Parkinson's Disease and Gut Microbiota

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Keywords

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Abstract

Background: Parkinson's disease (PD) is caused by abnormal aggregation of α -synuclein fibrils, called the Lewy bodies, in the central nervous system. Accumulating knowledge points to the notion that α -synuclein fibrils start from the dorsal vagal nucleus and ascend to the locus ceruleus and the substantia nigra (SN). Even in healthy elderly subjects without motor or cognitive impairment, α -synuclein fibrils are frequently observed in the brain and sometimes in the intestinal neural plexus. Enteroendocrine cells have a direct synapse to the vagal afferents, and the vagal nucleus has synaptic pathways to the SN and the striatum. Intestinal bacteria are likely to be involved in the formation of intestinal α -synuclein fibrils. **Summary:** A nonparametric meta-analysis of intestinal microbiota in PD in 5 countries, as well as scrutinization of the other reports from the other countries, indicates that mucin-degrading *Akkermansia* is increased in PD and that short-chain fatty acid (SCFA)-producing bacteria are decreased in PD. Both dysbiosis should increase the intestinal permeability, which subsequently facilitates exposure of the intestinal neural plexus to toxins like lipopolysac-

charide and pesticide, which should lead to abnormal aggregation of α -synuclein fibrils. Decreased SCFA also downregulates regulatory T cells and fails to suppress neuronal inflammation. **Key Messages:** Therapeutic intervention may be able to be established against these mechanisms. Additional biochemical, cellular, and animal studies are required to further dissect the direct association between intestinal microbiota and PD.

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Introduction

Parkinson's disease (PD) is the most commonly recognized movement disorder characterized by muscle rigidity, postural instability, gait disturbance, bradykinesia, and rest tremor. PD patients frequently exhibit nonmotor symptoms including mild-to-severe cognitive impairments. Gastrointestinal symptoms are also commonly observed nonmotor symptoms in PD patients affecting up to 80%. Braak et al. [1] examined Lewy bodies in autopsied PD patients without cognitive symptoms as well as in healthy subjects and found that Lewy bodies start from the dorsal vagal nucleus and ascend to the locus ceruleus and the substantia nigra. Clinically, constipation, rapid eye movement behavior disorder (RBD), and de-

pression frequently precede approximately 20, 10, and 5 years, respectively, before the onset of motor symptoms of PD [2].

Inflammatory bowel diseases, namely, ulcerative colitis and Crohn's disease, increase the incidence of PD by 22–35% [3]. Appendectomy performed >30 years ago reduces the incidence of PD by 19% [4]. These findings are in accordance with the notion that increased intestinal permeability is causally associated with PD. Epidemiological studies indicate that truncal vagotomy reduces a chance of developing PD by ~50% [5]. Enteroendocrine cells have a direct synapse to vagal afferents [6], and the vagal nucleus has synaptic pathways to the SN and the striatum [7]. Animal models also indicate trans-vagal prion-like transmission of α -synuclein fibrils [8]. Additionally, intraperitoneal administration of LPS increases intestinal permeability and causes accumulation of α -synuclein fibrils in the intestinal mucosa and dorsal vagal nucleus [9]. Furthermore, LPS promotes the formation of α -synuclein fibrils in vitro. In a mouse model of PD, germ-free mice have milder motor symptoms and milder constipation compared to specific pathogen-free mice [10]. Transplantation of fecal microbiota obtained from PD patients exacerbates motor symptoms and constipation more than that from healthy individuals. Association between intestinal microbiota and PD has been analyzed in each country [11, 12]. However, divergence of intestinal microbiota even in healthy subjects across countries has made it difficult to identify intestinal bacteria that are commonly changed in PD in the world. We recently reported a nonparametric meta-analysis of intestinal microbiota in PD in 5 countries [13]. This review will focus on gut dysbiosis shared across countries in PD patients and also on possible mechanisms of how gut dysbiosis is causally associated with the onset and development of PD.

Intestinal Bacteria

Because the compositions of the intestinal microbiota vary from country to country even in healthy individuals, gut dysbiosis observed in PD largely differ from report to report (Table 1). In addition, taxonomic identities are dependent on which database was used in the metagenome analysis and are different from report to report. Currently, SILVA is the most commonly used taxonomic database, but Greengenes, Ribosome Database Project (RDP), and NCBI are also sometimes used. We recently reported 16S ribosomal RNA (rRNA) gene sequencing of fecal

samples from 223 PD patients and 137 controls and meta-analyzed our dataset with 4 previously reported datasets of PD patients and controls [13]. We used the same analysis pipeline with the SILVA database for the 5 datasets. We found that enterobacteria that were increased in PD at the genus level were *Akkermansia* and *Catabacter* and those that were decreased in PD at the genus level were *Roseburia*, *Faecalibacterium*, and *Lachnospiraceae* ND3007. At the family level, Lactobacillaceae and Akkermansiaceae were increased in PD. In addition, *Akkermansia* was increased with progression of PD, whereas *Faecalibacterium* and *Roseburia* were decreased with progression of PD in our own dataset. Recent reports [14–16] with 100 or more PD patients also show an increase of *Akkermansia* and decrease of *Lachnospiraceae*, *Roseburia*, and *Faecalibacterium* in PD. *Lachnospiraceae*, *Roseburia*, and *Faecalibacterium* produce short-chain fatty acids (SCFAs), especially butyric acid. In addition, Lactobacillaceae is often reported to be increased in PD. However, the increase of Lactobacillaceae was largely due to a confounding effect of catechol-O-methyltransferase (COMT) inhibitor and partly due to a confounding effect of constipation. Lactobacillaceae was not significantly different between PD without taking a COMT inhibitor and healthy subjects [13]. Metagenome analysis of 16S rRNA sequencing data gives us relative abundance of each bacterium but not an absolute bacterial count. We previously analyzed absolute counts of 19 representative intestinal taxa that covered 71.3% of total intestinal bacteria using quantitative reverse transcription PCR of 16S rRNA and reported that the total intestinal bacterial count was lower in PD compared to healthy individuals [17]. The total intestinal bacterial count was also decreased in 2 years in PD [18]. The absolute counts of total intestinal bacteria have been rarely reported, and the pathological significance of reduced bacterial counts remains elusive.

As more and more studies have been conducted on a large number of cases, methods such as network analysis and pseudo-functional analysis have been introduced in addition to simple statistical estimation. Pseudo-functional analysis can be performed using PICRUSt2 with the 16S rRNA seq dataset. PICRUSt2 enables us to predict functional annotations of intestinal microbiota using the Kyoto Encyclopedia of Genes and Genomes (KEGG) orthologs (KOs). In gene expression analysis, Gene Set Enrichment Analysis (GSEA) is commonly used as a de facto standard tool. In GSEA, we substituted PICRUSt2-generated KOs for gene expression profiles and named this method as KEGG Orthology Set Enrichment Analy-

Table 1. Gut microbiota in Parkinson's disease

Dataset	First author	City, country ^a	Date ^b	PD [#]	Controls [#]	Sequencing	Primers
1	Scheperjans	Helsinki, Finland	Dec 2014	72	72	16S rRNA V1-3	27F/530R
2	Keshavarzian	Chicago, IL, USA	July 2015	38	36	16S rRNA V4	515F/806R
3	Hasegawa et al. [17]	Nagoya, Japan	Nov 2015	52	36	qRT-PCR	Not applicable
4	Unger et al. [22]	Homburg, Germany	Sep 2016	34	34	qPCR	Not applicable
5	Petrov	Tomsk, Russia	Dec 2016	89	66	16S rRNA V3-4	Not specified
6	Hill-Burns	Birmingham, AL, USA	Feb 2017	197	130	16S rRNA V4	515F/806R
7	Bedarf	Bonn, Germany	Apr 2017	31	28	Shotgun	Not applicable
8	Hopfner	Kiel, Germany	May 2017	29	29	16S rRNA V1-2	Not specified
9	Li	Beijing, China	May 2017	24	14	16S rRNA (region not specified)	Not specified
10	Qian	Shanghai, China	Mar 2018	45	45	16S rRNA V3-4	341F/806R
11	Lin	Guangzhou, China	May 2018	75	45	16S rRNA V4	V4F/V4R
12	Heintz-Buschart	Kassel, Germany ^c	Aug 2018	26	38	16S rRNA V4	515F/805R
13	Tan	Kuala Lumpur, Malaysia	Oct 2018	104	96	16S rRNA V3-4	Not specified
14	Barichella et al. [14]	Milan, Italy	Mar 2019	193	113	16S rRNA V3-V4	341F/785R
15	Aho	Helsinki, Finland	Jun 2019	64	64	16S rRNA V3-4	341F/785R
16	Li	Changchun, China	July 2019	51	48	16S rRNA V4	515F/806R
17	Pietrucci	Rome, Italy	Oct 2019	80	72	16S rRNA V3-V4	Not specified
18	Nishiwaki et al. [13]	Nagoya, Japan	Jun 2020	223	137	16S rRNA V3-4	341F/805R
19	Cristea [15]	British Columbia, Canada	July 2020	197	103	16S rRNA V4	515F/806R
20	Wallen et al. [16]	Birmingham, AL, USA	Jun 2020	323	184	16S rRNA V4	515F/806R

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sis (KOSEA) [13]. KOSEA revealed that metabolisms of butanoate and propionate were changed in the intestinal microbiota in PD. This is in accordance with decreased abundance of SCFA-producing bacteria in PD. KOSEA also showed an increase in the degradation of valine, leucine, isoleucine, and lysine. Similar results were obtained using MetaCyc metabolic pathways [15]. Control microbiota was enriched in pathways related to carbohydrate degradation, whereas PD microbiota was enriched in pathways related to nucleic acid degradation and amino acid metabolism. Interestingly, PD microbiota was also enriched in 2 fucose degradation pathways, where fucose is derived from N-linked glycans decorating host mucin proteins. According to the network analysis using SparCC, 2 networks were observed in PD [13]. One was composed of increased genera in PD, such as genera *Akkermansia* and *Christensenellaceae R-7 group*. The other was composed of decreased genera in PD, such as genera *Faecalibacterium*, *Roseburia*, and *Fusicatenibacter*. The genus *Christensenellaceae R-7 group* was a hub of the increased subcluster and connected to the genus *Akkermansia*. *Ak-*

kermansia and *Christensenellaceae R-7 group* might symbiotically play an important role in the development and/or progression of PD. Reduction of a network of SCFA-producing bacteria in PD was also reported by others [14, 16]. Based on these results, 2 major microbiota networks are changed in PD. When the dietary fibers are defective, *Akkermansia muciniphila* degrades the gut mucus layer and increases the intestinal permeability [19]. *Faecalibacterium* and *Roseburia* that are decreased in PD are butyrate-producing bacteria. Butyrate, as well as other molecules in SCFAs, induces the expression of anti-inflammatory cytokines by inhibiting histone deacetylase [20]. SCFAs also bind to G-protein-coupled receptors (e.g., GPR41, GPR43, and GPR109A) and exert an anti-inflammatory effect by increasing and/or activating regulatory T cells. The mucin-degrading *Akkermansia* and LPS-producing Gammaproteobacteria were increased in PD patients. Both dysbiosis should lead to increased intestinal permeability, motor impairment, nigral aggregation of α -synuclein fibrils, dopaminergic neuronal loss, and reduction in striatal dopamine (Fig. 1).

Fig. 1. Putative mechanisms of how gut dysbiosis cause the development and progression of PD. When the dietary fibers are defective, *Akkermansia muciniphila* degrades the gut mucus layer and increases the intestinal permeability. *Faecalibacterium* and *Roseburia* that are decreased in PD are butyrate-producing bacteria. Decreased butyrate and other SCFAs also decrease the gut mucus layer. Increased intestinal permeability is likely to expose the intestinal neural plexus to toxins like LPS and pesticides to cause abnormal aggregation of α -synuclein fibrils. In addition, SCFAs induce the expression of anti-inflammatory cytokines by inhibiting his-

tone deacetylase and upregulate Treg. Reduced SCFAs should aggravate neuroinflammation in the central nervous system. Intestinal acetate and propionate stimulate GPR41 and GPR43 to release PYY and GLP-1, which affect satiety and intestinal transit. Both dysbiosis should lead to increased intestinal permeability, motor impairment, nigral aggregation of α -synuclein fibrils, dopaminergic neuronal loss, and reduction in striatal dopamine. PD, Parkinson's disease; SCFAs, short-chain fatty acids; LPS, lipopolysaccharide; Treg, regulatory T cells.

Rapid eye movement sleep behavior disorder (RBD) frequently predisposes to α -synucleinopathy including PD, dementia with Lewy bodies, and multiple system atrophy. RBD patients sometimes have subtle motor and cognitive deficits, as well as constipation, before the onset of PD and other α -synucleinopathies. RBD is the most dependable hallmark of prodromal PD. LIGER is a topic model-based tool that was developed for the analysis of single-cell RNA seq (scRNA-seq) data. In scRNA-seq analysis, a set of genes are up- or downregulated in specific cells, and LIGER identifies such gene sets. This is analogous to intestinal microbiota, in which a set of bacteria are increased or decreased in specific individuals. We thus exploited LIGER to make unsupervised cluster-

ing of intestinal microbiota in controls, RBD patients, and PD patients and found 4 enterotypes of A, B, C, and D (Fig. 2) [21]. Severity of PD is classified by Hoehn and Yahr disease-rating scales 1–5, where 1 is the mildest form and 5 is the severest form. The proportion of controls in each enterotype was decreased in the order of enterotypes A to D, while the proportions of Hoehn and Yahr scales 3–5 were increased in the same order. Analysis of individual bacteria taxa revealed that the genus *Akkermansia* was significantly increased in RBD compared to controls. In contrast, SCFA-producing genera *Faecalibacterium*, *Roseburia*, and *Lachnospiraceae* ND3007 group were not different between RBD and controls, although *Faecalibacterium* tended to be decreased in RBD.

Fig. 2. Overall compositions of gut microbiota in controls, iRBD, and PD (Hoehn and Yahr disease-rating scales 1–5) in our dataset. **a** PCoA plot showing the center of gravity of the overall compositions of gut microbiota in 7 morbidity categories. Hoehn and Yahr scales are indicated by 1–5, where 1 is the mildest form and 5 is the severest form. Standard errors are indicated by whiskers. **b** Unsupervised clustering of overall compositions of gut microbiota in controls, iRBD, and PD by LIGER yielded 4 enterotypes. tSNE was adopted to visualize 4 clusters representing enterotypes A–D. **c** Fractional ratios of controls, iRBD, and Hoehn and Yahr scales

1–5 in each enterotype. Note that controls and iRBD are high in enterotype A, whereas severe PD patients are high in enterotype D. **d** Bacterial abundance in a total of 386 subjects was factorized into multiple factors. The first factor is color coded in each subject on a tSNE plot indicated in (b). SCFA-producing bacteria have high loadings in the first factor; individuals colored in blue carry a high proportion of SCFA-producing bacteria. PD, Parkinson's disease; iRBD, idiopathic rapid eye movement sleep behavior disorder; SCFA, short-chain fatty acid.

Thus, increased *Akkermansia* is likely to occur even in RBD, and decreased *Faecalibacterium* may be a hallmark to predict a transition from RBD to PD. We expect that administration of SCFAs and probiotic/prebiotic treatment to increase the production of SCFAs may be able to ameliorate the progression of α -synucleinopathy at the stage of RBD.

Metabolites by Intestinal Bacteria

Intestinal bacteria produce SCFAs, as well as vitamins B2, B6, B12, and K, folic acid, pantothenic acid, biotin (B7), serotonin, and polyamines. Serotonin promotes intestinal peristalsis. Intestinal SCFAs are decreased in PD [17, 22]. Serum polyamines are also decreased in PD [23].

Fig. 3. The microbial conversion of dietary fiber in the gut results in synthesis of the 3 major SCFAs, acetate, propionate, and butyrate. Acetate is produced from pyruvate via acetyl-CoA and also via the Wood-Ljungdahl pathway. Butyrate is synthesized from 2 molecules of acetyl-CoA, yielding acetoacetyl-CoA, which is further converted to butyryl-CoA via β -hydroxybutyryl-CoA and crotonyl-CoA. Propionate can be formed from PEP through the succinate pathway or the acrylate pathway, in which lactate is reduced to propionate. Microbes can also produce propionate through the propanediol pathway from deoxyhexose sugars, such as fucose and rhamnose. Representative intestinal bacteria that utilize the indi-

cated pathways are as follows: acetate from pyruvate via acetyl-CoA: most of the enteric bacteria. Wood-Ljungdahl pathway: *Blautia*, *Clostridium* spp., and *Streptococcus* spp. Propionate succinate pathway: *Bacteroides* spp. and *Veillonella* spp. Acrylate pathway: *Coproccoccus*. Butyrate-producing phosphotransbutyrylase/butyrate kinase route: *Coproccoccus*. Butyryl-CoA: acetate CoA-transferase route: *Coproccoccus*, *Eubacterium rectale*, *Eubacterium*, *Faecalibacterium prausnitzii*, and *Roseburia* spp. PEP, phosphoenolpyruvate; DHAP, dihydroxyacetonephosphate; SCFA, short-chain fatty acid.

We will focus on the roles of SCFAs and polyamines in this communication.

The major products from the microbial fermentative activity in the gut are SCFAs, in particular, acetate, propionate, and butyrate. However, when fermentable fibers are in short supply, microbes switch to energetically less-favorable sources for growth such as amino acids from dietary or endogenous proteins or dietary fats. Protein fermentation can contribute to the SCFA pool but mostly gives rise to branched-chain fatty acids such as isobutyrate, 2-methylbutyrate, and isovalerate, which exclusively originate from branched-chain amino acids

of valine, isoleucine, and leucine. The microbial conversion of dietary fiber in the gut results in the synthesis of the 3 major SCFAs, acetate, propionate, and butyrate (Fig. 3). Butyrate is a preferred energy source for colonocytes and is locally consumed, whereas other SCFAs drain into the portal vein. Propionate is metabolized in the liver and thus is present at low concentrations in the peripheral circulation, leaving acetate as the most abundant SCFA. Furthermore, acetate can cross the blood-brain barrier and reduce appetite via a central homeostatic mechanism. Intestinal acetate and propionate stimulate GPR41 and GPR43 to release PYY and GLP-1,

which affect satiety and intestinal transit. Luminal butyrate exerts anti-inflammatory effects by binding to GPR109A and also by inhibiting histone deacetylase. Furthermore, propionate can be converted into glucose by intestinal gluconeogenesis, leading to satiety and decreased hepatic glucose production [24]. The immune-suppressive mechanisms are indispensable for intestinal homeostasis. Besides its effects on intestinal epithelial cells, butyrate can also modulate the activity of the enteric nervous system. GPR41 is widely expressed in the peripheral nervous system, such as sympathetic ganglia, as well as vagal, dorsal root, and trigeminal ganglia [25]. They can act at distal sites such as the brain, modulating permeability, neurogenesis, and behavior of the host. Decreased intestinal SCFA is thus likely to be sufficient to promote α -synuclein-mediated exacerbation of PD symptoms. Further characterization of the link between microbiota and microglia is expected.

Polyamines (PAs) are defined as small polycationic molecules with a wide range of biological functions, including gene regulation, stress tolerance, cell proliferation, and cell differentiation. Ingested food is the main source of PAs in the lumen, and the majority of these compounds are absorbed in the upper part of the intestine. Therefore, the main source of PA levels in the lower part of the gut should be gut microbiota [26]. PAs in the colonic lumen are transferred to the bloodstream through the colonic mucosa. The availability of cellular PAs contributes to tissue homeostasis, epithelial cell division, and apoptosis in the gastrointestinal mucosa by regulating the expression of various growth-related genes [27]. Putrescine and spermidine are the most common PAs in bacteria. As far as we know, no bacteria carry an enzyme to transduce spermidine to spermine. Little is known about the production and degradation of biogenic amines by the gut microbiota, especially PAs. The genus *Bacteroides* has a CASDC homolog that is essential for spermidine biosynthesis [28]. However, many colonic microbial species do not have a complete synthetic pathway for producing PAs [29]. Arginine is converted to ornithine and further to putrescine in bacteria. Arginine is also converted to agmatine and further to putrescine in the following 2 bacteria. The acid-tolerant system of *E. coli* produces agmatine from arginine in a low pH environment. *Enterococcus faecalis* metabolizes agmatine to yield putrescine via the agmatine/putrescine antiporter in the agmatine deiminase pathway [30]. The presence of other bacteria, such as *Bifidobacterium* spp. that produce acidity in the gut, is advantageous for putrescine production.

Summary

Our current knowledge on the association between intestinal microbiota and PD indicates 2 pathomechanisms in the PD intestine. First, the decrease of SCFA-producing bacteria and the increase of mucin-degrading *Akkermansia* are likely to increase the intestinal permeability to expose the intestinal neural plexus to toxins like lipopolysaccharide and pesticides, which should lead to abnormal aggregation of α -synuclein fibrils. The increased intestinal permeability is underscored by decreased serum LPS-binding protein in PD [17, 22]. Second, the decrease of SCFA-producing bacteria also aggravates microglia-mediated inflammation in the central nervous system. Therapeutic intervention to modify these intestinal maladies may be able to be established. Metagenomic analyses of intestinal microbiota using next-generation sequencers have accelerated the elucidation of taxonomic changes in PD. However, many of the intestinal bacteria are difficult to culture or remain uncultured. In particular, most of butyrate-producing bacteria cannot be cultured. In addition, even when the whole genome sequences of intestinal bacteria are available, gene annotations remain largely unidentified. It is critical to establish gene annotations of intestinal bacteria. Currently, KEGG is a dependable database for analyzing intestinal microbiota, but we expect that KEGG orthology becomes more extensive and more comprehensive. For example, it is currently unclear whether the presence of functional genes in bacteria leads to the extracellular secretion of metabolites. Given that bacteria consume energy to produce metabolites, most of the metabolites are predicted to be consumed intracellularly. Most of the metabolites secreted are no longer needed for the bacteria, or secreted, for example, for self-preservation of a low pH environment, as we observe in the acid-tolerant system of *E. coli*. Accumulating knowledge supports the notion that intestinal microbiota indeed affects the development and progression of PD. Further studies, however, are required to dissect the exact molecular mechanisms directly linking intestinal dysbiosis to PD.

Conflict of Interest Statement

The authors have no conflicts of interest to disclose.

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Author Contributions

M. Hirayama reviewed all abstracts and articles and drafted, revised, and approved the final manuscript. K. Ohno reviewed and approved the final manuscript. All authors read and approved the final manuscript.

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