aggregation of α -synuclein (Klann et al., 2022; Santos et al., 2022; Mahbub et al., 2024). Several years before the onset of motor symptoms in PD patients, aggregates of this protein can already be detected in intestinal neurons, indicating that intestinal pathology may predate central lesions, and environmental factors that disrupt the intestinal microecology may be early triggers for the onset of PD.

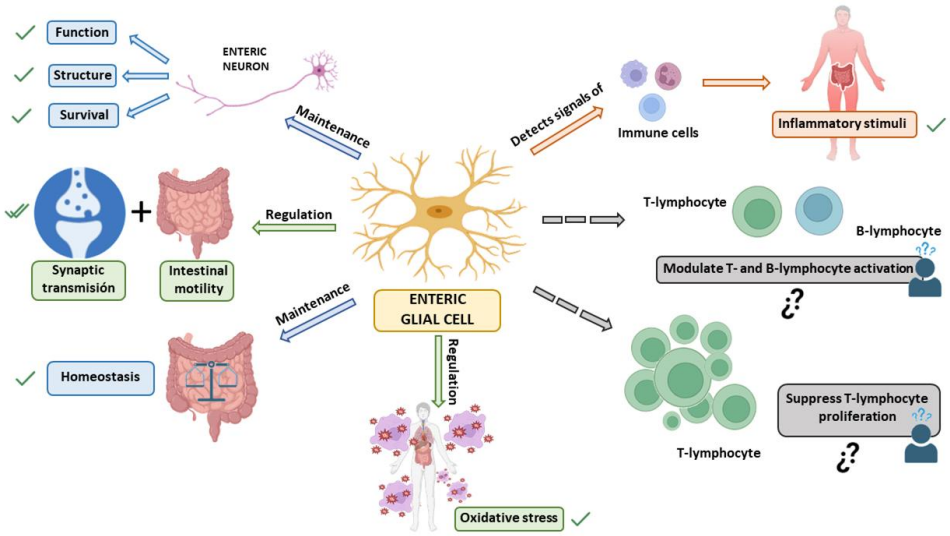

Figure 1 Functions of enteric glial cells (EGCs) (Adopted from Montalban-Rodriguez et al., 2024)

4.2 Pathological cascades of intestinal pathology that spread to the central nervous system through pathways such as the vagus nerve

The stepwise spread of α -synuclein pathology from the intestine to the brain is the core content of the gut-brain axis hypothesis. According to the Braak hypothesis, misfolded α -synuclein can be retroactive from the ENS to the central nervous system in a prion-like manner along the vagus nerve. It first affects the dorsal motor nucleus of the brainstem vagus nerve and then spreads to regions such as the substantia nigra, leading to the loss of dopaminergic neurons and the appearance of typical motor symptoms (Santos et al., 2022; Montalban-Rodriguez et al., 2024; Oliver et al., 2025). Clinical observations have shown that vagotomy is associated with a reduced risk of Parkinson's disease (PD) and that GI symptoms such as constipation occur earlier than motor symptoms, all of which provide indirect support for this model.

In addition to the vagus nerve, the humoral pathway may also be involved in the spread of intestinal pathology to the central nervous system: when the intestinal and blood-brain barriers are damaged, bacterial products and pro-inflammatory cytokines can enter the circulation, cross the barriers, induce neuroinflammation and promote further misfolding of α -synuclein in the central nervous system (Hill et al., 2021; Mahbub et al., 2024). Intestinal glial cells and various immune mediators play a key role in amplifying and transmitting enterogenic inflammatory signals to the brain. The interaction between neuro-humoral mechanisms highlights the complexity of the gut-brain axis pathology in PD and also suggests multiple potential therapeutic intervention targets (Santos et al., 2022; Montalban-Rodriguez et al., 2024).

4.3 The interaction among mitochondrial dysfunction, oxidative stress and genetic susceptibility

Dopaminergic neurons in the substantia nigra are inherently fragile and prone to injury. Pathological changes caused by intestinal flora disorder and abnormal folding of α-synuclein can be intertwined with mitochondrial dysfunction and oxidative stress to form a vicious cycle, jointly accelerating the degeneration and death of neurons (Lei et al., 2021). Microbial metabolites such as short-chain fatty acids and LPS can affect the working state of mitochondria and closely link the composition of the gut microbiota with the survival of neurons (Mahbub et al., 2024).

Genetic predisposition to the disease interacts with environmental and microbial factors, jointly altering the risk and progression rate of Parkinson's disease: Changes in related genes increase the risk of disease and also alter the