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Letter to published article ‘Mild Chronic Colitis Triggers Parkinsonism in LRRK2 Mutant Mice Through Activating TNF- α Pathway’

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With interest, we read the article by Lin et al. on the possible role of LRRK2 and gut inflammation in the development of Parkinson's disease.¹ Using a transgenic mouse model overexpressing the G2019S mutation of the human LRRK2 gene, they showed that transgenic animals are more vulnerable to DSS-induced colitis than controls littermates with gut hyperpermeability and an increased intestinal expression of pattern-recognition receptors. These changes in the gastrointestinal tract were associated with parkinsonism features including locomotor defect, microglia activation and dopaminergic neuron loss in the central nervous system.¹

In order to reinforce the findings obtained in mice, the authors performed a set of additional experiments with human samples. The expression of LRRK2 was analyzed by immunohistochemistry in colonic biopsies from 19 PD patients (7 with LRRK2 genetic variants G2385R or R1628P, 12 without LRRK2 mutations) and 7 age-matched controls. The percentage of cells immunoreactive for LRRK2 was higher in PD when compared to controls. Among PD subjects, the number of LRRK2-positive cells was higher in those with the LRRK2 genetic risk variants G2385R and R1628P compared to those without LRRK2 mutations.¹ The authors summarize their findings by saying that 'Our findings from human participants are supportive of the observations from the LRRK2 G2019S chronic colitis mice'. Although we agree with the authors that their findings obtained in human samples are potentially interesting, we would like to draw their attention to a recently published article by our group in which we analyzed LRRK2 expression in the human gastrointestinal tract. In keeping with previous findings obtained in mice², we first showed that the distribution of LRRK2 in the human GI tract was not limited to the immune cells but also extended to the two main plexuses of the human ENS, namely the submucosal and myenteric plexus³ (Figure 1a). Using sigmoid biopsy lysates from 12 PD patients (all Caucasian with no family history of PD) and 11 age-matched controls, we also showed that both LRRK2 expression and kinase activity were significantly reduced in the colon of PD patients when compared to age-matched controls³ (and Figure 1b for experiments with lysates from 6 additional PD subjects and 6 controls). In light of these observations, we believe that the findings from Lin and collaborators obtained with human samples raises more questions than answers. Are the cells that stained positive for LRRK2 in the gastrointestinal biopsies neuronal, immune or both? Is there any difference in the number of LRRK2 positive cells between PD subjects without LRRK2 mutation and controls? What are

the phosphorylation status and kinase activity of LRRK2 in these samples? These questions underscore the fact that future research should be conducted to better characterize the expression levels and kinase activity of LRRK2 in the human gastrointestinal tract under physiological conditions as well as in subjects with idiopathic PD and LRRK2-associated parkinsonism.

Legend to Figure

Figure 1. Expression levels of LRRK2 in the enteric nervous system under physiological condition and in PD. (a) Anti-LRRK2 antibody was used to detect LRRK2 in the myenteric ganglia in a control subject; beta III-tubulin (β III-tub) antibody was used to specifically label neurons. Scale bar is 50 μ m **(b)** Sigmoid biopsies lysates from 6 PD patients and 6 controls (C) were subjected to immunoblot analysis using antibodies against LRRK2 (rabbit monoclonal anti-LRRK2, 1:1,000; MJFF2, c41-2, Abcam, Paris, France); to ensure equal protein loading, membranes were probed with anti- β -actin antibody (1:10,000; A5441, Sigma, Saint-Quentin Fallavier, France). LRRK2 immunoreactive bands were measured using image J (version 1.51), normalized to the optical densities of β -actin and expressed as percentage of controls. GraphPad Prism software version 9.1.1 (GraphPad Software Inc., La Jolla, California, United States) was used for statistical analysis. For statistical comparison between groups, a Mann-Whitney test was performed. All data shown are mean \pm standard error of the mean (SEM). Data correspond to mean \pm SEM, * $p < 0.05$. The sampling of human colon was approved by the Fédération des bibliothèques of the University Hospital of Nantes. Regarding sigmoid biopsies sampling, the study protocol was approved by the local Committee on Ethics and Human Research (Comité de Protection des Personnes Ouest VI), and registered on ClinicalTrials.gov (ColoBioParker, identifier NCT01353183).

Authors Roles

All authors initially discussed the presented concepts. PD wrote the first draft and the figure. All authors edited the manuscript.

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Pascal Derkinderen has nothing to disclose. Adrien de Guilhem de Lataillade has nothing to disclose. Michel Neunlist has nothing to disclose. Malvyne Rolli-Derkinderen has nothing to disclose.

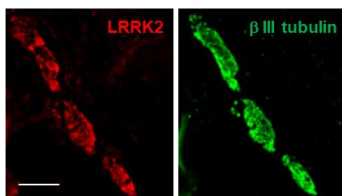
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(a)



(b)

