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REVIEW ARTICLE

The gut-brain axis in the pathogenesis of Parkinson's disease

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ABSTRACT

Parkinson's disease (PD) is the second most common neurodegenerative disease. Its pathological markers include Lewy bodies and Lewy neuritis, which primarily affect the substantia nigra. However, in recent years, mounting evidence suggests that PD is a multifocal neurodegenerative process that influences several neuronal structures aside from the substantia nigra, one of which is the enteric nervous system. Many clinical studies have reported that patients with PD experience gastrointestinal dysfunction for many years before the onset of motor symptoms. Emerging evidence indicates that α-synuclein deposition may start in the enteric nervous system and then propagate to the central nervous system. The gut-brain axis plays an important role in PD pathogenesis. Recent evidence suggests that these interactions may be primarily affected by the intestinal microbiota. In this review, the authors discuss recent research, and illustrate how changes in the composition of the gut microbiota may trigger inflammation, thus contributing to neurodegeneration in PD.

1 Neurodegenerative diseases

Neurodegenerative diseases are characterized by the progressive loss of neurons in the nervous system. The most common neurodegenerative diseases include Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis, and Huntington's disease, among others. The etiology and pathogenesis of these diseases remain largely unknown. Aging is the major risk factor for these diseases. Aging is accompanied by a series of cellular and functional impairments, such as cell dysfunction, genomic and protein instability, and impaired mitochondrial function. Thus, age-related vulnerability to neurodegenerative disease occurs on a background of organ functional decline.

The neurodegenerative diseases share common pathological characteristics of aberrant protein aggregation and deposition. Each neurode-

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generative disease is associated with the accumulation of major and specific misfolded proteins, such as tau and Aβ in AD, α-synuclein in PD, and huntingtin in Huntington's disease. Pathological accumulation of misfolded neuronal proteins leads to synaptic dysfunction and neuronal death and, thus, patients experience problems with movement, abstract thinking, cognition, emotional feelings, memory, and other abilities.

2 Gastrointestinal pathology in PD

As the second most common multisystem neurodegenerative disease, PD is associated with both motor and non-motor symptoms. The deposition of Lewy bodies and Lewy neurites containing misfolded α-synuclein (α-Syn) aggregation in neuronal perikaryal and neuronal processes, and the selective loss of midbrain dopaminergic (DA) neurons in the substantia nigra pars compacta are hallmarks of PD, and eventually lead to motor impairment including bradykinesia, tremor, and postural instability [1, 2].

Except for the above-mentioned degenerative changes in midbrain DA neurons, which are responsible for motor symptoms in PD, widespread neuropathological changes in the autonomic nervous system, lower brainstem, cerebral cortex, and olfactory structures are also found in individuals with PD [3–6]. It has become increasingly evident that extranigral pathology is associated with a broad spectrum of non-motor symptoms in PD [7, 8]. Gastrointestinal (GI) dysfunction is a prominent nonmotor manifestation of PD, which usually occurs at the very early stage of the disease, years before the appearance of motor symptoms. GI symptoms usually include excessive salivation, constipation, dysphagia, esophageal motility disorder, and gastric dysfunction. Constipation is usually the first symptom of PD, and affects up to 80% of PD patients. Furthermore, some studies have found that patients with PD experience constipation for more than 20 years before the onset of motor symptoms [6, 7, 9, 10]. Furthermore, an animal study found that the A53T α-Syn mice display significant GI dysfunction prior to the motor impairments and CNS α-Syn pathology [11]. According to Braak's hypothesis, the pathological process of PD initiates in the enteric nervous system (ENS). Hence, α-Syn-associated neurodegeneration in the ENS is a manifestation of the onset of motor symptoms in PD patients [4, 12]. Several neuropathological research studies have suggested that there is deposition of α-Syn-immunoreactive Lewy neurites and Lewy bodies in the GI tract, even up to 20 years before the onset of PD motor symptoms [13–15]. However, the specific relationship between ENS and central nervous system (CNS) pathologies remains largely unknown.

3 Innervation of the GI tract

Based on the topographic distribution of Lewy bodies in PD patients, Braak and colleagues hypothesized that α-Syn pathology initiates in ENS, and then spreads to the brain. Because early α-Syn aggregation is commonly found in structures providing parasympathetic innervation to the intestine in the early stages of PD, the vagal nerve may serve as the conduit of communication between the gut and brain [3, 5, 16].

Normal intestinal physiological processes, such as absorption of nutrients, and induction of mucosal and systemic immune response, are dependent on the GI tract. Gut motility is controlled by extrinsic input from the dorsal motor nucleus of the vagus (DMV) and paravertebral sympathetic ganglia, but also by local reflexes mediated by intrinsic neurons of the ENS [17–20]. Parasympathetic output originates in the DMV of the medulla and the sacral parasympathetic nucleus of the spinal cord [21, 22]. Sympathetic output originates from the prevertebral ganglia [23, 24].

4 Gut microbiota in PD

The gut is a complicated organ and is home to 100 trillion bacteria, which outnumber the cells of the human body by a factor of 10. The gut microbiota includes approximately 3 million genes, 150 times greater than the human genome. More interestingly, for most individuals, one-third of the gut microbiota is the same among the population, while two-thirds is special to each subject [25]. A diverse and balanced gut microbiota— and its subsequent maintenance—plays a fundamental role in the health status of the host. Some research has shown that alterations in gut microbiota composition in humans are related to PD, and that these changes may be a risk factor for PD. According to a study by Scheperjans, different bacterial families of gut microbiota are closely associated with PD motor phenotypes. *Enterobacteriaceae* in patients with postural balance disorder and abnormal gait phenotype were found to be significantly more abundant in tremor-positive patients. Furthermore, the severity of these symptoms is positively correlated with the concentration of *Enterobacteriaceae* [26]. In contrast, another group reported that the abundance of *Enterobacteriaceae* did not differ among PD phenotypes [27]. Both teams found that bacterial overgrowth in the small intestines of patients with PD was related to worse motor function [28, 29]. In addition, there is a strong correlation between *Helicobacter pylori* infection in the GI tract and the deterioration of motor function in patients with PD [30–32]. In fact, Braak also hypothesized that sporadic PD may be triggered by an unknown pathogen reaching the gut, which is then transported to the brain [3].

Recently, the concept of "gut-brain axis" has been introduced and largely accepted. In the past few years, some research has found that the gut microbiota has a profound impact on the CNS [33]. In 2016, Mazmanian et al. found that gut microbiota promotes motor and GI dysfunction [34]. When gut bacteria are eliminated by antibiotics, or under germ-free conditions, α-Syn-overexpressing (ASO) mice exhibited reduced motor deficits compared with mice harboring a complex microbiota. At the same time, they observed much less α-Syn pathology in the substantia nigra of germ-free ASO animals compared with control ASO mice with microbiota in the GI tract [34]. Moreover, Michel et al. found that Pink1 knockout mice showed a significant decrease of dopaminergic axonal varicosities in the striatum after intestinal infection with bacteria. These mice exhibited PD-like motor impairment which can be alleviated by levodopa treatment [35]. Clinical investigations have demonstrated that the microbiomes of PD patients were significantly different from those of control subjects [26, 36, 37]. To determine whether human gut microbes affect PD onset and progression, researchers collected fecal samples from patients with PD and healthy controls, and transferred them into germ-free animals. As a result, PD-derived gut microbiota not only had a strong effect on the microbial communities but also exacerbated motor dysfunction [34].

5 Inflammation and PD

As mentioned above, the correlation between changes in the gut microbiota and PD has been established. However, how different microbial populations change and their physiological outcomes remain unclear. One clinical investigation reported that the expression of pro-inflammatory cytokines (tumor necrosis factor-alpha, interferon-gamma, and interleukin-1 [IL-1] and IL-1β) were increased in colonic biopsies obtained from PD patients [38]. Another study measured immune- and angiogenesis-related proteins in human stool, and found that the levels of immune factors in PD patients were higher than controls [39].

Nevertheless, whether changes in the gut microbiota cause the production of pro-inflammatory cytokines in the gut of PD patients remains elusive. Recent studies have shown that short-chain fatty acids, one of many gut microbiota metabolites, promote microglia to fully mature and le ad to an inflammatory response [40]. Similar results were observed by Sarkis and colleagues in animal models [34]. Moreover, other groups have found that microglia activation and neuroinflammation alter neuronal function and increase cell death in PD models [41, 42]. Recently, another clinical investigation found that patients with inflammatory bowel disease (IBD) had a higher risk of PD when compared with non-IBD individuals [43]. All these results indicate that GI inflammation plays an important role in the development of PD pathology.

Inflammation has long been speculated to be a key contributor to the pathogenesis of PD. In one study, pro-inflammatory lipopolysaccharides (LPS) were reported to initiate the degeneration of DA neurons in the substantia nigra of rodents [44–46]. Moreover, environmental factors, such as the pesticide rotenone, in combination with LPS, worked synergistically to induce the selective degeneration of DA neurons [47]. These results provided evidence that inflammation is an important mediator in the pathogenesis of PD.

Inflammation, however, is a "double-edged sword" in PD. Inflammation is the first line of defense against infections and injuries. However, an excessive inflammatory response is harmful to host cells [48]. α-Syn is known to aggregate in an inflammatory environment, which activates microglia [49]. The over-activated microglia cause damage to neurons [41, 50]. Due to the inability of neurons to divide and recover from damage, neurons are highly vulnerable to auto-destructive immune and inflammatory processes [51–53]. This physiological property may prevent neurons from recovering neurological function at sites of inflammation and even exacerbate neuronal damage.

6 Transmission of pathological α-Syn from the gut to the brain

Misfolded protein aggregates are key pathological hallmarks of neurodegenerative disorders. Protein aggregation occurs through "nucleation seed" polymerization model, and is not a random process [54, 55]. Stable "seeds" are formed in the nucleation phase. One widely accepted view is that the seeds play an important role in the initiation and development of disease [56]. These seeds can recruit and convert the normal protein, generating aggregated oligomers, which in turn results in the formation and propagation of amyloid fibrils [57].

The fibrils are not only a key pathological characteristic of neurodegeneration, but also the reason for neurodegeneration. In the early stages of neurodegeneration, pathological changes, such as aggregated fibrils of misfolded proteins and neurological disorder, are localized in a confined area of the nervous system. However, in later stages, such changes become more prevalent and dispersed, indicating that pathological fibrils spread throughout the nervous system. Mounting evidence indicates that misfolded fibrillar forms of α-Syn self-propagate and spread among interconnected regions of the CNS, suggesting that cell-to-cell transmission of pathological proteins may explain disease progression [58–63]. Recently, it has been proposed that pathological misfolded proteins spread between neurons in a prion-like manner within the nervous system [64]. The concept of the prion was first proposed by S.B. Prusiner, who purified the scrapie agent, and found that is a protein with the capability of replicating without nucleic acid. The prion diseases are caused by the conformational change of normal cellular protein into an abnormal form, termed "prions", which then serve as templates, further induce the

misfolding of normal proteins. It is now believed that this induced conformational self-propagation plays a major role in many neurodegenerative diseases, including PD and AD [65, 66].

The misfolded α-Syn fibrils can induce monomeric α-Syn to misfold in the same cell. The α-Syn then aggregates and is released into the extracellular space. The aggregates can enter a new cell, the misfolded α-Syn fibrils further seed soluble α-Syn into a misfolded and aggregated form. Thus, the misfolded protein can act as a template for inducing monomeric α-Syn to misfold and spread disease from one cell to another [67–70]. Recently, researchers have provided direct evidence of gut-brain α-Syn transmission in rodent models. Li and colleagues found that pathological α-Syn fibrils derived from PD patients migrate from the GI tract to the brain through the vagus nerve in a rat model. At the same time, they even observed similar phenomena when injecting preformed artificial oligomeric and fibrillar α-Syn into the GI tract [71]. In a parallel study, the authors injected α-Syn performed fibrils into the duodenal and pyloric muscular layer of mice, and found that aggregates of pathological α-Syn can spread from the gut to the brain through the vagus nerve. What's more, the α-Syn pathology was accompanied by loss of dopaminergic neurons and was also associated with PD-like motor and non-motor symptoms [72]. Another study led by Nathalie Van Den Berge found that pathological α-Syn can spread along both the sympathetic and parasympathetic pathways in transgenic rats that overexpressed a human form of α-Syn [73]. All these new rodent models provide useful tools to explore the specific relationship between the gut-brain axis and PD pathology.

7 Conclusions

Dysbiosis in the GI tract may be a cause of PD and other neurodegenerative diseases. The balance of gut microbes is important for maintaining the health of the brain and gut. Changes in gut microorganisms affect the development and function of the CNS through the gut-brain axis; the hypothesis is illustrated in Fig. 1. Thus, it is important to study the relationship between the human gut microbiome and its functions in health and diseases. Based on current evidence, we propose that altered microbiota in the gut promotes the aberrant aggregation of α-Syn by enhancing inflammation. The aggregated α-Syn fibrils further self-aggregate and spread to the CNS through the gut-brain axis. A better understanding of gut-brain interactions in PD may provide new insights into early diagnosis and lead to novel therapeutic methods.

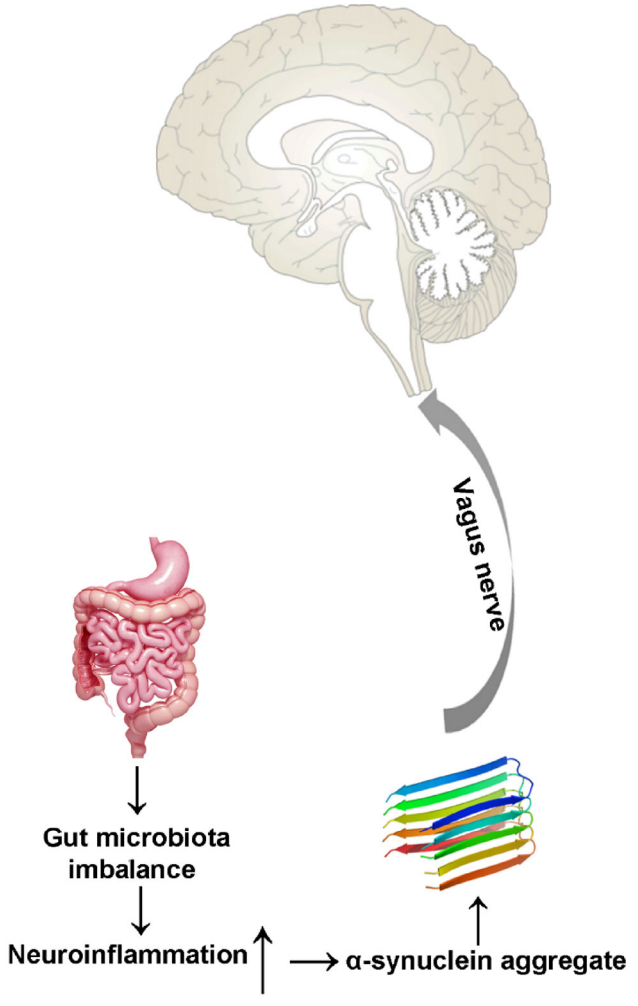

Fig. 1 Gut microorganisms affect the function of the central nervous system through the gut-brain axis.

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Conflict of interests

All contributing authors have no conflict of interests to declare.

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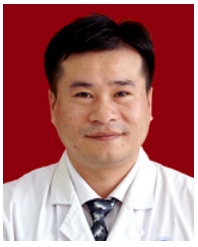

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