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Are LRRK2 mysteries lurking in the gut?

Adrien de Guilhem de Lataillade^a, Carolina Pellegrini^b, Michel Neunlist^a, Malvyne Rolli-Derkinderen^a, and Pascal Derkinderen^{a*}

^aNantes Université, CHU Nantes, INSERM, The enteric nervous system in gut and brain disorders, F-44000 Nantes, France. ^b Unit of Histology and Embryology, Department of Clinical and Experimental Medicine, University of Pisa.

Corresponding author:

Pascal Derkinderen, Inserm U1235 Nantes, 1 rue Gaston Veil, 44035 Nantes, France. Tel: +33(0)240165202, Fax: +33(0)240165203, E-mail: pascal.derkinderen@univ-nantes.fr; derkinderenp@yahoo.fr. Orcid ID: 0000-0001-8792-2582

Author Email Addresses:

Adrien de Guilhem de Lataillade (adrien_dgdl@live.fr)

Carolina Pellegrini (carolina.pellegrini87@gmail.com)

Michel Neunlist (michel.neunlist@univ-nantes.fr)

Malvyne Rolli-Derkinderen (malvyne.derkinderen@univ-nantes.fr)

Pascal Derkinderen (derkinderenp@yahoo.fr; pascal.derkinderen@univ-nantes.fr)

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Abstract

Gut-brain axis and inflammation are two hot topics in Parkinson's disease. In this setting, the Leucine-rich repeat kinase 2 (*LRRK2*) gene, which encodes the eponym protein has attracted much attention. *LRRK2* is not only the gene most commonly associated with Parkinson's disease but also a susceptibility gene for Crohn's disease, thereby suggesting that it may sit at the crossroads of gastrointestinal inflammation, Parkinson's, and Crohn's disease. In contrast to the accumulated data on LRRK2 in the CNS, research on LRRK2 in the digestive tract is still in its infancy and the scope of the present review article is therefore to review existing studies on LRRK2 in the gastrointestinal tract in both physiological and pathological conditions. In the light of current data on LRRK2 in the gastrointestinal tract, we discuss if LRRK2 could be or not regarded as a molecular link between gut inflammation, PD and CD and we suggest directions for future research.

Introduction

In the last 25 years, there has been a proliferation of literature showing that Parkinson's disease (PD) is not only a disorder of the brain, but also of the gastrointestinal (GI) tract and, more broadly, of the gut-brain axis. GI symptoms occur in almost every PD patient at some point (1, 2) and autopsy studies have consistently shown that alpha-synuclein deposits, the pathological hallmark of the disease, are found in the enteric nervous system (ENS) in nearly every case examined pathologically (3, 4). These and other observations led Braak to put forth the hypothesis, now bearing his name, stipulating that PD might be triggered by a hitherto unknown neurotropic pathogen, which initially affects the gut where it leads to alpha-synuclein aggregation, then spreading via the vagus nerve to enter the brain (5). This bottom-up hypothesis, still widely argued, has ignited heated debates among the movement disorders community (6–10). Nevertheless, if such a hypothesis is supported, the intestinal epithelial barrier, which is highly sensitive to intestinal inflammation, should be porous enough to allow the passage of a neurotropic pathogen that will trigger the pathological process in the nearby enteric neurons (11). This logically prompted several groups to investigate intestinal inflammation in PD patients and, although preliminary, existing studies showed that GI inflammation may indeed occur in the gut at least in some PD subjects (12, 13). The genetic findings showing that the *LRRK2* gene (encoding leucine-rich repeat serine/threonine-protein kinase 2), which has emerged as the gene most commonly associated with both familial and sporadic PD, is also a major susceptibility gene for Crohn's disease (CD) further support the link between GI inflammation and PD (14). It has thus been recently suggested that *LRRK2* may sit at a crossroads between PD, GI inflammation and CD (15, 16) and several research groups including ours have thus started to investigate *LRRK2* in the GI tract. Here, after a brief overview on tissue distribution and cell biology of *LRRK2*, we will focus on reviewing the current state of knowledge on *LRRK2* expression, activity and phosphorylation in the GI tract in both physiological and pathological conditions. In the light of current data on *LRRK2* in the GI tract, we discuss if *LRRK2* could be or not regarded as a molecular link between GI inflammation, PD and CD and suggest directions for future research.

1. A brief overview of *LRRK2*

LRRK2 gene mutations were first identified in 2004 as a cause of autosomal dominant PD (17, 18) and this gene subsequently emerged as one of the most frequently associated with familial and apparently sporadic form of the disease (19). As mentioned above, *LRRK2* has also been identified by genome-wide association studies as a major susceptibility gene for CD (Figure 1) (20, 21). *LRRK2* encodes a large 286-kDa Ser/Thr kinase of 2527 amino acids (Mata et al. 2006), which in addition to the kinase domain, also contains a GTPase and several potential protein–protein interaction domains (Figure 1) (17, 18, 22). In general, the most common mutations in *LRRK2*-associated PD, such as G2019S and R1441C show higher kinase activity (23), which is classically monitored by measuring the amount of

phosphorylation at Thr73 of the LRRK2 substrate Rab10 (24) (Figure 1). LRRK2 is ubiquitously expressed, but highly abundant in the kidney, lungs, pancreas, brain (25) and various peripheral immune cells (26). Since its discovery in 2004, the physiological functions of LRRK2 are a topic of intense investigation and LRRK2 has been associated with a set of cellular functions including synaptic vesicle recycling, control of neurites morphology, regulation of autophagy/lysosomal functions (reviewed in (27, 28)).

2. LRRK2 distribution and functions in the normal gut

The first paper on the expression of LRRK2 in the GI tract was published in 2010. To identify which cell types in intestinal tissue express LRRK2, Gardet et al. immunostained colonic biopsies of patients with CD (29). For each subject, a pair of biopsy specimens was collected, one from an inflamed area and one from a noninflamed area, the latter being regarded as 'control' condition. When LRRK2 was costained with cell-specific markers, LRRK2 was observed in some immune cells of the lamina propria, such as macrophages, dendritic cells, and B lymphocytes but not in mast cells, NK cells, epithelial cells or enteric neurons (Figure 2) (29). A more detailed immunohistochemical study performed in the mouse small intestine showed that, although not present in epithelial cells *per se*, LRRK2 was highly-expressed in lysozyme-positive Paneth cells that are scatteredly distributed throughout the epithelial lining (30). LRRK2 deficiency was associated with a loss of lysozyme in Paneth cells and a change in microbiota composition, which rendered LRRK2 knockout mice more susceptible to intestinal infection (30). Taken as whole, these first observations suggested that LRRK2 is involved in intestinal homeostasis by modulating commensals and mucosal immunity.

It took a few years for the first article on LRRK2 expression in the ENS to be published. This paper showed that, other than in immune cells, LRRK2 is also expressed in the myenteric neurons of the small intestine (31). In two subsequent studies, we showed that LRRK2 was also expressed in the myenteric and submucosal plexus of the adult human colon (32, 33). Using confocal immunofluorescence microscopy of myenteric ganglia from control cases, we identified LRRK2 immunoreactivity over the entire thickness of the ganglia, not only in neurons but also in enteric glial cells (33) (Figure 2). In both cell types, LRRK2 staining was mainly observed in the cytoplasmic perinuclear region (33). Given the key role of the ENS in the regulation of digestive functions, the presence of LRRK2 in both enteric neurons and glial cells raised questions about the potential roles of this protein in the gut. In order to tackle this question, the group of Tatsunori Maekawa used LRRK2 knockout mice to investigate if LRRK2 is involved in gut physiology. They showed that *LRRK2* invalidation was associated with an upregulation of mRNA encoding for major intestinal bioactive peptides involved in the regulation of GI functions, such as vasoactive intestinal peptide, substance P and neuropeptide Y (31). In a subsequent study, the same research group investigated GI motility in their LRRK2 knockout model and showed that these mice were resistant to the restraint stress-induced GI dysmotility that is usually observed in wild-type animals (34). It should however be noted that LRRK2-KO mice had normal GI motility in the absence of stress. Taken together, these data suggest that LRRK2 may be involved in the regulation of

digestive functions but that its role is more likely incidental rather than primary. Further studies are needed not only to clarify the details of this possible interplay between LRRK2 and neuropeptides but also to determine whether the expression of LRRK2 in enteric neurons is ubiquitous or limited to specific neurochemical subtypes. It will be also important to evaluate the possible roles of LRRK2 on gut functions that are compromised in both PD and CD, such as intestinal permeability.

3. The interplay between enteric LRRK2, CD and experimental colitis

In their seminal paper on the topic, Gardet and collaborators showed that LRRK2 mRNA levels were markedly higher in biopsy specimens from inflamed area compared with noninflamed tissue collected in the same patient with CD (29). We recently confirmed these findings by showing that the expression of LRRK2 was higher at both protein and messenger levels in colonic biopsies from CD patients when compared to control subjects (32). Such an upregulation was also observed in mice with dextran sulfate sodium (DSS)-induced colitis, the most widely used animal model for inflammatory bowel disease (32). Other studies have approached the problem in another way, investigating whether invalidation, overexpression or increased kinase activity of LRRK2 were capable of modulating GI inflammation. The three existing studies that used LRRK2-KO mice have had somewhat diverging results: in a first study, LRRK2 deficient mice had exacerbated DSS-induced colitis progression (35), whereas two subsequent reports showed that these mice were less sensitive to DSS-induced colitis than their wild-type littermate (36, 37) (Table 1). It is difficult to explain these discrepant results as the DSS protocols used in the different studies were very similar. However, additionally to the data obtained with LRRK2 deficient mice, two of the aforementioned studies (36, 37) together with two recent reports (38, 39) showed that LRRK2 G2019S and R1441C transgenic mice (two mutations known to increase LRRK2 kinase activity and to be associated with familial PD) were more sensitive to DSS-induced colitis than their littermate controls (Table 1). Taken as a whole, these data strongly suggest that increased LRRK2 expression/activity rather than decreased LRRK2 expression underlies the increased susceptibility to colitis in mice.

	DSS	Effects of LRRK2 deficiency on DSS-induced colitis/WT mice
LRRK2 KO 8wk male (37)	2% 36-60 kDa, 8 d	Improved Less epithelial alteration and neutrophil infiltrates Alleviated weight loss
LRRK2 KO C57BL/6J mice 6 and 8 wk (36)	3% 36-50 kDa (8 d DSS-2 d water) x 3	Improved Clinically and histologically less severe (slight effect, NS)
LRRK2 KO C57BL/6J mice 6 and 8 wk (35)	3% and 5% 36-60 kDa 8 d	Worsened More rapid weight loss, diarrhea and bloody stools More inflammatory infiltrates and thickened walls

Table 1. Existing studies that compared the severity of DSS-induced colitis between LRRK2-KO and wild-type (WT) mice. NS : non significant.

	DSS	Effects of LRRK2 overexpression on DSS-induced colitis/WT mice
Tg LRRK2 KI R1441C (37)	2% MW ? 7 d	Worsened More weight loss More severe loss of crypts and goblet cells, more infiltration of PMN
Tg LRRK2 G2019S C57BL/6J mice 6-8 wk (38)	2.5% 40 kDa 7d/m for 5 m	Worsened Reduction in colon length More bloody stools, more severe epithelial loss Enhanced pro-inflammatory cytokine secretion in colon Increased intestinal permeability, decreased expression of ZO-1
Tg LRRK2 G2019S C57BL/6J mice 8-10 wk (39)	0.5-2% 40 kDa 28 d	Worsened Reduction in colon length More epithelium damage, more destructure of crypt architecture, more infiltration of immune cells, more oedema
LRRK2 G2019S C57BL/6J mice 6 and 8 wk (36)	3% 36-50 kDa (8 d DSS-2 d water) x 3	Worsened More epithelium damage, more severe loss of crypts and goblet cells, more inflammatory infiltrate Enhanced pro-inflammatory cytokine secretion in colon

Table 2. Existing studies that compared the severity of DSS-induced colitis between LRRK2 transgenic and wild-type (WT) mice. PMN : polymorphonuclear neutrophils ; ZO-1 : Zonula occludens-1.

4. The interplay between enteric LRRK2, PD and experimental parkinsonism

As far as we are aware, there are three independent existing studies on gut expression of LRRK2 in PD. Two of these studies used colonic biopsies (32, 40) whereas the third one used post-mortem full thickness segments of the colon (33). We will not discuss the paper by Lin et al. (38), which likely corresponds to a sub-study from the same group (40). Using sigmoid biopsy lysates that were analyzed by Western blot, we showed that LRRK2 expression was significantly reduced in the colon of PD patients (n=12) when compared to age-matched controls (n=11) ; this was accompanied by a lower kinase activity in PD samples relative to controls, as evaluated by Rab10 phosphorylation at Thr73 (32). The other biopsy-based study on LRRK2 and PD gut found somewhat opposite results. In this study, the expression of LRRK2 was analyzed by immunohistochemical staining in colonic biopsy specimens from 51 PD subjects (3 with LRRK2 R1441H or I2012T mutations, 9 with the PD risk variant G2385R) and 40 controls and the cells immunoreactive for LRRK2 in the submucosa and lamina propria were counted and expressed as a cell ratio (40). The percentage of cells immunoreactive for LRRK2, which were mainly located in the lamina propria and thus likely of immune origin (see Figure 1), was higher in PD subjects relative to controls. The number of LRRK2-positive cells was higher in PD subjects with LRRK2 mutations and genetic risk variants compared with those without LRRK2 mutations. Additionally, a few clinico-pathological correlations showed that colonic LRRK2 expression correlated positively with UPDRS part III motor scores in “off” state and negatively with the MMSE score, suggesting that a higher LRRK2 expression level was associated with the severity of both motor

symptoms and cognitive functions (40). How could these two studies have yielded such divergent results? Although there is no definitive explanation, some points are worth discussing. First, although the two studies used colonic biopsies specimens, they were technically different. While we used biopsy lysates, which contains, besides epithelial cells, a mixture of submucosal enteric glial cells, submucosal neurons and immune cells (41), Liao et al. used paraffin-embedded samples and counted LRRK2 immunopositive cells. It is likely that the latter approach favors the analysis of immune cells at the expense of neuronal cells, which are largely overlooked when paraffin embedded-tissues are used. Second, the number of LRRK2-positive cells was higher in PD subjects with LRRK2 mutations and genetic risk variants compared with those without LRRK2 mutations and therefore the significant increase in LRRK2-positive cells in PD cases was likely driven by the few cases with LRRK2 mutations and risk variants. In contrast to the submucosal plexus, the myenteric plexus, which is also a target of the disease is not accessible to routine GI biopsies (41). This prompted us to analyze the expression levels of LRRK2 in full thickness segments of colon (transverse and sigmoid), which contain both plexuses, in pathologically confirmed Lewy body disorders (n=16) and non-Lewy body disorders cases (n=12). LRRK2 immunofluorescence intensity was not different between the two groups, either in the myenteric or submucosal plexus (33).

Data from animal models on the possible interplay between LRRK2, colitis and experimental parkinsonism are still scarce. The findings obtained with colonic biopsies from PD subjects prompted us to investigate LRRK2 expression in an animal model of enteric synucleinopathy. We used a transgenic mouse model of human synucleinopathies expressing the A53T mutant alpha-synuclein, which exhibit age-dependent alpha-synuclein accumulation in the ENS (42) and observed a decrease in LRRK2 expression in the colon of old mice (from 10 to 21 months) when compared to one-month old animals (32). LRRK2 G2019S transgenic mice develop relatively mild CNS abnormalities with a decrease in extra-cellular dopamine levels but without loss of dopaminergic neurons (43). This led to the assumption that factors others than the genetic mutations are needed to trigger PD process and that gut inflammation might be one of these facilitators. In line with this hypothesis, one recent report showed that DSS-induced colitis was associated with locomotor defect and dopaminergic neuronal loss in LRRK2 G2019S mice, two features that were not observed in animals without colitis (40). It should be however noted that another independent study was unable to replicate these findings (39). Indeed, in this study, no neuronal loss was observed in the substantia nigra of LRRK2 G2019S mice with colitis and a parkinsonian phenotype could be only observed in these mice when human alpha-synuclein was overexpressed in the substantia nigra (39).

5. LRRK2 in the gut, still some work to be done

Since the discovery of *LRRK2* as a common genetic risk factor for both PD and CD, it has been suggested that LRRK2 could be a link between GI inflammation and these two disorders (15, 16). As we have seen, data obtained in LRRK2 transgenic mice transgenic strongly suggest

that an increase in the expression and/or activity of LRRK2 exacerbate experimental colitis in mice but the link between such a colitis and the development of experimental parkinsonism is however still tenuous (38, 39). In addition, the results we obtained from digestive biopsies clearly showed opposite LRRK2 expression and activity between PD and CD suggesting that these two disorders, despite their genetic links, differs mechanistically. Thus, as it stands, the assumption that LRRK2 sits at the crossroads of GI inflammation, CD and PD remains to be proven.

In the discussion of the potential link between CD, PD via LRRK2, one of the main pitfalls comes from the ubiquitous expression of LRRK2. As discussed earlier, LRRK2 in the GI tract is present in a wide variety of cells, including both immune (including macrophages and B lymphocytes) and non-immune cells (enteric neurons and glial cells) and the list may not be complete. In addition to epithelial cells, all of these cells can be captured by the biopsy forceps used for GI endoscopy, even if it is limited to a few neuronal processes for the enteric neurons. This makes it difficult to analyze LRRK2 expression from biopsies, either by immunohistochemistry or Western blot. The latter, by providing a cell lysate, only performs an overall analysis of the expression levels or phosphorylation status of LRRK2 without being able to specify the cell type involved whereas quantification of IHC can be difficult especially for cells that are few in number and sparsely distributed in small-sized samples such as biopsies. In this respect, the use of complete sections of the colon could prove useful but they are limited to surgery or postmortem sampling. So how to move forward? Although a recent paper showed that LRRK2 in immune cells was critically involved in the development of DSS-induced colitis, it is unlikely that such an animal model will help us further in deciphering the role of LRRK2 in both IBD and PD. This model is indeed not an accurate mimic of human IBD not only because massive epithelial cell damage which is the primary effect of DSS in mice is unlikely to be a primary mechanism of the human disease but also because the immune response differs between the two disorders (44). Instead of using animal models, it is therefore crucial to carry out additional studies with GI samples from PD and CD subjects. These studies could greatly benefit from novel approaches, such as microdissection spatial transcription, which should not allow us only to determine in which cell types of the gut wall LRRK2 is dysregulated but also the local features that could contribute to disease in both PD and CD (45).

Legends to figures

Figure 1. LRRK2 domains and variants associated with PD and IBD. The main regions of the LRRK2 protein comprise an armadillo repeat domain, an ankyrin repeat domain, a mitogen-activated protein kinase kinase kinase domain, a GTPase domain (C-terminal of Roc (COR) domain) and a WD40 repeat domain. The respective locations of the LRRK2 variants and their association with inflammatory bowel disease and/or Parkinson's disease. Variants associated with IBD (intestine), those associated with PD (brain) are shown symbol. Red symbols indicate increased disease risk, while green ones indicate decreased disease risk.

Figure 2. Transverse section of the GI tract recapitulating the cell types that express LRRK2 and their location in the gut wall. (a) LRRK2 is expressed by Paneth cells which are located at the bottom of small intestinal crypts and by immune cells such as macrophages and B lymphocytes, primarily located in the lamina propria. LRRK2 is also found in the two main cell types of the enteric nervous system, namely enteric neurons and glial cells, in both the submucosal and myenteric plexus. **(b)** Human colonic tissue from a control subject was stained with LRRK2 (red) in both myenteric (right panel) and submucosal ganglia (left panel) were delineated with anti- β III-tubulin antibodies (green).

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Figure 1

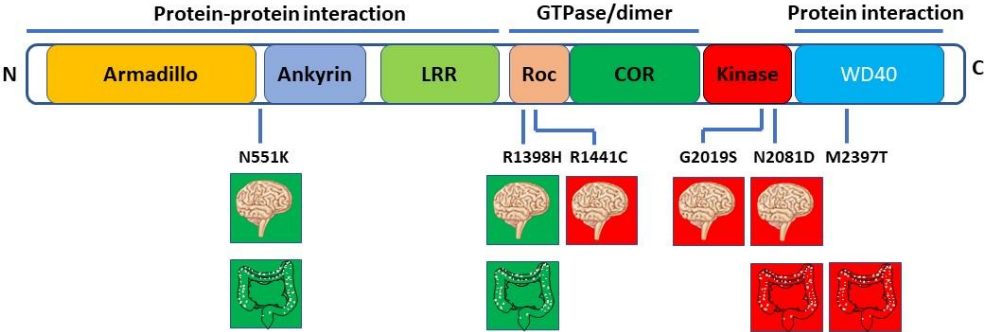


Figure 2

