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REVIEW ARTICLE

Intestinal Microbiota and Sclerosis Lateral Amyotrophic

Microbiota Intestinal e Esclerose Lateral Amiotrófica

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ABSTRACT

The human gastrointestinal tract contains numerous microorganisms. This intestinal microbiota (IM) has a mutualistic relationship with the human organism, and it plays a fundamental role in regulating metabolic, endocrine, and immunological functions. Intestinal dysbiosis is associated with phenotypes of many chronic and inflammatory diseases. This association is explained by the functions of the IM and the existing bi-directional communication of the microbiota-intestine-brain axis. Studies have uncovered new evidence between the IM and neurodegenerative diseases recently, including amyotrophic lateral sclerosis (ALS). Given this, the present narrative review discusses didactically about IM, its functions, its relationship with the neuroimmune-endocrine system, and its association with neurodegenerative diseases, with emphasis on ALS.

PALAVRAS-CHAVE
Disbiose
Doenças neurodegenerativas
Esclerose lateral amiotrófica
Microbiota intestinal

RESUMO

O trato gastrintestinal humano é povoado por uma grande quantidade de microrganismos. Essa microbiota intestinal (MI) tem uma relação de mutualismo com o organismo humano e desempenha papel fundamental na regulação de funções metabólicas, endócrinas e imunológicas. A disbiose intestinal está associada a fenótipos de várias doenças crônicas e inflamatórias. Essa associação é explicada pelas funções da MI e a existente comunicação bidirecional do eixo microbiota-intestino-cérebro. Nos últimos anos, estudos têm mostrado novas evidências entre a MI e as doenças neurodegenerativas, incluindo a esclerose lateral amiotrófica (ELA). Diante disso, essa revisão narrativa discorre de forma didática sobre a MI, suas funções, sua relação com o sistema neuro-imuno-endócrino e sua associação com as doenças neurodegenerativas, com ênfase na EL

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INTRODUCTION

The term intestinal microbiota (IM) indicates the set of microorganisms that inhabit the intestine. When the microorganisms within a particular habitat and their genetic material are considered, it is termed the microbiome. Recently, IM has been the target of several studies. Although this field still lacks clarification, the functions of IM and its interaction with the host have promising potential in determining an individual's state of health or disease. This information has widened the range for etiological understanding and new therapeutic targets. The microorganisms that populate the human intestine have a mutualistic relationship with the host and regulate innumerable processes related to its metabolism, immunity, and neuroendocrine system. Intestinal dysbiosis is a condition where there is an imbalance between beneficial and pathogenic microorganisms, resulting in the pathogenesis of innumerable diseases, which influences the composition of the IM (bidirectional cause-effect relationship)[1]. Here, we discuss the IM, its functions, role in the neuro-immuno-endocrine system, relationship with amyotrophic lateral sclerosis (ALS), and IM modulation in the ALS clinical condition.

INTESTINAL MICROBIOTA AND HUMAN MICROBIOME

The human microbiota is the set of microorganisms (bacteria, fungi, viruses, protozoa), with a predominance of bacteria (95%), that live symbiotically (mutualistic relationship) in various sites of the human body: oral cavity, genital organs, respiratory tract, gastrointestinal tract, etc[2,3]. Each of these sites is populated by a predominant profile of bacteria. Although there is stability in the profile of taxonomic phyla at specific sites, there is substantial variance among individuals[2]. It is estimated that the human gut contains more than 1 kg of bacteria[4] and its microbiota comprises approximately 10^{13} to 10^{14} cells, representing a close to 1:1 ratio of microorganism cells to human cells. Thus, we are as much bacteria as we are humans[1,5,6]. However, each individual has a unique microbial signature.

Bacterial taxonomy classification follows the hierarchical system of phyla, classes, orders, families, genera, and species (Figure 1). A single phylum may contain several types of bacteria. The dominant phyla of human IM are Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria, Fusobacteria, and Verrucomicrobia. Firmicutes and Bacteroidetes represent 90% of the IM[7]. An appropriate ratio of the abundance of *Firmicutes* to *Bacteroidetes* can be a parameter of gut health. This ratio varies during different life stages and in certain diseases. We previously estimated this ratio in children, adults, and older adults to be 0.4, 10.9, and 0.6, respectively[8]. An increased *Firmicutes*/*Bacteroidetes* abundance ratio has been associated with intestinal dysbiosis, type 2 diabetes mellitus, obesity, irritable bowel syndrome, and autism[7]. A decreased ratio was related to weight loss[8].

The gastrointestinal tract, particularly the stomach, duodenum, jejunum, ileum, and colon, harbor predominant bacterial genera, with a greater concentration in the large intestine[9]. IM refers to the set of microorganisms located only in the intestine. After birth, the infant's gastrointestinal tract is quickly colonized, but throughout life, several factors related to the host influence the composition of the IM (Figure 2). Thus, IM is dynamic and can be modulated in favor of better health.

Scientific evidence indicates that early exposure to IM in the male and female reproductive tracts at conception, delivery, and gestation substantially impacts child development during the first 1,000 days of life[10]. The prenatal, neonatal, and postnatal factors have been discussed as proper windows of opportunity for modulation of IM composition[11]. The type of delivery, for instance, influences IM composition. Children born via vaginal delivery present a higher concentration of *Lactobacillus* in the first days of life, whereas those born via cesarean section have depletion of this genus and, in contrast, present a higher concentration of the genera *Bacteroides* and/or *Clostridium*[12].

Each bacterial strain harbors thousands of genes, and the collective bacterial genome of the entire bacterial population within a human contains approximately 100 times more genes than the human genome itself. The human microbiome refers to the entire set of microorganisms and their respective genes[6]. Genome sequencing projects of the human microbiome such as the Human Microbiome Project (HMP) and Metagenomics of the Human Intestinal Tract (MetaHIT) have significantly advanced the knowledge in this field[1].

FUNCTIONS OF THE INTESTINAL MICROBIOTA

The IM is a vital organ that participates in the host's physiology through mutualistic participation. The host provides nutrients that the intestinal microorganisms need to survive and proliferate; in turn, these microorganisms perform numerous functions in the organism. Six of these functions are discussed below (Figure 3). Most of these functions are mediated by metabolites synthesized by the IM, such as short-chain fatty acids (SCFAs), which exert pleiotropic effects.

Production of SCFAs

Dietary fibers are fermented by IM generating SCFA as end products[1]. The main dietary fibers for bacterial fermentation and SCFA production are resistant to starch, inulin, oat bran, wheat bran, cellulose, guar gum, and pectin. The SCFAs are carboxylic acids with aliphatic tails of 1 to 6 carbons. The most common SCFAs are acetate, propionate, and butyrate, accounting for approximately 95% or more of all SCFAs[13]. Other less common SCFAs are valeric and caproic acids. Bacteroidetes (gram-negative) and Firmicutes (gram-positive) are the most abundant phyla in the gut. Members of Bacteroidetes produce more acetate and propionate, whereas bacteria of Firmicutes produce more butyrate. Acetate is the most abundant SCFA in the gut and can be converted to butyrate[14]. The SCFAs are used locally by enterocytes or transported by the bloodstream to other organs.

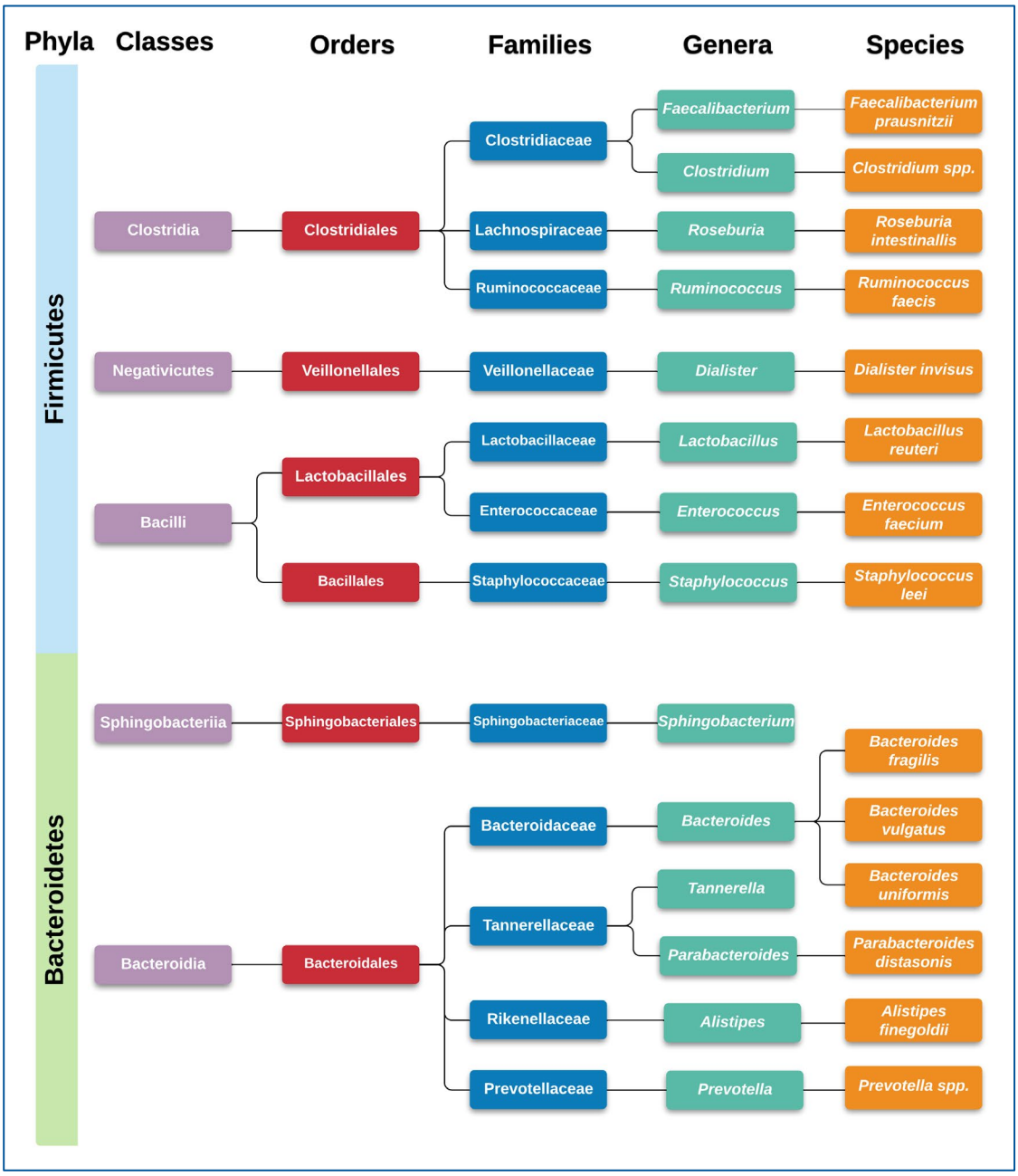

Figure 1 — Examples of the main bacterial phyla of the gut microbiota and their taxonomic classification. Adapted from Rinninella et al.[7].

Energy substrate supply

SCFAs are considered postbiotics and perform several functions in the body[15]. One of the main functions of SCFAs is to act as an energy substrate for the host. They contribute approximately 10% of the daily energy requirements used in metabolic processes. Approximately 60%-70% of the energy used by colonocytes originates from the oxidation of SCFAs, with a preference for butyrate. Most of the SCFAs are taken up by the liver, where they serve as energy substrates for hepatic gluconeogenesis. Besides acting as an energy source, butyrate also regulates processes such as autophagy and cellular respiration[1,13].

Vitamin synthesis

The IM is responsible for synthesizing some vitamins, independent of dietary intake. The IM produces eight vitamins: niacin, biotin, riboflavin, thiamin, pantothenic acid, folate, pyridoxine, and cobalamin. Bacteroidetes is the major phylum of bacteria that produce B-complex vitamins[16]. Vitamin K2 (menaquinone) is produced anaerobically by the intestinal bacteria *Bacteroides fragilis*, *Eubacterium lentum*, *Enterobacter agglomerans*, *Serratia marcescens*, and *Enterococcus faecium*[1]. Thus, IM indirectly influences several biochemical reactions and metabolic pathways, depending on the functions performed by each of these vitamins.

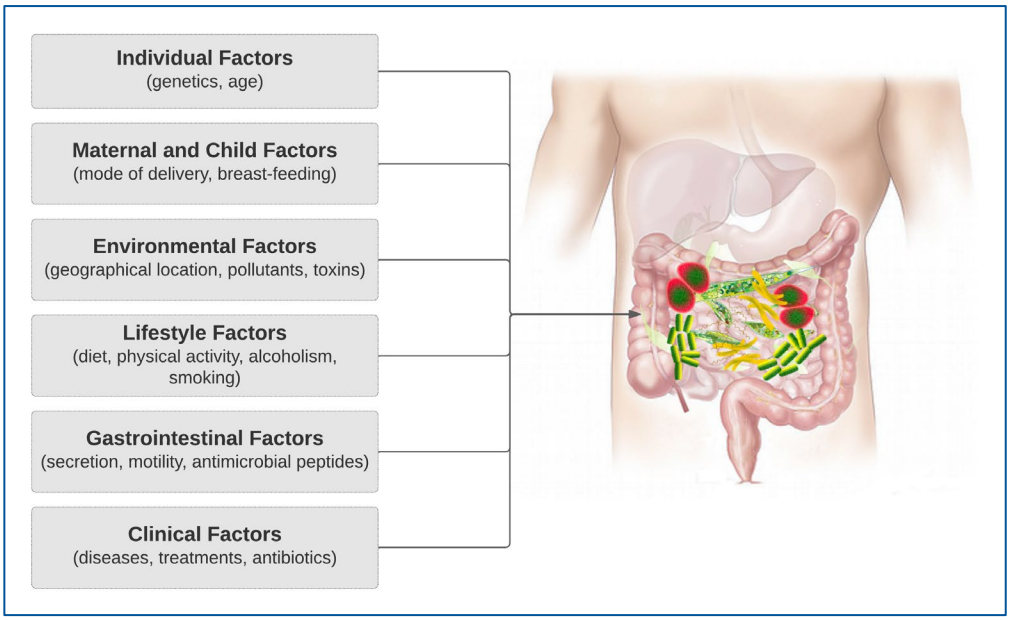

Figure 2 — Factors influencing the intestinal microbiota. Adapted from Clarke et al.[9].

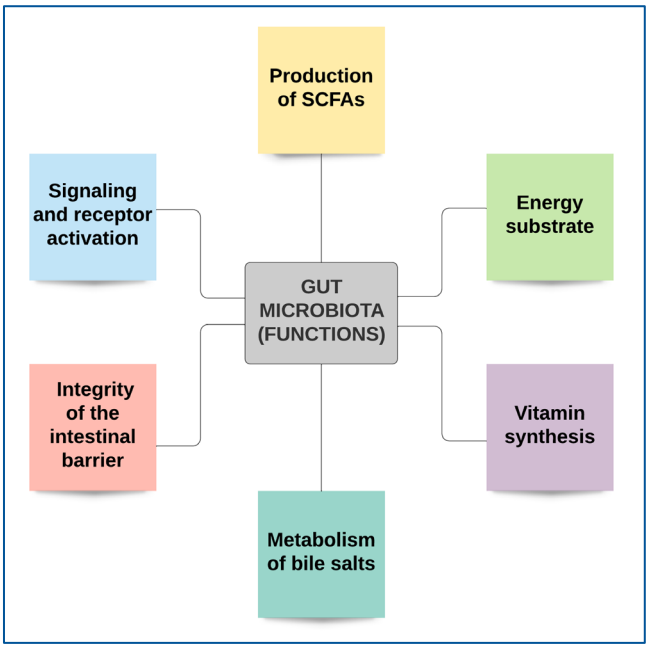

Figure 3 — Functions of the gut microbiota in humans. SCFA: short chain fatty acids. Source: the authors.

Metabolism of bile salts

IM participates in the metabolism of bile salts in the host. In humans, 95% of bile acids are reabsorbed in the distal ileum. The remaining 5% that are not absorbed are bioconverted or deconjugated into secondary bile acids by hydrolases secreted by colonic bacteria such as *Clostridium* spp. to be partially reabsorbed and transported back to the liver for the conjugation process. Primary and secondary bile acids can activate farnesoid X receptor signaling, regulating bile acid production, glucose metabolism, and hepatic autophagy. Additionally, secondary bile acids activate the *TCR5* gene, which, in turn, activates the cyclic adenosine 3',5'-monophosphate signaling pathway that induces the expression of several genes with great physiological importance. Furthermore, secondary bile acids exert antimicrobial effects that help modulate the composition of IM and protect the host against infectious microorganisms[1].

Maintenance of the integrity of the intestinal barrier

The IM also participates in maintaining the integrity of the intestinal barrier. The mucus layer forms the intestinal defense system, a strong junction between the cells, secretion of antimicrobial peptides, and the gut-associated lymphoid tissue (GALT). The mucus layer in the intestine is formed by glycoproteins called mucins. The deficiency of these proteins generates inflammation in the mucosa and increases intestinal permeability[17]. Butyrate can increase the expression of genes encoding mucins (e.g., *MUC2* gene) and other proteins associated with the strong junctions between intestinal cells. Furthermore, butyrate stimulates the production of antimicrobial peptides, contributing to the integrity of the intestinal barrier[14,18]. During intestinal dysbiosis, there is an increase in intestinal permeability, resulting in the translocation of pathogenic microorganisms and metabolites into the bloodstream, generating inflammatory and immune-mediated responses[1].

Signaling and receptor activation

The two primary signaling mechanisms of SCFAs comprise inhibition of histone deacetylases (HDACs) and activation of G protein-coupled receptors (GPCRs). SCFAs, especially butyrate and propionate, inhibit HDAC activity, causing increased histone acetylation,

loosening of DNA/chromatin, and activation of gene expression[17]. This epigenetic control is associated with an anti-inflammatory phenotype and is reviewed in other articles[17,19,20]. GPCRs are sensors of various nutrients, including fatty acids, and act in several signaling pathways. GPR43 is the primary receptor for SCFAs and is expressed throughout the gastrointestinal tract and adipose tissue. The GPR43 receptor is involved in the mechanisms by which SCFAs regulate intestinal immunity and inflammatory response in the body via the chemotaxis of neutrophils and cytokine expression[21]. The uptake of SCFAs by GPR43 receptors regulates the release of peptide YY and glucagon-like peptide 1, indirectly contributing to the anorexigenic effect and insulin release, respectively[17]. Thus, CBFA may play an essential role in body weight regulation. Our previous study concluded that the activation of GPCRs by SCFAs helps physiological functions such as colonic motility, colonic blood irrigation, and uptake of fluids and electrolytes[22].

INTESTINAL MICROBIOTA AND NEURO-IMMUNO-ENDOCRINE SYSTEM

The IM plays an essential role in the immune system, which has been demonstrated in germ-free mice. These animals present reduced immunoglobulin A (IgA) production in the GALT, reduced Peyer's patches, and altered expression of toll-like receptors, which recognize metabolites of IM and are involved in the innate immune response. In addition, approximately 45% of the genes induced by IM participate in immune response[23].

The IM is also important in the development of the enteric nervous system. Germ-free mice have fewer enteric neurons, low neuronal excitability, and low intestinal motility. This was also observed in mice with toll-like receptor genes 2 and 4 *(TLR2* and *TLR4)* silenced[24]. *TLR2* gene expression in enteric glial cells is increased by certain microorganisms, indicating a relationship between IM and toll-like metabolic pathways with diseases associated with the nervous system[24].

Gut bacteria can produce and regulate several neurotransmitters. *Bifidobacterium infantis* increases plasma levels of tryptophan, a precursor of serotonin; *Candida*, *Streptococcus*, *Escherichia*, and *Enterococcus* spp. can produce serotonin; *Lactobacillus* and *Bifidobacterium* spp. can produce gamma-aminobutyric acid (GABA); *Escherichia*, *Bacillus*, and *Saccharomyces* spp. can produce noradrenaline; *Bacillus* can produce dopamine, and *Lactobacillus* can produce acetylcholine. Due to the difficulty in crossing the blood-brain barrier, these neurotransmitters produced by the MI act on the enteric nervous system[4].

SCFAs also directly influence immune cells (intestinal epithelial cells, neutrophils, monocytes and macrophages, dendritic cells) and markedly impact the innate and acquired immune response. This influence occurs via signaling pathways, such as, for example, activation of GPCRs and inhibition of HDACs. Thus, SCFAs possess the capacity to modulate several cellular processes, such as gene expression, chemotaxis, phagocytosis, differentiation, proliferation, and apoptosis[25].

From the above-described features of the microbial species in the gut and the effect of the products of their metabolism (such as SCFAs), a broad-scale interaction between the IM and neuroimmune-endocrine system is evident. The gut-brain axis has been extended to the microbiota-intestine-brain axis[24]. Communication in this axis occurs via the vagus nerve and the hypothalamic-pituitary-adrenal axis. However, this communication is quite complex and encompasses several pathways. The authors inferred that there are possibly five communication routes between the IM and the brain[26] (Figure 4).

INTESTINAL MICROBIOTA AND ALS

Intestinal dysbiosis is associated with the pathogenesis of various diseases related to the gastrointestinal tract and other organs as well[27]. The composition of the IM affects the intestine and distant organs such as the brain. Gut dysbiosis interferes with nervous system function through the microbiota-intestine-brain axis communication pathways and has been associated with several neurological diseases, such as autistic spectrum disorder, multiple sclerosis, Alzheimer's disease, Parkinson's disease, and ALS[24,28]. Interestingly, animal models or individuals with these neural diseases present a dysbiotic IM compared to healthy controls. Even more intriguing is that the type of dysbiotic IM was similar among patients with the same neural disorder[24,29,30].

ALS is a neurodegenerative disease that affects the upper and lower motor neurons. It occurs in 1 to 3 cases per 100,000 people and is slightly more frequent in men than in women (ratio 1.2–1.5:1)[31]. The cause of ALS is multifactorial and includes genetic and environmental factors. More than 30 genes may be involved in the pathogenesis of ALS. This reflects its clinical and phenotypic heterogeneity. Traditionally, ALS is divided into familial (5%–15% of cases) and sporadic (85%–95% of cases) forms. The pathophysiology of ALS is not yet fully understood, but several mechanisms may be involved in neurodegeneration (Figure 5). This disease has an unfavorable prognosis, and its survival rate after the onset of symptoms is, on average, 3 to 5 years[31]. The role of IM in ALS was indicated in studies during recent years; much, however, still needs to be unveiled. IM may be involved in the pathophysiology of ALS and may be an important therapeutic target.

Animal models of ALS have been fundamental in investigating ALS pathophysiology and its molecular, cellular, and physiological mechanisms. The most explored among several existing models is the G93A mouse with the SOD1 gene mutation[32]. Although this point mutation represents only 15 to 20% of the cases of familial ALS, authors agree that G93A mice clearly reproduce most of the pathological mechanisms of ALS observed in human patients[33].

Wu et al.34 demonstrated, for the first time, the occurrence of intestinal permeability and dysbiosis in mice with ALS (G93A). These animals presented damage in the barrier function, with reduced expression of two proteins (ZO1 protein and Cadherin-E) involved in the

occluder and adherent junctions of the intestinal epithelium. Additionally, the authors also observed a marked increase in Paneth cells, specialized in secreting antimicrobial peptides in the presence of pathogens. For IM, reduced levels of *Butyrivibrio fibrisolvens*, *Firmicutes peptostreptococcus*, and *Escherichia coli* were found in the mice with ALS[34].

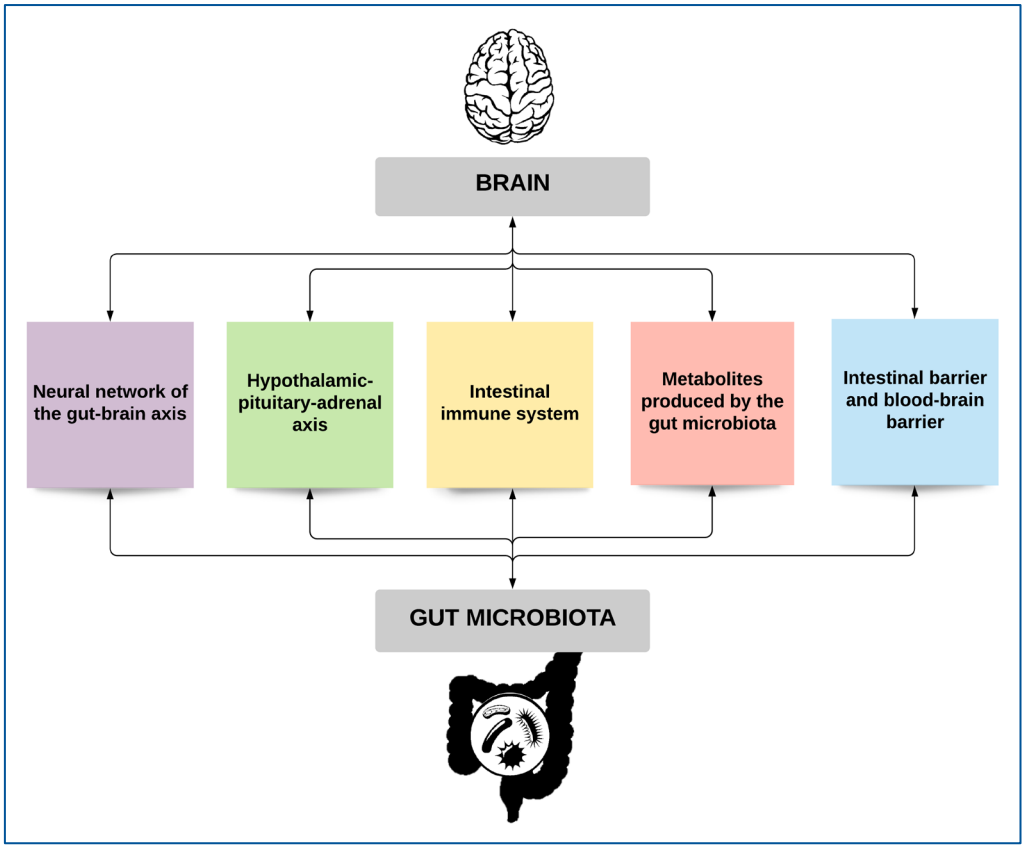

Figure 4 — Five possible communication pathways of the microbiota-gut-brain axis. Adapted from Wang and Wang[26].

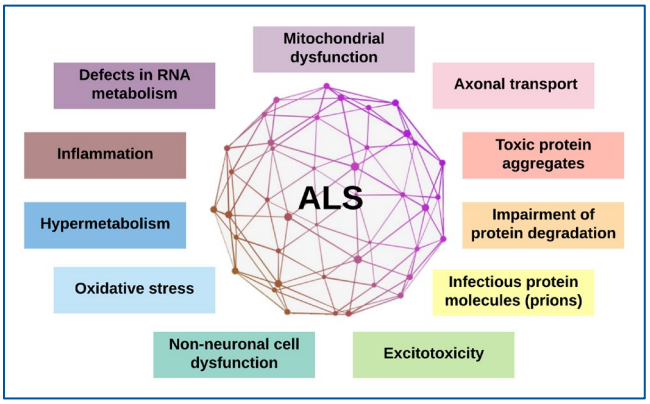

Figure 5 — Possible mechanisms involved in the pathophysiology of ALS, implicated in neurodegeneration. Source: the authors.

Chinese researchers found interesting results when comparing the MI of six patients with ALS with five healthy individuals. Despite the small sample size, the researchers observed that 37% of the operational bacterial taxonomic units differed between these groups. Among healthy individuals, increased *Firmicutes* (phylum), *Clostridia* (class), *Clostridiales* (order), *Lachnospiraceae*, and Family_XIII (family), *Oscillibacter*, *Anaerostipes*, and *Lachnospiraceae* (genera) abundances were observed. In patients with ALS, an increase in *Bacteroidetes* (phylum), *Bacteroidia* (class), *Bacteroidales* (order), and *Dorea* (genus) abundance was observed[35]. Furthermore, the IM of patients with ALS showed a low Firmicutes/Bacteroidetes abundance ratio and decreased number of Oscillibacter, Anaerostipes, and Lachnospiraceae members (beneficial bacteria). This dysbiosis may influence the pathogenesis process of ALS via mechanisms or pathways involving the production of nitric oxide, GABA, SCFA, and lipopolysaccharide (LPS)[35]. Considering that bacteria of the genus *Anaerostipes* and members *Lachnospiraceae* are butyrate producers, we can assume that butyrate production by patients with ALS may be reduced[24].

In a longitudinal study, Di Gioia et al.30 also observed differences in IM composition among patients with ALS compared to that of healthy individuals. The phylum Cyanobacteria was more abundant in patients and appeared to be involved in the pathogenesis of ALS.

Furthermore, the authors observed interdependence between the relative abundance of some families of bacteria and clinical parameters of body mass index, functional scale, and forced vital capacity in the group of patients.

Butyrate and its derivatives have been considered multifunctional molecules with therapeutic potential for several neurological diseases. The neuroprotective effects of butyrate are explained by its action on mitochondrial activity, GPCRs, histone acetylation, and homeostasis of the intestinal microbiome[36]. In a study on mice, butyrate was found to exert anti-inflammatory activity in the primary culture of microglia cells with LPS-induced inflammation. Its anti-inflammatory action resulted from inhibiting the nuclear factor kappa beta signaling pathway. This is probably related to the capacity of butyrate to inhibit HDAC activity and promote the expression of genes related to anti-inflammatory pathways[37].

Ryu et al.38 demonstrated that phenylbutyrate administration in mice with ALS (G93A) could slow the death of motor neurons by modulating several transcriptional and post-translational pathways. An example of these pathways is the inhibition of HDACs. In another study, mice with ALS (G93A) were found to have intestinal dysbiosis and weakened junctions between intestinal epithelial cells. Mice treated with sodium butyrate (2% concentration in water) lost less weight and survived longer than the control group. Furthermore, a correction of dysbiosis, a decrease in intestinal permeability of mice treated with butyrate, and an increase in the abundance of butyrate-producing bacteria in the IM were observed[39].

In a phase 2 clinical study conducted on 26 patients with ALS, during 20 weeks of treatment, sodium phenylbutyrate, an SCFA, was shown to be safe and tolerated at doses of 9 to 21 g/day[40]. Additionally, it was observed that the lower dose of 9 g/day was efficient to increasing the histone acetylation pattern[40]. A multicenter, randomized, double-blind study on 177 patients with defined ALS demonstrated that the oral supplementation of sodium phenylbutyrate with tauroursodeoxycholic acid for 24 weeks contributed to the slowing of functional decline in patients with ALS, as evaluated by the revised functional scale, ALSFRS-R[41].

Although studies regarding IM in patients with ALS are scarce[42], McCombe et al.[3] published a narrative review discussing the possible role of IM in the pathogenesis of ALS (Figure 6). This review made the following observations: 1) Some IM bacteria can produce toxins, such as LPS. These toxins can cross the intestinal barrier and enter the body in intestinal dysbiosis and increase permeability. Some of them reach the nervous system where they have neurotoxic actions; 2) patients with ALS may present with changes in the energy homeostasis, such as hypermetabolism and more substantial weight loss. Studies show that resting energy expenditure has a positive relationship with the number of intestinal bacteria and a negative relationship with the abundance of Firmicutes[3]. This suggests that reducing Firmicutes contributes to higher energy expenditure and more substantial weight loss in these patients; 3) Dysphagic patients with ALS have low food intake. Deficiency of energy and essential nutrients may modify the composition of the IM, as already seen in patients with anorexia nervosa; 4) Chronic activation of the microglia and progressive neuroinflammation are part of the pathogenesis of ALS. Dysbiosis leads to an inflammatory state and may influence the immune system of patients with ALS, contributing to disease progression; 5) Patients with ALS may present with gastrointestinal alterations (delayed gastric emptying, delayed intestinal transit, constipation). It is possible that intestinal dysbiosis affects enteric neurons and contributes to the onset or worsening of these changes; 6) The IM produces circulating neurotransmitters that, with the microbiota-intestine-brain axis, can contribute to depression and cognitive and behavioral changes, which is observed in ALS patients[3].

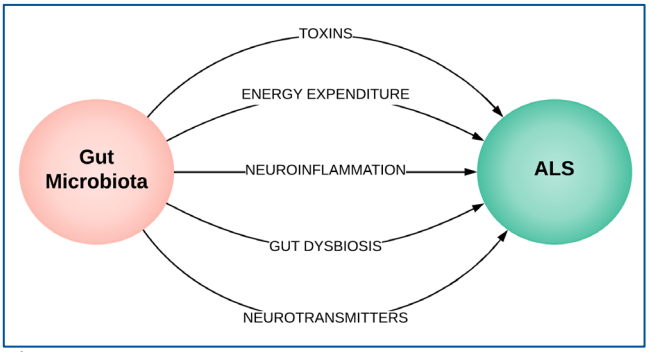

Figure 6 — Possible associations of gut microbiota in the pathogenesis and progression of ALS. Source: the authors.

MODULATION OF INTESTINAL MICROBIOTA IN ALS

ALS is a multifactorial disease, and alternative therapies may be helpful in its treatment[43]. Considering the function and interaction of IM with the host and its possible relation in the pathogenesis and progression of ALS, the modulation of IM in patients with ALS seems to be an important therapeutic target, which can be achieved by diet, prebiotics, probiotics, postbiotics, and fecal transplantation.

Diet

Diet has an immediate impact on the composition of IM. However, the dietary approach to modulating IM must be instituted long-term. This is because short-term dietary modifications cause rapid changes in IM composition, but the magnitude of these changes is still insufficient to change the enterotype of the individual[27]. Generally, it is said that a diet rich in vegetables and low in refined carbohydrates and fast foods favors a balanced IM (eubiosis). There is also evidence that a diet rich in fruits and vegetables is associated with a better functional state in ALS patients[44]. However, it is essential to remember that in patients with ALS, the implementation of any diet that favors IM should also be associated with an adequate energy intake[3]. Hypercaloric diets may benefit ALS patients[45], and dietary variety contributes to a more diverse microbiome[46].

Prebiotics

Prebiotics are nondigestible food compounds that confer health benefits to the host by modulating the IM[47]. These compounds are selectively fermentable by gut bacteria, inducing the growth of beneficial bacteria and the production of CBFA. The most common prebiotics are oligofructose, inulin, galactooligosaccharides, breast milk oligosaccharides, and lactulose. They are present in wheat, onions, bananas, honey, garlic, leeks, and chicory and can also be added to food[48]. Legumes such as peas and chickpeas are also rich in fermentable fiber and improve the intestinal barrier and IM[49]. The use of prebiotics may be a useful nutritional strategy in patients with ALS, despite the lack of clinical trials on prebiotics in this population[3].

Probiotics

Probiotics are live strains of selected microorganisms that confer health benefits to the host when administered in adequate amounts. Probiotic strains must meet established criteria for safety, functionality, and technological utility[47]. Although some strains have unique properties that confer certain neurological, immunological, and antimicrobial activities, it has been recognized that different strains may act similarly and synergistically, especially concerning resistance to colonization, the regulation of intestinal transit, or normalization of dysbiosis[48]. Probiotic supplementation can be a coadjuvant strategy in preventing or treating neurodegenerative diseases[50]. In ALS, probiotics have been highlighted as one of the innovative therapies[51]. There is still no evidence on which probiotic strains would be the most suitable for supplementation in patients with ALS. Clinical trials need to be conducted, considering the pathophysiology of the disease, the specific efficacy of the probiotic strain(s), and the quality, formulation, and dosage of the product[52].

Postbiotics

Postbiotics are by-products or metabolites generated by the fermentation of probiotic bacteria, such as those of the genus *Lactobacillus* and *Bifidobacterium*. Examples of probiotics are SCFAs, enzymes, peptides, teichoic acids, peptidoglycan muropeptides, endopolysaccharides, exopolysaccharides, cell surface proteins, vitamins, plasmalogens, and organic acids. These by-products are also believed to promote host health and are a safe therapeutic alternative[15]. Although the mechanisms of action of postbiotics are not yet fully understood, it is hypothesized that these by-products may influence various host cellular pathways, including proliferation, differentiation, migration, and cell death[53].

With prebiotics and probiotics, postbiotics assist in treating intestinal dysbiosis and, consequently, promote better functioning of the gastrointestinal tract, immune system, and nervous system[49]. Butyrate SCFA, considered a postbiotic, had a beneficial effect in restoring intestinal dysbiosis and increasing survival in mice with ALS (G93A)[39]. Therefore, it may be plausible to add butyrate to the diet of ALS patients[3]. The beneficial effects of postbiotic phenylbutyrate have been demonstrated in some clinical trials conducted with animal models or ALS patients[38,40,41].

The IM is capable of producing and metabolizing secondary bile salts. One of these is tauroursodeoxycholic acid (TUDCA), also considered a postbiotic. TUDCA improves intestinal barrier function, alters the composition of IM[54] and exerts anti-apoptotic, anti-inflammatory, antioxidant, and neuroprotective effects[55]. In a randomized, double-blind clinical trial on patients with ALS, it was observed that the use of TUDCA was well tolerated and was associated with less deterioration of the functional status of patients compared to that seen for the placebo[56]. This fact also demonstrates another therapeutic possibility of a postbiotic in ALS.

Fecal Microbiota Transplantation (FMT)

FMT transfers fecal microbiota from healthy donors to affected recipients. Although fecal transfer from one individual to another is reported in ancient Chinese medicine, this practice only resurfaced centuries later as a more efficient therapeutic possibility in pseudomembranous enterocolitis[57] and recurrent *C. difficile* infection[58]. Currently, TMF has been the target of several clinical trials involving neurological, psychiatric, neoplastic, autoimmune/inflammatory, infectious, gastrointestinal, and cardiometabolic disorders[59]. The trial master file has emerged as a promising strategy to restore the gut dysbiosis involved with the pathophysiology of neurodegenerative diseases[60]. Research involving TMF still faces numerous challenges regarding the form of administration, recipient colonization resistance, adverse effects, cost-effectiveness, and protocol standardization[59]. In our recent review of TMF in neurological disorders, we discussed 34 studies with human or animal models[61]. We noted several animal studies supported by some case reports affirming the positive effects of TMF for multiple sclerosis and Parkinson's disease.

There are still limitations of studies and evidence regarding epilepsy, Tourette's syndrome, diabetic neuropathy, stroke, Alzheimer's disease, and Guillain-Barré syndrome. There are still no clinical trials on TMF in patients with ALS, although this treatment has already been proposed for this population[3]. The protocol of the first clinical trial (multicenter, randomized, double-blind; FETR-ALS *Study Protocol*) was published[62], using TMF as a therapeutic intervention in early-stage ALS but with results yet to be published.

CONCLUSION

IM can individually modulate several physiological and behavioral activities from the microbiota-intestine-brain axis. The study of IM in neurodegenerative diseases, such as ALS, is an important field of research. Evidence shows signs of dysbiosis in patients or animal models with ALS. However, it is unknown whether

dysbiosis is a primary condition of ALS or secondary to dietary changes (anorexia, dysphagia, low food intake, enteral diet). IM may be a factor involved in the pathogenesis of ALS and, therefore, a promising therapeutic target; it can be modulated by diet, using prebiotics, probiotics and postbiotics, and TMF. Given this, representative and well-designed methodological studies must be conducted to clarify the knowledge gaps in this area and provide evidence of possible modulators of IM and their benefits in patients with ALS.

REFERENCES

1. Kho ZY, Lal SK. The human gut microbiome - a potential controller of wellness and disease. Front Microbiol. 2018;9:1835. https://doi.org/10.3389/fmicb.2018.01835
2. Cho I, Blaser MJ. The human microbiome: at the interface of health and disease. Nat Rev Genet. 2012;13(4):260-70. https://doi.org/10.1038/nrg3182
3. McCombe PA, Henderson RD, Lee A, Lee JD, Woodruff TM, Restuadi R, et al. Gut microbiota in ALS: possible role in pathogenesis? Expert Rev Neurother. 2019;19(9):785-805. https://doi.org/10.1080/14737175.2019.1623026
4. Dinan TG, Cryan JF. The microbiome-gut-brain axis in health and disease. Gastroenterol Clin N Am. 2017;46:77-89. https://doi.org/10.1016/j.gtc.2016.09.007
5. Sender R, Fuchs S, Milo R. Revised estimates for the number of human and bacteria cells in the body. PLoS Biol. 2016;14(8):e1002533. https://doi.org/10.1371/journal.pbio.1002533
6. Ding RX, Goh WR, Wu RN, Yue XQ, Luo X, Khine WWT, et al. Revisit gut microbiota and its impact on human health and disease. J Food Drug Anal. 2019;27(3):623-31. https://doi.org/10.1016/j.jfda.2018.12.012
7. Rinninella E, Raoul P, Cintoni M, Franceschi F, Miggiano GAD, Gasbarrini A, et al. What is the healthy gut microbiota composition? A Changing ecosystem across age, environment, diet, and diseases. Microorganisms. 2019;7(1):14. https://doi.org/10.3390/microorganisms7010014
8. Mariat D, Firmesse O, Levenez F, Guimarães V, Sokol H, Doré J, et al. The Firmicutes/Bacteroidetes ratio of the human microbiota changes with age. BMC Microbiol. 2009;9:123. https://doi.org/10.1186/1471-2180-9-123
9. Clarke G, Sandhu KV, Griffin BT, Dinan TG, Cryan JF, Hyland NP. Gut Reactions: Breaking down xenobiotic-microbiome interactions. Pharmacol Rev. 2019;71(2):198-224. https://doi.org/10.1124/pr.118.015768
10. Selma-Royo M, Tarrazó M, García-Mantrana I, Gómez-Gallego C, Salminen S, Collado MC. Shaping microbiota during the first 1000 days of life. Adv Exp Med Biol. 2019;1125:3-24. https://doi.org/10.1007/5584_2018_312
11. Milani C, Duranti S, Bottacini F, Casey E, Turroni F, Mahony J, et al. The first microbial colonizers of the human gut: composition, activities, and health implications of the infant gut microbiota. Microbiol Mol Biol Rev. 2017;81(4):e00036-17. https://doi.org/10.1128/MMBR.00036-17
12. Thursby E, Juge N. Introduction to the human gut microbiota. Biochem J. 2017;474(11):1823-36. https://doi.org/10.1042/BCJ20160510
13. den Besten G, van Eunen K, Groen AK, Venema K, Reijngoud DJ, Bakker BM. The role of short-chain fatty acids in the interplay between diet, gut microbiota, and host energy metabolism. J Lipid Res. 2013;54(9):2325-40. https://doi.org/10.1194/jlr.R036012
14. Venegas DP, la Fuente MK, Landskron G, González MJ, Quera R, Dijkstra G, et al. Short chain fatty acids (SCFAs)-mediated gut epithelial and immune regulation and its relevance for inflammatory bowel diseases. Front Immunol. 2019;20:277. https://doi.org/10.3389/fimmu.2019.00277
15. Amoroso C, Perillo F, Strati F, Fantini MC, Caprioli F, Facciotti F. The role of gut microbiota biomodulators on mucosal immunity and intestinal inflammation. Cells. 2020;9(5):1234. https://doi.org/10.3390/cells9051234
16. Yadav M, Verma MK, Chauhan NS. A review of metabolic potential of human gut microbiome in human nutrition. Arch Microbiol. 2018;200(2):203-17. https://doi.org/10.1007/s00203-017-1459-x
17. Tan J, McKenzie C, Potamitis M, Thorburn AN, Mackay CR, Macia L. The role of short-chain fatty acids in health and disease. Adv Immunol. 2014;121:91-119. https://doi.org/10.1016/B978-0-12-800100-4.00003-9
18. Liu H, Wang J, He T, Becker S, Zhang G, Li D, et al. Butyrate: A double-edged sword for health? Adv Nutr. 2018;9(1):21-9. https://doi.org/10.1093/advances/nmx009
19. Lin MY, de Zoete MR, van Putten JP, Strijbis K. Redirection of epithelial immune responses by short-chain fatty acids through inhibition of histone deacetylases. Front Immunol. 2015;6:554. https://doi.org/10.3389/fimmu.2015.00554
20. Li M, van Esch BCAM, Henricks PAJ, Folkerts G, Garssen J. The anti-inflammatory effects of short chain fatty acids on lipopolysaccharide- or tumor necrosis factor α-stimulated endothelial cells via activation of GPR41/43 and inhibition of HDACs. Front Pharmacol. 2018;9:533. https://doi.org/10.3389/fphar.2018.00533
21. Yang G, Chen S, Deng B, Tan C, Deng J, Zhu G, et al. Implication of G protein-coupled receptor 43 in intestinal inflammation: a mini-review. Front Immunol. 2018;9:1434. https://doi.org/10.3389/fimmu.2018.01434
22. Tazoe H, Otomo Y, Kaji I, Tanaka R, Karaki SI, Kuwahara A. Roles of short-chain fatty acids receptors, GPR41 and GPR43 on colonic functions. J Physiol Pharmacol. 2008;59 (Suppl 2):251-62. PMID: 18812643
23. Gaboriau-Routhiau V, Rakotobe S, Lécuyer E, Mulder I, Lan A, Bridonneau C, et al. The key role of segmented filamentous bacteria in the coordinated maturation of gut helper T cell responses. Immunity. 2009;31(4):677-689. https://doi.org/10.1016/j.immuni.2009.08.020
24. Marietta E, Horwath I, Taneja V. Microbiome, immunomodulation, and the neuronal system. Neurotherapeutics. 2018;15:23-30. https://doi.org/10.1007/s13311-017-0601-4
25. Corrêa-Oliveira R, Fachi JL, Vieira A, Sato FT, Vinolo MA. Regulation of immune cell function by short-chain fatty acids. Clin Transl Immunology. 2016;5(4):e73. https://doi.org/10.1038/cti.2016.17
26. Wang HX; Wang YP. Gut microbiota-brain axis. Chin Med J. 2016;129(19):2372-2380. https://doi.org/10.4103/0366-6999.190667
27. Gagliardi A, Totino V, Cacciotti F, Iebba V, Neroni B, Bonfiglio G, et al. Rebuilding the gut microbiota ecosystem. Int J Environ Res Public Health. 2018;15(8):1679. https://doi.org/10.3390/ijerph15081679
28. Benakis C, Martin-Gallausiaux C, Trezzi JP, Melton P, Liesz A, Wilmes P. The microbiome-gut-brain axis in acute and chronic brain diseases. Curr Opin Neurobiol. 2020;61:1-9. https://doi.org/10.1016/j.conb.2019.11.009
29. Sasmita AO. Modification of the gut microbiome to combat neurodegeneration. Rev. Neurosci. 2019;30:795-805. https://doi.org/10.1515/revneuro-2019-0005
30. Di Gioia D, Cionci NB, Baffoni L, Amoruso A, Pane M, Mogna L, et al. A prospective longitudinal study on the microbiota composition in amyotrophic lateral sclerosis. BMC Med. 2020;18(1):153. https://doi.org/10.1186/s12916-020-01607-9
31. van Es MA, Hardiman O, Chio A, Al-Chalabi A, Pasterkamp RJ, Veldink JH, et al. Amyotrophic lateral sclerosis. Lancet. 2017;390(10107):2084-98. https://doi.org/10.1016/S0140-6736(17)31287-4
32. Gois AM, Mendonça DMF, Freire MAM, Santos JR. In vitro and in vivo models of amyotrophic lateral sclerosis: an updated overview. Brain Res Bull. 2020;159:32-43. https://doi.org/10.1016/j.brainresbull.2020.03.012
33. Bonifacino T, Zerbo RA, Balbi M, Torazza C, Frumento G, Fedele E, et al. Nearly 30 years of animal models to study

amyotrophic lateral sclerosis: a historical overview and future perspectives. Int J Mol Sci. 2021;22(22):12236. https://doi.org/10.3390/ijms222212236
34. Wu S, Yi J, Zhang YG, Zhou J, Sun J. Leaky intestine and impaired microbiome in an amyotrophic lateral sclerosis mouse model. Physiol Rep. 2015;3(4):e12356. https://doi.org/10.14814/phy2.12356
35. Fang X, Wang X, Yang S, Meng F, Wang X, Wei H, et al. Evaluation of the microbial diversity in amyotrophic lateral sclerosis using high-throughput sequencing. Front Microbiol. 2016;7:1479. https://doi.org/10.3389/fmicb.2016.01479
36. Bourassa MW, Alim I, Bultman SJ, Ratan RR. Butyrate, neuroepigenetics and the gut microbiome: Can a high fiber diet improve brain health? Neurosci Lett. 2016;625:56-63. https://doi.org/10.1016/j.neulet.2016.02.009
37. Huuskonen J, Suuronen T, Nuutinen T, Kyrylenko S, Salminen A. Regulation of microglial inflammatory response by sodium butyrate and short-chain fatty acids. Br J Pharmacol. 2004;141(5):874-80. https://doi.org/10.1038/sj.bjp.0705682
38. Ryu H, Smith K, Camelo SI, Carreras I, Lee J, Iglesias AH, et al. Sodium phenylbutyrate prolongs survival and regulates expression of anti-apoptotic genes in transgenic amyotrophic lateral sclerosis mice. J Neurochem. 2005;93(5):1087-98. https://doi.org/10.1111/j.1471-4159.2005.03077.x
39. Zhang YG, Wu S, Yi J, Xia Y, Jin D, Zhou J, et al. Target intestinal microbiota to alleviate disease progression in amyotrophic lateral sclerosis. Clin Ther. 2017;39(2):322-36. https://doi.org/10.1016/j.clinthera.2016.12.014
40. Cudkowicz ME, Andres PL, Macdonald SA, Bedlack RS, Choudry R, Brown Jr. RH, et al. Phase 2 study of sodium phenylbutyrate in ALS. Amyotroph Lateral Scler. 2009;10(2):99-106. https://doi.org/10.1080/17482960802320487
41. Paganoni S, Macklin EA, Hendrix S, Berry JD, Elliott MA, Maiser S, et al. Trial of sodium phenylbutyrate-taurursodiol for amyotrophic lateral sclerosis. N Engl J Med. 2020;383(10):919-30. https://doi.org/10.1056/NEJMoa1916945
42. Wright ML, Fournier C, Houser MC, Tansey M, Glass J, Hertzberg VS. Potential role of the gut microbiome in ALS: a systematic review. Biol Res Nurs. 2018;20(5):513-21. https://doi.org/10.1177/1099800418784202
43. Cai M, Yang EJ. Complementary and alternative medicine for treating amyotrophic lateral sclerosis: A narrative review. Integr Med Res. 2019;8(4):234-9. https://doi.org/10.1016/j.imr.2019.08.003
44. Nieves JW, Gennings C, Factor-Litvak P, Hupf J, Singleton J, Sharf V, et al. Association between dietary intake and function in amyotrophic lateral sclerosis. JAMA Neurol. 2016;73(12):1425-32. https://doi.org/10.1001/jamaneurol.2016.3401
45. Wills AM, Hubbard J, Macklin EA, Glass J, Tandan R, Simpson EP, et al. Hypercaloric enteral nutrition in patients with amyotrophic lateral sclerosis: a randomised, double-blind, placebo-controlled phase 2 trial. Lancet. 2014;383(9934):2065-72. https://doi.org/10.1016/S0140-6736(14)60222-1
46. Heiman ML, Greenway FL. A healthy gastrointestinal microbiome is dependent on dietary diversity. Mol Metab. 2016;5(5):317-20. https://doi.org/10.1016/j.molmet.2016.02.005
47. Markowiak P, Śliżewska K. Effects of probiotics, prebiotics, and synbiotics on human health. Nutrients. 2017;9(9):1021. https://doi.org/10.3390/nu9091021
48. Guarner F, Khan AG, Garisch J, Eliakim R, Gangl A, Thomson A, et al. World Gastroenterology Organisation Global Guidelines - Probiotics and Prebiotics. World Gastroenterology Organisation, 2017. 35p. https://doi.org/10.1097/MCG.0b013e3182549092
49. Maguire M, Maguire G. Gut dysbiosis, leaky gut, and intestinal epithelial proliferation in neurological disorders: towards the development of a new therapeutic using amino acids, prebiotics, probiotics, and postbiotics. Rev Neurosci. 2019;30(2):179-201. https://doi.org/10.1515/revneuro-2018-0024
50. Kuraszkiewicz B, Goszczyńska H, Podsiadły-Marczykowska T, Piotrkiewicz M, Andersen P, Gromicho M, et al. Potential Preventive Strategies for Amyotrophic Lateral Sclerosis. Front Neurosci. 2020;14:428. https://doi.org/10.3389/fnins.2020.00428
51. Liscic RM, Alberici A, Cairns NJ, Romano M, Buratti E. From basic research to the clinic: innovative therapies for ALS and FTD in the pipeline. Mol Neurodegener. 2020;15(1):31. https://doi.org/10.1186/s13024-020-00373-9
52. Sniffen JC, McFarland LV, Evans CT, Goldstein EJC. Choosing an appropriate probiotic product for your patient: An evidence-based practical guide. PLoS One. 2018;13(12):e0209205. https://doi.org/10.1371/journal.pone.0209205
53. Russo E, Giudici F, Fiorindi C, Ficari F, Scaringi S, Amedei A. immunomodulating activity and therapeutic effects of short chain fatty acids and tryptophan post-biotics in inflammatory bowel disease. Front Immunol. 2019;10:2754. https://doi.org/10.3389/fimmu.2019.02754
54. Wang W, Zhao J, Gui W, Sun D, Dai H, Xiao L, et al. Tauroursodeoxycholic acid inhibits intestinal inflammation and barrier disruption in mice with non-alcoholic fatty liver disease. Br J Pharmacol. 2018;175(3):469-84. https://doi.org/10.1111/bph.14095
55. Daruich A, Picard E, Boatright JH, Behar-Cohen F. Review: The bile acids urso- and tauroursodeoxycholic acid as neuroprotective therapies in retinal disease. Mol Vis. 2019;25:610-24. PMCID: PMC6817734
56. Elia AE, Lalli S, Monsurrò MR, Sagnelli A, Taiello AC, Reggiori B, et al. Tauroursodeoxycholic acid in the treatment of patients with amyotrophic lateral sclerosis. Eur J Neurol. 2016;23(1):45-52. https://doi.org/10.1111/ene.12664
57. Eiseman B, Silen W, Bascom GS, Kauvar AJ. Fecal enema as an adjunct in the treatment of pseudomembranous enterocolitis. Surgery. 1958;44:854-9. PMID:13592638
58. van Nood E, Vrieze A, Nieuwdorp M, Fuentes S, Zoetendal EG, de Vos WM, et al. Duodenal infusion of donor feces for recurrent Clostridium difficile. N Engl J Med. 2013;368(5):407-15 https://doi.org/10.1056/NEJMoa1205037
59. Leshem A, Horesh N, Elinav E. Fecal Microbial Transplantation and its potential application in cardiometabolic syndrome. Front Immunol. 2019;10:1341. https://doi.org/10.3389/fimmu.2019.01341
60. Tilocca B, Pieroni L, Soggiu A, Britti D, Bonizzi L, Roncada P, et al. Gut-brain axis and neurodegeneration: state-of-the-art of meta-omics sciences for microbiota characterization. Int J Mol Sci. 2020;21(11):4045. https://doi.org/10.3390/ijms21114045
61. Vendrik KEW, Ooijevaar RE, de Jong PRC, Laman JD, van Oosten BW, van Hilten JJ, et al. Fecal microbiota transplantation in neurological disorders. Front Cell Infect Microbiol. 2020;10:98. https://doi.org/10.3389/fcimb.2020.00098
62. Mandrioli J, Amedei A, Cammarota G, Niccolai E, Zucchi E, D'Amico R, et al. FETR-ALS Study Protocol: A randomized clinical trial of fecal microbiota transplantation in amyotrophic lateral sclerosis. Front Neurol. 2019;10:1021. https://doi.org/10.3389/fneur.2019.01021

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