LRRK2 in Infection: Friend or Foe?

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**ABSTRACT:** In the field of Parkinson’s disease (PD) research, leucine-rich repeat kinase 2 (LRRK2) remains one of the most enigmatic kinases. LRRK2 pathogenic mutations result in increased kinase activity, making LRRK2 an attractive therapeutic target for PD. For over 10 years, the identification of a bona fide substrate and a physiological function for LRRK2 has been elusive, and only recently, Rab GTPases were identified as substrates for LRRK2 kinase activity. Additionally, LRRK2 gene expression data shows that LRRK2 is expressed at low levels in neurons and at high levels in cells of the immune system. These findings shifted research efforts from neuronal toxicity of LRRK2 mutations to the function of LRRK2 in both vesicle trafficking and the immune system, which has resulted in novel insights into the role of LRRK2 during infection and immunity. In this Perspective, we summarize the latest findings highlighting LRRK2 as a central regulator of vesicular trafficking, infection, immunity, and inflammation, speculating how LRRK2 function could influence neuronal pathology in PD.

**KEYWORDS:** LRRK2, infection, inflammation, Parkinson’s disease, tuberculosis

In the field of Parkinson’s disease (PD) research, leucine-rich repeat kinase 2 (LRRK2) remains one of the most enigmatic kinases. LRRK2 pathogenic mutations result in increased kinase activity, making LRRK2 an attractive therapeutic target for PD. For over 10 years, the identification of a bona fide substrate and a physiological function for LRRK2 has been elusive, and only recently, Rab GTPases were identified as substrates for LRRK2 kinase activity. Additionally, LRRK2 gene expression data shows that LRRK2 is expressed at low levels in neurons and at high levels in cells of the immune system. These findings shifted research efforts from neuronal toxicity of LRRK2 mutations to the function of LRRK2 in both vesicle trafficking and the immune system, which has resulted in novel insights into the role of LRRK2 during infection and immunity. In this Perspective, we summarize the latest findings highlighting LRRK2 as a central regulator of vesicular trafficking, infection, immunity, and inflammation, speculating how LRRK2 function could influence neuronal pathology in PD.

**ELUSIVE FUNCTION OF THE KINASE LRRK2**

LRRK2 is a large multidomain protein that includes, among other domains, a kinase and a GTPase domain. Since its identification, evidence shows that mutations in the LRRK2 gene are associated with both familial and idiopathic forms of PD. Disease-causing mutations cluster in the kinase and GTPase domain, and it is now widely accepted that they result in gain-of-function of the kinase, indicating that alterations in enzymatic activity underlie disease progression. The most common mutation associated with PD, G2019S, is found in ~5% of familial PD cases in Europe and North America and can be detected in up to 20–40% of PD patients of Ashkenazi Jewish or Berber Arab ancestry. Because of its prevalence and the strong link between LRRK2 kinase activity and PD, LRRK2 represents an attractive therapeutic target and several pharmaceutical and biotech companies have ongoing drug discovery programs to develop selective LRRK2 kinase inhibitors for PD treatment.

From the viewpoint of fundamental biology, however, the precise molecular and cellular function of LRRK2 still remains elusive. Only recently, Rab GTPases were identified as bona fide substrates that are phosphorylated by LRRK2, confirming previous reports connecting LRRK2 and intracellular trafficking.

Gene and protein expression data show that LRRK2 is highly expressed in cells of the immune system, in particular myelocytic cells. Altogether, these studies support the idea that LRRK2 is primarily implicated in intracellular trafficking and immunity, opening a new perspective in the context of the immunological component of PD pathology. The idea of an association between LRRK2 and inflammation was primarily based on a genome wide association study showing that genetic polymorphisms in LRRK2 are associated with multibacillary leprosy. Leprosy reactions are acute immune-related inflammatory episodes against *M. leprae* that occur during the chronic course of leprosy. These reactions predominated in individuals classified as multibacillary and are responsible for irreversible nerve damage. Subsequently,

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studies in the Han Chinese population confirmed that LRRK2 is a susceptible gene in leprosy. 8

- LRRK2 FUNCTION IN INTRACELLULAR TRAFFICKING: Rab GTPases LEAD THE WAY

Eukaryotic cells differ fundamentally from prokaryotes by possessing internal membranous compartments: the organelles. Intracellular organelles are spatially segregated but functionally connected by the trafficking of different cargos from one compartment to another by the processes of membrane fusion and fission. The control of trafficking events between organelles is critical for the majority of cellular responses that are regulated by a family of small GTPases, Rab proteins. LRRK2 is functionally associated with a number of intracellular pathways such as endocytosis, phagocytosis, and autophagocytosis as well as lysosomal and retromer function.7 LRRK2 is implicated in intracellular trafficking via regulation of several Rab GTPases such as Rab7, Rab29, and Rab32. However, in these studies, the link between LRRK2 kinase activity and Rab protein function was not entirely clear.10,11 The identification of Rab GTPases as physiological LRRK2 substrates was a major breakthrough in the LRRK2 research field1 and provided a mechanistic link between LRRK2 and vesicle trafficking. Functionally, these findings argue that LRRK2 modulates a distinct set of Rab GTPase effector functions by regulating effector binding. This study also implies that LRRK2 might regulate processes that are beyond the currently described roles of these Rab GTPases in endocytosis, exocytosis, and membrane recycling. More importantly, these observations opened the possibility to indirectly monitor LRRK2 activation by measuring Rab GTPase phosphorylation. Several Rab proteins were identified as substrates of LRRK2 such as Rab8, Rab10, Rab12, and Rab35, implying that LRRK2 might control a significant number of intracellular pathways ranging from endocytosis to autophagocytosis and phagocytosis.12 Whereas it is clear that different subsets of Rab GTPases can be phosphorylated by LRRK2,5,13 how exactly phosphorylation by LRRK2 regulates vesicular trafficking is less clear. For example, only a minor fraction of the Rab intracellular pool is phosphorylated, and it has been reported that over 50 Rab proteins are phosphorylated by LRRK2. Some of the implicated Rab proteins such as Rab8A are widely expressed in both immune and nonimmune cells, but others such as Rab43 show a cell-type specific expression pattern.14,15 This strongly suggest a cell-type specific spatiotemporal control of Rab GTPase phosphorylation (see below), and further studies in this area will shed light into this.

- LRRK2 ROLE IN BACTERIAL INFECTION: BENEFIT OR DRAWBACK?

Vesicular trafficking and Rab GTPase function is critical for the development of the immune response.15 It was therefore thought that LRRK2 may have a role in vesicle-trafficking-dependent immune responses. One of the key pathways of the innate immune response to pathogens is phagocytosis, where professional phagocytes ingest bacterial pathogens and deliver them along the phagosomal pathway to lysosomes for degradation. LRRK2 is highly expressed in macrophages but also in dendritic cells and neutrophils, suggesting that increased LRRK2 activity may regulate immune function during infection.

In recent years, several studies implicating LRRK2 in infection emerged, in particular in response to bacterial pathogens. One of the first studies that experimentally examined the function of LRRK2 in innate immunity found that LRRK2 contributes to the restriction of the enteric pathogen Salmonella by macrophages in vitro.16 This finding was confirmed in vivo by demonstrating that mice lacking LRRK2 are more susceptible to peritoneal inflammation, resulting in impaired control of Salmonella and increased mortality of infected mice.17 This study also investigated the effect of the LRRK2 kinase inhibitor GSK2578215A in vivo and demonstrated that LRRK2 kinase inhibition increases mouse susceptibility to Salmonella infection.17 Similarly, LRRK2 knockout (KO) mice showed increased susceptibility to oral but not systemic infection with the foodborne pathogen Listeria monocytogenes18 (Table 1).

| Table 1. Empirical Evidence of LRRK2 Association with Bacterial Infections |
|-----------------|-----------------|-----------------|-----------------|
| pathogen        | main cells      | LRRK2 function  | inflammatory profile |
| Salmonella      | macrophages     | restriction      | reduced IL-1B (LRRK2 KO) |
| Mycobacterium   | macrophages     | permissive       | high Type II IFN and low Type I IFN (LRRK2 KO) |
| tuberculosis    | (lung)           |                  |                  |

In contrast to enteric pathogens, inhibitors of LRRK2 kinase activity enhanced restriction of the intracellular pathogen Mycobacterium tuberculosis by human and mouse macrophages.19 Macrophages lacking LRRK2 were able to control M. tuberculosis significantly better when compared to wild type macrophages.19 In agreement with a permissive role of LRRK2, LRRK2 KO mice infected via aerosol with M. tuberculosis showed an early protective effect against the infection.19 Thus, the absence of LRRK2 seems to be beneficial for the host and results in M. tuberculosis control in vitro and in vivo (Table 1). These apparently contradicting results could be due to different functions of LRRK2 in cell types other than macrophages that are important for the control of fast growing Gram-negative pathogens in the gut, such as Paneth cells. Potential differences in LRRK2 function between gut immune cells and, for example, resident tissue macrophages could be of special interest since single-nucleotide polymorphisms (SNPs) in LRRK2 contribute to chronic inflammatory diseases in the gut such as Crohn’s disease and ulcerative colitis (see below).

It will be interesting to define if increased susceptibility of the LRRK2 KO mice to Salmonella and Listeria infection translates into protection by LRRK2 gain-of-function mutations such as the G2019S mutation. Since some of the pathogenic mutations in LRRK2 are very prevalent in human populations, it is tempting to speculate that gain of function mutations in LRRK2 are protective against certain types of infection in specific human populations and might therefore have constituted an evolutionary advantage.

- TOWARD A CELL TYPE-SPECIFIC LRRK2 FUNCTION?

As mentioned earlier, immune cells express LRRK2 at variable and relatively high levels. Additionally, activation of immune receptors such as Toll-like receptors (TLRs) regulates LRRK2...
phosphorylation and LRRK2 localization to membranes.\textsuperscript{20,21} Elucidating cell type-specific mechanisms of LRRK2 activation and function is therefore crucial to define if the response to bacterial pathogens is similarly affected by LRRK2-mediated alterations in immune function.

In macrophages, the increased susceptibility of mice lacking LRRK2 to \textit{Salmonella Typhimurium} infection is associated with the reduced activation of the NLR family CARD domain-containing protein 4 (NLRC4) inflammasome and failure to mount an appropriate inflammatory response.\textsuperscript{17} LRRK2 interacts and phosphorylates the NLRC4 inflammasome, suggesting a Rab GTPase-independent mechanism of action.\textsuperscript{17}

In brain macrophages (microglia), LRRK2 also regulates phagocytosis of latex bead particles and \textit{E. coli} via interactions with actin regulator Wiskott-Aldrich syndrome protein-family verproline (WAVE).\textsuperscript{15} However, this seems to be dependent on the macrophage type and the phagocytic target since other studies have reported either no effect or increased phagocytosis.\textsuperscript{19} Moreover, LRRK2 regulates lysosomal function and phagosome maturation in macrophages, since lysosomes of macrophages lacking LRRK2 are more proteolytic and contain higher levels of lysozyme.\textsuperscript{19} Phagosomes from macrophages lacking LRRK2 contain low levels of PI3P associated with a deficient recruitment of the Class III phosphatidylinositol-3 kinase complex, a well-known regulator of phagosome maturation.\textsuperscript{19} LRRK2 is functionally associated with autophagy, an important innate immune mechanism.\textsuperscript{23,24}

However, the altered phagosome maturation phenotype seems to be independent of autophagic targeting of \textit{M. tuberculosis}, suggesting a specific function for LRRK2 on phagosomal membranes. It is possible that altered recruitment of Rab GTPases and their effectors are able to modulate lipid signaling and organelle function. However, the mechanism underlying the LRRK2-dependent regulation of phosphoinositide levels and signaling on endolysosomal membranes remains to be further investigated.

Paneth cells are secretary immune cells of the gut important for the control of intestinal bacteria.\textsuperscript{16} The susceptibility of LRRK2 KO mice to \textit{L. monocytogenes} gut infection is due to the defective sorting of the antibacterial enzyme lysozyme in these cells. LRRK2 regulates lysozyme sorting via Rab2a recruitment into secretory vesicles, in agreement with the idea that Rab GTPases are LRRK2 substrates. Given the pleiotropic effects of LRRK2 function in different cell types, we argue that LRRK2 most likely has cell type-specific functions as differential Rab GTPase subsets are present in different cells, thereby allowing LRRK2 to regulate distinct vesicle trafficking pathways.

LRRK2 is expressed in additional immune cells that have a major impact on pathogen control during infections, such as dendritic cells and neutrophils.\textsuperscript{26} but so far, the role of LRRK2 in pathogen restriction in these cells is poorly characterized. There is some indication that mouse neutrophils lacking LRRK2 display impaired migratory and antimicrobial responses, and interestingly, idiopathic PD patients have increased neutrophil LRRK2 levels.\textsuperscript{26} Given the abundance of neutrophils and their importance during the acute phase of pathogen control and the crucial role of dendritic cells in the induction of adaptive immune responses, these aspects of potential LRRK2 function during immune responses represent an exciting field of research in the future.

Collectively, a growing body of evidence highlights the pleiotropic effect of LRRK2 on vesicle-mediated trafficking pathways and links this kinase to immunity and infection. Outcomes of LRRK2 kinase inhibition on immunity to pathogens might depend on the cell type or organ, as vesicle trafficking pathways play different roles in response to extracellular and intracellular pathogens and might be cell-type specific. Therefore, it is tempting to postulate that there is an organ-specific function for LRRK2. During gut immunity, LRRK2 could be implicated in secretion of antimicrobial components important in the response to bacterial pathogens in the gut whereas, in lung immunity, LRRK2 could function at the intracellular level in alveolar macrophages or dendritic cells that will contribute to the immune response.

### LRRK2 AND INFLAMMATION: BIRDS OF A FEATHER

There is data showing elevated levels of pro-inflammatory cytokines in blood from patients with several forms of PD. Although the changes in cytokine levels are relatively small, the results are consistent with inflammation of the peripheral and central nervous system in PD patients with or without LRRK2 association.\textsuperscript{27}

There is also considerable evidence, mostly coming from animal models, that neuronal degeneration and inflammation are linked.\textsuperscript{28} PD is a complex disease that results from the interplay between genetic predisposition and possibly external triggers. Clinical data suggest that a causative factor could be the inflammation caused by bacterial or viral infections.\textsuperscript{29} In the clinics, PD patients with viral and bacterial infections show marked motor and cognitive deterioration.\textsuperscript{29} Additionally, anti-
TNF-α (TNF-α, tumor necrosis factor alpha) therapy in inflammatory bowel disease (IBD) patients greatly reduced their risk of developing PD, further strengthening the possible causal link between peripheral inflammation and neurodegeneration in PD50 (Figure 1).

More recently, mutations in the LRRK2 gene have also emerged as a risk factor for inflammatory bowel disease (IBD) and Crohn’s disease (CD), which is characterized by aberrant inflammatory processes.31 The N2081D LRRK2 mutation, associated with increased CD risk, is similar to the PD associated G2019S mutation, located in the kinase domain and believed to increase kinase activity.31 Additionally, the PD G2019S mutation was associated with increased CD risk in an Ashkenazi Jewish patient cohort,32 suggesting the presence of shared LRRK2 alleles in CD and PD. This may have major implications for the treatment of these diseases and provide crucial information on cross-talks between chronic inflammation and PD. The dysregulation of inflammatory processes in LRRK2 mutation carriers is enigmatic and may be either causal or consequential to PD and IBD disease development. Given that changes in the microbiota are associated with inflammation, another potential link between LRRK2 and inflammation is the reported alterations on gut microbiome in PD patients33 and in mouse models of PD.34

LRRK2 activates the NLRC4 inflammasome as well as the pro-inflammatory transcription factors nuclear factor of activated T-cells (NFAT) and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB). However, the function of LRRK2 in pro-inflammatory signaling after immune stimulation seems to depend on the context. Despite the finding that TLR2 and TLR4 stimulation induces LRRK2 phosphorylation on S935, LRRK2 KO macrophages do not have an altered pattern of pro-inflammatory cytokines secretion after TLR2 or TLR4 stimulation,30 indicating that LRRK2 function might be regulated by PAMP signaling without affecting downstream cytokine responses. Similarly, other studies did not observe significant differences in cytokine secretion in LRRK2 KO or LRRK2 overexpressing mouse dendritic cells in response to TLR2 or TLR4 stimulation.34 However, there were increased cytokine responses to the dead yeast particle zymosan, a TLR2, and Dectin-1 ligand in dendritic cells.35 This was explained by an increased NFAT-dependent inflammatory response to Dectin-1 stimulation. This effect seems to be independent of LRRK2 kinase activity, suggesting a “scaffold” function for LRRK2 in this context.36

On the other hand, when LRRK2 is overexpressed in mouse dendritic cells, a system that is functionally more akin to carrying a LRRK2 gain-of-function mutations, a substantial increase in pro-inflammatory responses and NFAT activation is observed.35 These findings suggest that LRRK2 kinase activity could be the driving factor behind the production in inflammatory cytokines. In agreement with this notion, LRRK2 kinase inhibitors efficiently reduce TNF-α responses to zymosan, although at very high concentrations.36 It is likely that differences in cellular systems account for these discordant observations in dendritic cells, and more studies are required to define the role of immune cell activation in LRRK2 function.

LRRK2 regulates the secretion of the anti-inflammatory cytokine IL-10 (IL, interleukin) in mouse macrophages after infection with M. tuberculosis but had very little effect on inflammatory cytokines such as TNF-α or IL-6.37 M. tuberculosis is able to trigger Dectin-1 signaling in macrophages and activate similar signaling pathways as fungi.37 During chronic M. tuberculosis infection in mice, the absence of LRRK2 results in enhanced secretion of pro-inflammatory cytokines, with high levels of IFN-γ (IFN, interferon) but an almost complete absence of the Type I IFN-α.19 Most likely, these results are not a direct consequence of LRRK2 affecting transcription factor activation but might be related to a downstream alteration in pathogen clearance or eventually communication between immune cells. Therefore, if the pro-inflammatory LRRK2-dependent responses in vivo are the cause or a consequence that leads to pathology requires further investigation. LRRK2 is also required for NLRP3 inflammasome activation and competent IL-1β secretion in response to Salmonella Typhimurium infection.17 NLRP4 inflammasome activation was LRRK2 kinase-dependent as it was reduced by kinase inhibitor treatment and absent when LRRK2 kinase-dead mutants were expressed. Accordingly, expression of the G2019S LRRK2 mutant resulted in aberrant NLRP4 inflammasome activation.17

Altogether, these data clearly support the idea that LRRK2 contributes to cytokine-mediated inflammatory responses. Evidence showing a formal demonstration of an anti-inflammatory effect for LRRK2 kinase inhibitors is limited, and further studies are needed to define the effect of LRRK2 kinase activity on inflammation. Of interest, current data indicates that LRRK2 might be only affecting selected signaling pathways, such as C-type lectin receptor responses or specific inflammasome signaling pathways. Since phagolysosomes constitute major signaling platforms that orchestrate intra-cellular receptor activation and cytokine responses, it is possible that the role of LRRK2 on inflammation can be related to its vesicular function.

LRRK2 AS A THERAPEUTIC TARGET IN BOTH PD AND INFECTIOUS DISEASES?

Because it is now accepted that LRRK2 can modulate immune responses, the effect of LRRK2 inhibitors on the immune system and the response to infection needs to be carefully considered and studied. For example, it is critical to define whether LRRK2 kinase inhibition results in either an increased risk to or protection from infection in relevant animal models. The current knowledge is restricted to a limited group of bacterial pathogens, and the outcome of LRRK2 kinase inhibition on infection with viral or fungal pathogens is poorly characterized. Because LRRK2 can be activated downstream of C-type lectin receptors, such as the primary pattern recognition receptors for fungal pathogens Dectin-1, this might be of special importance. Similarly, the reduced Type-I IFN responses to M. tuberculosis raises the question if LRRK2 inhibitors could be useful as a drug target beyond PD. In the context of infection and inflammation, the condition that LRRK2 kinase inhibitors need to cross the blood brain barrier, a bottleneck for many suitable kinase inhibitors in PD, could be less important for systemic treatment.

After a decade of research, LRRK2 kinase inhibitors are entering clinical trials for PD. The small molecule LRRK2 inhibitor DNL201 from Denali Therapeutics was shown to be safe in an acute dose-escalation study with healthy volunteers.38 Results are very promising and indicate that treatment with DNL201 is able to inhibit LRRK2 without side effects in

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humans. Although this is a relatively small trial in healthy individuals and potential side effects of long-term LRRK2 kinase inhibition remain unknown, the results suggest that acute inhibition of LRRK2 is not increasing the risk of systemic infection. Initial studies in animal models using LRRK2 inhibitors raised some safety concerns by demonstrating a size increase in type-II alveolar pneumocytes and an intracellular accumulation of multivesicular bodies. However, in humans, heterozygous loss-of-function mutations of LRRK2 have been reported, resulting in a 50% reduction in LRRK2 protein levels and, so far, have not been associated with increased risk of disease.

Studies demonstrating LRRK2 activation in patients with idiopathic PD or other PD causing mutations in proteins other than LRRK2 such as the vacuolar protein sorting-associated protein 35 (Vps35) D620N raised the prospect of a common disease mechanisms in PD and broader application potential of LRRK2 kinase inhibitors. Data showing a function for LRRK2 in the endo-phago-lysosomal pathway highlights the convergence of LRRK2 regulation of lysosomal function in both infection and PD. Alterations in lysosomal functions are well established as an underlying cause for neurodegenerative diseases, and in the case of PD, lysosomal dysfunction is becoming more accepted as a major risk factor for developing disease. It is likely that LRRK2 feeds into common intracellular pathways during infection and PD. As such, the study of LRRK2 function in infectious disease might be informative about PD disease etiology (Figure 1).

The studies discussed here contribute to the idea that inflammation can represent a therapeutic target in LRRK2-associated PD. Successful immunotherapeutic approaches for PD have yet to be developed, but targeting the immune response in patients with the onset of PD symptoms could represent an advantageous strategy to explore in the future. One of the main challenges for the upcoming period of LRRK2 research in the context of infection is to define the physiological activators of LRRK2 signaling in immune cells. Given that LRRK2 is highly expressed in these cells, an attractive idea is that microbial infections or even microbially dysregulation as in IBD could trigger certain forms of PD in patients with a predisposed genetic background. Novel and potent LRRK2 activators will help elucidate LRRK2 downstream signaling events and LRRK2 function. Additionally, this would allow for the development of robust read-outs for target engagement in vivo and PD biomarker development that could aid diagnosis and analysis of disease progression. Finally, some important questions remain to be answered: First, does PD start in the brain or in the periphery? Second, do environmental triggers, such as infection, contribute to the onset of neurodegenerative symptoms in PD?

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■ ABBREVIATIONS
CD, Crohn’s disease; IBD, inflammatory bowel disease; IFN, interferon; IL, interleukin; KO, knockout; LRRK2, leucine-rich repeat kinase 2; NFAT, nuclear factor of activated T-cells; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NLRRC4, NLR family CARD domain-containing protein 4; PD, Parkinson’s disease; SNP, singlenucleotide polymorphism; TLR, Toll-like receptor; TNF-α, tumor necrosis factor alpha; Vps35, vacuolar protein sorting-associated protein 35; WAVE, Wiskott-Aldrich syndrome protein-family verproline

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