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Exploring Gut Microbiota and Alzheimer's Disease: From Mechanisms to Interventions

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Abstract: Alzheimer's disease (AD) is a neurodegenerative disorder of the central nervous system characterized by insidious onset and progressive development. Its core clinical manifestations include cognitive decline, memory impairment, and personality and behavioral changes. Currently, there are no curative treatments available clinically, and the underlying pathogenesis remains incompletely understood. In recent years, with the rapid advancement of microbiome technologies, the gut-brain axis has emerged as a prominent research focus in neurodegenerative diseases. Extensive studies have demonstrated that gut microbiota dysbiosis participates in the initiation and progression of AD through multiple pathways, including immune inflammation, metabolic disturbances, neural signaling, and blood-brain barrier damage. Modulating gut microbiota homeostasis offers a novel target for early prevention, control, and clinical intervention of AD. This paper systematically reviews the association mechanisms between gut microbiota and AD, summarizes the research progress of mainstream interventions such as probiotics, prebiotics, dietary interventions, and fecal microbiota transplantation, analyzes the current limitations and deficiencies in existing research, and looks forward to future research directions, aiming to provide a theoretical reference for the development of novel prevention and treatment strategies for AD.

Keywords: Gut microbiota; Alzheimer's disease; Gut-brain axis; Pathogenesis; Intervention strategies

Introduction

The gut microbiota is a microbial community colonizing the human gastrointestinal tract, forming a vital "microecological organ" in the human body. It facilitates bidirectional communication between the gut and the central nervous system via the gut-brain axis and is extensively involved in physiological processes such as immune regulation, substance metabolism, and neurotransmitter synthesis. The gut-brain axis primarily relies on neural, immune, endocrine, and metabolic pathways to transmit signals and maintain normal brain physiological functions. When the structure of the gut microbiota becomes imbalanced and its diversity declines, the intestinal barrier function is compromised, peripheral inflammatory responses are activated, and abnormal signals can be transmitted to the central nervous system through multiple pathways, triggering neuroinflammation, neuronal damage, and promoting the onset of neurodegenerative diseases [1]. In recent

years, numerous clinical and basic studies have confirmed that Alzheimer's disease (AD) patients exhibit significant gut microbiota dysbiosis, with the degree of dysbiosis closely correlated with the severity of cognitive impairment and disease progression. Targeted modulation of the gut microbiota has thus emerged as a novel research direction for AD prevention and treatment. Based on recent cutting-edge studies both domestically and internationally, this article systematically elucidates the core mechanisms by which the gut microbiota mediates AD pathogenesis, summarizes the current research status of various microbiota-targeted interventions, analyzes existing research bottlenecks, and provides new insights for the precise prevention and treatment of AD.

1. Core Mechanisms of Gut Microbiota Involvement in Alzheimer's Disease Pathogenesis

Under normal physiological conditions, the human gut microbiota maintains a stable structure and rich diversity, with Firmicutes and Bacteroidetes serving as the dominant phyla, their ratio remaining in dynamic balance. In AD patients, however, the gut microbiota exhibits significant dysbiosis: the abundance of harmful bacteria such as Proteobacteria and Escherichia coli markedly increases, while beneficial bacteria like Bifidobacteria, Lactobacilli, and Butyricicoccus experience substantial declines, accompanied by a notable reduction in microbial diversity. This disrupted gut microbiota mediates AD pathological damage through multiple dimensions by impairing the homeostasis of the gut-brain axis, with core mechanisms primarily including immune-inflammatory activation, metabolite imbalance, blood-brain barrier disruption, and neurotransmitter dysregulation.

1.1 Mediating Peripheral and Central Chronic Inflammatory Responses

Chronic low-grade inflammation is a core driving factor in the onset and progression of AD, while gut microbiota imbalance serves as a significant source triggering systemic chronic inflammation. The excessive proliferation of harmful gut bacteria releases endotoxins such as lipopolysaccharide (LPS). When intestinal barrier integrity is compromised and permeability increases, LPS can cross the intestinal mucosa and enter the bloodstream, triggering systemic low-grade inflammation. Peripheral inflammatory factors can then pass through the impaired blood-brain barrier into the central nervous system, activating microglia in the brain.

Microglia are the primary immune cells in the central nervous system. When excessively activated, they release large amounts of pro-inflammatory factors such as tumor necrosis factor-α and interleukin-6, disrupting central immune homeostasis [2]. Persistent neuroinflammation inhibits neuronal repair, accelerates neuronal apoptosis, and simultaneously promotes abnormal Aβ deposition and excessive phosphorylation of tau proteins, forming a vicious cycle of "inflammation–pathological damage–more severe inflammation." Clinical studies have found that levels of LPS and pro-inflammatory factors in the peripheral blood of AD patients are significantly higher than in healthy individuals and are positively correlated with Aβ burden in the brain and the degree of cognitive impairment. This further confirms the critical role of the gut microbiota-mediated inflammatory pathway in the pathogenesis of AD.

1.2 Imbalance of Gut Microbiota Metabolites Regulating Neurodegenerative Diseases

The gut microbiota can produce various bioactive substances through metabolizing dietary nutrients. Some metabolites can cross the blood-brain barrier and directly regulate physiological functions of the central nervous system. Among these metabolites, imbalances in short-chain fatty acids, bile acids, and others are closely associated with the pathological progression of AD. Short-chain fatty acids (SCFAs), primarily butyrate, acetate, and propionate, are key products of dietary fiber fermentation by beneficial gut bacteria. They play roles in maintaining intestinal barrier integrity, exerting anti-inflammatory effects, protecting neurons, and inhibiting Aβ aggregation. In AD patients, reduced abundance of SCFA-producing gut bacteria leads to insufficient SCFA levels in both peripheral circulation and the brain. This deficiency impairs effective suppression of neuroinflammation and weakens blood-brain barrier protection, thereby exacerbating neural damage [3].

1.3 Impairing Blood-Brain Barrier Integrity

The blood-brain barrier is a critical structure that maintains the stability of the internal environment

in the central nervous system, preventing peripheral harmful substances from infiltrating brain tissues. The homeostasis of the gut microbiota is essential for preserving the structural and functional integrity of the blood-brain barrier. Dysbiosis-induced peripheral inflammation and endotoxin entry into the bloodstream can damage endothelial cells of the blood-brain barrier, reduce the expression of tight junction proteins, and lead to an abnormal increase in its permeability.

After the breakdown of the blood-brain barrier, inflammatory factors, toxins, and abnormal proteins from peripheral circulation can extensively invade the central nervous system. On one hand, they directly damage neurons and glial cells; on the other hand, they induce abnormal deposition of Aβ and excessive phosphorylation of tau protein in the brain, forming neurofibrillary tangles and exacerbating the typical pathological changes of AD. Concurrently, damage to the blood-brain barrier further impedes the clearance of metabolic waste from the brain, leading to the accumulation of toxic substances and accelerating cognitive decline.

1.4 Impaired Neurotransmitter Synthesis and Signal Transduction

The intestine is known as the "second brain." The gut microbiota can regulate the synthesis and secretion of peripheral neurotransmitters, thereby influencing central nervous system signaling through the gut-brain axis. Over 90% of the serotonin in the human body is synthesized by intestinal enterochromaffin cells, and the gut microbiota is a key factor regulating serotonin synthesis and release. Imbalance in the gut microbiota can lead to disruptions in peripheral serotonin secretion, subsequently affecting central nervous system pathways involved in mood regulation and cognitive memory. Meanwhile, disrupted microbiota can inhibit the synthesis of protective neurotransmitters such as gamma-aminobutyric acid (GABA) and dopamine, resulting in abnormal neuronal excitability, decreased synaptic plasticity, and impairments in learning and memory functions, aligning with the core cognitive deficits observed in AD patients. Furthermore, the gut microbiota can transmit abnormal peripheral signals directly to cognitive-related brain regions, such as the brainstem and hippocampus, via the vagus nerve, directly interfering with central nervous system function and contributing to the pathogenesis of AD.

2. Targeted Gut Microbiota Interventions for Alzheimer's Disease

Given the close association between gut microbiota and AD, targeting the regulation of gut microbiota homeostasis and restoring the function of the gut-brain axis have emerged as novel intervention strategies for AD. Current mainstream intervention approaches include dietary intervention, supplementation with probiotics and prebiotics, fecal microbiota transplantation, and lifestyle regulation. These interventions work by reshaping the gut microbiota structure, alleviating neuroinflammation, protecting neurons, and improving cognitive function, demonstrating promising application prospects in both basic research and clinical exploration of AD [4].

2.1 Dietary Intervention

Diet is the most direct and safe method to regulate the structure of gut microbiota. Long-term dietary patterns can significantly alter microbial abundance and diversity, thereby influencing the risk of AD. Studies confirm that the Mediterranean diet and high dietary fiber intake can notably enrich beneficial gut bacteria, promote the synthesis of short-chain fatty acids (SCFAs), maintain intestinal barrier integrity, alleviate systemic and central nervous system inflammation, and reduce AD risk in the elderly. These dietary patterns emphasize vegetables, fruits, whole grains, deep-sea fish, and nuts, which are rich in dietary fiber, unsaturated fatty acids, and antioxidants. These components provide nutritional substrates for beneficial bacteria and inhibit the proliferation of harmful microbes.

Conversely, a Western-style diet high in fat and sugar and heavily processed can disrupt the balance of gut microbiota, reduce microbial diversity, trigger dysbiosis, exacerbate neuroinflammation and brain pathology, and accelerate cognitive decline.

2.2 Probiotics and Prebiotics Interventions

Probiotics are beneficial active microorganisms for the body. Common strains such as Bifidobacterium, Lactobacillus, and Clostridium butyricum can directly supplement beneficial gut bacteria and reshape the gut microbiota structure. Basic experiments have confirmed that supplementing with specific probiotics significantly improves intestinal flora disorders in AD model mice, reduces peripheral LPS and pro-inflammatory cytokine

levels, alleviates excessive activation of microglia in the brain, decreases Aβ deposition, and enhances learning and memory abilities in mice. Clinical studies have also found that long-term supplementation with compound probiotics in AD patients can effectively increase gut microbiota diversity, alleviate cognitive impairment, and improve emotional and behavioral abnormalities in patients.

Prebiotics are dietary polysaccharides that cannot be digested and absorbed by the human body. They selectively promote the proliferation of beneficial intestinal bacteria, activate their metabolic activity, and indirectly regulate microbial homeostasis. Common prebiotics such as fructooligosaccharides, inulin, and dietary fibers can enhance the synthesis of short-chain fatty acids (SCFAs) in the gut, repair the intestinal barrier, and suppress inflammatory responses. Compared to probiotics, prebiotics exhibit greater stability, higher tolerance, and are less susceptible to degradation by gastric acid, enabling long-term regulation of the gut microbiota. Currently, the combined intervention of probiotics and prebiotics (synbiotics) has emerged as a research hotspot. Their synergistic effects allow for more efficient restoration of gut microbiota homeostasis and exert neuroprotective functions, representing a significant direction in adjuvant interventions for AD.

2.3 Fecal Microbiota Transplantation

Fecal microbiota transplantation (FMT) is an intervention method that involves transferring intestinal microbiota from healthy individuals into the patient's gut, rapidly and thoroughly reshaping the gut microbiome. It is currently one of the most effective approaches for regulating intestinal microbiota. Multiple animal experiments have shown that transplanting fecal microbiota from healthy mice into AD model mice can significantly correct microbiota disorders, repair the intestinal barrier and blood-brain barrier, inhibit neuroinflammation, reduce cerebral Aβ deposition and tau protein phosphorylation, and markedly improve cognitive function in mice.

Clinical case studies have also confirmed that fecal microbiota transplantation can improve the gut microbiota structure in patients with early-stage AD, delay cognitive decline progression, and demonstrate good safety. However, research on fecal microbiota transplantation for AD intervention is still in its early stages, facing issues such as inconsistent donor screening criteria, non-standardized transplantation dosages and treatment durations, unknown long-term efficacy, and infection risks associated with invasive procedures. As a result, it cannot yet be widely applied in clinical practice. Large-scale, long-term follow-up clinical trials are still needed to verify its effectiveness and safety.

3. Research Limitations and Prospects

3.1 Current Research Limitations

Current research on the association between gut microbiota and Alzheimer's disease has made some progress, but several limitations remain. Firstly, studies predominantly focus on correlational analyses, where most differences in microbiota composition merely confirm associations with the clinical status of AD. It remains difficult to establish causal relationships between microbiota dysbiosis and AD onset, and specific AD-causative or protective microbial groups have yet to be definitively identified. Secondly, gut microbiota exhibits significant inter-individual variability, influenced by factors such as age, diet, geography, and genetics. As a result, findings across different studies often diverge, making it challenging to establish unified diagnostic and interventional criteria based on microbiota. Thirdly, existing intervention studies are mostly limited to animal experiments or small-scale clinical observations. There is a lack of large-sample, multicenter, long-term follow-up randomized controlled trials, and the optimal dosage, duration, and target populations for various interventions remain unclear. The long-term safety and efficacy of these interventions also require further validation. Fourthly, research into the molecular mechanisms by which microbiota modulate AD remains relatively superficial, often staying at the level of broad pathways. The specific molecular targets through which microbial metabolites regulate neuropathological damage still need to be further elucidated.

3.2 Future Research Directions

Future research should focus on two core directions: causal mechanisms and clinical translation. First, leveraging multi-omics integrated technologies to precisely identify AD-specific differential microbiota and key metabolites, elucidating the molecular

mechanisms by which microbiota dysbiosis mediates AD pathogenesis and clarifying the precise regulatory network of the gut-brain axis. Second, conducting large-scale clinical studies with standardized research protocols to determine optimal intervention strategies—such as probiotics, prebiotics, and fecal microbiota transplantation—and establish a standardized microbiota-targeted intervention system. Third, exploring the feasibility of using gut microbiota as biomarkers for early screening, diagnosis, and disease progression assessment of AD, enabling early warning and precise screening. Finally, developing novel functional formulations and precise probiotic strains targeting the gut microbiota, combined with individualized dietary and lifestyle intervention plans, to construct a comprehensive, precise, and personalized prevention and management system for AD.

Conclusion

The gut microbiota profoundly participates in the occurrence and progression of AD via the gut-brain axis, engaging multiple pathways such as immune inflammation, metabolic regulation, barrier damage, and neural signal transduction. Gut microbiota dysbiosis serves as a significant peripheral trigger for AD pathogenesis. Gut microbiota-targeted interventions, including dietary modulation, probiotic supplementation, and fecal microbiota transplantation, can effectively reshape gut microecological homeostasis, repair central nervous system damage, and delay cognitive decline, thereby opening up novel avenues for AD prevention and treatment. Although current research still faces challenges such as unclear causal mechanisms, incomplete clinical translation, and inconsistent intervention standards, the deep integration of microbiome science, neuroscience, and clinical medicine will undoubtedly establish gut microbiota-targeted interventions as a core direction for early prevention and clinical adjunctive therapy of AD in the future, offering fresh theoretical support and technical means for tackling neurodegenerative diseases.

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