widely exists in the enteric nervous system (ENS) and intestinal mucosa (Chiang and Lin, 2025). The Braak hypothesis suggests that Parkinson's disease may originate in the gut: misfolded α -synuclein first appears in the enteric nervous system and then spreads along the vagus nerve to the central nervous system like prions (Montalban-Rodriguez et al., 2024). Both human and animal experiments can support this view. For instance, α -synuclein aggregates can be detected in intestinal neurons several years before the onset of motor symptoms in patients with Parkinson's disease. Inoculation of α -synuclein fibrils into the intestines of mice can lead to lesions similar to Lewy bodies in their brainstems. In addition, this diffusion also relies on the complete vagus nerve pathway.

The evidence for the "gut origin" theory comes from environment-related studies. When the gut is exposed to toxic substances or when the gut microbiota is imbalanced, it may cause misfolding of local α -synuclein (Chiang and Lin, 2025). Intestinal glial cells play a key role in this process. Their activation and reactivity changes are closely related to the pathological changes and inflammatory responses of α -synuclein (Montalban-Rodriguez et al., 2024). In addition, a small amount of α -synuclein can also be found in intestinal endocrine cells. These abnormally folded proteins will directly contact intestinal neurons along neural pathways and gradually spread from the intestinal epithelium to the central nervous system. Overall, these findings provide strong support for the Braak hypothesis and also highlight the significant role of the enteric nervous system in the pathogenesis of Parkinson's disease.

3.3 Findings related to intestinal barrier dysfunction, "leaky gut", and mucosal immune activation

Poor intestinal barrier function, commonly known as "leaky gut", is regarded as an important cause of Parkinson's disease. Under normal circumstances, the intestinal epithelial barrier not only enables nutrients to be absorbed smoothly but also prevents harmful bacteria and toxins from entering the body. The intestinal barrier integrity of patients with Parkinson's disease is disrupted, specifically manifested as increased intestinal permeability, elevated levels of tight junction marker protein zonulin, and endotoxemia may also occur (Skjærbæk et al., 2021; Derkinderen et al., 2025). These changes are usually associated with intestinal flora disorders and chronic enteritis, which may trigger a systemic immune response and subsequently cause neuroinflammation in the central nervous system. These factors are regarded as important links connecting intestinal lesions and neurodegeneration (Dodiya et al., 2020; Metta et al., 2021; Munoz-Pinto et al., 2024).

Mucosal immune activation is another distinct feature of Parkinson's disease. Studies have found that the levels of pro-inflammatory cytokines increase in the intestines and peripheral blood of patients with Parkinson's disease, and immune cells such as monocytes and T cells can also invade the central nervous system. Toll-like receptors on the surface of small intestinal glial cells are crucial in immune responses and maintaining intestinal barrier function. Their functional disorders can aggravate inflammation and promote pathological changes in α -synuclein (Figure 1) (Montalban-Rodriguez et al., 2024). Animal experiments have shown that intestinal inflammation caused by intestinal barrier damage or microbiota disorder can accelerate neurodegenerative changes and make the symptoms of Parkinson's disease more severe. This indicates that restoring intestinal barrier function and regulating mucosal immunity may become methods for intervention and even change the disease process to a certain extent (Dodiya et al., 2020; Metta et al., 2021).

4 Examine the pathogenesis of Parkinson's disease from the perspective of the gut-brain axis

4.1 Environmental factors induce intestinal flora imbalance and misfolding of α -synuclein

Environmental conditions such as diet, toxic substances, infections and the use of antibiotics can significantly alter the flora in the intestines, causing an imbalance in the flora. This can cause lipopolysaccharide (LPS) produced by bacteria to enter the bloodstream, thereby triggering systemic and local immune responses (Klann et al., 2022; Mahbub et al., 2024; Oliver et al., 2025). When this immune response is activated, it will cause misfolding and accumulation of the core protein of Parkinson's disease - α -synuclein, leaving hidden dangers for subsequent pathological changes (Santos et al., 2022).

Abnormal aggregation of α -synuclein may first occur in the enteric nervous system (ENS). Experiments have confirmed that specific intestinal bacteria, environmental toxins and poor diet can all affect or exacerbate the