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EDITORIAL

LRRK2 Expression in the Enteric Nervous System: ENSuring Its Significance

Pascal Derkinderen[1,2,3]

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The hypothesis that the gut is a second brain arose in the early 1900s, when it was discovered that enteric nervous system (ENS) control of intestinal motility and secretion was largely independent of influences from the central nervous system (CNS). The ENS contains as many neurons as the spinal cord; the functional and chemical diversity of enteric neurons closely resembles that of the CNS. The ENS controls gut motility and secretion via local reflexes regulated by the liberation of specific neuromediators synthesized by functionally defined enteric neurons [1]. For example, among the most common neurotransmitters in the ENS, vasoactive intestinal peptide (VIP) and nitric oxide are often expressed in inhibitory muscle motoneurons, whereas acetylcholine and substance P are expressed in excitatory motoneurons. Aside from its well-recognized influences on gastrointestinal motility disorders, it has become evident over the last 20 years that the ENS is also substantially involved in Parkinson's and Crohn's diseases. At some point in the disease course, gastrointestinal symptoms occur in almost every Parkinson's disease (PD) patient, clinical observations supported by *postmortem* studies that demonstrated the presence of alpha-synuclein inclusions, the defining neuropathological hallmark of the disease, in the ENS of almost all Parkinsonian subjects [2]. In Crohn's disease, a number of studies consistently reported quantitative and qualitative changes in the neurochemical composition of enteric neurons in the small intestine and in the rectum [3, 4]. Remarkably, genome-wide association studies identified leucine-rich repeat kinase 2 (LRRK2), the most common gene implicated in the pathogenesis of autosomal dominant PD, as one of the susceptibility genes for Crohn's disease [5]. These genetic data have been supported by a recent Taiwanese epidemiological study, which reported an increased risk of PD among individuals with Crohn's disease [6].

Despite the growing interest in LRRK2 as a regulator of gut functions, existing studies have focused on its expression and functions in intestinal immune cells; no available prior data exist regarding the potential influence of LRRK2 on the ENS. In this context, the aim of the study by Maekawa et al. [7] published in this issue of *Digestive Diseases and Sciences* was to investigate the expression profile and the possible influence of LRRK2 on the ENS. Using wild-type and LRRK2-deficient mice, they showed that, other than in immune cells, LRRK2 is also expressed in enteric neurons of the small intestine (Fig. 1). When compared to wild-type mice, the lack of expression of LRRK2 altered mRNA abundance coding for the major intestinal neuronal peptides, with a significant increase in VIP mRNA associated with a significant decrease in the amounts of mRNAs for substance P and neuropeptide Y [7].

The strength of this article lies in the fact that it is the first study showing that LRRK2 is expressed by enteric neurons and that this protein might be involved in the regulation of ENS and more generally of gut functions. These results reinforce the notion that the bidirectional signaling between the gastrointestinal tract and the brain, i.e., the brain–gut axis, is not only regulated at hormonal and immunological levels but also at neuronal levels. Nevertheless, the preliminary results obtained by Maekawa and collaborators raise more questions than provide

✉ Pascal Derkinderen
derkinderenp@yahoo.fr; pascal.derkinderen@chu-nantes.fr

[1] INSERM, U913, 1, rue Gaston Veil, 44035 Nantes Cedex 1, France

[2] Department of Neurology, CHU Nantes, 44093 Nantes, France

[3] Nantes University, 44035 Nantes, France

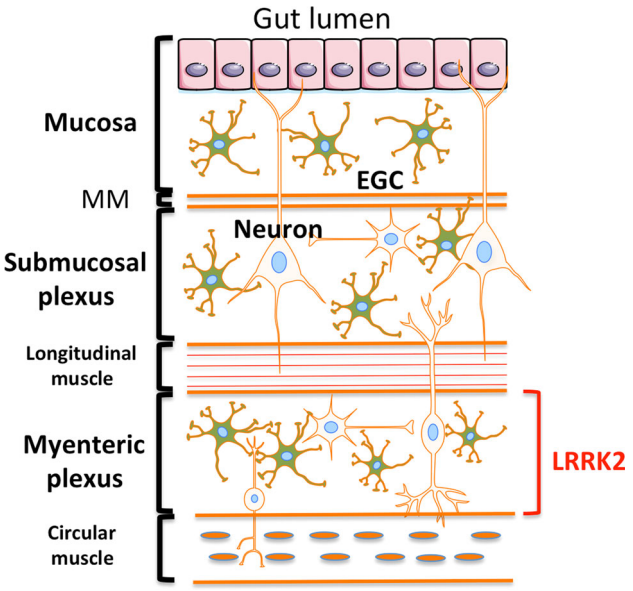

Fig. 1 Cross section of the intestinal wall depicting the results from Maekawa et al. [7] LRRK2 immunostaining is observed in the mouse myenteric plexus in the small intestine and may therefore affect ENS physiology [7]. Specifically related to this study, four questions remain: Is LRRK2 expression in the ENS limited to specific neurochemical subtypes? Do the enteric glial cells (EGC) express LRRK2? Are LRRK2-positive neurons also present in the submucosal plexus? What are the roles of LRRK2 on gastrointestinal functions motility and permeability? MM: *muscularis mucosae*

answers on LRRK2 and ENS physiology. Further research is needed to determine whether the expression of LRRK2 in the ENS is ubiquitous or limited to specific neurochemical subtypes and whether the enteric glial cells, which are the enteric counterpart of the CNS astrocytes, also express LRRK2. Moreover, because the immunohistochemical analysis performed by Maekawa et al. [7] was limited to the myenteric plexus of the mouse small intestine, it is essential to analyze in detail the expression levels of the protein along the entire digestive tract and across the gastrointestinal wall not only in rodent but also in human samples. Another key issue will be to evaluate the effects of LRRK2 deficiency on principal gastrointestinal functions such as motility and permeability (Fig. 1).

The findings of the current research could also be relevant for PD research. Based on the topographic distribution of alpha-synuclein inclusions established after autopsy from PD patients, Braak and coworkers assumed that the gastrointestinal tract may be the trigger site for PD pathology, which would subsequently spread through the vagus nerve to the brain [2]. This 'gut-to-brain' hypothesis, still widely argued, has ignited heated debates among the movement disorders community. Nevertheless, if such a hypothesis is supported, the ENS and the microbiota are both likely to have fundamental contributions to disease pathogenesis. In a recent survey, Sampson et al. [8] evaluated the contributions of the gut microbiota toward the principal gastrointestinal and motor features observed in Parkinsonian patients in an alpha-synuclein transgenic mouse model of PD. Transgenic mice grown under germ-free conditions exhibited milder symptoms than did mice with conventional gut microbiota. Furthermore, when germ-free transgenic mice received the microbiota from patients with PD, their motor dysfunction worsened, strongly suggesting that gut microbiota influence the severity and thus the clinical progression of PD. Although interesting and provocative, these results, far from definitive, need to be replicated in another animal model of PD. Given the possible contributions of LRRK2 to the ENS, it would be tempting to evaluate the effect of microbiota from PD patients in LRRK2 transgenic mice, such as mice bearing the G2019S LRRK2 mutation [9].

In conclusion, the findings presented in the study by Maekawa et al. [7] provide new insights into the physiology of the ENS and more generally into the 'molecular' links between the gut and the brain. More studies evaluating the expression and the roles of LRRK2 in the ENS could clarify whether these results might be of interest for a better understanding and management of Parkinson's and Crohn's diseases.

References

1. Schemann M, Neunlist M. The human enteric nervous system. *Neurogastroenterol Motil.* 2004;16(Suppl 1):55–59.
2. Derkinderen P, Rouaud T, Lebouvier T, Bruley des Varannes S, Neunlist M, De Giorgio R. Parkinson disease: the enteric nervous system spills its guts. *Neurology*. 2011;77:1761–1767.
3. Villanacci V, Bassotti G, Nascimbeni R, et al. Enteric nervous system abnormalities in inflammatory bowel diseases. *Neurogastroenterol Motil*. 2008;20:1009–1016.
4. Schneider J, Jehle EC, Starlinger MJ, et al. Neurotransmitter coding of enteric neurones in the submucous plexus is changed in non-inflamed rectum of patients with Crohn's disease. *Neurogastroenterol Motil*. 2001;13:255–264.
5. Barrett JC, Hansoul S, Nicolae DL, et al. Genome-wide association defines more than 30 distinct susceptibility loci for Crohn's disease. *Nat Genet*. 2008;40:955–962.
6. Lin J-C, Lin C-S, Hsu C-W, Lin C-L, Kao C-H. Association between Parkinson's disease and inflammatory bowel disease: a nationwide Taiwanese retrospective cohort study. *Inflamm Bowel Dis*. 2016;22:1049–1055.
7. Maekawa T, Shimayama H, Tsushima H, et al. LRRK2: an emerging new molecule in the enteric neuronal system that quantitatively regulates neuronal peptides and IgA in the gut. *Dig Dis Sci*. (Epub ahead of print). doi:10.1007/s10620-017-4476-3.
8. Sampson TR, Debelius JW, Thron T, et al. Gut microbiota regulate motor deficits and neuroinflammation in a model of Parkinson's disease. *Cell*. 2016;167:1469–1480.e12.
9. Yue M, Hinkle KM, Davies P, et al. Progressive dopaminergic alterations and mitochondrial abnormalities in LRRK2 G2019S knock-in mice. *Neurobiol Dis*. 2015;78:172–195.