Parkinson’s disease (PD) is characterized by motor symptoms and non-motor symptoms chiefly attributed to the loss of dopaminergic neurons in the substantia nigra pars compacta [1]. Approximately 3 million PD patients suffer from motor deficits including tremors, muscle rigidity, bradykinesia and psychological abnormality [2]. The main pathological change of PD is the degeneration and death of dopaminergic neurons in the substantia nigra pars compacta, which leads to a significant decrease in dopamine content in the striatum. The pathogenesis of PD is fairly complex. Genetic factors, environmental factors, aging, oxidative stress, and inflammation may be related to the degeneration and death of PD dopaminergic neurons [3]. There are five main classes of drugs currently available to treat PD, including dopamine receptor agonists, monoamine oxidase B inhibitors, catechol-oxo-methyltransferase inhibitors, anticholinergic drugs, and amantadine. However, these drugs can only relieve the condition of PD patients, but not block it, and most have side effects. That is, there are still no effective therapeutic drugs to prevent PD.

Intestinal flora is the gut microbes in the human body, and there are about 10 trillion bacteria in the human intestine. Intestinal flora can synthesize different vitamins and amino acids which are necessary for human growth and development and participate in the metabolism of sugars and proteins [4, 5]. Currently, studies have demonstrated that the imbalance of intestinal flora is closely related to the occurrence and development of cardiovascular diseases [6], obesity [7] and nervous system diseases [8]. Targeting the gut microbiota has become an effective treatment strategy for these diseases.

“Gut-first theory” has gradually become the mainstream of PD pathogenesis. The Braak hypothesis indicates that α-synuclein (α-syn) can spread from the intestinal flora via the vagus nerve to the ventral midbrain and selectively damages dopamine neurons of the substantia nigra pars compacta through the analysis of human pathology [9, 10]. In this paper of Neuron, Kim et al. provide first and direct evidence that α-syn aggregation initiating in the gut and spreads from the gut to the brain via the vagus nerve, which supports the idea that the gut could be a starting point for PD [11]. The short-chain fatty acids (SCFAs) metabolized from gut microbes has been found to be tightly linked to neuroinflammatory responses and α-syn-dependent motor deficits [12]. Gut microbes modulate microglia activation through production of microbial metabolites, namely SCFAs, and depletion of gut microbes decrease microglia activation [13]. Furthermore, α-syn immunizations induce intestinal inflammation, and neuron loss in the gut, which provides a further evidence for “gut-first theory” [14].

An increasing number of studies have proved that PD is accompanied by dysbiosis of intestinal flora and alterations of microbial metabolites. Multiple studies have accumulated to show that the gut microbiota of PD patients differs from that of healthy people. The researchers found that in people with PD, the number of certain strains increased significantly, while the number of others decreased. Investigations have found a high prevalence of Helicobacter pylori among PD patients [15]. Recent studies have revealed an increase in the Lactobacillaceae family and Verrucomicrobiaceae family (including the genus Akkermansia), coupled with a decreased abundance of Lachnospiraceae families (including the genus Roseburia) and Prevotellaceae [16, 17]. Metabolites derived from the microbiota have a significant effect on immune and inflammatory response. SCFAs, also known as volatile fatty acids, are the main metabolites produced by bacterial fermentation, mainly including butyric acid, acetic acid, valeric acid and caprylic acid [18]. SCFAs has important biological functions, such as providing energy, anti-inflammatory effects, immune regulation, and maintaining intestinal integrity [19, 20]. The number of SCFAs producing bacteria in the colon of PD patients was observably reduced, while the concentration of SCFAs mixture in the faeces and the absolute concentration of individual acetic acid, propionic acid and butyric acid were also significantly decreased [21, 22]. SCFAs not only reinforce the integrity of the blood brain barrier, but affect the physiology of cells in the central nervous system, such as the activation of microglia [13, 23]. Besides, studies have shown that increasing the abundance of SCFAs producing strains can effectively alleviate the symptoms of PD [24, 25]. This imbalance of microorganisms and their metabolites may lead to changes in the internal environment of the gut, which in turn affects the health of neurons [15, 26, 27]. Hence, the regulation of intestinal flora and its metabolites is an effective strategy for the treatment of PD.

Collectively, the treatment of PD should follow the principle of early detection and early treatment due to the high failure rate of drug development. However, the early screening and diagnosis of PD mainly rely on blood and urine, and the success rate is low. Considering the close relationship between intestinal flora and PD, 16s sequencing accompanied with metabolomics of faeces should be added to the early diagnosis of PD. Targeting intestinal flora will also become a promising strategy in the drug discovery of PD. Nevertheless, studies on the gut-to-brain axis is still preliminary, and an in-depth mechanism revealing how beneficial or pathogenic microbial populations regulate the occurrence and development of PD needs to be explored, enhancing the potential of gut microbiota to the treatment of PD and as a detection index for the early screening of PD.

References


Author contribution
Conceptualization: Yiran Sun; Original draft preparation: Chenchen Yan, Yiran Sun; Review and editing: Chenchen Yan and Yiran Sun.

Competing interests
The authors declare no conflicts of interest.

Acknowledgments
This study was financially supported by Henan Youth Science Foundation of Henan Province (No. 232300421310); Postdoctoral Foundation of China (No. 2022M711080); The National Natural Science Foundation of China (No. 82274612); Program for Science & Technology Innovation Talents in Universities of Henan Province (No. 23HASTI044); Innovative Research Team (in Science and Technology) in University of Henan Province (21RTSTSSN026); Henan Province Traditional Chinese Medicine Scientific Research Special Project (No. 2022ZYD211); Joint Research Fund of Science and Technology R&D Plan of Henan Province (NO. 222301420068).

Abbreviations
PD, Parkinson’s disease; α-syn, α-synuclein; SCFAs, short-chain fatty acids.

Citation

Executive editor: Xin-Yun Zhang.
Received: 05 September 2023, Accepted: 06 September 2023, Available online: 08 September 2023.
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