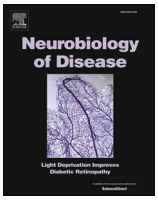
Neurobiology of Disease 169 (2022) 105724

Contents lists available at ScienceDirect

Neurobiology of Disease

journal homepage: www.elsevier.com/locate/ynbdi



LRRK2 as a target for modulating immune system responses

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ARTICLE INFO

Keywords:
LRRK2
Parkinson's disease
Immune system
Inflammation
Kinase inhibitors
Biomarkers

ABSTRACT

Mutations in the Leucine-Rich Repeat Kinase 2 (LRRK2) gene are associated with familial and sporadic cases of Parkinson's disease (PD) but are also found in patients with immune- related disorders, such as inflammatory bowel disease (IBD) and leprosy, linking LRRK2 to the immune system. Supporting this genetic evidence, in the last decade LRRK2 was robustly shown to modulate inflammatory responses at both systemic and central nervous system level. In this review, we recapitulate the role of LRRK2 in central and peripheral inflammation in PD and inflammatory disease models. Moreover, we discuss how LRRK2 inhibitors and anti- inflammatory drugs may be beneficial at reducing disease risk/progression in LRRK2-mutation carriers and manifesting PD patients, thus supporting LRRK2 as a promising disease-modifying PD strategy.

1. Introduction

The *LRRK2* gene, encoding Leucine-Rich Repeat kinase 2 (LRRK2), represents a common genetic cause of Parkinson's disease (PD), harboring both highly penetrant, rare missense mutations and common non-coding variants associated with PD risk (Kluss et al., 2019). Moreover, genetic variation in the *LRRK2* locus is associated with survival in progressive supranuclear palsy (PSP) (Jabbari et al., 2021). Despite the established role of LRRK2 in neurodegeneration, genetic variations in the *LRRK2* gene also modify the risk of inflammatory bowel disorders (IBD), such as Crohn's disease (CD) (Hui et al., 2018), and infectious diseases such as leprosy (Zhang et al., 2009). Interestingly, patients with IBD have a 35% increased risk of PD (Lin et al., 2016), while the *LRRK2* R1628P PD risk variant is protective in leprosy by reducing type-1 reaction and nerve damage (Fava et al., 2019). As such, *LRRK2* exerts pleiotropic effects on neurological, infectious and inflammatory disorders (Provenzano and Deleidi, 2021).

LRRK2 belongs to the family of ROCO proteins, characterized by the presence of the bidomain ROC (Ras of complex proteins) and COR (C-terminal of ROC). ROC functions as a GTPase with lower affinity for GTP compared to small GTPases (Wauters et al., 2019), whereas COR operates as a dimerization device (Cogo et al., 2022; Wauters et al., 2019). Another signaling output in LRRK2 is a serine-threonine kinase domain, which autophosphorylates LRRK2 *in cis* at multiple sites, including S1292 in vivo, and phosphorylates a subset of Rab GTPases to regulate a variety of vesicular trafficking events (Bonet-Ponce and Cookson, 2021; Sheng et al., 2012; Steger et al., 2016). Although the multilevel and bidirectional crosstalk between kinase and GTPase activities is not entirely understood, in the cellular milieu the GTPase activity is required to shuttle LRRK2 at the appropriate target compartments where the kinase can phosphorylate its substrates (Iannotta et al., 2020). LRRK2 also contains protein-to-protein interaction domains, covering scaffolding roles during signal transduction, e.g. recruitment by Rab29 via ANK domain at the trans-Golgi or stressed lysosomes (Purlyte et al., 2018) and association with synaptic vesicle proteins via WD40 domain (Cirnaru et al., 2014). PD-segregating mutations reside in the catalytic core of the protein and can affect either the kinase (G2019S and I2020T) or the GTPase (N1347H, R1441C/G/H and Y1699C) activities. Despite all mutations increase substrate phosphorylation as a common outcome, the tissue and substrate specificity vary depending on whether the

Abbreviation: LRRK2, leucine-rich repeat kinase 2; PD, Parkinson's disease; IBD, inflammatory bowel disease; CNS, central nervous system; ANK, ankyrin repeats; PSP, progressive supranuclear palsy; ROC, Ras of complex proteins; COR, C-terminal of ROC; SNpc, substantia nigra pars compacta; CD, Crohn's disease; PDE4, phosphodiesterase 4; NFATc2, nuclear factor of activated T cells cytoplasmic 2; KO, knock-out; iPD, idiopathic Parkinson's disease; PNS, peripheral nervous system; RBD, REM sleep behavior disorder; AAV, adeno-associated viral; NSAIDs, nonsteroidal anti-inflammatory drugs; PBMCs, peripheral blood mononuclear cells; BMDMs, bone marrow-derived macrophages; hiPSC, human induced pluripotent stem cells; LB, Lewy bodies.

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https://doi.org/10.1016/j.nbd.2022.105724
Received 16 February 2022; Received in revised form 7 April 2022; Accepted 8 April 2022
Available online 12 April 2022

mutation is in the kinase (G2019S) or in the ROC (R1441C/G) domain (Fan et al., 2021; Iannotta et al., 2020; Kluss et al., 2021), indicating a degree of pleiotropy, which is supported by the clinical and pathological heterogeneity across carriers of different LRRK2 mutations.

From the functional standpoint, LRRK2 has been linked to multiple cellular processes, including autophagy, endolysosomal pathways, synaptic vesicles trafficking, cytoskeletal dynamics and transcription/translation, through binding with a variety of interactors and phosphorylation of a subset of RAB GTPases (Bonet-Ponce and Cookson, 2021; Iannotta and Greggio, 2021). Furthermore, phosphorylation/dephosphorylation of Ser910 and Ser935 regulates binding with 14–3-3 proteins and LRRK2 subcellular localization (Nichols et al., 2010).

LRRK2 is expressed in multiple tissues and organs, with high expression levels in the brain, lungs, kidneys and circulating immune cells. Within the brain, LRRK2 is found in neurons, microglia and astrocytes, with high expression in medium spiny neurons of the striatum, which receive the dopaminergic projecting fibers from the substantia nigra pars compacta (SNpc) (Iannotta et al., 2020; West et al., 2014).

Here we review the role of LRRK2 in central and peripheral inflammation in PD and inflammatory disease models. We further discuss how LRRK2 inhibition and anti-inflammatory drugs may be beneficial at reducing disease risk/progression in LRRK2-mutation carriers and LRRK2-PD patients.

2. Role of LRRK2 in central and peripheral immune systems

In 2010, six years after the identification of *LRRK2* as a gene mutated in familiar PD (Paisán-Ruíz et al., 2004; Zimprich et al., 2004), Gardet and colleagues reported for the first time a link between LRRK2 and the immune system, showing that the kinase was highly expressed in inflamed intestinal tissues and relocalized to phagocytosed bacteria during macrophage infection (Gardet et al., 2010). This work was the prelude to a long series of studies which consolidated the function of LRRK2 as an immune response regulator both in the CNS and in the periphery (Lee et al., 2017). Although there are discordant results as to whether LRRK2 plays beneficial or detrimental roles during infection (Herbst and Gutierrez, 2019), the involvement of its activity in different steps of inflammatory signaling is unquestionable. In addition, the role of LRRK2 in inflammation is corroborated by genome-wide association studies (GWAS) which highlighted how *LRRK2* variants can increase or decrease the risk of IBDs (De Lange et al., 2017; Liu et al., 2015) and leprosy (Ahmadi Rastegar and Dzamko, 2020; Fava et al., 2016). Importantly, the N2081D variant, sitting closed to the hyperactive PD G2019S mutation, increases the risk for Crohn's disease (CD) through augmented kinase activity (Hui et al., 2018), overall suggesting that a chronic enhancement of systemic inflammation through abnormal LRRK2 activity in combination with other genetic or non-genetic co-factors (e.g. aging, environmental exposure, diet) can result in a disease condition.

Based on this genetic evidence, a number of studies explored the role of LRRK2 in immune cells and the impact of LRRK2 mutations in the inflammatory responses associated with PD. LRRK2 has been consistently detected, both under resting and stimulated conditions, across various subsets of peripheral and brain immune cells, comprising neutrophils, monocytes, dendritic cells, microglia and astrocytes (Ahmadi Rastegar and Dzamko, 2020). To date, it is well-established that LRRK2, through its kinase activity, controls several cellular pathways important for immune system functions such as secreting inflammatory mediators, phagocyting debris, pathogen and/or dying cells, and chemotaxis-mediated migration to sites of damage (Filippini et al., 2021; Lee et al., 2017; Russo et al., 2014a). Moreover, accumulating evidence reported that even LRRK2 GTPase function is implicated in the inflammatory response (Li et al., 2021, 2015, 2014), corroborating LRRK2 as a main player of the immune system.

2.1. Generation of inflammatory mediators

In microglia and astrocytes, LRRK2 carrying the hyperactive PD G2019S or R1441G mutation, leads to an increase of inflammatory cytokines and chemokines production in response to different challenges (Caesar et al., 2014; Gillardon et al., 2012; Ho et al., 2017; Russo et al., 2018; Sonninen et al., 2020). In contrast, LRRK2 knock-out (KO) (Kim et al., 2012, 2019; Russo et al., 2019, 2015) or pharmacological inhibition (Kim et al., 2019; Marker et al., 2012; Moehle et al., 2012; Munoz et al., 2015; Russo et al., 2015) has the opposite effect, indicating that LRRK2 kinase activity positively controls the generation of inflammatory mediators. To this regard, we demonstrated that LRRK2 regulates phosphodiesterase 4 (PDE4) activity and the levels of cAMP, thus modulating PKA-NFkB p50 inhibitory pathway and the consequent inflammatory response upon LPS or aggregated alpha-synuclein priming (Russo, 2019; Russo et al., 2018, 2015). In addition to PKA-NFkB signaling, it has been recently shown that LRRK2 promotes the inflammatory cascade through the activation of the nuclear factor of activated T cells cytoplasmic 2 (NFATc2) pathway (Kim et al., 2020). Interestingly, the involvement of LRRK2 in neuroinflammation has been confirmed also by in vivo studies. Transgenic mice with LRRK2 G2019S exhibited increased microgliosis, astrogliosis, neuroinflammatory response under PD pathological conditions (Bieri et al., 2019; Daher et al., 2015; Lin et al., 2009). In agreement with these findings, LRRK2 KO animals displayed attenuated neuroinflammatory effects upon different inflammatory challenges (Chen et al., 2018b; Daher et al., 2014; Puccini et al., 2015). Overall, these results position LRRK2 as a pro-inflammatory mediator in the CNS.

In contrast to what observed in brain cells, the direction of the effect that LRRK2 produces on inflammatory cytokines/chemokines generation is still under debate in systemic immune cells. In peripheral macrophages, pathogenic LRRK2 G2019S mutation (Moehle et al., 2015) or LRRK2 genetic deletion (Dzamko et al., 2012; Liu et al., 2011; Wandu et al., 2015) does not affect the secretion of LPS-driven inflammatory cytokines. Instead, dendritic cells with LRRK2 KO exhibited increased activation of NFkB pathway and inflammatory cytokines upon stimulation with LPS (Kubo et al., 2020), while LPS and zymosan stimulation of RAW264.7 murine macrophages reduces IL-10 release in T1348N-LRRK2 and LRRK2 KO (GTP-deficient binding) lines (Nazish et al., 2021). In agreement, LRRK2 GTP-binding inhibitors dampen the inflammatory response and TNFα release in peripheral lymphoblast cells (Li et al., 2021).

Conflicting results have been reported even in in vivo studies of systemic immune disorders. In animal models of colitis, both the overexpression of LRRK2 wild-type and its gene deletion have been shown to cause exacerbated colitis and increased inflammation (Liu et al., 2011; Takagawa et al., 2018). In a mouse model of sepsis, the G2019S mutation showed protection against bacterial infection (Shutinoski et al., 2019), whilst the same study showed that G2019S pups infected with reovirus-causing encephalitis exhibited higher mortality compared to control animals (Shutinoski et al., 2019), overall indicating that the exact relation between LRRK2 and peripheral immune system requires further investigation and that LRRK2 kinase activity may be beneficial or detrimental depending on the type of pathogen and inflammatory insult.

Collectively, LRRK2 seems to play distinct roles in immune cells in a cell-type dependent manner. Future research should aim at directly comparing immune cells from the periphery and CNS, from the same animals and under standardized experimental conditions.

2.2. Phagocytosis

Evidence for a role of LRRK2 in phagocytosis is contrasting. Independent studies showed that LRRK2 genetic (Kim et al., 2018; Panagiotakopoulou et al., 2020) and pharmacological inhibition attenuate microglial phagocytosis (Marker et al., 2012), while LRRK2 G2019S

pathological mutation enhances the ability of cells to phagocyte (Kim et al., 2018; Panagiotakopoulou et al., 2020), suggesting that LRRK2 positively modulates phagocytosis. Conversely, other groups showed that pathogenic LRRK2 G2019S (Moehle et al., 2015), LRRK2 deletion and pharmacological inhibition do not affect the phagocytic abilities of both brain and peripheral immune cells (Lee et al., 2020; Maekawa et al., 2016a; Schapansky et al., 2014), but rather impacts phagosome's maturation (Härtlova et al., 2018). To this regard, it has been shown that LRRK2 can affect phagosome formation and functionality via regulation of specific downstream Rab partners, including Rab5, Rab8 and Rab10 (Kim et al., 2018; Lee et al., 2020; Maekawa et al., 2016b). Specifically, LRRK2 KO microglia showed increased phagocytic function due to an increment of Rab5 positive endosomes (Maekawa et al., 2016b). While, in BMDM cells, LRRK2 G2019S-mediated activation of LRRK2-Rab5 pathway has been associated with an increased phagocytic activity (Kim et al., 2018). LRRK2 has been reported to recruit its RAB8a and RAB10 substrates also at maturing phagosomes in macrophages (Lee et al., 2020), in agreement with its recognized role in the downstream steps of vesicle delivery to the lysosome (Bonet-Ponce and Cookson, 2021). During mycobacterial infection and consequent phagosomal membrane damage, LRRK2-mediated Rab8a phosphorylation, but not Rab10, is increased, pointing to the existence of stimulus-specific responses (Herbst et al., 2020). Moreover, under pathogenic conditions, LRRK2 G2019S sequesters Rab8a to lysosomes dysregulating iron uptake in activated hiPSC-derived microglia, suggesting that LRRK2 can affect iron homeostasis during neuroinflammation (Mamais et al., 2021).

Thus, the state-of-the-art suggests that the impact of LRRK2 on phagocytosis is still unresolved and will require further investigation. Indeed, different particles (e.g. obsolete synapses, different bacteria or viruses, amyloid proteins) may stimulate different internalization pathways (e.g. clathrin-mediated vs. clathrin independent) and LRRK2 may play specific rather than general roles under defined conditions.

2.3. Migration

Several studies suggest the involvement of LRRK2 in the migration process that immune cells undertake to reach the site of injury or infection (Filippini et al., 2021; Russo et al., 2014b). In microglial cells, LRRK2 appears to negatively regulate cell motility and migration. Specifically, LRRK2 KO (Ma et al., 2016) or knock-down microglia (Choi et al., 2015) exhibited elevated migratory ability compared to wild-type cells. Accordingly, microglia isolated from LRRK2 G2019S transgenic mice displayed an attenuated motility compared to control cells, which is rescued by the treatment with LRRK2 GSK2578215A kinase inhibitor (Choi et al., 2015). In contrast to what observed in brain cells, peripheral macrophages with LRRK2 G2019S mutation displayed opposite effects with increased migration activity that is rescued upon LRRK2 kinase inhibitors (Moehle et al., 2015).

2.4. Effects of LRRK2 mutations

The two most common PD-linked LRRK2 mutations are the G2019S located in the kinase domain and the R1441C/G in the GTPase/ROC domain, with the majority of the studies focusing on these mutations. While the glycine-to-serine substitution at position 2019 within the kinase activation loop causes an enhancement of the kinase intrinsic activity by affecting the Vmax (Covy and Giasson, 2010), the R1441C/G mutations hamper GTP hydrolysis, resulting in an abnormal GTP-bound state and consequent prolonged access to and phosphorylation of cellular substrates. Accordingly, in brain and peripheral mouse tissues, LRRK2 G2019S displays increased autophosphorylation but normal substrate (Rab10) phosphorylation (GTPase activity is unaffected), whilst R1441C does not impact autophosphorylation but augments Rab10 phosphorylation (Fan et al., 2021; Iannotta et al., 2020; Kluss et al., 2021). Further supporting this model, the ROC-interacting kinase PAK6 phosphorylates 14–3-3 proteins reducing LRRK2-mediated Rab10 phosphorylation in wild-type and G2019S but not in R1441G expressing cells (Cogo et al., 2022). A R1441G specific effect on Rab10 phosphorylation has been recently confirmed in human peripheral blood neutrophils, suggesting that LRRK2 PD patients with R1441C/G mutations may mount a different inflammatory response as compared to G2019S patients (Fan et al., 2021). Neutrophils are phagocytic cells of the innate immune system that are quickly recruited to the site of infection upon pro-inflammatory signals during the acute phase of inflammation, especially during bacterial infections (Liew and Kubes, 2019). As LRRK2-dependent Rab10 phosphorylation and recruitment is needed for phagosome maturation (Lee et al., 2020), we can predict that R1441G displays enhanced phagocytosis in neutrophils compared to G2019S cells. A side-by-side comparison of G2019S vs. R1441C/G mutations in different immune cells may disclose mutation-specific effects and disease biomarkers. Of interest, this mutation-specific effect on Rab10 phosphorylation may be restricted to certain cell populations (e.g. immune cells) as phospho-T73-Rab10 levels in astrocytes carrying LRRK2-G2019S are nearly two-fold higher than wild type (Wang et al., 2021). The possibility that different LRRK2 mutations act through different mechanisms depending on the cell type is thrilling and clearly deserves further investigation, especially for the potential therapeutic implications. Indeed, a systemic inhibition of LRRK2 activity may not turn beneficial in the long run, considering the peripheral side effects observed in rodent and non-human primates (Fell et al., 2015; Fuji et al., 2015). Lowering LRRK2 activity only in tissues where LRRK2 mutations exert a gain of function effect (e.g. immune cells vs. neurons) may be the way to prevent or limit unwanted side effects. If future research further corroborates this scenario, targeting strategies for tissue-specific drug delivery may be needed (Zhao et al., 2020).

One important consideration to make is that, despite several studies nominated LRRK2 as a crucial regulator of microglia functions, independent investigations performed on mouse and human brain tissues failed to detect LRRK2 in microglial cells (Biskup et al., 2006; Dzamko, 2017; Dzamko et al., 2017; Higashi et al., 2007; Iannotta et al., 2020; Mandemakers et al., 2012; Sharma et al., 2011; Westerlund et al., 2008). These observations suggest that more work needs to be done to solve the discrepancy between in vitro and in vivo experimental models. To this regard, a recent preprint by Langston and co-workers may start to shed some light into the complex regulation of cell-type specific LRRK2 expression. The authors found that a non-coding risk factor variant in *LRRK2* confers an expression quantitative trait loci (eQTL) specifically in microglia and macrophages through epigenetic mechanisms (Langston et al., 2021). These findings may have a broader implication on the existence of a microglial-specific regulation of LRRK2 expression upon inflammatory or phagocytic stimuli, supporting the importance of investigating cell-type- and genotype-specific effect on individual cell populations.

3. Targeting LRRK2-linked inflammation as therapeutic approach: Cellular and preclinical studies

To date, it is well accepted that LRRK2 is a positive modulator of brain immune response; therefore, the potential anti-inflammatory properties of LRRK2 inhibitors are started to be considered as disease modifying treatment for PD. In this section, we briefly summarize cellular and preclinical studies assessing the ability of LRRK2 inhibitors, at both kinase and GTPase level, to mitigate the neuroinflammatory effects exerted by mutant LRRK2.

Compelling evidence demonstrated that microglial and astrocytic cells treated with different inhibitory molecules of LRRK2 kinase activity exhibited an attenuated inflammation in response to different challenges, such as LPS, HIV-1 protein, manganese and alpha-synuclein fibrils (Kim et al., 2020; Kluss et al., 2019; Marker et al., 2012; Moehle et al., 2012; Munoz et al., 2015; Russo et al., 2015). Moreover, LRRK2 pharmacological inhibition has been reported to prevent additional

immune cell functions, including the enhanced motility of microglia carrying LRRK2 G2019S mutation (Choi et al., 2015) and phagocytosis (Marker et al., 2012). Altogether, these findings indicate that LRRK2 kinase inhibition may prevent the pro-inflammatory response and its related effects under pathological conditions. Importantly, targeting LRRK2-related inflammation has been proven beneficial when translated in preclinical models. Van der Perren et al., (Van der Perren et al., 2021) observed a significant attenuation of alpha-synuclein–induced neuroinflammation, with reduced microglial activation and $CD4^+$ and $CD8^+$ T cell infiltration, in the adeno-associated viral (AAV) vector-based PD model treated with the third generation, type I LRRK2 kinase inhibitor MLi-2. In an earlier study, Daher and colleagues showed that the exacerbated neuroinflammation and neurodegeneration observed in the G2019S-LRRK2 transgenic rats could be mitigated by administration of the second generation PF-06447475 LRRK2 inhibitor (Daher et al., 2015), further confirming that lowering LRRK2 kinase activity has an anti-inflammatory effect.

Recent studies showed that also the modulation of LRRK2 GTPase activity, which orchestrates kinase activity in cells (Cogo et al., 2022), may be beneficial for the brain immune system. Two studies by Wanli Smith and co-workers reported that inhibition of LRRK2 GTP binding, through compound 68 and its novel analog FX214, results in attenuation of the neuroinflammatory response and related neurodegeneration in G2019S-LRRK2 BAC transgenic mice after LPS-induced priming (Li et al., 2015, 2014). With the caution in mind that GTP competitive inhibitors have more off-target effects compared to ATP competitors (Cox et al., 2014), at least in small GTPases, these observations strengthen the idea that LRRK2-linked inflammation could represent a therapeutic target for diseases with a neuroinflammatory component. Moreover, the discoveries that pharmacological inhibition of LRRK2 can be neuroprotective in preclinical models of PD (Chan and Tan, 2017; Chen et al., 2018a) and appears safe after phase I clinical evaluations (Tolosa et al., 2020), place LRRK2 at the center of disease modifying PD strategies. However, it should be considered that, despite intense research effort over the past decade, the contribution of LRRK2 in peripheral and brain inflammation remains to be validated in human tissues that may differ with diverse aspects from rodents.

4. Lowering inflammation as a therapeutic avenue in LRRK2-linked PD?

Neuroinflammation and impaired immune system responses have been robustly linked to PD and are thought to represent critical components of PD susceptibility and progression (Tan et al., 2020). A first evidence comes from genetic and bioinformatic studies, which highlighted that PD and autoimmune and/or inflammatory diseases share common genes and pathways (Tan et al., 2020). Second, brain imaging revealed the presence of activated microglia in PD brain patients (Gerhard et al., 2006). Third, alterations in the microbioma, by influencing the inflammatory state of the gut, affect neuronal health through the gut-brain connections of the enteric system (Houser and Tansey, 2017). Last, anti-inflammatory drugs were shown be protective against PD (Gagne and Power, 2010) although other studies failed to replicate this association (Poly et al., 2019).

With respect to LRRK2-PD, we already discussed the vast genetic evidence linking the kinase with immune-related and inflammatory disorders (Wallings et al., 2020). Increased peripheral inflammatory markers has been reported in a PD cohort with LRRK2 G2019S and LRRK2 R1441G carriers (Brockmann et al., 2016; Dzamko et al., 2016) and, importantly, in a cohort of asymptomatic LRRK2 G2019S carriers (Dzamko et al., 2016). Moreover, neuroimaging studies reported nigrostriatal dysfunction and neuroinflammation in LRRK2 non-manifesting carriers (Gersel Stokholm et al., 2020). These observations support the possibility of early treatments with LRRK2 inhibitors in individuals with a positive family history for LRRK2 mutation combined with signs of neuroinflammation. To this regard, type I LRRK2 inhibitors (BIIB122/DNL151) are under clinical evaluation and already met safety and biomarker goals in phase I trials (ClinicalTrials.gov; NCT04056689). If approved, these molecules could be used as personalized therapies for LRRK2 mutation carriers and, possibly, for other PD patients affected by a neuroinflammatory phenotype combined with enhanced LRRK2 activity. In this context, recent studies showed that idiopathic PD (iPD) patients present enhanced LRRK2 activity (Di Maio et al., 2018) and LRRK2 inhibition prevents endolysosomal defects in iPD patient cells (Rocha et al., 2020), supporting the possibility of extending LRRK2-based therapies to iPD patients with enhanced LRRK2 function. One important caveat of ongoing LRRK2 trials is that target engagement is assessed by measuring decreased pRab10 and pS935-LRRK2 in PBMCs or whole blood cells (ClinicalTrials.gov; NCT04056689). Whether these pharmacodynamic readouts genuinely reflect LRRK2 activity in the CNS of subjects administered with the inhibitor is unclear. Of potential concern, phosphorylation of Rab10 is insensitive to LRRK2 inhibition in the brain of knock-in G2019S mice, while it fully responds in peripheral organs (Kluss et al., 2021). Conversely, pRab12 appears a more reliable biomarker of LRRK2 kinase activity in the mouse CNS (Kluss et al., 2021). This observation highlights the importance of identifying biomarker readouts in the blood that are tightly coupled with LRRK2 activity in the brain.

Given the established role of LRRK2 in gut inflammation, one interesting question to ask is whether LRRK2-PD starts from the periphery and later spread into the CNS through the enteric neuron connections. Alpha-synuclein is the major component of Lewy bodies (LBs), complex intraneuronal inclusions present in the SNpc and other brain regions of patients with PD and other synucleinopathies (Spillantini et al., 1997). However, according to the dual-hit-hypothesis (Hawkes et al., 2007), alpha-synuclein pathology may not start in the brain, but rather initiate in the olfactory bulb and digestive tract and then spread into the CNS by retrogradely travelling through the peripheral nervous system (PNS) connections. Although some PD patients exhibit a PNS-first phenotype which results in a REM sleep behavior disorder (RBD) when the pathology reaches the CNS, others present with a CNS-first phenotype where RBD is typically absent (Borghammer and Van Den Berge, 2019). Interestingly, RBD is not a common feature in early G2019S LRRK2-PD (Saunders-Pullman et al., 2015) arguing against the periphery-to-center spread of the pathology.

Of interest, while the clinical presentation of LRRK2-PD is similar to that of sporadic PD, the pathology is more variable and not always characterized by the presence of LBs. Intriguingly, absence of LBs correlates with the presence of motor phenotype, whereas non-motor symptoms such as dementia, anxiety, and orthostatic hypotension are more likely to occur in patients positive for LBs (Kalia et al., 2015). Strikingly, depositions of tau, typically present in Alzheimer's disease and other tauopathies, were shown to be more common than LBs (Henderson et al., 2019), suggesting that LRRK2-PD may intersect with other neurodegenerative pathologies.

Future studies examining the presence of alpha-synuclein and tau depositions in the gastrointestinal tract of LRRK2-PD patients and pre-symptomatic carriers will help defining the potential contribution of peripheral LRRK2 activity in pathology spreading. It is also possible that LRRK2-mediated peripheral inflammation triggers neuroinflammation by promoting the infiltration of peripheral macrophages or by increasing the amount circulating pro-inflammatory mediators that stimulate the transition of microglia and astrocytes into their reactive state leading to dopaminergic neuron degeneration. Supporting the former mechanism, West and collaborators found that pathological alpha-synuclein recruits monocytes infiltrating from the periphery to the brain through increased LRRK2 expression and Rab10 phosphorylation (Xu et al., 2022). Regarding the latter, Kozina et al. (Kozina et al., 2018) found that LPS-induced nigral loss in LRRK2 mutant mice is triggered by circulating pro-inflammatory molecules released by peripheral leukocytes rather than infiltrating cells or resident microglia. Supporting these findings, LRRK2 is highly expressed in neutrophils, monocytes and macrophages (Hakimi

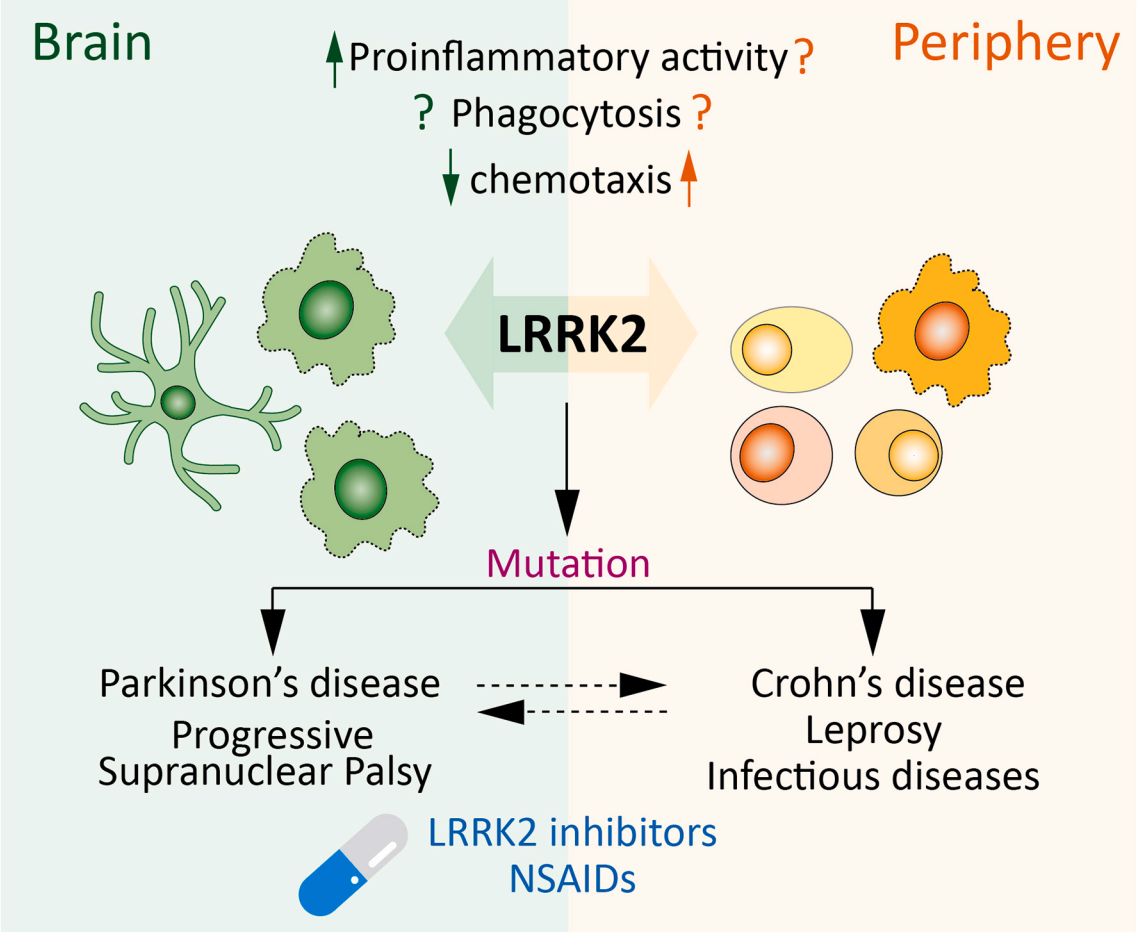

Fig. 1. LRRK2 regulates different cellular processes related to inflammation, including production of inflammatory mediators, phagocytosis and chemotaxis. However, central versus peripheral LRRK2 activity seems to impact these processes differently, although a uniform consensus is still lacking. Mutations in LRRK2 cause PD and modify risk for PSP while gene variant can predispose to systemic inflammatory diseases such as Crohn's disease and Leprosy. LRRK2 targeted therapies and nonsteroidal anti-inflammatory drugs hold the potential to act as disease modifying treatments by correcting the abnormal inflammatory component associated with LRRK2-PD.

et al., 2011; Wallings and Tansey, 2019). Moreover, LRRK2 levels in monocytes and B cells are increased in patients with PD (Cook et al., 2017).

Although the scenario is still not fully resolved, the role of LRRK2-dependent inflammation as a contributing factor in PD is supported by multiple evidence. However, if LRRK2 inhibitors impair the capacity of the kinase to trigger an appropriate immune response against infections, the side-effects could overweigh the benefits especially for those patients with a compromised immune system. Thus, personalized therapies with LRRK2 inhibitors or antisense oligonucleotides (BIIB094; NCT03976349) not only should consider the genetic (LRRK2-PD) or biomarker (iPD with increased LRRK2 activity) information but also the presence of comorbidities or preexisting conditions that result in patient immunodeficiency.

Further supporting the beneficial role of reducing inflammation in LRRK2-PD, a recent report highlighted that non-manifesting LRRK2 carriers are at reduced risk of PD if chronically treated with nonsteroidal anti-inflammatory drugs (NSAIDs) (San Luciano et al., 2020). Importantly, not only G2019S but also R1441C/G and risk variant carriers are protected by the regular use of ibuprofen or aspirin. Thus, NSAIDs may be useful as disease-preventing treatments for LRRK2 mutation carriers and disease-modifying treatments for manifesting LRRK2-PD patients. It is important to note that while the long term effects of chronic treatment with LRRK2 inhibitors are unknown at the moment (phase II clinical trials are ongoing), studies in rodents and non-human primates highlighted pulmonary side effects (Fell et al., 2015; Fuji et al., 2015). The therapeutic use of NSAIDs could therefore represent a potential alternative or complementary treatment to LRRK2 targeting therapies that may be beneficial for specific subgroups of PD patients.

5. Conclusions

Although the current literature appears to suggest that LRRK2 plays an opposite role in brain and peripheral immune cells, an overwhelming amount of data support LRRK2 as a positive regulator of neuroinflammation and that LRRK2-dependent inflammation could be a contributing factor in PD. Moreover, the important discoveries that LRRK2 inhibition or anti-inflammatory drugs can reduce the risk to develop/advance the disease place LRRK2 as a promising disease-modifying strategy for LRRK2-linked PD and iPD with enhanced LRRK2 function (Fig. 1). In this regard, ongoing and future clinical trials outcomes will help to understand the safety of chronic treatment with LRRK2 inhibitors and the potentiality of LRRK2 inhibition as a PD-modifying target.

Declaration of Competing Interest

None.

Acknowledgements

We are grateful for the financial support of the Michael J Fox Foundation (to E.G.), Italian Ministry of Research MUR (PRIN 2018 to L. B.), CARIPLO Foundation (grant ID: 2016-0428 to I.R.), Italian Ministry of Health (GR-2016-02362548 to I.R.) and Regional Foundation for Biomedical Research (grant ID:1737591 to I.R.).

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