Review Article

LRRK2 regulation of immune-pathways and inflammatory disease

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Mutations in the *leucine-rich-repeat kinase 2* (*LRRK2*) gene are associated with familial and sporadic cases of Parkinson's disease but are also found in immune-related disorders such as inflammatory bowel disease, tuberculosis and leprosy. LRRK2 is highly expressed in immune cells and has been functionally linked to pathways pertinent to immune cell function, such as cytokine release, autophagy and phagocytosis. Here, we examine the current understanding of the role of LRRK2 kinase activity in pathway regulation in immune cells, drawing upon data from multiple diseases associated with LRRK2 to highlight the pleiotropic effects of LRRK2 in different cell types. We discuss the role of the *bona fide* LRRK2 substrate, Rab GTPases, in LRRK2 pathway regulation as well as downstream events in the autophagy and inflammatory pathways.

Introduction

The *leucine-rich-repeat kinase 2* (*LRRK2*) gene encodes for a large, multidomain protein encompassing two enzymatic functions at its core. The catalytic core consists of the GTPase domain of the protein, and the serine/threonine kinase domain, which are surrounded by protein–protein interaction domains. The N-terminal harbours the armadillo, the ankyrin and the leucine-rich-repeat (LRR) domains. At the C-terminal, there is the WD40 domain, which has been demonstrated to be crucial for protein folding [1]. Given the multiple, highly diverse enzymatic and protein-interacting domains, it is likely that LRRK2 may have different binding partners in different cell types and be instrumental in many different cellular pathways.

Mutations in the *LRRK2* gene are the most frequent cause of familial Parkinson's disease (PD) [2], with seven pathogenic mutations, which cluster around the catalytic domains of the protein, identified. Clinically, mutant *LRRK2*-PD patients are often considered indistinguishable from sporadic patients. Therefore, deciphering the role of LRRK2 in PD pathogenesis may reveal common pathological mechanisms underlying idiopathic PD and is consequently of great research importance.

LRRK2 is highly expressed in immune cells and this expression is tightly regulated by immune stimulation. As well, LRRK2 has been biochemically linked to the pathways regulating inflammation as well as autophagy and phagocytosis. There is now mounting evidence that both systemic and central nervous system (CNS) inflammation play a role in PD pathophysiology [3]. Furthermore, polymorphisms in the *LRRK2* gene have now been linked to inflammatory diseases such as inflammatory bowel disease (IBD), tuberculosis (TB) and increased susceptibility to leprosy, highlighting a critical role of LRRK2 in inflammation.

This review will outline what is currently understood about LRRK2 function in the regulation of pathways in immune cells. The role of LRRK2 kinase activity in disease will be discussed, as well as recently identified, *bona fide* LRRK2 protein interactors and the role of LRRK2 in inflammatory signalling pathways and autophagy.

LRRK2 expression in immune cells

The activation of immune cell subsets is critical for a proper and effective immune response to pathogens. For example, activation of T cells leads to the development of cell-mediated immune mechanisms and increased antibody responses which are produced by activated B cells [4]. Human monocytes have been subdivided into different populations based on the surface expression of CD14 and CD16. CD14$^+$ classical monocytes have been observed to be phagocytic with decreased inflammatory attributes, whilst CD16$^+$ non-classical monocytes have been reported to display inflammatory characteristics and display properties for antigen presentation [5]. Activation of immune cells is a healthy response serving to protect and repair the body, however, chronic activation and therefore chronic inflammation is deleterious and damaging.

LRRK2 is a largely ubiquitously expressed protein, and is most abundant in the brain, kidney and lungs. However, increased expression in immune cells, specifically in response to pro-inflammatory signals, has been observed in many immune cell types, strongly implicating LRRK2 as a regulator of the immune response.

Increases in *LRRK2* mRNA and protein expression have been observed in response to interferon-γ (IFN-γ) treatment in human B cells, T cells, macrophages [6–9] and non-classical monocytes [9]. Similar increases in LRRK2 protein expression have been observed in response to the toll-like receptor 4 (TLR4) ligand, lipopolysaccharide (LPS) in bone-marrow-derived macrophages (BMDMs) [10] and primary murine-microglia [11] and the cytokine IL-1β [12] in human umbilical vein endothelial cells (HUVECs). Microglia have also been shown to up-regulate LRRK2 protein expression following cranial injection with LPS, as well as increased kinase activity [11].

It has been reported that PD-associated *LRRK2* mutations exacerbate LRRK2 expression levels in response to inflammatory stimuli, suggesting a role of LRRK2 in immune cells in PD [13]. This is supported by the observation that the loss of Lrrk2 decreases pro-inflammatory myeloid cells in the brains of rats and decreases neurodegenerative responses to both LPS and α-synuclein [14]. LRRK2 is also up-regulated in unstimulated cells in sporadic-PD neutrophils [15], B cells, T Cells, and CD16$^+$/CD14$^-$ non-classical monocytes [7]. Furthermore, inhibition of LRRK2 with multiple kinase inhibitors has been shown to decrease CD14, CD16 and MHC-II expression in human immune cells, suggesting that LRRK2 is playing a significant role in the activation of cells in response to inflammatory stimulation in a kinase-dependent manner [8].

LRRK2 kinase activity in disease

The increased kinase activity of LRRK2 mutants has been linked to the pathological function of LRRK2 in disease. However, when considering different diseases, cell types, and mutations, the role of LRRK2 kinase activity may not be quite as simple as originally thought (Table 1).

Inflammation and LRRK2 in PD

Genome-wide conjunctional analysis has previously identified 17 novel loci that overlap between PD and autoimmune diseases, including known PD loci adjacent to *GAK*, *HLA-DRB5*, *LRRK2* and *MAPT* for rheumatoid arthritis and IBD [30]. Furthermore, peripheral pro-inflammatory cytokine levels are higher in a percentage of asymptomatic subjects carrying the *G2019S-LRRK2* mutation [16], which consistently increases LRRK2 kinase activity [31-35], suggesting an early role of inflammation in a disease that may be driven by increased kinase levels. Interestingly, systemic LPS administration triggers significant increases in peripheral cytokines in mice expressing *R1441G-LRRK2* that exacerbate neuroinflammation in the brain, increases LRRK2 expression in neurons and causes neurodegeneration [17]. The *R1441G/C/H* mutations, which reside in the GTPase domain, fail to consistently increase LRRK2 kinase activity, with both increases [35–38] and no changes [33,34,39] reported. The role of LRRK2 kinase activity in inflammation observed in these *R1441G-LRRK2* mice is therefore unclear.

The effect of LRRK2 kinase inhibitors, LRRK2 knockdown or kinase-dead mutants has resulted in conflicting results in different immune cell types (Table 1). For example, data from HUVECs expressing the *G2019S-LRRK2* mutation demonstrate an increase in levels of VCAM-1, which is essential for immune cell trafficking, in response to IL-1β [12]. This phenotype was not recapitulated with the expression of the kinase-dead mutant, *K1347A*, indicating a kinase-dependent mechanism for LRRK2 in immune responses. This is further supported with evidence from knockout models suggesting a dampened immune response with the loss of LRRK2. For example, loss of *Lrrk2* in microglia increases α-synuclein uptake and clearance relative to microglia

Table 1 Summary of results on the role of LRRK2 kinase activity in disease

Cell-type	Methods	Results	Refs.
Parkinson's disease			
Asymptomatic patient serum	G2019S (GoF)	Increased pro-inflammatory cytokines	[16]
Peripheral leukocytes and serum, whole brain/midbrain	R1441G	Increased pro-inflammatory cytokines in the periphery and increase CNS inflammation and neurodegeneration in response to LPS	[17]
HUVECs	G2019S (GoF) K1347A (KD)	Increased VCAM-1 expression in GS in response to IL-1β	[12]
Microglia	*Lrrk2* KO	Increased α-synuclein uptake and clearance	[18]
Primary mouse microglia	*Lrrk2* KD RNAi Kinase inhibition	Decreased pro-inflammatory cytokines	[11]
Primary mouse microglia	*Lrrk2* KO Kinase inhibition	Decreased pro-inflammatory cytokines	[19]
BMDMs	*Lrrk2* KO	No changes in cytokine release	[10]
BMDMs	*Lrrk2* KO	No changes in cytokine release	[20]
Peripheral myeloid	*Lrrk2* KO G2019S (GoF)	Decreased phagocytosis in KO Increased phagocytosis in GS	[21]
Leprosy			
BMDMs	M2367T (GoF)	Increased pro-inflammatory cytokine transcription	[22]
—	R1628P (GoF)	Variant is T1R protective, PD risk factor	[23]
Bacterial infections			
BMDMs	Kinase inhibition *Lrrk2* KO	Increased Mtb control	[24]
Peritoneal macrophages	*Lrrk2* KO G2019S	KO: Impaired *ST* control GS: Increased caspase-1 activation and *ST* control	[25]
Paneth cells	*Lrrk2* KO	Increased susceptibility to *Lm*	[26]
Splenocytes, BMDMs, whole brain/midbrain	G2019S (GoF) D1994S (KD)	*ST:* GS increased bacterial control and survival Reovirus-induced encephalitis: GS increased mortality, ROS and α-synuclein in brain	
Inflammatory bowel disease			
—	N2081D (GoF)	Increased risk of CD	[27]
—	G2019S (GoF)	Increased in CD patients	[28]
BMDMs	*Lrrk2* KO	Increased colitis severity	[22]
BMDMs	*Lrrk2* overexpression Kinase inhibition	Increased colitis severity ameliorated by kinase inhibition	[29]

Abbreviations: GoF, Gain-of-function; KD, Kinase-dead; *ST, Salmonella typhimurium*; Lm, *Listeria monocytogenes*; ROS, reactive oxygen species.

from wild-type (WT) mice [18]. Furthermore, LRRK2 knockdown or kinase inhibition in primary microglia have been shown to decrease the production of the pro-inflammatory cytokines TNF and IL-1β [11,19]. However, many reports observe no differences in cytokine release with *Lrrk2*-knockout in BMDMs [10,20]. Interestingly, knockout of *Lrrk2* decreases phagocytosis in peripheral myeloid cells, whilst *G2019S-LRRK2* expression increases phagocytosis in these cells [21]. Collectively, these data suggest LRRK2 may play distinct roles in immune cells in a cell-type dependent manner. Interestingly, an opposing role of LRRK2 in peripheral and CNS innate immunity has recently been suggested [3], and future research would benefit from directly comparing immune cells from the periphery and CNS.

LRRK2 in leprosy and the lesson of pleiotropy

Leprosy is a chronic dermato-neurological infectious disease caused by *Mycobacterium leprae* (*M. Laprae*). It has been demonstrated that *LRRK2* variants are significantly associated with leprosy [40]. However, results evaluating the association of *LRRK2* variants with leprosy susceptibility have been inconsistent [41–43]. One complication of the disease is excessive inflammation termed as type-1 reactions (T1R) which can lead to pathological immune responses directed against peripheral nerve cells [44]. Eighteen single nucleotide polymorphisms (SNPs) in *LRRK2* have been shown to preferentially associate with T1R [45], which may underlie the previously reported inconsistencies. Specifically, one variant identified, *M2367T*, lies in the WD40 domain of LRRK2 and has previously been shown to increase LRRK2 protein turnover and therefore decrease enzymatic activity [46]. This subsequently increases pro-inflammatory cytokine transcription via NFAT translocation to the nucleus [22], suggesting that LRRK2 pathophysiology in leprosy may be due to a loss or decrease in function.

Intriguingly, antagonistic pleiotropic effects of LRRK2 in leprosy T1R and PD have recently been described. The *R1628P-LRRK2* gain-of-kinase function mutation has been shown to be protective for T1R but has been reported as a risk-variant for PD [23]. It was hypothesized that a reduction in apoptosis caused by the *R1628P* mutation underlies this effect, with apoptotic cells releasing multiple anti-inflammatory mediators [47] whilst also increasing inflammation if not cleared efficiently [48]. This would suggest that the lower yield of apoptotic debris in leprosy patients may protect against T1R whilst the reduction in anti-inflammatory molecules resulting from abrogated apoptosis is disease-promoting in the brain. This data, therefore, implies potential opposing effects of LRRK2 kinase activity on inflammation in the peripheral and CNS.

LRRK2 in tuberculosis and other bacterial infections

LRRK2 has been implicated in several bacterial infections. Interestingly, there are contrasting reports between the effects of kinase inhibition on different bacterial infections, with LRRK2 kinase inhibition enhancing the restriction of some bacteria or increasing susceptibility to infection for others.

TB is an infectious disease caused by the intracellular pathogen *Mycobacterium tuberculosis* (Mtb). Numerous SNPs in *LRRK2* are associated with susceptibility to mycobacterial infection [40,45]. A statistical meta-analysis of nine published datasets has recently demonstrated that *LRRK2* is a differentially expressed gene (DEG) in association with TB [49]. More specifically, LRRK2 also interacts with seven of the other DEGs identified in this study, including two components in the NRON complex through which LRRK2 inhibits the immune response transcription factor NFAT1 [22].

It has recently been demonstrated that LRRK2 kinase activity negatively regulates phagosome maturation via the recruitment of the Class III phosphatidylinositol-3 kinase (PI3K) complex and Rubicon, with kinase inhibition and LRRK2 deficiency enhancing Mtb control and decreasing Mtb burdens [24]. In contrast with the improved control of Mtb replication, loss of LRRK2 has been reported to impair control of the enteric pathogen *Salmonella typhimurium* via decreased NLRC4 inflammasome activation [6,25]. Intriguingly, the *G2019S-LRRK2* mutation, which increases LRRK2 kinase activity, enhanced caspase-1 activation and IL-1β production in response to NLRC4 inflammasome activation in macrophages infected with *S. typhimurium* [25]. Similarly, knockout of *Lrrk2* increases susceptibility to the oral infection to a different enteric pathogen, *Listeria monocytogenes* [26]. Similar antagonistic pleiotropic effects of the gain-of-kinase function *G2019S* mutation have recently been reported in models of sepsis and encephalitis [50]. It was observed that the *G2019S* mutation controlled infection better, with reduced bacterial growth and longer survival during sepsis; an effect which was dependent on myeloid cells and LRRK2 kinase activity. However, animals with reovirus-induced encephalitis that expressed the *G2019S* mutation exhibited increased mortality, increased reactive oxygen species and higher concentrations of α-synuclein in the brain. Such data implies potential opposing effects of LRRK2-mediated inflammation in the CNS versus the periphery. Collectively, these data point towards the potential of LRRK2 having pleiotropic effects on bacterial control and inflammation dependent on the bacterial infection (the concept of LRRK2 being a pleiotropic actor at both the genetic and molecular level has recently been reviewed [51]).

LRRK2 in inflammatory bowel disease

IBD is composed of two major subtypes; Crohn's disease (CD) and ulcerative colitis (UC). The two can be distinguished by the distribution of chronic inflammatory changes. UC is typically confined to the colon, whilst

CD is known to affect both the ileum and colon, and is associated with deep, transmural inflammation. Patients with IBD have a 22% increased risk of PD compared with non-IBD individuals [52]. With regards to LRRK2, genetic variances and mutations in the *LRRK2* gene have been demonstrated to increase the risk of developing PD in both CD [30] and UC [52] patients.

The role of LRRK2 kinase activity in IBD is still unclear. *LRRK2* has been identified by GWAS as a major susceptibility gene for CD [53], and the gain-of-function variant, *N2081D*, has recently been identified and shown to increase the risk of CD two-fold in at-risk populations [27]. The *G2019S* mutation, which increases kinase activity, has been shown to be increased in CD patients in the Ashkenazi Jewish population [28]. Furthermore, the down-regulation of LRRK2 was previously shown to enhance the susceptibility to dextran sulfate sodium salt (DSS)-induced colitis [22], suggesting a loss of LRRK2 activity may increase the risk for inflammation in the gut. This is in agreement with increased expression in the secretory immunoglobulin A, IgA, observed in the intestines of *Lrrk2* deficient mice [54]. IgA is produced by intestinal B cells and is a crucial factor for maintaining a healthy intestinal tract barrier in terms of pathogen elimination, and increased IgA has been reported in patients with IBD [55]. However, in a mouse model of DSS-induced colitis, overexpression of the *Lrrk2* gene causes increased severity in colitis, which was ameliorated with LRRK2 kinase inhibitors [29]. From this data, it is still not clear if the role of LRRK2 in IBD is due to a loss- or gain-of-function. What is apparent, however, is that LRRK2 is crucial for normal inflammatory responses, and alterations in LRRK2 activity or expression levels can increase inflammation in the gut.

LRRK2 and Rab GTPases in immune cells

Many proteins have been reported to be directly regulated by LRRK2, however, the number of these that have been validated and replicated by numerous groups is small [56]. Recent studies have identified a subset of Rab GTPases, including Rab3, Rab5, Rab7, Rab8, Rab10, Rab12, Rab35, Rab39b, Rab43 and Rab7L1, as *bona fide* substrates of LRRK2 in cells [37,38,57,58].

Rab GTPases are key organizers of intracellular membrane trafficking and have been heavily implicated in a range of neurodegenerative diseases (reviewed in detail in [59]). Intracellular membrane trafficking and the immune function of cells are linked in multiple ways and this coordination is critical for dynamic and specialized immune defences. Interestingly, these specialized immune functions include phagocytosis and phagosome maturation, autophagy and antigen presentation [60], which have all been suggested to be regulated by LRRK2.

Phagocytosis is crucial for the clearance of dying cells and microbial pathogens. Proteomic studies have unveiled a network of Rab proteins that are associated with phagosomes and are highly essential for their maturation [61]. For example, Rab5 is present on early phagosomes where they regulate their fusion with early endosomes [61,62]. LRRK2 has been shown to form a complex with the protein WAVE2 (Wiskott–Aldrich syndrome protein-family verproline 2) and colocalize with Rab5a during phagosome-early endosome fusion in BMDMs [21]. Furthermore, G2019S-LRRK2 expression in these cells was shown to increase phagocytic activity, potentially due to altered Rab5a activity levels. This is in contrast with a report from *Lrrk2*-knockout (*Lrrk2*-KO) microglia, that showed increased uptake and clearance of α-synuclein with the loss of LRRK2 due to increases in Rab5 positive endosomes [18]. Thus, it seems that LRRK2 and its interacting partners may regulate phagocytosis in a cell-type-specific manner.

Rab7 is typically associated with late phagosomes and facilitates the fusion of these vesicles with lysosomes. Interestingly, many studies have demonstrated that PD-associated *LRRK2* mutations have deleterious effects on Rab7 functions. For example, G2019S-LRRK2 decreases Rab7 activity, leading to decreased degradative receptor trafficking [63], and lysosomal defects can be rescued upon Rab7 inhibition in LRRK2-PD patient fibroblasts [64]. A recent study has suggested that LRRK2-mediated deficits in Rab7 function are not due to direct phosphorylation of Rab7, but rather via the interaction between LRRK2 and it's substrate, Rab8A [65]. Interestingly, Rab8A has been shown to modulate TLR4-dependent immune responses [66]. This signalling pathway has been shown to modulate phosphorylation of LRRK2 as well as its subsequent cellular localization, dimerization and translocation to membranes [20,67,68], suggesting a bi-directional regulatory effect of LRRK2 and its Rab substrates.

Rab10 is known to regulate phagosomal recycling [69] and has been shown to be phosphorylated in human peripheral blood mononuclear cells [70] and isolated human neutrophils [71] by LRRK2. Furthermore, both PD and CD-associated pathogenic mutations and risk variants increase phosphorylation of Rab10 at the amino acid residue threonine 73 in patient macrophages [27]. However, this increase in Rab10 phosphorylation was

not replicated in patient neutrophils, suggesting a cell-type dependent effect of LRRK2-mediated Rab10 phosphorylation [15]. With regards to the functional effects of this interaction with Rab10, LRRK2 is recruited to the lysosome upon lysosomal overload stress, alongside Rab7L1, where it stabilizes Rab10 and Rab8 through phosphorylation [72]. Furthermore, knockout of *Lrrk2* increases vacuolization and lipofuscin autofluorescence, indicating that LRRK2 may protect against lysosomal enlargement and up-regulates lysosomal secretion during lysosomal stress. These findings also suggest that under stress-conditions, phosphorylated Rab GTPases acquire novel functions from those under steady-state conditions. It has been suggested that the roles of Rab8 and Rab10 on stressed lysosomes are different from their physiological functions documented in recycling phagosomes [72].

Collectively, these data highlight the complex and pertinent role of the interaction between LRRK2 and Rab GTPases in immune cell homeostasis (Figure 1). It is clear from these reports that both LRRK2 and Rab GTPases are capable of regulating immune cell function in a cell-type-specific manner. Whether or not the interaction between LRRK2 and different Rab GTPases is also cell-type dependent, and dependent on stress-conditions or different immune challenges, is of high interest for future research.

Events downstream of LRRK2 in immune cells

Previous evidence has shown that LRRK2 is involved in numerous pathways, including transcription, mitochondrial function and neurotransmitter release. In the context of immune cells, however, two cellular pathways are of particular interest and will be reviewed in detail: immune signalling and autophagy.

LRRK2 and inflammatory signalling pathways

The mitogen-activated protein kinase pathways (MAPK) were among the first to be investigated as potentially relating to LRRK2. MAPK pathways comprise of three proteins situated in a cascade, with different subtypes leading to the activation of different effectors involved in a range of functions such as apoptosis and inflammation. LRRK2 has been shown to bind to and phosphorylate MAP2K-3, -4, -6 and -7 [73,74], with increased kinase activity leading to hyperphosphorylation and dopaminergic neuronal death [75]. More recently, it has been demonstrated that LRRK2 kinase activity plays a critical role in manganese-induced inflammation and toxicity via downstream activation of MAPK signalling in both macrophages and microglia [76].

As previously discussed, LRRK2 has been shown to inhibit responses to infection via the NRON complex [49]. Interestingly, the NRON complex inhibits NFAT1 transcription, which modulates cytokine expression. LRRK2 has been shown to negatively modulate NFAT1 translocation to the nucleus, with LRRK2 deficiency conferring enhanced susceptibility to experimentally induced colitis in mice due to increased inflammation [22], highlighting converging LRRK2-mediated mechanisms between diseases.

LRRK2 has also been heavily implicated in NF-κB signalling. A recent transcriptomics study revealed that microglia from *Lrrk2*-KO mice exhibit a decreased inflammatory response with LPS or α-synuclein pre-formed fibril (PFF) treatment [77]. Interestingly, the NF-κB transcriptional regulator, NFKBIZ, was significantly decreased in *Lrrk2*-KO microglia in response to α-synuclein PFF. This is in agreement with previously reported findings from *Lrrk2*-KO microglia, where increases in the inhibitory p50 homodimer was observed, leading to an attenuated inflammatory response [19]. This was shown to be a downstream consequence of increased PKA activity, known to be negatively regulated by LRRK2 [78]. It has also been observed that LRRK2 lies downstream of the β-glucan receptor, Dectin-1, leading to activation of the NF-κB components TAK1 complex and TRAF6, increasing pro-inflammatory cytokine secretion [29]. Interestingly, Dectin-1 receptor signalling is also known to induce the LRRK2-associated NFAT signalling pathway [79]. As well, LRRK2 has recently been shown to phosphorylate RCAN1, a protein inhibitor of calcineurin, the main activator of NFAT transcriptional responses, leading to the increased transcriptional activity of NF-κB and IL-8 production [80].

Collectively, this data on LRRK2 in MAPK, NFAT1 NF-κB and RCAN1 signalling highlights that LRRK2 is situated downstream of multiple affecters and can regulate multiple inflammatory pathways via different mechanisms (Figure 2).

LRRK2, autophagy and the lysosome in immune cells

The degradative pathway of autophagy plays a crucial role in regulating different aspects of the innate and adaptive immune systems and is intrinsically linked to phagocytosis due to the convergence of both pathways on the lysosome (Figure 1). Furthermore, due to its role in the maintenance of biological homeostasis in
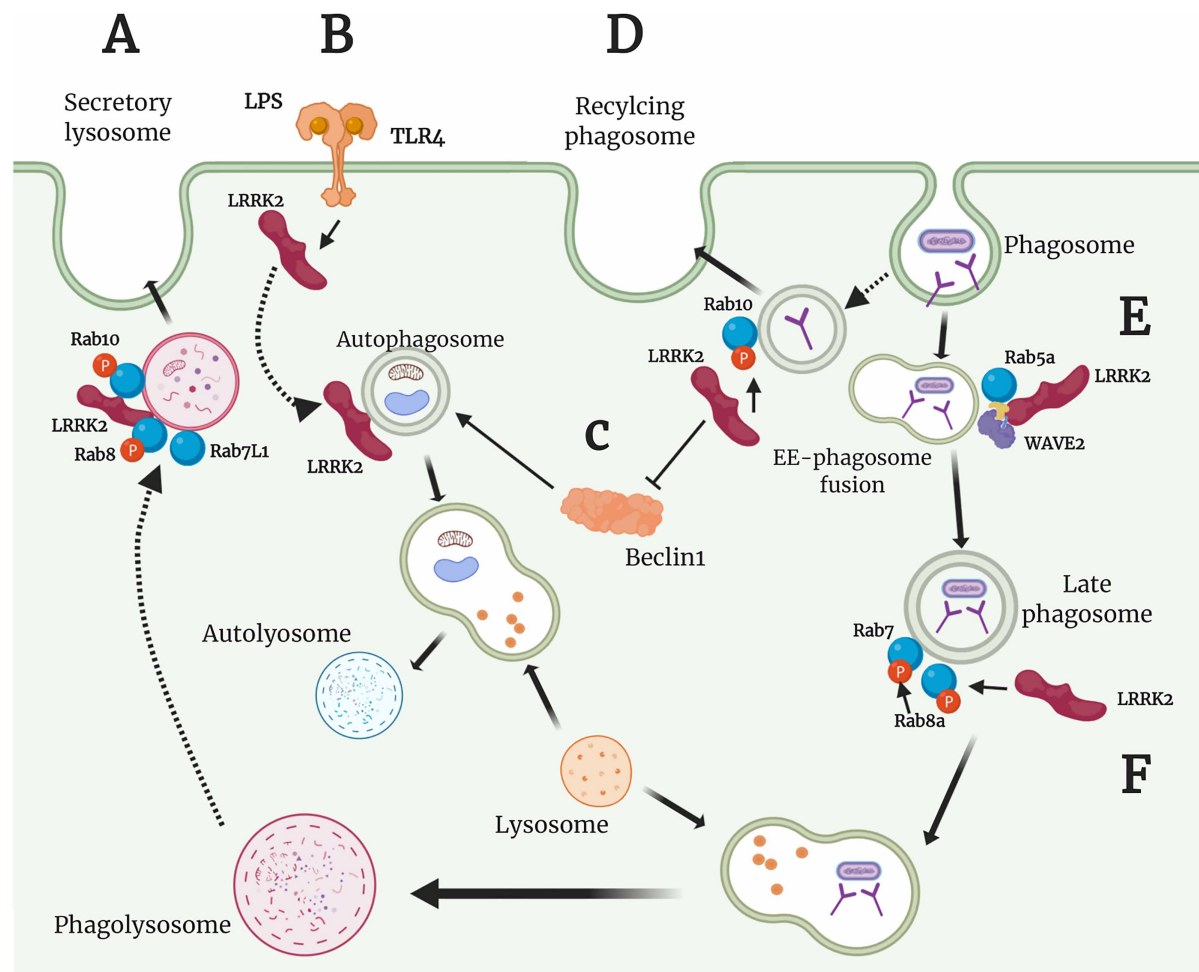
Figure 1. LRRK2 in phagocytosis and autophagy in immune cells.
(**A**) LRRK2 stabilizes Rab10 and Rab8 onto secretory lysosomes via phosphorylation during cellular stress. (**B**) LRRK2 is recruited to autophagosomes upon LPS treatment. (**C**) LRRK2 inhibits autophagic flux via Beclin-1 inhibition. (**D**) LRRK2 phosphorylates Rab10, which is found on recycling phagosomes. (**E**) LRRK2 modulates phagosome fusion with early endosomes via WAVE2 complex formation and Rab5a interaction. (**F**) LRRK2 phosphorylates Rab7 via the phosphorylation of Rab8a, mediating late phagosome and lysosome function.

conditions of stress, dysregulation or disruption of autophagy has been linked to IBD [81], PD [82,83] and host defence of Mtb [84] and other bacterial infections [85]. The macroautophagy pathway (hereby referred to as autophagy) arises from the formation of a phagophore that engulfs cargo for degradation and encloses to become an autophagosome. The autophagosome will then fuse with a lysosome to form mature autolysosome at which point contents can be degraded.

LRRK2 was first shown to regulate autophagy specifically in immune cells in 2014 where LPS-stimulation of monocytic cell lines increased LRRK2 translocation to autophagosome membrane, with loss of LRRK2 leading to autophagic deficits [67]. Furthermore, it has recently been demonstrated in a mouse macrophage cell line that, upon lysosomal overload stress, LRRK2 is recruited to the lysosome, alongside Rab7L1, where it stabilizes Rab8 and Rab10 through phosphorylation [72]. In the same study, it was also shown that the knockout of Lrrk2 increases vacuolization and lipofuscin autofluorescence, indicating that LRRK2 may protect against lysosomal enlargement and up-regulates lysosomal secretion during lysosomal stress in immune cells.

Collectively, this data suggests LRRK2 is functionally beneficial for the autophagy pathway. However, there are contradictions in the literature. For example, Lrrk2 overexpression in mouse bone-marrow-derived dendritic cells causes inhibition of autophagy via Beclin-1 inactivation [29]. This Beclin-1 mediated inhibition of
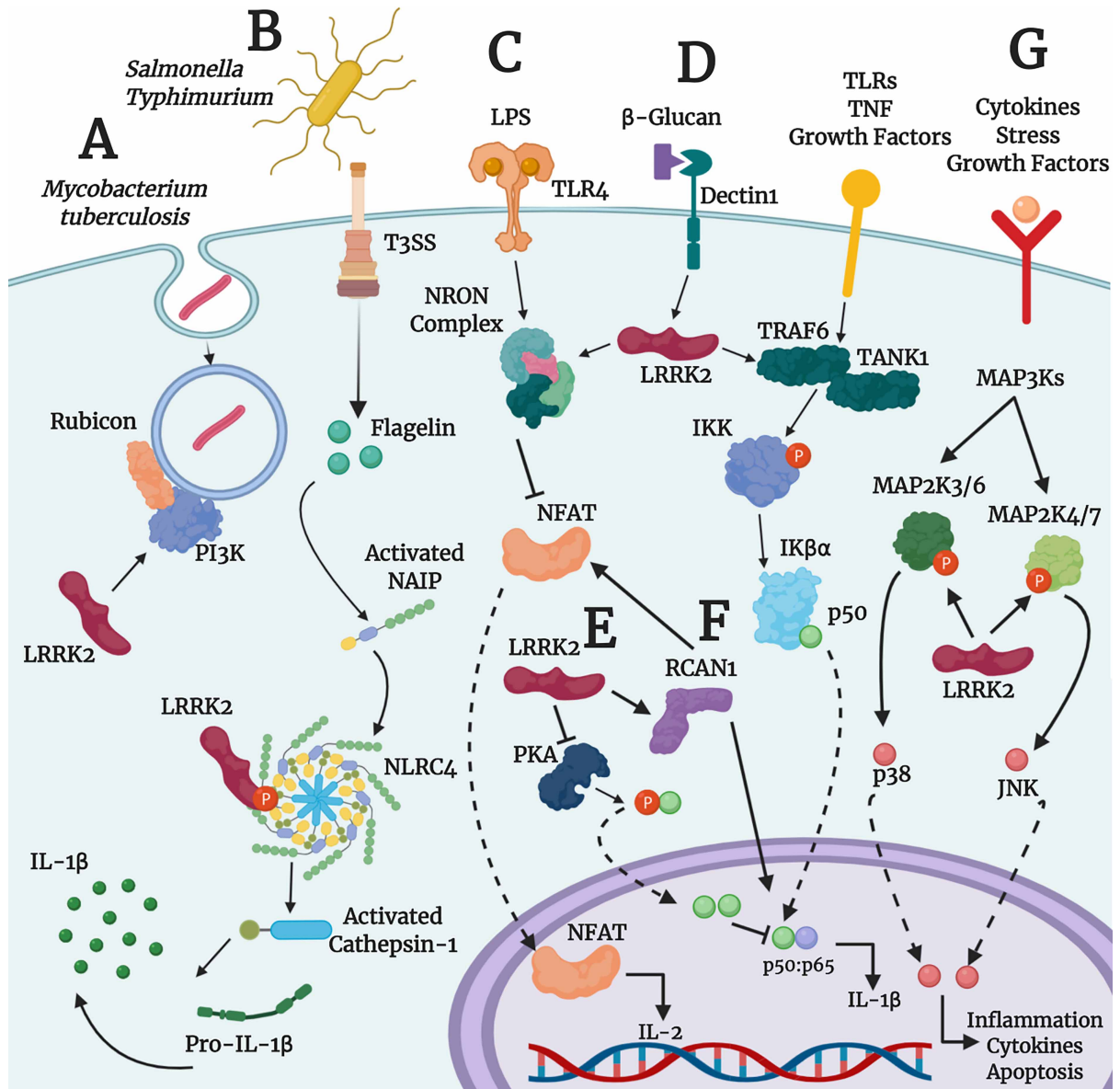
Figure 2. LRRK2 and inflammatory signalling.

(**A**) LRRK2 regulates *Mycobacterium tuberculosis* control and phagocytosis via PI3K complex and Rubicon inhibition. (**B**) LRRK2 regulates inflammation in response to *Salmonella* by forming a complex with and phosphorylating the **NLRC4** inflammasome, modulating IL-1β production. (**C**) LRRK2 interacts with the NRON complex, mediating NFAT translocation and LPS-induced inflammation. (**D**) LRRK2 lies downstream of the Dectin-1 receptor and modulates NF-κB-signalling via TRAF6 and TANK1 interaction. (**E**) LRRK2 mediates NF-κB-signalling via PKA inhibition. (**F**) LRRK2 phosphorylates RCAN1 regulating NF-κB and NFAT signalling (**G**) LRRK2 phosphorylates key components of the MAPK pathway, MAP2K3/6 and MAP2K4/7, leading to p38 and JNK nuclear translocation and increased inflammatory responses.

autophagy by LRRK2 has previously been reported in astrocytes [86]. One consequence of autophagy inhibition mediated by LRRK2 signalling is that it leads to increased LRRK2 [29] and therefore may further exacerbate LRRK2-mediated inflammation. Interestingly, there is evidence that NF-κB can inhibit autophagy via the up-regulation of NEDD4, a signalling component that can cause Beclin-1 cleavage as does LRRK2 [87]. NF-κB activation and autophagy, therefore, have reciprocal effects on each other; whether the effects of LRRK2 on these pathways are independent or linked is currently unknown and will be of interest to future research.

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Table 2 Summary of results on the role of LRRK2 in autophagy

Model	LRRK2 gene	Effects on autophagy	Refs.
In vitro/cell culture models			
SH-SY5Y	hLRRK2 cDNA (GS)	↑ Autophagic vacuoles	[89]
HEK293	BAC hLRRK2 (WT & RC)	↑ Autophagic vacuoles	[90]
HEK293	Human LRRK2 cDNA (WT and GS)	↑ Autophagic vacuoles	[91]
iPSC derived vmDA neurons	GS and WT	↑ Autophagic vacuoles and ↓ autophagic flux	[92]
Human fibroblasts	GS and WT	↓ Autophagic vacuoles	[93]
Human fibroblasts	GS, RC, YC and WT	Inhibited LC3-II response to starvation	[94]
HEK293	hLRRK2 cDNA (GS)	↓ LC3-II levels	[95]
RAW264.7	**Endogenous**	**↓ Membrane recruitment with autophagy stimulation**	[67]
SH-SY5Y	Endogenous	↑ LC3-II and p62 with Lrrk2 kinase inhibition	[96]
Primary *C. elegans* DA neurons	LRRK2 cDNA (GS and WT)	↑ Autophagic vacuoles and accelerated age-related loss of autophagy	[97]
Human fibroblasts	GS and control	↓ LC3-II levels and ↑ autophagic flux	[98]
Primary mouse astrocytes	**BAC mLRRK2 (GS, RC, YC)**	**↑ Lysosome size and ↓ pH**	[99]
Human fibroblasts	GS and control	↑ Lysosome size and calcium release	[64]
H4 neuroglioma cells	Endogenous	LRRK2 kinase inhibition ↑ LC3-II in a Beclin1 dependent manner	[100]
HEK293	hLRRK2 cDNA (WT GS, RC, DA, GR)	LRRK2 binds to p62 and ↓ p62 phosphorylation	[101]
Primary rat astrocytes	**Endogenous**	**LRRK2 kinase inhibition ↑ ULK1 phosphorylation**	[86]
BMDMs	**BAC mLRRK2**	**↓ Autophagic flux**	[29]
RAW264.7	**hLRRK2 cDNA**	**LRRK2 regulates lysosomal secretion via Rab8/10 and Rab7L1**	[72]
Primary cortical neurons	GS-knock-in	↓ Autophagic flux with ↑ lysosomal pH	[102]
Primary cortical neurons	BAC hLRRK2 (WT, GS, RC)	↓ Autophagic flux with ↑ lysosomal pH in RC neurons	[103]
Human fibroblasts	GS and control	↓ Autophagic vacuoles and mitophagy	[104]
In vivo models			
Transgenic mouse	hLRRK2 cDNA (GS, RC and WT)	Enlarged and ↑ autophagic vacuoles	[105]
Lrrk2⁻/⁻ mouse	KO	↑ p62 in kidneys	[106]
Lrrk2⁻/⁻ mouse	KO	Age-dependent biphasic alterations in LC3-II levels in kidneys	[107]
Lrrk2⁻/⁻ rat	KO	↑ Increased lysosomes in kidneys	[108]
Transgenic mouse	hLRRK2 cDNA (RC)	No changes	[109]
AV striatal injected rat	hLRRK2 WT/GS cDNA	No changes	[110]
KI mouse	GS	↑ LC3-II levels	[111]
Non-human primate	Endogenous	↓ Lysosomal dysregulation in urine after kinase inhibition	[112]

Table 2 Summary of results on the role of LRRK2 in autophagy Part 2 of 2

Model	LRRK2 gene	Effects on autophagy	Refs.
KI mouse	GS	↓ LAMP1 and LC3-I (*in vivo*)	[102]
Human post-mortem	GS, iPD and control	↓ LAMP1 and p62 in BG	[113]

Studies in immune cells are highlighted in bold. ↑= increased, ↓= decreased.
Abbreviations: RC, R1441C; GS, G2019S; WT, wild-type; YC, Y1699C; DA, D1994A ; GR, G2385R; vmDA, ventral-midbrain dopaminergic neurons; KI, knock-in; iPD, idiopathic PD; BAC, bacterial-artificial-chromosome.

Autophagy is now one of the most intensively studied pathways in the LRRK2 field, however, many aspects are still not fully understood, and results often conflicting. Discrepancies in the literature may be a result from the use of different cell types used in this research (Table 2). The 'date-hub' hypothesis describes two types of 'hubs' in protein interaction networks; 'party hubs', which interact with most of their partners simultaneously at the same time and space, and 'date hubs', which bind their different partners at different times or locations. The potential for LRRK2 behaving as a 'date-hub' has been discussed in the literature [88] and may explain the discrepancies reported. Under the perspective of the date-hub hypothesis, LRRK2 may be capable of interacting with different proteins. Therefore, LRRK2 could control different cellular pathways (or modulate the same pathway differentially) based on the expression of LRRK2 activators and partners and the complexes formed in a cell-type-specific manner. Furthermore, it is noticeable that, although autophagy is an intensively studied pathway regarding LRRK2, only a small proportion of those studies has been carried out in immune cells. As well, despite the crucial role autophagy and the lysosome play in regulating different aspects of the innate and adaptive immune systems, mechanistic insight into how LRRK2's role in autophagy and lysosome function impacts inflammatory pathways in immune cells remains unknown, and is an important area for further research.

Concluding remarks

Research over the last decade has increased our understanding of the pathophysiological role of LRRK2 in disease and supports the role of LRRK2 in inflammation and immune cell function. Rab GTPases have been identified as *bona fide* LRRK2 substrates, and LRRK2 regulates phagocytosis, cell-signalling and autophagy in immune cells. What is apparent from the current literature regarding leprosy, bacterial infection and PD, is a distinct role of LRRK2 in inflammation in a cell-specific manner. Interestingly, Rab GTPases in immune cells are recruited differentially to phagosomes and other cellular organelles based on cell-type and extracellular stimuli [114,115]. Given the important role of Rab GTPases in LRRK2 function and in immune cell function, more research is required in order to unequivocally establish the *bona fide* interacting partners of LRRK2 in different immune cell types under different conditions. Furthermore, additional research is required in order to establish the involvement of LRRK2 in inflammatory pathways in different immune cell types. Specifically, further research is required to unveil the cell-type dependent manner in which LRRK2 kinase activity regulates these different cellular pathways. LRRK2 kinase inhibitors have been discussed for their potential therapeutic effects in diseases such as PD where aberrant LRRK2 kinase activity is apparent. However, a loss of LRRK2 kinase activity may lead to an increased risk of infection and inflammation in the periphery, as suggested by data discussed here. Therefore, such malignant side effects would need to be taken into consideration if such inhibitors were to be therapeutically beneficial.

Understandably, a large percentage of the research aiming to understand LRRK2 enzymatic function has focused on its kinase activity. Kinases are appealing drug targets for pharmaceutical companies due to the fact that these enzymes are considered highly druggable and can be targeted by small-molecule chemistry. However, this also means that there is still uncertainty about the contribution of GTPase activity to cellular toxicity in immune cells. Although many model organisms with interesting phenotypes have been developed based upon familial mutations in the GTPase domain of LRRK2, mechanistic insight into the contribution of GTPase activity is so far lacking [116]. As well, it is important to consider that the enzymatic core of LRRK2 is surrounded by protein–protein interaction domains, which have received considerably less research attention over the last decade. The *G2385R* mutation, which is located in the WD40 domain of LRRK2, is a risk factor for PD [117],

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emphasizing the need for future research on the role of these protein–protein interaction domains in disease. Understanding how LRRK2 GTPase activity and its role as a scaffolding protein contributes to such phenotypes in immune cells will be challenging and may rely in the future upon genetic or pharmacological manipulations.

Perspectives

- LRRK2 has been implicated in multiple processes critical for immune cell function. Unveiling pathological mechanisms of mutations in immune cells is of great importance for research on PD, IBD and bacterial infections

- LRRK2 can regulate inflammatory pathways in multiple cell types via different mechanisms. The current literature highlights the pertinent role of the interaction between LRRK2 and Rab GTPases in immune cell homeostasis.

- Discrepancies in the literature highlight cell-type dependent effects of LRRK2 on immune cell function. Future research will benefit from a direct comparison between immune cells and identifying *bona fide* substrates of LRRK2 in different cell types and under different immune conditions.

Abbreviations

BMDMs, bone-marrow-derived macrophages; CD, Crohn's disease; CNS, central nervous system; DEG, differentially expressed gene; DSS, extran sulfate sodium salt; HUVECs, human umbilical vein endothelial cells; IBD, inflammatory bowel disease; IFN-γ, interferon-γ; LPS, lipopolysaccharide; LRR, leucine-rich-repeat; LRRK2, leucine-rich-repeat kinase 2; *Lrrk2*-KO, *Lrrk2*-knockout; MAPK, mitogen-activated protein kinase pathways; Mtb, *Mycobacterium tuberculosis*; PBMCs, peripheral blood mononuclear cells; PD, Parkinson's disease; PFF, pre-formed fibril; PI3K, phosphatidylinositol-3 kinase; ROS, reactive oxygen species; SNPs, single nucleotide polymorphisms; T1R, type-1 reactions; TB, tuberculosis; TLR4, toll-like receptor 4; UC, ulcerative colitis; WAVE2, Wiskott–Aldrich syndrome protein-family verproline 2; WT, wild-type.

Competing Interests

The authors declare that there are no competing interests associated with the manuscript.

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