

Research Progress on Correlation between Gut Microbiome and Amyotrophic Lateral Sclerosis

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Abstract: Amyotrophic Lateral Sclerosis (ALS), also known as motor neuron disease, is characterized by simultaneous degeneration of upper and lower motor neurons, resulting in muscle weakness, paralysis, and eventually death. However, research on its pathogenesis is currently unclear. Recently, many studies have found that the intestinal flora plays a direct or indirect role in the disease progression of ALS, including the release of neuroactive metabolites, increased intestinal permeability, and inducing metabolic disorders. Therefore, this article briefly reviews the correlation between intestinal microbiota and ALS in terms of pathology, aiming to provide new therapeutic targets for ALS.

Keywords: Amyotrophic lateral sclerosis; Gut microbiome; Metabolism

1. Introduction

Amyotrophic Lateral Sclerosis (ALS) is a heterogeneous neurodegenerative disease that occurs by the degeneration of upper and lower motor neurons, leading to motor and additional motor symptoms, manifested clinically as cognitive impairment, behavioral disorders, dysarthria and swallowing disorders, respiratory insufficiency, muscle spasms and atrophy[1]. Its pathological mechanism is intricate, and there is currently no unified conclusion. In general, mitochondrial damage, oxidative stress, glutamate excitatory toxicity, neuroinflammation, axonal transport system dysfunction, endoplasmic reticulum stress, protein aggregation, and metabolic abnormalities of RNA are considered key factors in the pathogenesis of ALS [2]. In recent years, many studies have found that intestinal flora disorders play an important role in the pathogenesis of ALS. This article reviews the association between intestinal flora disorders and amyotrophic lateral sclerosis, as well as its inflammation, immunity and metabolic mechanisms.

2. Gut Microbiome and ALS

Evidence collected from animal models and humans that the gut microbiota is associated with ALS suggests that there are distinct microbial signatures in ALS. In animal models, one study showed [3], SOD1G93A mice treated with butyrate restored intestinal homeostasis, improved neuromuscular function, and slowed the progression of ALS. In a small study of ALS patients, one study [4] compared the gut microbiome profiles of 16S RNA assays in 6 ALS patients and 5 healthy controls and found significant differences in gut microbes between ALS patients and healthy people. One study [5] performed 16S RNA sequencing on stool samples from 5 ALS patients and compared them with 96 healthy controls found that the microbial composition profile of ALS patients changed compared to the control group, 3 out of 5 patients had fewer beneficial bacteria, and the firmicutes/Bacteroides phylum ratio was reduced.

The above studies have confirmed the correlation between ALS and intestinal flora, and the changes of ALS intestinal microorganisms have two significant characteristics, first: the ratio of Firmicutes/Bacteroides is mainly abnormal; Second: the abundance of the dominant flora producing butyrate decreases. However, the above study was limited to the assessment of the microbial composition of ALS feces, so the results do not explain microbial differences within the gut. In addition, its research methods are usually limited to metagenomics methods, which are relatively single, and their overview of microbial diversity is quite limited. Given the variety of physiological effects between the gut microbiota and the many abnormal physiological processes in ALS, future studies

should focus on analyzing the composition of gut microbes in ALS patients and their impact on disease progression.

3. Gut Microbiome Releases Neuroactive Metabolites

In the process of human evolution, the microbes in the gut have established a "symbiotic" relationship with the host: the host meets the nutritional needs of the gut microbe through dietary intake; At the same time, gut microbes provide specific energy to the host. In addition, gut microbes are able to produce some neuroactive metabolites that affect the synthesis and release of relevant neurotransmitters and their precursors in the brain [6], and gut microbes can directly stimulate intestinal chromaffin cells to produce some neurotransmitters, which can enter the brain through the blood-brain barrier and affect the function of the central nervous system. One study [7] found that the abundance of *A. muciniphila* in SOD1G93A mice decreased with disease progression compared to control by using untargeted metabolomics analysis and metagenomics. In addition, the study found that *A. muciniphila* alleviated the disease process in ALS-model mice, and that mice treated with *A. muciniphila* had elevated levels of niacinamide (NAM), a specific substance required for energy transduction, signaling pathways, and antioxidant mechanisms, and NAM has been shown to lead to ALS-related neurodegeneration [8]. One study showed [9] that ALS patients had lower concentrations of NAM in serum and cerebrospinal fluid compared to healthy subjects, and relatively low expression of bacterial genes capable of synthesizing NAM in their feces. These studies support the idea that the gut microbiota can produce compounds that can penetrate the blood-brain barrier and affect neuronal function.

4. Gut Microbiome Increases Intestinal Permeability

Intestinal epithelial cells act as a barrier between the environment and human tissues, and their role is to prevent the entry of microorganisms and macromolecules. In a healthy state, the body absorbs nutrients primarily through intestinal transport mechanisms. Intestinal bacteria and their metabolites, primarily Short-chain Fatty Acids (SCFA), maintain the integrity of the intestinal epithelial barrier by regulating the growth and differentiation of intestinal epithelial cells, tight junction protein expression, and alterations in mucosal permeability [10]. Studies have shown that increased intestinal permeability is associated with abnormal changes in tight junctions between intestinal epithelial cells, and changes in the specific composition of intestinal flora can damage tight junctions between cells, thereby disrupting the intestinal epithelial barrier and increasing mucosal permeability. One study showed [11], prior to the onset of ALS symptoms, impaired tight junction structure, increased intestinal permeability, elevated levels of inflammatory cytokine IL-17, and significantly reduced expression levels of connexin ZO-1 and cadherin in the gut of SOD1G93A mice compared to the control group, which may be responsible for increased intestinal permeability and leakage. In addition, there was an abnormal increase in the number of intestinal Paneth cells in the SOD1G93A mouse model, as well as a decrease in the dominant bacteria producing butyrate, *Vibrio fibrolyticus*, *Escherichia coli* and Firmicutes, Paneth cells are specialized intestinal epithelial cells, whose main function is to detect microorganisms and secrete antimicrobial peptides, which can directly affect the intestinal environment, and decreased levels of antimicrobial peptides and lysozyme-1 were observed in the intestines of SOD1G93A mice, indicating dysfunction of Paneth cells. The above results reflect the population transfer of dysbiota in the gut of ALS model mice.

5. Gut Microbiome Cause High Metabolism

The main function of the intestine is to digest the diet and absorb nutrients, and normally, some small molecules can spread through the intestinal barrier. In terms of nutrition and energy metabolism, the intestinal flora can promote nutrient absorption, vitamin synthesis, and weight regulation [12-13]. The interaction between the human body and the intestinal flora determines the relevant metabolic response, and the ability of intestinal bacteria such as the wall bacteria to obtain energy from the diet is enhanced, which predisposes the host to gain weight and develop obesity. Metabolic disorders have been reported to be often associated with altered abundance of proteobacteria such as facultative anaerobic bacteria. In the human body, some proteobacteria contribute to intestinal health, and proteobacteria can not only affect metabolic function, but also promote changes in the gut microbiota. Studies have shown [14] that the energy balance of ALS patients has been severely altered, resulting in metabolic disorders in ALS patients, extensive weight loss in ALS patients, which may be caused by

ALS patients' own motor symptoms, and an increase in basal metabolism is also an important cause of their weight loss. Intestinal dysbacteriosis may be responsible for altered ALS metabolism. One study showed[15]that certain microbes in the gut, inversely correlated with energy metabolism, demonstrated that a decrease in specific bacterial phylums would help increase energy metabolism.

6. Future Clinical Treatment Direction

At present, the treatment of ALS is relatively lacking, and the two drugs commonly used in clinical practice: riluzole and riladafone, can only relieve some motor symptoms, but cannot improve the final outcome of ALS patients, so new clinical interventions are urgently needed. With the in-depth study of intestinal flora and ALS, intestinal flora is expected to be a new target for the treatment of ALS. Fecal microbe transplantation (FMT), dietary supplement therapy, probiotic therapy, etc. have become promising new methods for the treatment of ALS.

6.1 Fecal Microbe Transplantation

FMT is currently the most effective gut microbiota intervention, and one study[16] reported an FMT treatment for ALS patient whose symptoms improved at 12 months follow-up, in addition, dynamic microbial and metabolomic analysis of blood and stool samples from this patient found an increase in beneficial gut microbial communities in this patient. Conversely, some bacteria with potentially neurotoxic or pro-inflammatory activity, such as Proteobacteria, are significantly reduced. However, at present, there are few studies on the treatment of ALS by FMT, and more in-depth research should be carried out in the future in order to provide more basis for FMT as an adjunct to the treatment of ALS.

6.2 Dietary Supplement

The intestinal flora can produce chemicals and affect intestinal cells, so dietary supplements supplementing the beneficial chemicals that produce microorganisms can be used as a treatment for ALS, such as butyrate, bile acids and niacinamide, animal experiments have shown that butyrate supplementation can alleviate the symptoms of ALS mice, there is also a specific link between bile acids and the imbalance of gut microbes, the gut microbiota can convert bile acids into taurine deoxycholic acid (TUDCA), which is a high-quality secondary bile salt, It relieves endoplasmic reticulum stress [17]. In addition, NAM supplementation has also been shown to improve motor symptoms in ALS mice [18].

6.3 Probiotic

Studies have proved that prebiotic and probiotic treatment can improve intestinal dysbiosis and increase beneficial microorganisms. Polyphenols are prebiotics that synthesize bioactive chemicals that have been shown to have neuroprotective effects, prevent neuroinflammation, maintain brain homeostasis, and promote the improvement of cognitive function [19-20]; polyphenols can inhibit the growth of enteric pathogens and stimulate the growth of beneficial bacteria, thereby protecting the intestine, so supplementation with polyphenols facilitates the production of beneficial chemicals, thereby achieving the effect of preventing ALS.

7. Summary and Outlook

In summary, a large number of animal and human studies have demonstrated a potential direct or indirect link between intestinal flora and amyotrophic lateral sclerosis, and intestinal flora can affect the pathogenesis of amyotrophic lateral sclerosis by releasing neuroactive metabolites, regulating immunity, metabolism, synthesizing neurotoxins and increasing intestinal permeability, but more direct research evidence is needed to clarify the causal relationship between intestinal flora and amyotrophic lateral sclerosis. At present, the domestic research on the correlation and mechanism of intestinal flora and amyotrophic lateral sclerosis is still in its infancy, and more in-depth basic and clinical research is needed in the future to explain the mechanism of action of intestinal flora on amyotrophic lateral sclerosis, better prevent and treat amyotrophic lateral sclerosis, and bring good news to patients suffering from the disease.

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