw et al., 2013; Solana et al., 2012; Thomas and Schroder, 2013). By contrast, functional alterations affecting chemotaxis, free radical and chemokine production decrease with age (Bandaranayake and Shaw, 2016; Fortin et al., 2008; Goldberg et al., 2020; Gupta, 2014; Hazeldine and Lord, 2015; Khanfer et al., 2012; Müller et al., 2019). These observations speak for changes in associated signalling pathways such as MAPK, phosphatidylinositol-4,5-bisphosphate 3 kinase (PI3K) and protein kinase B (Akt) in innate immune cells downstream of membrane receptors affecting signalosome formation (Fortin et al., 2008; Larbi et al., 2005). This complex age-related dysregulation of innate immune responses together with life-long pathogen, allergen, and toxin exposure in context of genetic changes affects the individual risk of developing PD. We will focus here on some important examples of the emerging evidence for an interplay between central and peripheral innate immune function, genetic risk and aging affected by related cell signalling dysfunction.

As indicated above, evidence for an importance of the PD kinase LRRK2 in peripheral innate immune function is accumulating with a role for LRRK2 in bacterial and autoimmune diseases. LRRK2 is highly expressed in peripheral innate immune cells with accumulating evidence suggesting higher expression levels in people harbouring genetic pathogenic mutations linked to inflammatory bowel disease and PD (Bliederhaeuser et al., 2016; Cook et al., 2017; Gardet et al., 2010). LRRK2 expression was shown to be further increased during innate immune cell signalling stimulation following TLR4 receptor activation with LPS and stimulation with INFγ, likely regulating expression through a *LRRK2* promoter binding site (Gardet et al., 2010). Whereas exact LRRK2 mediated signalling regulation in innate immune cells seems to depend on the context of cell type, immune challenge, and genetic background, changes in several pathways leading to NFkB and NFAT signalling pathway activation have been suggested. These include TLR, C-type lectin receptors (CLRs) and inflammasome regulated pathways. Even though mostly investigated in other cell types, *in vivo* or in post-mortem tissue, other LRRK2 signalling pathways such as receptor interacting protein kinase (RIPK) and Wnt signalling with importance in innate immune response pathways and aging are likely to be important, as well (Royce et al., 2019). LRRK2 has been shown to physically interact with components of both these pathways with clear indications for signalling activation (Berwick et al., 2019; Berwick and Harvey, 2012; Harvey and Outeiro, 2019; Law et al., 2014; Salašová et al., 2017; Sancho et al., 2009; Yan and Liu, 2017).

3.1. Wnt signalling in aging

Canonical Wnt signalling has a positive effect in preventing neurodegeneration in PD and AD partly by affecting peripheral and central immune responses including glia responses in the subventricular zone maintaining striatal plasticity. During aging Wnt signalling is increasingly downregulated and less effective in promoting neuronal regeneration mediated by an interplay between astrocytes and microglia. Consequently, aged microglia are less effective in augmenting toxic insults and inducing neurogenesis. Instead, they are increasingly harmful (Bayod et al., 2015; Cho et al., 2019; Kase et al., 2019; Marchetti et al., 2020). Other insults including genetic factors such as *LRRK2* and *PRKN* mutations, that have been linked to dysregulated Wnt signalling, are likely to further accelerate this age dependent process during PD pathogenesis (Berwick and Harvey, 2014; Berwick and Harvey, 2012).

3.2. TLR responses in aging

TLR responses in innate immune cells are not just affected by aging but also impaired in PD (da Silva et al., 2016; Shaw et al., 2013). TLR expression might be affected by aging depending on the investigated species but pathway function seems more consistently downregulated leading to a decrease in TLR-induced TNF and IL-6 production (Asquith et al., 2012; Boehmer et al., 2005; Boehmer et al., 2004; Boyd et al., 2012; Renshaw et al., 2002; van Duin et al., 2007). For example, human monocytes from aged individuals were shown to have a decreased TNF and IL-6 expression in response to TLR1/TLR2 stimulation. In addition, an associated decrease in MAPK signalling was demonstrated (Nyugen et al., 2010; van Duin et al., 2007). Impaired STAT1-dependent downregulation of TLR3 responses were further shown in virus exposed aged macrophages leading to continuous detrimental TLR3 activation (Kong et al., 2008). In summary, complex immune signalling pathways dysregulation caused by changes in PD associated genetic variation are further exacerbated during aging contributing to the pathogenesis of the disease.

4. Therapeutic strategies modulating neuroinflammation

As outlined above, neuroinflammation is considered a phenomenon dramatically affecting PD progression and therefore a target for neuroprotective or disease-modifying therapies. The ultimate goal and a challenge is to develop compounds that will halt the detrimental effects of neuroinflammation and restore a balanced microenvironment in the brain.

Multiple studies have detected elevated levels of proinflammatory cytokines such as IL-1β, IL-6, TNFα and IFNγ in brain parenchyma, cerebrospinal fluid (CSF) and peripheral blood mononuclear cells (PBMC) of PD patients (Reale et al., 2009; Tan et al., 2020). Moreover, several polymorphisms in cytokine-coding genes have been reported and might increase the probability of developing PD. For example, IL-1β at amino acid position 511, IL-6 polymorphism at position 174 and TNF-α polymorphism at position 308 are more common in PD patients than in

healthy controls (Arman et al., 2010; Bachiller et al., 2018; Håkansson et al., 2005; Krüger et al., 2000).These cytokines and chemokines are released by innate immune cells including activated microglia and play an important role as molecular modulators of inflammation. They form a cytokine network, controlled partially by NF-kB, which is also reported to be activated in PD brain (Hunot et al., 1997; Mattson and Camandola, 2001; Mogi et al., 2007). Activation of microglia leads to upregulation of complement receptors that exacerbate dopaminergic-associated neurotoxicity (Schwab et al., 2020). In addition, the local brain inflammation increases the permeability of the blood-brain barrier (BBB) causing the infiltration of adaptive immune cells, including macrophages, as well as T and B cells (Garretti et al., 2019). Both local innate and infiltrated adaptive immune components participate in the clearance of neuron-released α-synuclein. As this complex multifactorial process fails with aging or due to PD-mutations, the total balance is shifting toward a proinflammatory state and increased oxidative stress damaging susceptible dopaminergic neurons.

In addition to increased levels of specific proinflammatory cytokines in the brain of PD patients, altered infiltrated T cell populations can also contribute to the neuroinflammatory microenvironment through modulation of the microglial reactivity (Garretti et al., 2019). Specifically, it's been suggested that the number and proportion of brain infiltrated T effector (Teff) and T regulatory (Treg) cells might interact with microglia and either cause the secretion of proinflammatory cytokines such as IL-17,TNFα, IFNγ or have the capacity to harness microglia by secreting immune suppressive factors including IL-4, IL-10, TNFβ and attenuate inflammation respectively (Olson and Gendelman, 2016; Schwab et al., 2020).

It's been proposed that an initial role of the activated microglia seems to be beneficial at the early stages of PD. However, with disease progression the activated microglia begin to exert a neurotoxic effect (Yan et al., 2014). Overall, the possible therapeutic strategies, which may downregulate inflammatory processes, could be important as well as an optimal timing of intervention. To these ends, the chronic use of non-steroidal anti-inflammatory drugs (NSAIDs) has been suggested to reduce the risk of developing PD (Gelders et al., 2018). Although different studies have presented conflicting data and this question remains to be investigated, the growing evidence supports a fundamental role of brain and systemic inflammation as a therapeutic target in PD risk and progression (Cardinale et al., 2021; Gao et al., 2011; Manthripragada et al., 2011; Wahner et al., 2007).

Some additional therapeutic strategies, which may influence the brain's microenvironment toward a less inflammatory state, might include regulation of cytokines levels directly through immunosuppressive drugs or through modulation of the microglial receptors or by changes in specific T cells populations (Harms et al., 2021; Tan et al., 2020). In this context, the NF-kB pathway is among the main pathways involved in the inflammatory process in PD and accompanied by cytokine production (Bachiller et al., 2018). NF-kB inhibition has been shown to reduce microglial activation and mRNA levels of TNF-α, IL-1β and iNOS in the SNpc, preventing dopaminergic neuronal loss and improving motor ability in mice exposed to MPTP (Ghosh et al., 2007). Direct inhibition of microglial activation or IL1 and TNF-neutralizing antibodies (already approved by the FDA) could prevent an acquisition of the reactive astrocytic phenotype, which is involved in PD. It's been reported that anti-TNF therapy, tested in patients suffering from inflammatory bowel disease, was associated with substantially reduced PD incidence (Pajares et al., 2020). Numerous studies have shown an elevated level of another critical inflammatory cytokine, IFN-γ, in substantia nigra of PD patients (Yan et al., 2014). Immunomodulation of IFN-γ activity, produced by microglia and T lymphocytes, could have some protective effect for dopaminergic neurons. The importance of IFN-γ in the death of dopaminergic neurons induced by MPTP (*in vivo*) and rotenone (*in vitro*) has been reported (Mount et al., 2007).

It has been shown that TLR 2 and 4 that recognize different forms of α-synuclein are upregulated in microglia and monocytes in PD patients. While both receptors are initiating an inflammatory response upon interaction with α-synuclein, TLR2 activation further results in neuronal degeneration and death, while TLR4 also promotes the clearance of a-synuclein supporting some protective role (Harms et al., 2021). It has been suggested that blocking TLR2 with anti-TLR2-antibody could be neuroprotective, while activation or overexpression of TLR4 might have a protective effect in rodent models of a-synucleinopathies (Kim et al., 2018; Venezia et al., 2017).

Since various types of T cells have been implicated in PD pathogenesis they could also represent a therapeutic target (Tan et al., 2020). For example, the pharmaceutical induction of Treg numbers and function with recombinant human granulocyte macrophage-colony stimulating factor (rhGM-CSF, sargramostim) has been shown to attenuate neuroinflammation, decrease microgliosis and increase survival of dopaminergic neurons in mouse and rat models of PD. Sargamostim was well-tolerated in a phase 1 clinical trial in PD patients and increased Tregs without affecting Teff numbers (Gendelman et al., 2017). Additional promising immunomodulatory agents such as Anti-CD3 mAbs and the neuropeptide vasoactive intestinal peptide (VIP) also have shown to suppress microglial activation and reduce neuronal degeneration in animal models of PD by increasing Treg number and function (Schwab et al., 2020).

NLRP3 inflammasome also represents a potential target for modulation of immune responses. Several preclinical studies have presented evidence that numerous plant-derived chemicals might have inhibitory functions on NLRP3 inflammasome assembly and activation. Lee and colleagues summarized that several single compounds derived from natural extraction and herbal medicines could modulate the intracellular signaling cascade of the NLRP3 inflammasome/caspase-1/IL-1β axis, suppressing NLRP3 inflammasome activation in microglia (Lee et al., 2021). Accumulating evidence suggests that specific modulation of the NLRP3 inflammasome may be a promising therapeutic target in PD (Holbrook et al., 2021). There are several therapies that have shown their efficacies in treating autoinflammatory diseases through targeting the inflammasome effector IL-1β. Those include IL-1 receptor antagonist (anakinra), IL-1β neutralizing antibody (canakinumab) and soluble decoy receptor for IL-1β and IL-1α (rilonacept). Currently those are not used in clinical trials of PD probably due to their poor penetration of the blood-brain barrier (Duan et al., 2020). In animal models of PD, the NLRP3 inhibitor MCC950 has been shown to block activation of microglial inflammasome and effectively mitigate motor deficits and nigrostriatal dopaminergic degeneration (Gordon et al., 2018). Future research is needed to identify pharmacological mechanisms and develop therapeutic compounds that will serve as NLRP3 modulators with the goal of prevention and treatment of neurodegenerative disorders through neuroinflammatory regulation. In summary, different immunomodulatory therapies targeting the components of the innate as well as adaptive immune system may reduce the production of factors that contribute to neurotoxicity and might be beneficial for patients with PD.

5. Conclusions

A central role of inflammation in neurodegenerative diseases has become increasingly documented in the literature. The study of genetic causes of PD has in particular identified multiple cell biological and signalling pathways that affect immune signalling further compromised during aging (Fig. 1). These pathways are all potential targets for disease modifying treatment with the caveat that a balance between immune stimulation and immunosuppression needs to be maintained during a potentially long-term PD therapeutic intervention. However, therapeutic advances combining new target identification with increasingly specific biological therapies hold promise for the future.

References

Aflaki, E., Moaven, N., Borger, D.K., Lopez, G., Westbroek, W., Chae, J.J., Marugan, J., Patnaik, S., Maniwang, E., Gonzalez, A.N., Sidransky, E., 2016. Lysosomal storage and impaired autophagy lead to inflammasome activation in Gaucher macrophages. Aging Cell 15, 77–88. https://doi.org/10.1111/acel.12409.

Arman, A., Isik, N., Coker, A., Candan, F., Becit, K.S., List, E.O., 2010. Association between sporadic Parkinson disease and interleukin-1 beta -511 gene polymorphisms in the Turkish population. Eur. Cytokine Netw. 21, 116–121. https://doi.org/10.1684/ecn.2010.0186.

Asquith, M., Haberthur, K., Brown, M., Engelmann, F., Murphy, A., Al-Mahdi, Z., Messaoudi, I., 2012. Age-dependent changes in innate immune phenotype and function in rhesus macaques (Macaca mulatta). Pathobiol. Aging Age Relat. Dis. 2 https://doi.org/10.3402/pba.v2i0.18052.

Austin, S.A., Floden, A.M., Murphy, E.J., Combs, C.K., 2006. Alpha-synuclein expression modulates microglial activation phenotype. J. Neurosci. 26, 10558–10563. https://doi.org/10.1523/JNEUROSCI.1799-06.2006.

Bachiller, S., Jiménez-Ferrer, I., Paulus, A., Yang, Y., Swanberg, M., Deierborg, T., Boza-Serrano, A., 2018. Microglia in Neurological Diseases: A Road Map to Brain-Disease Dependent-Inflammatory Response. Front. Cell. Neurosci. 12, 488. https://doi.org/10.3389/fncel.2018.00488.

Bailey, K.L., Smith, L.M., Heires, A.J., Katafiasz, D.M., Romberger, D.J., LeVan, T.D., 2019. Aging leads to dysfunctional innate immune responses to TLR2 and TLR4 agonists. Aging Clin. Exp. Res. 31, 1185–1193. https://doi.org/10.1007/s40520-018-1064-0.

Bandaranayake, T., Shaw, A.C., 2016. Host Resistance and Immune Aging. Clin. Geriatr. Med. 32, 415–432. https://doi.org/10.1016/j.cger.2016.02.007.

Bandres-Ciga, S., Diez-Fairen, M., Kim, J.J., Singleton, A.B., 2020. Genetics of Parkinson disease: an introspection of its journey towards precision medicine. Neurobiol. Dis. 137, 104782 https://doi.org/10.1016/j.nbd.2020.104782.

Barber, G.N., 2015. STING: infection, inflammation and cancer. Nat. Rev. Immunol. 15, 760–770. https://doi.org/10.1038/nri3921.

Bayod, S., Felice, P., Andrés, P., Rosa, P., Camins, A., Pallàs, M., Canudas, A.-M., 2015. Downregulation of canonical Wnt signaling in hippocampus of SAMP8 mice. Neurobiol. Aging 36, 720–729. https://doi.org/10.1016/j.neurobiolaging.2014.09.017.

Beilina, A., Van Der Brug, M., Ahmad, R., Kesavapany, S., Miller, D.W., Petsko, G.A., Cookson, M.R., 2005. Mutations in PTEN-induced putative kinase 1 associated with recessive parkinsonism have differential effects on protein stability. Proc. Natl. Acad. Sci. U. S. A. 102, 5703–5708. https://doi.org/10.1073/pnas.0500617102.

Berwick, D.C., Harvey, K., 2012. The importance of Wnt signalling for neurodegeneration in Parkinson's disease. Biochem. Soc. Trans. 40, 1123–1128. https://doi.org/10.1042/BST20120122.

Berwick, D.C., Harvey, K., 2014. The regulation and deregulation of Wnt signaling by PARK genes in health and disease. J. Mol. Cell Biol. 6, 3–12. https://doi.org/10.1093/jmcb/mjt037.

Berwick, D.C., Heaton, G.R., Azeggagh, S., Harvey, K., 2019. LRRK2 Biology from structure to dysfunction: research progresses, but the themes remain the same. Mol. Neurodegener. 14, 49. https://doi.org/10.1186/s13024-019-0344-2.

Billingsley, K.J., Bandres-Ciga, S., Saez-Atienzar, S., Singleton, A.B., 2018. Genetic risk factors in Parkinson's disease. Cell Tissue Res. 373, 9–20. https://doi.org/10.1007/s00441-018-2817-y.

Bliederhaeuser, C., Zondler, L., Grozdanov, V., Ruf, W.P., Brenner, D., Melrose, H.L., Bauer, P., Ludolph, A.C., Gillardon, F., Kassubek, J., Weishaupt, J.H., Danzer, K.M., 2016. LRRK2 contributes to monocyte dysregulation in Parkinson's disease. Acta Neuropathol. Commun. 4, 123. https://doi.org/10.1186/s40478-016-0396-2.

Blumenthal, A., Ehlers, S., Lauber, J., Buer, J., Lange, C., Goldmann, T., Heine, H., Brandt, E., Reiling, N., 2006. The Wingless homolog WNT5A and its receptor Frizzled-5 regulate inflammatory responses of human mononuclear cells induced by microbial stimulation. Blood 108, 965–973. https://doi.org/10.1182/blood-2005-12-5046.

Boehmer, E.D., Goral, J., Faunce, D.E., Kovacs, E.J., 2004. Age-dependent decrease in Toll-like receptor 4-mediated proinflammatory cytokine production and mitogen-activated protein kinase expression. J. Leukoc. Biol. 75, 342–349. https://doi.org/10.1189/jlb.0803389.

Boehmer, E.D., Meehan, M.J., Cutro, B.T., Kovacs, E.J., 2005. Aging negatively skews macrophage TLR2- and TLR4-mediated pro-inflammatory responses without affecting the IL-2-stimulated pathway. Mech. Ageing Dev. 126, 1305–1313. https://doi.org/10.1016/j.mad.2005.07.009.

Boyd, A.R., Shivshankar, P., Jiang, S., Berton, M.T., Orihuela, C.J., 2012. Age-related defects in TLR2 signaling diminish the cytokine response by alveolar macrophages during murine pneumococcal pneumonia. Exp. Gerontol. 47, 507–518. https://doi.org/10.1016/j.exger.2012.04.004.

Braak, H., Del Tredici, K., Rüb, U., de Vos, R.A.I., Jansen Steur, E.N.H., Braak, E., 2003. Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol. Aging 24, 197–211. https://doi.org/10.1016/s0197-4580(02)00065-9.

Brochard, V., Combadière, B., Prigent, A., Laouar, Y., Perrin, A., Beray-Berthat, V., Bonduelle, O., Alvarez-Fischer, D., Callebert, J., Launay, J.-M., Duyckaerts, C., Flavell, R.A., Hirsch, E.C., Hunot, S., 2009. Infiltration of CD4+ lymphocytes into the brain contributes to neurodegeneration in a mouse model of Parkinson disease. J. Clin. Invest. 119, 182–192. https://doi.org/10.1172/JCI36470.

Brown, M., Strudwick, N., Suwara, M., Sutcliffe, L.K., Mihai, A.D., Ali, A.A., Watson, J.N., Schröder, M., 2016. An initial phase of JNK activation inhibits cell death early in the endoplasmic reticulum stress response. J. Cell Sci. 129, 2317–2328. https://doi.org/10.1242/jcs.179127.

Buhlman, L., Damiano, M., Bertolin, G., Ferrando-Miguel, R., Lombès, A., Brice, A., Corti, O., 2014. Functional interplay between Parkin and Drp1 in mitochondrial fission and clearance. Biochim. Biophys. Acta 1843, 2012–2026. https://doi.org/10.1016/j.bbamcr.2014.05.012.

Camargos, S.T., Dornas, L.O., Momeni, P., Lees, A., Hardy, J., Singleton, A., Cardoso, F., 2009. Familial Parkinsonism and early onset Parkinson's disease in a Brazilian movement disorders clinic: phenotypic characterization and frequency of SNCA, PRKN, PINK1, and LRRK2 mutations. Mov. Disord. 24, 662–666. https://doi.org/10.1002/mds.22365.

Cardinale, A., Calabrese, V., de Iure, A., Picconi, B., 2021. Alpha-Synuclein as a Prominent Actor in the Inflammatory Synaptopathy of Parkinson's Disease. Int. J. Mol. Sci. 22, 6517. https://doi.org/10.3390/ijms22126517.

Cerri, S., Ghezzi, C., Ongari, G., Croce, S., Avenali, M., Zangaglia, R., Di Monte, D.A., Valente, E.M., Blandini, F., 2021. GBA Mutations Influence the Release and Pathological Effects of Small Extracellular Vesicles from Fibroblasts of Patients with Parkinson's Disease. Int. J. Mol. Sci. 22, 2215. https://doi.org/10.3390/ijms22042215.

Chahine, L.M., Qiang, J., Ashbridge, E., Minger, J., Yearout, D., Horn, S., Colcher, A., Hurtig, H.I., Lee, V.M.-Y., Van Deerlin, V.M., Leverenz, J.B., Siderowf, A.D., Trojanowski, J.Q., Zabetian, C.P., Chen-Plotkin, A., 2013. Clinical and biochemical differences in patients having Parkinson disease with vs without GBA mutations. JAMA Neurol. 70, 852–858. https://doi.org/10.1001/jamaneurol.2013.1274.

Chandran, R., Kumar, M., Kesavan, L., Jacob, R.S., Gunasekaran, S., Lakshmi, S., Sadasivan, C., Omkumar, R.V., 2019. Cellular calcium signaling in the aging brain. J. Chem. Neuroanat. 95, 95–114. https://doi.org/10.1016/j.jchemneu.2017.11.008.

Chen, C.-Y., Weng, Y.-H., Chien, K.-Y., Lin, K.-J., Yeh, T.-H., Cheng, Y.-P., Lu, C.-S., Wang, H.-L., 2012. (G2019S) LRRK2 activates MKK4-JNK pathway and causes degeneration of SN dopaminergic neurons in a transgenic mouse model of PD. Cell Death Differ. 19, 1623–1633. https://doi.org/10.1038/cdd.2012.42.

Chen, J., Ren, Y., Gui, C., Zhao, M., Wu, X., Mao, K., Li, W., Zou, F., 2018. Phosphorylation of Parkin at serine 131 by p38 MAPK promotes mitochondrial dysfunction and neuronal death in mutant A53T α-synuclein model of Parkinson's disease. Cell Death Dis. 9, 1–15. https://doi.org/10.1038/s41419-018-0722-7.

Cho, C.H., Yoo, K.H., Oliveros, A., Paulson, S., Hussaini, S.M.Q., van Deursen, J.M., Jang, M.-H., 2019. sFRP3 inhibition improves age-related cellular changes in BubR1 progeroid mice. Aging Cell 18, e12899. https://doi.org/10.1111/acel.12899.

Clark, I.E., Dodson, M.W., Jiang, C., Cao, J.H., Huh, J.R., Seol, J.H., Yoo, S.J., Hay, B.A., Guo, M., 2006. Drosophila pink1 is required for mitochondrial function and interacts genetically with parkin. Nature 441, 1162–1166. https://doi.org/10.1038/nature04779.

Cook, D.A., Kannarkat, G.T., Cintron, A.F., Butkovich, L.M., Fraser, K.B., Chang, J., Grigoryan, N., Factor, S.A., West, A.B., Boss, J.M., Tansey, M.G., 2017. LRRK2 levels in immune cells are increased in Parkinson's disease. npj Parkinson's Dis. 3, 1–12. https://doi.org/10.1038/s41531-017-0010-8.

Cosín-Roger, J., Ortiz-Masiá, D., Calatayud, S., Hernández, C., Esplugues, J.V., Barrachina, M.D., 2016. The activation of Wnt signaling by a STAT6-dependent macrophage phenotype promotes mucosal repair in murine IBD. Mucosal Immunol. 9, 986–998. https://doi.org/10.1038/mi.2015.123.

da Silva, D.J., Borges, A.F., Souza, P.O., de Souza, P.R., Cardoso, C.R.B., Dorta, M.L., de Oliveira, M.A.P., Teixeira, A.L., Ribeiro-Dias, F., 2016. Decreased Toll-Like Receptor 2 and Toll-Like Receptor 7/8-Induced Cytokines in Parkinson's Disease Patients. Neuroimmunomodulation 23, 58–66. https://doi.org/10.1159/000443238.

De Maeyer, R.P.H., Chambers, E.S., 2021. The impact of ageing on monocytes and macrophages. Immunol. Lett. 230, 1–10. https://doi.org/10.1016/j.imlet.2020.12.003.

Decressac, M., Mattsson, B., Lundblad, M., Weikop, P., Björklund, A., 2012. Progressive neurodegenerative and behavioural changes induced by AAV-mediated overexpression of α-synuclein in midbrain dopamine neurons. Neurobiol. Dis. 45, 939–953. https://doi.org/10.1016/j.nbd.2011.12.013.

Duan, Y., Kelley, N., He, Y., 2020. Role of the NLRP3 inflammasome in neurodegenerative diseases and therapeutic implications. Neural Regen. Res. 15, 1249–1250. https://doi.org/10.4103/1673-5374.272576.

Emmenegger, M., De Cecco, E., Hruska-Plochan, M., Eninger, T., Schneider, M.M., Barth, M., Tantardini, E., de Rossi, P., Bacioglu, M., Langston, R.G., Kaganovich, A., Bengoa-Vergniory, N., Gonzalez-Guerra, A., Avar, M., Heinzer, D., Reimann, R., Häsler, L.M., Herling, T.W., Matharu, N.S., Landeck, N., Luk, K., Melki, R., Kahle, P. J., Hornemann, S., Knowles, T.P.J., Cookson, M.R., Polymenidou, M., Jucker, M., Aguzzi, A., 2021. LAG3 is not expressed in human and murine neurons and does not modulate α-synucleinopathies. EMBO Mol. Med. 13, e14745 https://doi.org/10.15252/emmm.202114745.

Ferrara, J.L., Abhyankar, S., Gilliland, D.G., 1993. Cytokine storm of graft-versus-host disease: a critical effector role for interleukin-1. Transplant. Proc. 25, 1216–1217.

Fortin, C.F., Larbi, A., Lesur, O., Douziech, N., Fulop, T., 2006. Impairment of SHP-1 down-regulation in the lipid rafts of human neutrophils under GM-CSF stimulation contributes to their age-related, altered functions. J. Leukoc. Biol. 79, 1061–1072. https://doi.org/10.1189/jlb.0805481.

Fortin, C.F., McDonald, P.P., Lesur, O., Fülöp, T., 2008. Aging and neutrophils: there is still much to do. Rejuvenation Res. 11, 873–882. https://doi.org/10.1089/rej.2008.0750.

Franceschi, C., Bonafè, M., Valensin, S., Olivieri, F., De Luca, M., Ottaviani, E., De Benedictis, G., 2000. Inflamm-aging. An evolutionary perspective on immunosenescence. Ann. N. Y. Acad. Sci. 908, 244–254. https://doi.org/10.1111/j.1749-6632.2000.tb06651.x.

Fülöp, T., Larbi, A., Witkowski, J.M., 2019. Human Inflammaging. Gerontology 65, 495–504. https://doi.org/10.1159/000497375.

Funayama, M., Hasegawa, K., Kowa, H., Saito, M., Tsuji, S., Obata, F., 2002. A new locus for Parkinson's disease (PARK8) maps to chromosome 12p11.2-q13.1. Ann. Neurol. 51, 296–301.
Gao, X., Chen, H., Schwarzschild, M.A., Ascherio, A., 2011. Use of ibuprofen and risk of Parkinson disease. Neurology 76, 863–869. https://doi.org/10.1212/WNL.0b013e31820f2d79.
Gardet, A., Benita, Y., Li, C., Sands, B.E., Ballester, I., Stevens, C., Korzenik, J.R., Rioux, J. D., Daly, M.J., Xavier, R.J., Podolsky, D.K., 2010. LRRK2 is involved in the IFN-gamma response and host response to pathogens. J. Immunol. 185, 5577–5585. https://doi.org/10.4049/jimmunol.1000548.
Garretti, F., Agalliu, D., Lindestam Arlehamn, C.S., Sette, A., Sulzer, D., 2019. Autoimmunity in Parkinson's Disease: The Role of α-Synuclein-Specific T Cells. Front. Immunol. 10, 303. https://doi.org/10.3389/fimmu.2019.00303.
Gelders, G., Baekelandt, V., Van der Perren, A., 2018. Linking Neuroinflammation and Neurodegeneration in Parkinson's Disease. J Immunol Res 2018, e4784268. https://doi.org/10.1155/2018/4784268.
Gendelman, H.E., Zhang, Y., Santamaria, P., Olson, K.E., Schutt, C.R., Bhatti, D., Shetty, B.L.D., Lu, Y., Estes, K.A., Standaert, D.G., Heinrichs-Graham, E., Larson, L., Meza, J.L., Follett, M., Forsberg, E., Siuzdak, G., Wilson, T.W., Peterson, C., Mosley, R.L., 2017. Evaluation of the safety and immunomodulatory effects of sargramostim in a randomized, double-blind phase 1 clinical Parkinson's disease trial. NPJ Parkinsons Dis. 3, 10. https://doi.org/10.1038/s41531-017-0013-5.
Ghosh, A., Roy, A., Liu, X., Kordower, J.H., Mufson, E.J., Hartley, D.M., Ghosh, S., Mosley, R.L., Gendelman, H.E., Pahan, K., 2007. Selective inhibition of NF-kappaB activation prevents dopaminergic neuronal loss in a mouse model of Parkinson's disease. Proc. Natl. Acad. Sci. U. S. A. 104, 18754–18759. https://doi.org/10.1073/pnas.0704908104.
Gloeckner, C.J., Schumacher, A., Boldt, K., Ueffing, M., 2009. The Parkinson disease-associated protein kinase LRRK2 exhibits MAPKKK activity and phosphorylates MKK3/6 and MKK4/7, in vitro. J. Neurochem. 109, 959–968. https://doi.org/10.1111/j.1471-4159.2009.06024.x.
Goldberg, E.L., Shaw, A.C., Montgomery, R.R., 2020. How Inflammation Blunts Innate Immunity in Aging. Interdiscip. Top Gerontol. Geriatr. 43, 1–17. https://doi.org/10.1159/000504480.
Gomez-Pinedo, U., Matias-Guiu, J., Sanclemente-Alaman, I., Moreno-Jimenez, L., Montero-Escribano, P., Matias-Guiu, J.A., 2020. Is the brain a reservoir organ for SARS-CoV2? J. Med. Virol. 92, 2354–2355. https://doi.org/10.1002/jmv.26046.
Gordon, R., Albornoz, E.A., Christie, D.C., Langley, M.R., Kumar, V., Mantovani, S., Robertson, A.A.B., Butler, M.S., Rowe, D.B., O'Neill, L.A., Kanthasamy, A.G., Schroder, K., Cooper, M.A., Woodruff, T.M., 2018. Inflammasome inhibition prevents α-synuclein pathology and dopaminergic neurodegeneration in mice. Sci. Transl. Med. 10, eaah4066. https://doi.org/10.1126/scitranslmed.aah4066.
Grünewald, A., Breedveld, G.J., Lohmann-Hedrich, K., Rohé, C.F., König, I.R., Hagenah, J., Vanacore, N., Meco, G., Antonini, A., Goldwurm, S., Lesage, S., Dürr, A., Binkofski, F., Siebner, H., Münchau, A., Brice, A., Oostra, B.A., Klein, C., Bonifati, V., 2007. Biological effects of the PINK1 c.1366C>T mutation: implications in Parkinson disease pathogenesis. Neurogenetics 8, 103–109. https://doi.org/10.1007/s10048-006-0072-y.
Gupta, S., 2014. Role of dendritic cells in innate and adaptive immune response in human aging. Exp. Gerontol. 54, 47–52. https://doi.org/10.1016/j.exger.2013.12.009.
Hadjadj, J., Yatim, N., Barnabei, L., Corneau, A., Boussier, J., Smith, N., Péré, H., Charbit, B., Bondet, V., Chenevier-Gobeaux, C., Breillat, P., Carlier, N., Gauzit, R., Morbieu, C., Pène, F., Marin, N., Roche, N., Szwebel, T.-A., Merkling, S.H., Treluyer, J.-M., Veyer, D., Mouthon, L., Blanc, C., Tharaux, P.-L., Rozenberg, F., Fischer, A., Duffy, D., Rieux-Laucat, F., Kernéis, S., Terrier, B., 2020. Impaired type I interferon activity and inflammatory responses in severe COVID-19 patients. Science 369, 718–724. https://doi.org/10.1126/science.abc6027.
Håkansson, A., Westberg, L., Nilsson, S., Buervenich, S., Carmine, A., Holmberg, B., Sydow, O., Olson, L., Johnels, B., Eriksson, E., Nissbrandt, H., 2005. Interaction of polymorphisms in the genes encoding interleukin-6 and estrogen receptor beta on the susceptibility to Parkinson's disease. Am. J. Med. Genet. B Neuropsychiatr. Genet. 133B, 88–92. https://doi.org/10.1002/ajmg.b.30136.
Halleskog, C., Schulte, G., 2013. Pertussis toxin-sensitive heterotrimeric G(αi/o) proteins mediate WNT/β-catenin and WNT/ERK1/2 signaling in mouse primary microglia stimulated with purified WNT-3A. Cell. Signal. 25, 822–828. https://doi.org/10.1016/j.cellsig.2012.12.006.
Halleskog, C., Mulder, J., Dahlström, J., Mackie, K., Hortobágyi, T., Tanila, H., Kumar Puli, L., Färber, K., Harkany, T., Schulte, G., 2011. WNT signaling in activated microglia is proinflammatory. Glia 59, 119–131. https://doi.org/10.1002/glia.21081.
Halleskog, C., Dijksterhuis, J.P., Kilander, M.B.C., Becerril-Ortega, J., Villaescusa, J.C., Lindgren, E., Arenas, E., Schulte, G., 2012. Heterotrimeric G protein-dependent WNT-5A signaling to ERK1/2 mediates distinct aspects of microglia proinflammatory transformation. J. Neuroinflammation 9, 111. https://doi.org/10.1186/1742-2094-9-111.
Harms, A.S., Ferreira, S.A., Romero-Ramos, M., 2021. Periphery and brain, innate and adaptive immunity in Parkinson's disease. Acta Neuropathol. 141, 527–545. https://doi.org/10.1007/s00401-021-02268-5.
Harvey, K., Outeiro, T.F., 2019. The role of LRRK2 in cell signalling. Biochem. Soc. Trans. 47, 197–207. https://doi.org/10.1042/BST20180464.
Hatano, Y., Li, Y., Sato, K., Asakawa, S., Yamamura, Y., Tomiyama, H., Yoshino, H., Asahina, M., Kobayashi, S., Hassin-Baer, S., Lu, C.-S., Ng, A.R., Rosales, R.L., Shimizu, N., Toda, T., Mizuno, Y., Hattori, N., 2004. Novel PINK1 mutations in early-onset parkinsonism. Ann. Neurol. 56, 424–427. https://doi.org/10.1002/ana.20251.
Hazeldine, J., Lord, J.M., 2015. Innate immunesenescence: underlying mechanisms and clinical relevance. Biogerontology 16, 187–201. https://doi.org/10.1007/s10522-014-9514-3.
Heneka, M.T., McManus, R.M., Latz, E., 2018. Inflammasome signalling in brain function and neurodegenerative disease. Nat. Rev. Neurosci. 19, 610–621. https://doi.org/10.1038/s41583-018-0055-7.
Holbrook, J.A., Jarosz-Griffiths, H.H., Caseley, E., Lara-Reyna, S., Poulter, J.A., Williams-Gray, C.H., Peckham, D., McDermott, M.F., 2021. Neurodegenerative Disease and the NLRP3 Inflammasome. Front. Pharmacol. 12, 643254 https://doi.org/10.3389/fphar.2021.643254.
Hooper, C., Sainz-Fuertes, R., Lynham, S., Hye, A., Killick, R., Warley, A., Bolondi, C., Pocock, J., Lovestone, S., 2012. Wnt3a induces exosome secretion from primary cultured rat microglia. BMC Neurosci. 13, 144. https://doi.org/10.1186/1471-2202-13-144.
Hsu, C.H., Chan, D., Greggio, E., Saha, S., Guillily, M.D., Ferree, A., Raghavan, K., Shen, G.C., Segal, L., Ryu, H., Cookson, M.R., Wolozin, B., 2010. MKK6 binds and regulates expression of Parkinson's disease-related protein LRRK2. J. Neurochem. 112, 1593–1604. https://doi.org/10.1111/j.1471-4159.2010.06568.x.
Hui, K.Y., Fernandez-Hernandez, H., Hu, J., Schaffner, A., Pankratz, N., Hsu, N.-Y., Chuang, L.-S., Carmi, S., Villaverde, N., Li, X., Rivas, M., Levine, A.P., Bao, X., Labrias, P.R., Haritunians, T., Ruane, D., Gettler, K., Chen, E., Li, D., Schiff, E.R., Pontikos, N., Barzilai, N., Brant, S.R., Bressman, S., Cheifetz, A.S., Clark, L.N., Daly, M.J., Desnick, R.J., Duerr, R.H., Katz, S., Lencz, T., Myers, R.H., Ostrer, H., Ozelius, L., Payami, H., Peter, Y., Rioux, J.D., Segal, A.W., Scott, W.K., Silverberg, M. S., Vance, J.M., Ubarretxena-Belandia, I., Foroud, T., Atzmon, G., Peer, I., Ioannou, Y., McGovern, D.P.B., Yue, Z., Schadt, E.E., Cho, J.H., 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. https://doi.org/10.1126/scitranslmed.aai7795.
Hunot, S., Brugg, B., Ricard, D., Michel, P.P., Muriel, M.-P., Ruberg, M., Faucheux, B.A., Agid, Y., Hirsch, E.C., 1997. Nuclear translocation of NF-κB is increased in dopaminergic neurons of patients with Parkinson disease. Proc. Natl. Acad. Sci. U. S. A. 94, 7531–7536.
Iwata, A., Maruyama, M., Kanazawa, I., Nukina, N., 2001. α-Synuclein Affects the MAPK Pathway and Accelerates Cell Death *. J. Biol. Chem. 276, 45320–45329. https://doi.org/10.1074/jbc.M103736200.
James, L.M., Georgopoulos, A.P., 2020. Shared Human Leukocyte Antigen (HLA) Coverage in dementia and Parkinson's disease. J. Neurol. Neuromed. 5.
Johnson, M.E., Stecher, B., Labrie, V., Brundin, L., Brundin, P., 2019. Triggers, Facilitators, and Aggravators: Redefining Parkinson's Disease Pathogenesis. Trends Neurosci. 42, 4–13. https://doi.org/10.1016/j.tins.2018.09.007.
Kane, L.A., Lazarou, M., Fogel, A.I., Li, Y., Yamano, K., Sarraf, S.A., Banerjee, S., Youle, R. J., 2014. PINK1 phosphorylates ubiquitin to activate Parkin E3 ubiquitin ligase activity. J. Cell Biol. 205, 143–153. https://doi.org/10.1083/jcb.201402104.
Kannarkat, G.T., Boss, J.M., Tansey, M.G., 2013. The role of innate and adaptive immunity in Parkinson's disease. J. Parkinsons Dis. 3, 493–514. https://doi.org/10.3233/JPD-130250.
Kannarkat, G.T., Cook, D.A., Lee, J.-K., Chang, J., Chung, J., Sandy, E., Paul, K.C., Ritz, B., Bronstein, J., Factor, S.A., Boss, J.M., Tansey, M.G., 2015. Common Genetic Variant Association with Altered HLA Expression, Synergy with Pyrethroid Exposure, and Risk for Parkinson's Disease: An Observational and Case-Control Study. NPJ Parkinsons Dis. 1, 15002. https://doi.org/10.1038/npjparkd.2015.2.
Kase, Y., Otsu, K., Shimazaki, T., Okano, H., 2019. Involvement of p38 in Age-Related Decline in Adult Neurogenesis via Modulation of Wnt Signaling. Stem Cell Rep. 12, 1313–1328. https://doi.org/10.1016/j.stemcr.2019.04.010.
Khanfer, R., Carroll, D., Lord, J.M., Phillips, A.C., 2012. Reduced neutrophil superoxide production among healthy older adults in response to acute psychological stress. Int. J. Psychophysiol. 86, 238–244. https://doi.org/10.1016/j.ijpsycho.2012.09.013.
Kilander, M.B.C., Halleskog, C., Schulte, G., 2011. Recombinant WNTs differentially activate β-catenin-dependent and -independent signalling in mouse microglia-like cells. Acta Physiol (Oxford) 203, 363–372. https://doi.org/10.1111/j.1748-1716.2011.02324.x.
Kim, C., Ho, D.-H., Suk, J.-E., You, S., Michael, S., Kang, J., Joong Lee, S., Masliah, E., Hwang, D., Lee, H.-J., Lee, S.-J., 2013. Neuron-released oligomeric α-synuclein is an endogenous agonist of TLR2 for paracrine activation of microglia. Nat. Commun. 4, 1562. https://doi.org/10.1038/ncomms2534.
Kim, K.S., Marcogliese, P.C., Yang, J., Callaghan, S.M., Resende, V., Abdel-Messih, E., Marras, C., Visanji, N.P., Huang, J., Schlossmacher, M.G., Trinkle-Mulcahy, L., Slack, R.S., Lang, A.E., Team (CLINT), C.L. in I., Park, D.S, 2018. Regulation of myeloid cell phagocytosis by LRRK2 via WAVE2 complex stabilization is altered in Parkinson's disease. PNAS 115, E5164–E5173. https://doi.org/10.1073/pnas.1718946115.
Kim, J., Pajarillo, E., Rizor, A., Son, D.-S., Lee, J., Aschner, M., Lee, E., 2019. LRRK2 kinase plays a critical role in manganese-induced inflammation and apoptosis in microglia. PLoS One 14, e0210248. https://doi.org/10.1371/journal.pone.0210248.
Kitada, T., Asakawa, S., Hattori, N., Matsumine, H., Yamamura, Y., Minoshima, S., Yokochi, M., Mizuno, Y., Shimizu, N., 1998. Mutations in the parkin gene cause autosomal recessive juvenile parkinsonism. Nature 392, 605–608. https://doi.org/10.1038/33416.
Klein, C., Djarmati, A., Hedrich, K., Schäfer, N., Scaglione, C., Marchese, R., Kock, N., Schüle, B., Hiller, A., Lohnau, T., Winkler, S., Wiegers, K., Hering, R., Bauer, P., Riess, O., Abbruzzese, G., Martinelli, P., Pramstaller, P.P., 2005. PINK1, Parkin, and DJ-1 mutations in Italian patients with early-onset parkinsonism. Eur. J. Hum. Genet. 13, 1086–1093. https://doi.org/10.1038/sj.ejhg.5201455.
Kong, K.-F., Delroux, K., Wang, X., Qian, F., Arjona, A., Malawista, S.E., Fikrig, E., Montgomery, R.R., 2008. Dysregulation of TLR3 impairs the innate immune

response to West Nile virus in the elderly. J. Virol. 82, 7613–7623. https://doi.org/10.1128/JVI.00618-08.
Krashia, P., Cordella, A., Nobili, A., La Barbera, L., Federici, M., Leuti, A., Campanelli, F., Natale, G., Marino, G., Calabrese, V., Vedele, F., Ghiglieri, V., Picconi, B., Di Lazzaro, G., Schirinzi, T., Sancesario, G., Casadei, N., Riess, O., Bernardini, S., Pisani, A., Calabresi, P., Viscomi, M.T., Serhan, C.N., Chiurchiù, V., D'Amelio, M., Mercuri, N.B., 2019. Blunting neuroinflammation with resolvin D1 prevents early pathology in a rat model of Parkinson's disease. Nat. Commun. 10, 3945. https://doi.org/10.1038/s41467-019-11928-w.
Krüger, R., Hardt, C., Tschentscher, F., Jäckel, S., Kuhn, W., Müller, T., Werner, J., Woitalla, D., Berg, D., Kühnl, N., Fuchs, G.A., Santos, E.J., Przuntek, H., Epplen, J.T., Schöls, L., Riess, O., 2000. Genetic analysis of immunomodulating factors in sporadic Parkinson's disease. J. Neural Transm. (Vienna) 107, 553–562. https://doi.org/10.1007/s007020070078.
Kulich, S.M., Chu, C.T., 2001. Sustained extracellular signal-regulated kinase activation by 6-hydroxydopamine: implications for Parkinson's disease. J. Neurochem. 77, 1058–1066. https://doi.org/10.1046/j.1471-4159.2001.00304.x.
L'Episcopo, F., Tirolo, C., Serapide, M.F., Caniglia, S., Testa, N., Leggio, L., Vivarelli, S., Iraci, N., Pluchino, S., Marchetti, B., 2018. Microglia Polarization, Gene-Environment Interactions and Wnt/β-Catenin Signaling: Emerging Roles of Glia-Neuron and Glia-Stem/Neuroprogenitor Crosstalk for Dopaminergic Neurorestoration in Aged Parkinsonian Brain. Front. Aging Neurosci. 10, 12. https://doi.org/10.3389/fnagi.2018.00012.
Lampe, J.B., Gossrau, G., Herting, B., Kempe, A., Sommer, U., Füssel, M., Weber, M., Koch, R., Reichmann, H., 2003. HLA typing and Parkinson's disease. Eur. Neurol. 50, 64–68. https://doi.org/10.1159/000072500.
Larbi, A., Douziech, N., Fortin, C., Linteau, A., Dupuis, G., Fulop, T., 2005. The role of the MAPK pathway alterations in GM-CSF modulated human neutrophil apoptosis with aging. Immun. Ageing 2, 6. https://doi.org/10.1186/1742-4933-2-6.
Larbi, A., Fülöp, T., Pawelec, G., 2008. Immune receptor signaling, aging and autoimmunity. Adv. Exp. Med. Biol. 640, 312–324. https://doi.org/10.1007/978-0-387-09789-3_21.
Law, B.M.H., Spain, V.A., Leinster, V.H.L., Chia, R., Beilina, A., Cho, H.J., Taymans, J.-M., Urban, M.K., Sancho, R.M., Blanca Ramírez, M., Biskup, S., Baekelandt, V., Cai, H., Cookson, M.R., Berwick, D.C., Harvey, K., 2014. A direct interaction between leucine-rich repeat kinase 2 and specific β-tubulin isoforms regulates tubulin acetylation. J. Biol. Chem. 289, 895–908. https://doi.org/10.1074/jbc.M113.507913.
Lee, J.S., Shin, E.-C., 2020. The type I interferon response in COVID-19: implications for treatment. Nat. Rev. Immunol. 20, 585–586. https://doi.org/10.1038/s41577-020-00429-3.
Lee, J.-Y., Nagano, Y., Taylor, J.P., Lim, K.L., Yao, T.-P., 2010. Disease-causing mutations in parkin impair mitochondrial ubiquitination, aggregation, and HDAC6-dependent mitophagy. J. Cell Biol. 189, 671–679. https://doi.org/10.1083/jcb.201001039.
Lee, H., Flynn, R., Sharma, I., Haberman, E., Carling, P.J., Nicholls, F.J., Stegmann, M., Vowles, J., Haenseler, W., Wade-Martins, R., James, W.S., Cowley, S.A., 2020. LRRK2 Is Recruited to Phagosomes and Co-recruits RAB8 and RAB10 in Human Pluripotent Stem Cell-Derived Macrophages. Stem Cell Rep. 14, 940–955. https://doi.org/10.1016/j.stemcr.2020.04.001.
Lee, J.H., Kim, H.J., Kim, J.U., Yook, T.H., Kim, K.H., Lee, J.Y., Yang, G., 2021. A Novel Treatment Strategy by Natural Products in NLRP3 Inflammasome-Mediated Neuroinflammation in Alzheimer's and Parkinson's Disease. Int. J. Mol. Sci. 22, 1324. https://doi.org/10.3390/ijms22031324.
Lesage, S., Brice, A., 2009. Parkinson's disease: from monogenic forms to genetic susceptibility factors. Hum. Mol. Genet. 18, R48–R59. https://doi.org/10.1093/hmg/ddp012.
Li, Y., Tomiyama, H., Sato, K., Hatano, Y., Yoshino, H., Atsumi, M., Kitaguchi, M., Sasaki, S., Kawaguchi, S., Miyajima, H., Toda, T., Mizuno, Y., Hattori, N., 2005. Clinicogenetic study of PINK1 mutations in autosomal recessive early-onset parkinsonism. Neurology 64, 1955–1957. https://doi.org/10.1212/01.WNL.0000164009.36740.4E.
Liu, J., Halene, S., Yang, M., Iqbal, J., Yang, R., Mehal, W.Z., Chuang, W.-L., Jain, D., Yuen, T., Sun, L., Zaidi, M., Mistry, P.K., 2012. Gaucher disease gene GBA functions in immune regulation. Proc. Natl. Acad. Sci. U. S. A. 109, 10018–10023. https://doi.org/10.1073/pnas.1200941109.
Maekawa, T., Sasaoka, T., Azuma, S., Ichikawa, T., Melrose, H.L., Farrer, M.J., Obata, F., 2016. Leucine-rich repeat kinase 2 (LRRK2) regulates α-synuclein clearance in microglia. BMC Neurosci. 17, 77. https://doi.org/10.1186/s12868-016-0315-2.
Manthripragada, A.D., Schernhammer, E.S., Qiu, J., Friis, S., Wermuth, L., Olsen, J.H., Ritz, B., 2011. Non-steroidal anti-inflammatory drug use and the risk of Parkinson's disease. Neuroepidemiology 36, 155–161. https://doi.org/10.1159/000325653.
Mao, X., Ou, M.T., Karuppagounder, S.S., Kam, T.-I., Yin, X., Xiong, Y., Ge, P., Umanah, G.E., Brahmachari, S., Shin, J.-H., Kang, H.C., Zhang, J., Xu, J., Chen, R., Park, H., Andrabi, S.A., Kang, S.U., Gonçalves, R.A., Liang, Y., Zhang, S., Qi, C., Lam, S., Keiler, J.A., Tyson, J., Kim, D., Panicker, N., Yun, S.P., Workman, C.J., Vignali, D.A.A., Dawson, V.L., Ko, H.S., Dawson, T.M., 2016. Pathological α-synuclein transmission initiated by binding lymphocyte-activation gene 3. Science 353, aah3374. https://doi.org/10.1126/science.aah3374.
Marchetti, B., Tirolo, C., L'Episcopo, F., Caniglia, S., Testa, N., Smith, J.A., Pluchino, S., Serapide, M.F., 2020. Parkinson's disease, aging and adult neurogenesis: Wnt/β-catenin signalling as the key to unlock the mystery of endogenous brain repair. Aging Cell 19, e13101. https://doi.org/10.1111/acel.13101.
Matsumine, H., Saito, M., Shimoda-Matsubayashi, S., Tanaka, H., Ishikawa, A., Nakagawa-Hattori, Y., Yokochi, M., Kobayashi, T., Igarashi, S., Takano, H., Sanpei, K., Koike, R., Mori, H., Kondo, T., Mizutani, Y., Schäffer, A.A., Yamamura, Y., Nakamura, S., Kuzuhara, S., Tsuji, S., Mizuno, Y., 1997. Localization of a gene for an autosomal recessive form of juvenile Parkinsonism to chromosome 6q25.2-27. Am. J. Hum. Genet. 60, 588–596.
Mattson, M.P., Camandola, S., 2001. NF-κB in neuronal plasticity and neurodegenerative disorders. J. Clin. Invest. 107, 247–254. https://doi.org/10.1172/JCI11916.
Moehle, M.S., Webber, P.J., Tse, T., Sukar, N., Standaert, D.G., DeSilva, T.M., Cowell, R. M., West, A.B., 2012. LRRK2 Inhibition Attenuates Microglial Inflammatory Responses. J. Neurosci. 32, 1602–1611. https://doi.org/10.1523/JNEUROSCI.5601-11.2012.
Mogi, M., Kondo, T., Mizuno, Y., Nagatsu, T., 2007. p53 protein, interferon-gamma, and NF-kappaB levels are elevated in the parkinsonian brain. Neurosci. Lett. 414, 94–97. https://doi.org/10.1016/j.neulet.2006.12.003.
Mount, M.P., Lira, A., Grimes, D., Smith, P.D., Faucher, S., Slack, R., Anisman, H., Hayley, S., Park, D.S., 2007. Involvement of interferon-gamma in microglial-mediated loss of dopaminergic neurons. J. Neurosci. 27, 3328–3337. https://doi.org/10.1523/JNEUROSCI.5321-06.2007.
Müller, L., Di Benedetto, S., Pawelec, G., 2019. The Immune System and Its Dysregulation with Aging. Subcell. Biochem. 91, 21–43. https://doi.org/10.1007/978-981-13-3681-2_2.
Mullin, S., Stokholm, M.G., Hughes, D., Mehta, A., Parbo, P., Hinz, R., Pavese, N., Brooks, D.J., Schapira, A.H.V., 2021. Brain Microglial Activation Increased in Glucocerebrosidase (GBA) Mutation Carriers without Parkinson's disease. Mov. Disord. 36, 774–779. https://doi.org/10.1002/mds.28375.
Nalls, M.A., Pankratz, N., Lill, C.M., Do, C.B., Hernandez, D.G., Saad, M., DeStefano, A.L., Kara, E., Bras, J., Sharma, M., Schulte, C., Keller, M.F., Arepalli, S., Letson, C., Edsall, C., Stefansson, H., Liu, X., Pliner, H., Lee, J.H., Cheng, R., International Parkinson's Disease Genomics Consortium (IPDGC), Parkinson's Study Group (PSG) Parkinson's Research: The Organized GENetics Initiative (PROGENI), 23andMe, GenePD, NeuroGenetics Research Consortium (NGRC), Hussman Institute of Human Genomics (HIHG), The Ashkenazi Jewish Dataset Investigator, Cohorts for Health and Aging Research in Genetic Epidemiology (CHARGE), North American Brain Expression Consortium (NABEC), United Kingdom Brain Expression Consortium (UKBEC), Greek Parkinson's Disease Consortium, Alzheimer Genetic Analysis Group, Ikram, M.A., Ioannidis, J.P.A., Hadjigeorgiou, G.M., Bis, J.C., Martinez, M., Perlmutter, J.S., Goate, A., Marder, K., Fiske, B., Sutherland, M., Xiromerisiou, G., Myers, R.H., Clark, L.N., Stefansson, K., Hardy, J.A., Heutink, P., Chen, H., Wood, N. W., Houlden, H., Payami, H., Brice, A., Scott, W.K., Gasser, T., Bertram, L., Eriksson, N., Foroud, T., Singleton, A.B., 2014. Large-scale meta-analysis of genome-wide association data identifies six new risk loci for Parkinson's disease. Nat. Genet. 46, 989–993.
Nalls, M.A., Blauwendraat, C., Vallerga, C.L., Heilbron, K., Bandres-Ciga, S., Chang, D., Tan, M., Kia, D.A., Noyce, A.J., Xue, A., Bras, J., Young, E., von Coelln, R., Simón-Sánchez, J., Schulte, C., Sharma, M., Krohn, L., Pihlstrøm, L., Siitonen, A., Iwaki, H., Leonard, H., Faghri, F., Gibbs, J.R., Hernandez, D.G., Scholz, S.W., Botia, J.A., Martinez, M., Corvol, J.-C., Lesage, S., Jankovic, J., Shulman, L.M., Sutherland, M., Tienari, P., Majamaa, K., Toft, M., Andreassen, O.A., Bangale, T., Brice, A., Yang, J., Gan-Or, Z., Gasser, T., Heutink, P., Shulman, J.M., Wood, N.W., Hinds, D.A., Hardy, J.A., Morris, H.R., Gratten, J., Visscher, P.M., Graham, R.R., Singleton, A.B., 23andMe Research Team, System Genomics of Parkinson's Disease Consortium, International Parkinson's Disease Genomics Consortium, 2019. Identification of novel risk loci, causal insights, and heritable risk for Parkinson's disease: a meta-analysis of genome-wide association studies. Lancet Neurol. 18, 1091–1102. https://doi.org/10.1016/S1474-4422(19)30320-5.
Narendra, D., Tanaka, A., Suen, D.-F., Youle, R.J., 2008. Parkin is recruited selectively to impaired mitochondria and promotes their autophagy. J. Cell Biol. 183, 795–803. https://doi.org/10.1083/jcb.200809125.
Neumann, J., Schaale, K., Farhat, K., Endermann, T., Ulmer, A.J., Ehlers, S., Reiling, N., 2010. Frizzled1 is a marker of inflammatory macrophages, and its ligand Wnt3a is involved in reprogramming Mycobacterium tuberculosis-infected macrophages. FASEB J. 24, 4599–4612. https://doi.org/10.1096/fj.10-160994.
Nuytemans, K., Theuns, J., Cruts, M., Van Broeckhoven, C., 2010. Genetic Etiology of Parkinson Disease Associated with Mutations in the SNCA, PARK2, PINK1, PARK7, and LRRK2 Genes: A Mutation Update. Hum. Mutat. 31, 763–780. https://doi.org/10.1002/humu.21277.
Nyugen, J., Agrawal, S., Gollapudi, S., Gupta, S., 2010. Impaired functions of peripheral blood monocyte subpopulations in aged humans. J. Clin. Immunol. 30, 806–813. https://doi.org/10.1007/s10875-010-9448-8.
Olson, K.E., Gendelman, H.E., 2016. Immunomodulation as a neuroprotective and therapeutic strategy for Parkinson's disease. Curr. Opin. Pharmacol. 26, 87–95. https://doi.org/10.1016/j.coph.2015.10.006.
Paisán-Ruíz, C., Jain, S., Evans, E.W., Gilks, W.P., Simón, J., van der Brug, M., López de Munain, A., Aparicio, S., Gil, A.M., Khan, N., Johnson, J., Martinez, J.R., Nicholl, D., Carrera, I.M., Pena, A.S., de Silva, R., Lees, A., Martí-Massó, J.F., Pérez-Tur, J., Wood, N.W., Singleton, A.B., 2004. Cloning of the gene containing mutations that cause PARK8-linked Parkinson's disease. Neuron 44, 595–600. https://doi.org/10.1016/j.neuron.2004.10.023.
Pajares, M., Rojo, I., Manda, G., Boscá, L., Cuadrado, A., 2020. Inflammation in Parkinson's Disease: Mechanisms and Therapeutic Implications. Cells 9, 1687. https://doi.org/10.3390/cells9071687.
Pan, J., Xiao, Q., Sheng, C.-Y., Hong, Z., Yang, H.-Q., Wang, G., Ding, J.-Q., Chen, S.-D., 2009. Blockade of the translocation and activation of c-Jun N-terminal kinase 3 (JNK3) attenuates dopaminergic neuronal damage in mouse model of Parkinson's disease. Neurochem. Int. 54, 418–425. https://doi.org/10.1016/j.neuint.2009.01.013.
Pan, J., Qian, J., Zhang, Y., Ma, J., Wang, G., Xiao, Q., Chen, S., Ding, J., 2010. Small peptide inhibitor of JNKs protects against MPTP-induced nigral dopaminergic injury

via inhibiting the JNK-signaling pathway. Lab. Investig. 90, 156–167. https://doi.org/10.1038/labinvest.2009.124.
Paramel, G.V., Sirsjö, A., Fransén, K., 2015. Role of genetic alterations in the NLRP3 and CARD8 genes in health and disease. Mediat. Inflamm. 2015, 846782 https://doi.org/10.1155/2015/846782.
Parisiadou, L., Yu, J., Sgobio, C., Xie, C., Liu, G., Sun, L., Gu, X.-L., Lin, X., Crowley, N.A., Lovinger, D.M., Cai, H., 2014. LRRK2 regulates synaptogenesis and dopamine receptor activation through modulation of PKA activity. Nat. Neurosci. 17, 367–376. https://doi.org/10.1038/nn.3636.
Park, J., Lee, S.B., Lee, S., Kim, Y., Song, S., Kim, S., Bae, E., Kim, J., Shong, M., Kim, J.-M., Chung, J., 2006. Mitochondrial dysfunction in Drosophila PINK1 mutants is complemented by parkin. Nature 441, 1157–1161. https://doi.org/10.1038/nature04788.
Patrick, K.L., Bell, S.L., Weindel, C.G., Watson, R.O., 2019. Exploring the "Multiple-Hit Hypothesis" of Neurodegenerative Disease: Bacterial Infection Comes Up to Bat. Front. Cell. Infect. Microbiol. 9, 138. https://doi.org/10.3389/fcimb.2019.00138.
Pereira, C.P., Bachli, E.B., Schoedon, G., 2009. The wnt pathway: a macrophage effector molecule that triggers inflammation. Curr. Atheroscler. Rep. 11, 236–242. https://doi.org/10.1007/s11883-009-0036-4.
Polymeropoulos, M.H., Higgins, J.J., Golbe, L.I., Johnson, W.G., Ide, S.E., Di Iorio, G., Sanges, G., Stenroos, E.S., Pho, L.T., Schaffer, A.A., Lazzarini, A.M., Nussbaum, R.L., Duvoisin, R.C., 1996. Mapping of a gene for Parkinson's disease to chromosome 4q21-q23. Science 274, 1197–1199.
Rakovic, A., Grünewald, A., Kottwitz, J., Brüggemann, N., Pramstaller, P.P., Lohmann, K., Klein, C., 2011. Mutations in PINK1 and Parkin impair ubiquitination of Mitofusins in human fibroblasts. PLoS One 6, e16746. https://doi.org/10.1371/journal.pone.0016746.
Reale, M., Iarlori, C., Thomas, A., Gambi, D., Perfetti, B., Di Nicola, M., Onofrj, M., 2009. Peripheral cytokines profile in Parkinson's disease. Brain Behav. Immun. 23, 55–63. https://doi.org/10.1016/j.bbi.2008.07.003.
Renshaw, M., Rockwell, J., Engleman, C., Gewirtz, A., Katz, J., Sambhara, S., 2002. Cutting edge: impaired Toll-like receptor expression and function in aging. J. Immunol. 169, 4697–4701. https://doi.org/10.4049/jimmunol.169.9.4697.
Rogaeva, E., Johnson, J., Lang, A.E., Gulick, C., Gwinn-Hardy, K., Kawarai, T., Sato, C., Morgan, A., Werner, J., Nussbaum, R., Petit, A., Okun, M.S., McInerney, A., Mandel, R., Groen, J.L., Fernandez, H.H., Postuma, R., Foote, K.D., Salehi-Rad, S., Liang, Y., Reimsnider, S., Tandon, A., Hardy, J., St George-Hyslop, P., Singleton, A. B., 2004. Analysis of the PINK1 gene in a large cohort of cases with Parkinson disease. Arch. Neurol. 61, 1898–1904. https://doi.org/10.1001/archneur.61.12.1898.
Royce, G.H., Brown-Borg, H.M., Deepa, S.S., 2019. The potential role of necroptosis in inflammaging and aging. Geroscience 41, 795–811. https://doi.org/10.1007/s11357-019-00131-w.
Russo, I., Berti, G., Plotegher, N., Bernardo, G., Filograna, R., Bubacco, L., Greggio, E., 2015. Leucine-rich repeat kinase 2 positively regulates inflammation and down-regulates NF-κB p50 signaling in cultured microglia cells. J. Neuroinflammation 12, 230. https://doi.org/10.1186/s12974-015-0449-7.
Russo, I., Kaganovich, A., Ding, J., Landeck, N., Mamais, A., Varanita, T., Biosa, A., Tessari, I., Bubacco, L., Greggio, E., Cookson, M.R., 2019. Transcriptome analysis of LRRK2 knock-out microglia cells reveals alterations of inflammatory- and oxidative stress-related pathways upon treatment with α-synuclein fibrils. Neurobiol Dis 129, 67–78. https://doi.org/10.1016/j.nbd.2019.05.012. Epub 2019 May 15.PMID: 31102768.
Salašová, A., Yokota, C., Potěšil, D., Zdráhal, Z., Bryja, V., Arenas, E., 2017. A proteomic analysis of LRRK2 binding partners reveals interactions with multiple signaling components of the WNT/PCP pathway. Mol. Neurodegener. 12, 54. https://doi.org/10.1186/s13024-017-0193-9.
Sampson, T.R., Debelius, J.W., Thron, T., Janssen, S., Shastri, G.G., Ilhan, Z.E., Challis, C., Schretter, C.E., Rocha, S., Gradinaru, V., Chesselet, M.-F., Keshavarzian, A., Shannon, K.M., Krajmalnik-Brown, R., Wittung-Stafshede, P., Knight, R., Mazmanian, S.K., 2016. Gut Microbiota Regulate Motor Deficits and Neuroinflammation in a Model of Parkinson's Disease. Cell 167, 1469–1480.e12. https://doi.org/10.1016/j.cell.2016.11.018.
San Luciano, M., Tanner, C.M., Meng, C., Marras, C., Goldman, S.M., Lang, A.E., Tolosa, E., Schüle, B., Langston, J.W., Brice, A., Corvol, J.-C., Goldwurm, S., Klein, C., Brockman, S., Berg, D., Brockmann, K., Ferreira, J.J., Tazir, M., Mellick, G. D., Sue, C.M., Hasegawa, K., Tan, E.K., Bressman, S., Saunders-Pullman, R., Michael, J., Fox Foundation LRRK2 Cohort Consortium, 2020. Nonsteroidal Anti-inflammatory Use and LRRK2 Parkinson's Disease Penetrance. Mov. Disord. 35, 1755–1764. https://doi.org/10.1002/mds.28189.
Sanchez-Guajardo, V., Febbraro, F., Kirik, D., Romero-Ramos, M., 2010. Microglia acquire distinct activation profiles depending on the degree of alpha-synuclein neuropathology in a rAAV based model of Parkinson's disease. PLoS One 5, e8784. https://doi.org/10.1371/journal.pone.0008784.
Sancho, R.M., Law, B.M.H., Harvey, K., 2009. Mutations in the LRRK2 Roc-COR tandem domain link Parkinson's disease to Wnt signalling pathways. Hum. Mol. Genet. 18, 3955–3968. https://doi.org/10.1093/hmg/ddp337.
Satake, W., Nakabayashi, Y., Mizuta, I., Hirota, Y., Ito, C., Kubo, M., Kawaguchi, T., Tsunoda, T., Watanabe, M., Takeda, A., Tomiyama, H., Nakashima, K., Hasegawa, K., Obata, F., Yoshikawa, T., Kawakami, H., Sakoda, S., Yamamoto, M., Hattori, N., Murata, M., Nakamura, Y., Toda, T., 2009. Genome-wide association study identifies common variants at four loci as genetic risk factors for Parkinson's disease. Nat. Genet. 41, 1303–1307. https://doi.org/10.1038/ng.485.
Sauce, D., Dong, Y., Campillo-Gimenez, L., Casulli, S., Bayard, C., Autran, B., Boddaert, J., Appay, V., Elbim, C., 2017. Reduced Oxidative Burst by Primed Neutrophils in the Elderly Individuals Is Associated With Increased Levels of the CD16bright/CD62Ldim Immunosuppressive Subset. J. Gerontol. A Biol. Sci. Med. Sci. 72, 163–172. https://doi.org/10.1093/gerona/glw062.
Schaale, K., Neumann, J., Schneider, D., Ehlers, S., Reiling, N., 2011. Wnt signaling in macrophages: augmenting and inhibiting mycobacteria-induced inflammatory responses. Eur. J. Cell Biol. 90, 553–559. https://doi.org/10.1016/j.ejcb.2010.11.004.
Schwab, A.D., Thurston, M.J., Machhi, J., Olson, K.E., Namminga, K.L., Gendelman, H.E., Mosley, R.L., 2020. Immunotherapy for Parkinson's disease. Neurobiol. Dis. 137, 104760 https://doi.org/10.1016/j.nbd.2020.104760.
Shaw, A.C., Goldstein, D.R., Montgomery, R.R., 2013. Age-dependent dysregulation of innate immunity. Nat. Rev. Immunol. 13, 875–887. https://doi.org/10.1038/nri3547.
Shutinoski, B., Hakimi, M., Harmsen, I.E., Lunn, M., Rocha, J., Lengacher, N., Zhou, Y.Y., Khan, J., Nguyen, A., Hake-Volling, Q., El-Kodsi, D., Li, J., Alikashani, A., Beauchamp, C., Majithia, J., Coombs, K., Shimshek, D., Marcogliese, P.C., Park, D.S., Rioux, J.D., Philpott, D.J., Woulfe, J.M., Hayley, S., Sad, S., Tomlinson, J.J., Brown, E.G., Schlossmacher, M.G., 2019. Lrrk2 alleles modulate inflammation during microbial infection of mice in a sex-dependent manner. Sci. Transl. Med. 11, eaas9292. https://doi.org/10.1126/scitranslmed.aas9292.
Siuda, J., Jasinska-Myga, B., Boczarska-Jedynak, M., Opala, G., Fiesel, F.C., Moussaud-Lamodière, E.L., Scarffe, L.A., Dawson, V.L., Ross, O.A., Springer, W., Dawson, T.M., Wszolek, Z.K., 2014. Early-onset Parkinson's disease due to PINK1 p.Q456X mutation–clinical and functional study. Parkinsonism Relat. Disord. 20, 1274–1278. https://doi.org/10.1016/j.parkreldis.2014.08.019.
Sliter, D.A., Martinez, J., Hao, L., Chen, X., Sun, N., Fischer, T.D., Burman, J.L., Li, Y., Zhang, Z., Narendra, D.P., Cai, H., Borsche, M., Klein, C., Youle, R.J., 2018. Parkin and PINK1 mitigate STING-induced inflammation. Nature 561, 258–262. https://doi.org/10.1038/s41586-018-0448-9.
Smeyne, R.J., Noyce, A.J., Byrne, M., Savica, R., Marras, C., 2021. Infection and Risk of Parkinson's Disease. J. Parkinsons Dis. 11, 31–43. https://doi.org/10.3233/JPD-202279.
Solana, R., Tarazona, R., Gayoso, I., Lesur, O., Dupuis, G., Fulop, T., 2012. Innate immunosenescence: effect of aging on cells and receptors of the innate immune system in humans. Semin. Immunol. 24, 331–341. https://doi.org/10.1016/j.smim.2012.04.008.
Staal, F.J.T., Luis, T.C., Tiemessen, M.M., 2008. WNT signalling in the immune system: WNT is spreading its wings. Nat. Rev. Immunol. 8, 581–593. https://doi.org/10.1038/nri2360.
Sulzer, D., Alcalay, R.N., Garretti, F., Cote, L., Kanter, E., Agin-Liebes, J.P., Liong, C., McMurtrey, C., Hildebrand, W.H., Mao, X., Dawson, V.L., Dawson, T.M., Oseroff, C., Pham, J., Sidney, J., Dillon, M.B., Carpenter, C., Weiskopf, D., Phillips, E., Mallal, S., Peters, B., Frazier, A., Lindestam Arlehamn, C.S., Sette, A., 2017. T cells of Parkinson's disease patients recognize α–synuclein peptides. Nature 546, 656–661. https://doi.org/10.1038/nature22815.
Takagawa, T., Kitani, A., Fuss, I., Levine, B., Brant, S.R., Peter, I., Tajima, M., Nakamura, S., Strober, W., 2018. An increase in LRRK2 suppresses autophagy and enhances Dectin-1–induced immunity in a mouse model of colitis. Sci. Transl. Med. 10, eaan8162. https://doi.org/10.1126/scitranslmed.aan8162.
Tan, E.-K., Chao, Y.-X., West, A., Chan, L.-L., Poewe, W., Jankovic, J., 2020. Parkinson disease and the immune system — associations, mechanisms and therapeutics. Nat. Rev. Neurol. 16, 303–318. https://doi.org/10.1038/s41582-020-0344-4.
Tanji, K., Mori, F., Imaizumi, T., Yoshida, H., Matsumiya, T., Tamo, W., Yoshimoto, M., Odagiri, H., Sasaki, M., Takahashi, H., Satoh, K., Wakabayashi, K., 2002. Upregulation of alpha-synuclein by lipopolysaccharide and interleukin-1 in human macrophages. Pathol. Int. 52, 572–577. https://doi.org/10.1046/j.1440-1827.2002.01385.x.
Tansey, M.G., Goldberg, M.S., 2010. Neuroinflammation in Parkinson's disease: Its role in neuronal death and implications for therapeutic intervention. Neurobiol. Dis. Inflam. Neuropsychiatric Dis. 37, 510–518. https://doi.org/10.1016/j.nbd.2009.11.004.
Tansey, M.G., Wallings, R.L., Houser, M.C., Herrick, M.K., Keating, C.E., Joers, V., 2022. Inflammation and immune dysfunction in Parkinson disease. Nat. Rev. Immunol. https://doi.org/10.1038/s41577-022-00684-6.
Thomas, C.J., Schroder, K., 2013. Pattern recognition receptor function in neutrophils. Trends Immunol. 34, 317–328. https://doi.org/10.1016/j.it.2013.02.008.
van Duin, D., Mohanty, S., Thomas, V., Ginter, S., Montgomery, R.R., Fikrig, E., Allore, H. G., Medzhitov, R., Shaw, A.C., 2007. Age-associated defect in human TLR-1/2 function. J. Immunol. 178, 970–975. https://doi.org/10.4049/jimmunol.178.2.970.
Venezia, S., Refolo, V., Polissidis, A., Stefanis, L., Wenning, G.K., Stefanova, N., 2017. Toll-like receptor 4 stimulation with monophosphoryl lipid A ameliorates motor deficits and nigral neurodegeneration triggered by extraneuronal α-synucleinopathy. Mol. Neurodegener. 12, 52. https://doi.org/10.1186/s13024-017-0195-7.
Verma, A., Ebanks, K., Fok, C.-Y., Lewis, P.A., Bettencourt, C., Bandopadhyay, R., 2021. In silico comparative analysis of LRRK2 interactomes from brain, kidney and lung. Brain Res. 1765, 147503 https://doi.org/10.1016/j.brainres.2021.147503.
von Herrmann, K.M., Salas, L.A., Martinez, E.M., Young, A.L., Howard, J.M., Feldman, M.S., Christensen, B.C., Wilkins, O.M., Lee, S.L., Hickey, W.F., Havrda, M. C., 2018. NLRP3 expression in mesencephalic neurons and characterization of a rare NLRP3 polymorphism associated with decreased risk of Parkinson's disease. NPJ Parkinsons Dis. 4, 24. https://doi.org/10.1038/s41531-018-0061-5.
Wahner, A.D., Bronstein, J.M., Bordelon, Y.M., Ritz, B., 2007. Nonsteroidal anti-inflammatory drugs may protect against Parkinson disease. Neurology 69, 1836–1842. https://doi.org/10.1212/01.wnl.0000279519.99344.ad.
Wang, Z., Arat, S., Magid-Slav, M., Brown, J.R., 2018. Meta-analysis of human gene expression in response to Mycobacterium tuberculosis infection reveals potential

therapeutic targets. BMC Syst. Biol. 12, 3. https://doi.org/10.1186/s12918-017-0524-z.

Winklhofer, K.F., 2007. The parkin protein as a therapeutic target in Parkinson's disease. Expert Opin. Ther. Targets 11, 1543–1552. https://doi.org/10.1517/14728222.11.12.1543.

Wissemann, W.T., Hill-Burns, E.M., Zabetian, C.P., Factor, S.A., Patsopoulos, N., Hoglund, B., Holcomb, C., Donahue, R.J., 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. https://doi.org/10.1016/j.ajhg.2013.10.009.

Witoelar, A., Jansen, I.E., Wang, Y., Desikan, R.S., Gibbs, J.R., Blauwendraat, C., Thompson, W.K., Hernandez, D.G., Djurovic, S., Schork, A.J., Bettella, F., Ellinghaus, D., Franke, A., Lie, B.A., McEvoy, L.K., Karlsen, T.H., Lesage, S., Morris, H.R., Brice, A., Wood, N.W., Heutink, P., Hardy, J., Singleton, A.B., Dale, A. M., Gasser, T., Andreassen, O.A., 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. https://doi.org/10.1001/jamaneurol.2017.0469.

Yan, R., Liu, Z., 2017. LRRK2 enhances Nod1/2-mediated inflammatory cytokine production by promoting Rip2 phosphorylation. Protein Cell 8, 55–66. https://doi.org/10.1007/s13238-016-0326-x.

Yan, J., Fu, Q., Cheng, L., Zhai, M., Wu, W., Huang, L., Du, G., 2014. Inflammatory response in Parkinson's disease (Review). Mol. Med. Rep. 10, 2223–2233. https://doi.org/10.3892/mmr.2014.2563.

Yu, E., Ambati, A., Andersen, M.S., Krohn, L., Estiar, M.A., Saini, P., Senkevich, K., Sosero, Y.L., Sreelatha, A.A.K., Ruskey, J.A., Asayesh, F., Spiegelman, D., Toft, M., Viken, M.K., Sharma, M., Blauwendraat, C., Pihlstrøm, L., Mignot, E., Gan-Or, Z., 2021. Fine mapping of the HLA locus in Parkinson's disease in Europeans. npj Parkinsons Dis. 7, 1–7. https://doi.org/10.1038/s41531-021-00231-5.

Zhang, P., Katz, J., Michalek, S.M., 2009. Glycogen synthase kinase-3beta (GSK3beta) inhibition suppresses the inflammatory response to Francisella infection and protects against tularemia in mice. Mol. Immunol. 46, 677–687. https://doi.org/10.1016/j.molimm.2008.08.281.

Zhu, F., Li, C., Gong, J., Zhu, W., Gu, L., Li, N., 2019. The risk of Parkinson's disease in inflammatory bowel disease: A systematic review and meta-analysis. Dig. Liver Dis. 51, 38–42. https://doi.org/10.1016/j.dld.2018.09.017.

Zimprich, A., Biskup, S., Leitner, P., Lichtner, P., Farrer, M., Lincoln, S., Kachergus, J., Hulihan, M., Uitti, R.J., Calne, D.B., Stoessl, A.J., Pfeiffer, R.F., Patenge, N., Carbajal, I.C., Vieregge, P., Asmus, F., Müller-Myhsok, B., Dickson, D.W., Meitinger, T., Strom, T.M., Wszolek, Z.K., Gasser, T., 2004. Mutations in LRRK2 Cause Autosomal-Dominant Parkinsonism with Pleomorphic Pathology. Neuron 44, 601–607. https://doi.org/10.1016/j.neuron.2004.11.005.