REVIEW

Gut microbiota in muscular atrophy development, progression, and treatment: New therapeutic targets and opportunities

Shujie Chen,[1,2,3,10] Puxuan Zhang,[1,10] Huimin Duan,[1,2,3,10] Jie Wang,[8] Yuyueyang Qiu,[1,9] Zongbin Cui,[1] Yulong Yin,[5,6,*] Dan Wan,[5,6,*] and Liwei Xie[1,2,3,4,7,*]

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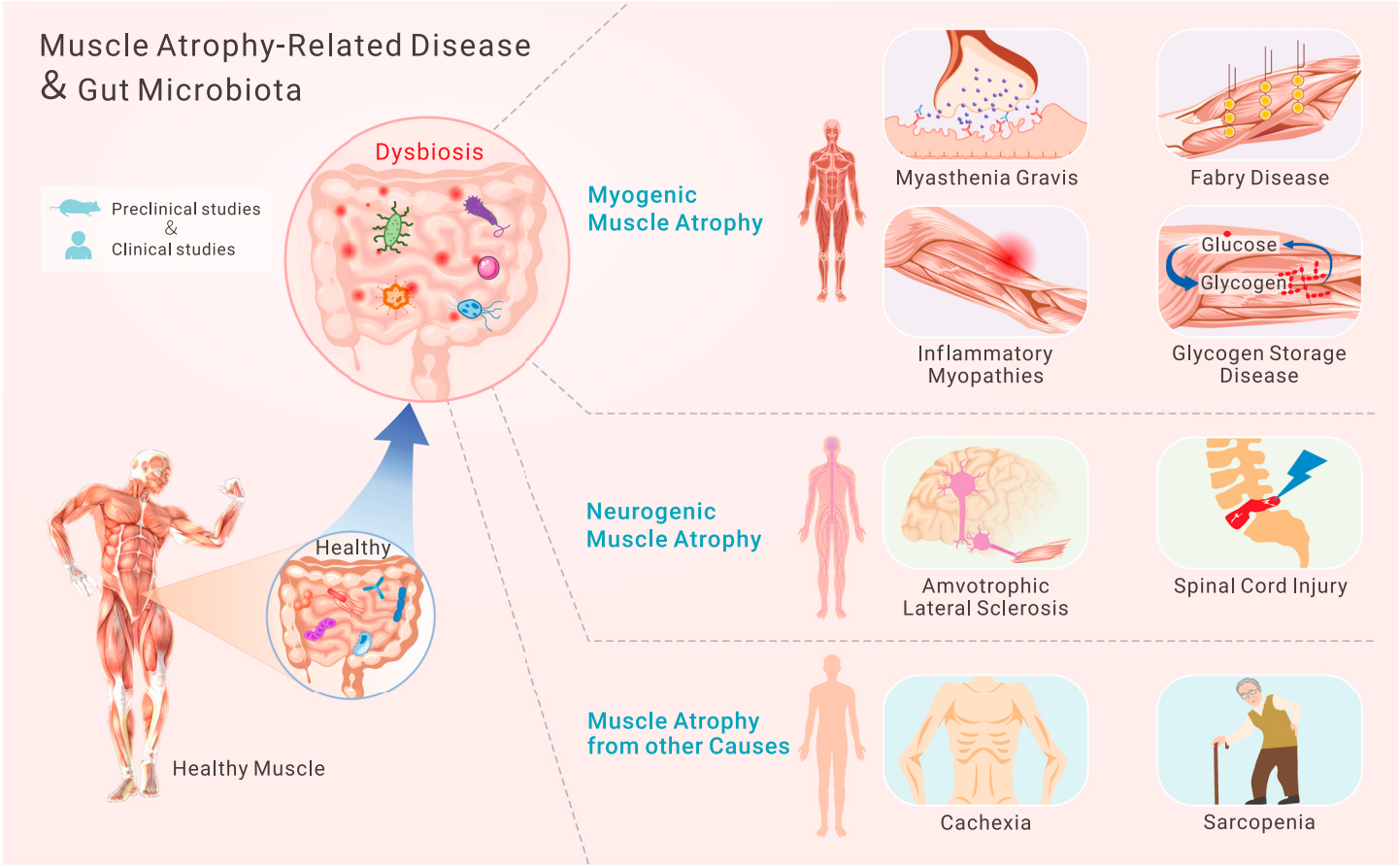
GRAPHICAL ABSTRACT



PUBLIC SUMMARY

- Understanding gut microbiota differences in muscle atrophy is crucial for effective interventions.
- Gut microbiota alterations may contribute to muscle atrophy through metabolites and inflammation.
- Modulating the gut microbiota shows promise for improving muscle performance and promoting disease recovery in animal models and clinical trials.

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Skeletal muscle atrophy is a debilitating condition that significantly affects quality of life and often lacks effective treatment options. Muscle atrophy can have various causes, including myogenic, neurogenic, and other factors. Recent investigation has underscored a compelling link between the gut microbiota and skeletal muscle. Discerning the potential differences in the gut microbiota associated with muscle atrophy-related diseases, understanding their influence on disease development, and recognizing their potential as intervention targets are of paramount importance. This review aims to provide a comprehensive overview of the role of the gut microbiota in muscle atrophy-related diseases. We summarize clinical and pre-clinical studies that investigate the potential for gut microbiota modulation to enhance muscle performance and promote disease recovery. Furthermore, we delve into the intricate interplay between the gut microbiota and muscle atrophy-related diseases, drawing from an array of studies. Emerging evidence suggests significant differences in gut microbiota composition in individuals with muscle atrophy-related diseases compared with healthy individuals. It is conceivable that these alterations in the microbiota contribute to the pathogenesis of these disorders through bacterium-related metabolites or inflammatory signals. Additionally, interventions targeting the gut microbiota have demonstrated promising results for mitigating disease progression in animal models, underscoring the therapeutic potential of modulating the gut microbiota in these conditions. By analyzing the available literature, this review sheds light on the involvement of the gut microbiota in muscle atrophy-related diseases. The findings contribute to our understanding of the underlying mechanisms and open avenues for development of novel therapeutic strategies targeting the gut-muscle axis.

INTRODUCTION

Muscle atrophy, a prevalent chronic muscle condition, arises from an imbalance between protein synthesis and breakdown, which governs muscle mass and fiber size.[1] Excessive protein breakdown and muscle loss pose severe risks, including death. Hence, maintaining optimal muscle health is crucial for preventing metabolic disorders and promoting healthy aging.[2] Muscle atrophy can be divided into three subgroups according to clinical etiology: physiological, pathologic, and neurogenic atrophy. Physiological atrophy, induced by muscle diseases and conditions that restrict motion, is characterized by being bedridden and a limited range of motion. However, with specific clinical treatment strategies, this type of atrophy can be reversed.[3] Pathologic atrophy is considered to be the result of cell injury and loss of stimulus in a specific region,[4] while neurogenic atrophy, the most severe form of muscle atrophy, results from disruption of the signaling pathway between the nerve and muscle.[5] The pathogenesis of muscle atrophy is regulated by local and external factors, such as gut microbiota metabolites.

Recently, the gut microbiome has attracted considerable attention from researchers. Its role in regulating host physiology by modulating multiple endogenous processes has been well studied. An increasing number of studies have identified a causal relationship between the gut microbiome and muscular diseases, revealing new possibilities for treating muscular dystrophy. The human gut harbors 10–100 trillion microorganisms with over 9.9 million microbial genes involved in regulating host physiology and pathophysiology.[6] A healthy gut typically contains 1,100–2,000 bacterial taxa belonging to 10 phyla, with 99% of the species dominated by the *Firmicutes* and *Bacteroidetes* phyla.[7] The composition of the gut microbiota varies among individuals because of differences in genetic background and host environment.[8] Aging-associated pathologic conditions, such as malnutrition and chronic diseases, also affect gut microbiota composition.[9] In contrast, healthy elderly people with a high life expectancy have a relatively high proportion of "good bacteria" with anti-inflammatory properties.[9] Given the essential roles of the gut microbiota in regulating host homeostasis, it is essential to identify regulatory mechanisms to prevent the development and progression of muscle atrophy-related diseases. Such an endeavor opens up the possibility of developing personalized and precise microbial treatments.

Over the past decades, numerous studies have uncovered the role of the gut microbiota in host immune function, brain activity, and the gut barrier.[10–13] In recent years, the connection between the gut and muscles has garnered increasing attention from researchers. Studies have demonstrated that the gut microbiota is associated with various aspects of skeletal muscle, including mass, function, and metabolism. This connection plays a role in maintaining metabolic balance, insulin sensitivity, and managing inflammation in the body. In a pre-clinical study involving germ-free (GF) mice, absence or imbalance of the gut microbiota induced phenotypic alterations in all types of skeletal muscles. This outcome can be partially attributed to the signaling pathway involving AMPK (AMP-activated protein kinase), FoxO3 (Forkhead box protein O3), and atrogin, highlighting the impact of the gut microbiota on skeletal muscle function.[14] The intestinal microbiome has been found to impact muscle function and quantity through various mechanisms, including increased activation of the BCAA (branched-chain amino acid) pathway,[15] higher levels of SCFAs (short-chain fatty acids),[16] improved iron absorption,[17] enhanced insulin sensitivity,[18] improved mitochondrial respiration,[18] improved glucose utilization,[19] strengthened intestinal barrier,[20] reduced inflammation,[18] decreased cytokine production,[19] and reduced negative effects of antibiotics on fermentation in the colon.[17] These effects have been observed in clinical and pre-clinical studies.

The interaction between gut bacteria and skeletal muscle physiology has gained significant attention because of its underlying mechanisms and clinical implications. This review summarizes recent findings from pre-clinical and clinical studies exploring the relationship between the gut microbiota and muscle

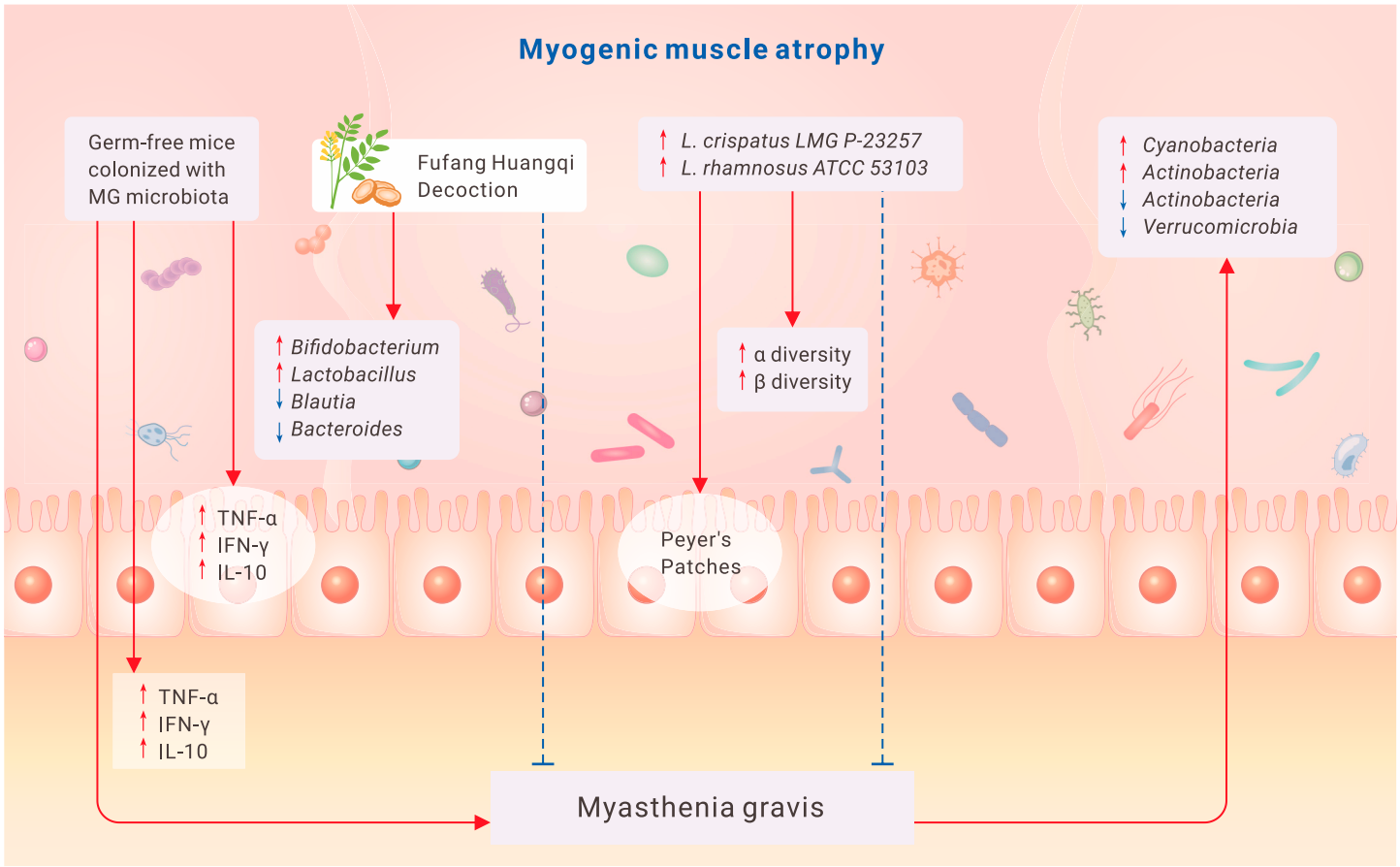

Figure 1. MG patients have obvious gut microbiota alterations In a fecal microbiota transplantation (FMT) experiment, colonizing GF mice with the microbiota of MG patients resulted in impaired locomotion and upregulation of host inflammatory cytokines.[23] The microbiota of MG patients who were administered fufang huangqi decoction and achieved remarkable alleviation of symptoms underwent alteration, with the abundance of *Blautia* and *Bacteroides* decreasing and *Bifidobacterium*, *Lactobacillus*, and *Roseburia* increasing.[24] The progression of the disease was benefitted by the administration of two probiotic strains of *Bifidobacterium* and *Lactobacillus* in the Lewis rat model of myasthenia gravis (EAMG). Probiotic interactions with Peyer's patches and greater α and β diversity in probiotic-treated EAMG were observed.[25] Blue arrows represent promotion effects. Red arrows represent inhibition effects.

diseases. By examining the evidence linking the gut microbiome and muscle diseases, this review aims to contribute to the development of preventive or therapeutic strategies that target modulation of the gut microbiota.

GUT MICROBIOTA AND MYOGENIC MUSCLE ATROPHY

Myasthenia gravis

Myasthenia gravis (MG) is a chronic autoimmune disease and neuromuscular disorder in which the transmission of nerve signals to the muscles is disturbed, resulting in skeletal muscle weakness. A hallmark of MG is the presence of B cell-produced antibodies against the acetylcholine receptor (AChR).[21] AChR is found in the postsynaptic membrane at the neuromuscular junction. It is associated with muscle-specific kinase (MUSK), lipoprotein-related protein 4 (LRP4), and agarin, all of which play important roles in muscle-related processes.[21] Muscle weakness is a key symptom of MG. The most common initial symptom is ocular muscle weakness. However, the symptoms of MG are often found in the bulbar, leg, axial, and respiratory muscles.[21] The most commonly used treatments for MG are thymectomy, prednisone (an immunosuppressant), and pyridostigmine (an acetylcholinesterase inhibitor).[21] Alterations in the composition of the gut microbiota may play a role in immune-mediated diseases by influencing immune activation and triggering pro- and anti-inflammatory responses to activate or inhibit immune responses.[22] Clinical and pre-clinical studies have shown a connection between MG symptoms and the gut microbiota (Figure 1).

Clinical studies were categorized based on the affected regions (i.e., ocular MG [OMG] and generalized MG [GMG]), and the age of the population (i.e., pediatric or adult MG). OMG is characterized by frailty of the eyelid and/or extraocular muscles, leading to fatigable ptosis and diplopia. Within 2 years, nearly 30%–80% of patients develop GMG. The gut microbiota in the MG group exhibits a significant decrease in α diversity compared with healthy individuals, suggesting that patients with MG have lower bacterial richness and evenness.[23,26–28] The β diversity of the gut microbiota of patients with MG is significantly different from that of healthy controls (HCs).[23,27–29] In a single-center observational study, 41 patients with MG were recruited and compared with 12 HCs and two other autoimmune diseases (Neuromyelitis Optica Spectrum Disorder [NIND] and Chronic Inflammatory Demyelinating Polyneuropathy [CIDP]).[26] The results revealed that four indices of α diversity (Shannon, Chao1, Simpson, and ACE) showed a significant difference between MG patients and HCs, and all four indices tended to be lower in the MG groups compared with the HCs. However, no differences were observed in α and β diversity among the MG, NIND, and CIDP groups, suggesting that immunological disorders may be related to gut microbiota dysbiosis. Compared with HCs, MG patients had a higher abundance of *Faecalibacterium* and Deltaproteobacteria in their feces.[26] Another clinical study compared two subtypes of MG (OMG and GMG) with HCs and found that the GMG group, but not the OMG group, had lower α diversity in the Chao, invSimpson, and Shannon indices, while the β diversity of GMG and OMG was significantly different from HCs.[27] According to data from a pediatric MG study, an altered fecal microbiota and reduced SCFAs may be crucial for the pathogenesis of pediatric MG. A total of 12,803 significantly dysregulated genes were detected between the MG group and HCs, with 238 co-abundant gene groups (CAGs). The results showed that the CAGs of *Clostridium bartlettii*, *Bilophila wadsworthia*, and *Bacteroides dorei* were enriched in the HC group, whereas *Prevotella copri* and *Bacteroides massiliensis* were the main sources of CAGs in the MG group. In addition, the levels of butyric and isobutyric acids in SCFAs differed between HCs and patients with MG. At the species level of the gut microbiome, *Lactobacillus sanfranciscensis* and *Prevotella nanceiensis* were strongly correlated with blood butyric acid levels. *B. dorei*,

Erysipelotrichaceae bacterium 3_1_53, and *Eubacteriaceae bacterium ACC19a* are positively associated with blood isobutyric acid. Of these species, the other four bacterial species were enriched in HCs, whereas only *Erysipelotrichaceae bacterium 3_1_53* was enriched in MG.[30] The remaining three clinical studies included 267 subjects, consisting of 133 adult patients with MG and 134 adult HCs. Two studies examined the diversity between MG and HCs and similarly concluded that patients with MG had lower microbiome diversity and richness. In particular, MG patients had lower levels of *Clostridium* and *Eubacterium* and more *Streptococcus* and *Parasutteralla* at the genus level.[28] At the family level, Bacteroidetes and Fusobacteria were upregulated, whereas Actinobacteria was downregulated in MG.[23] In another study, *Verrucomicrobiaceae*, *Bifidobacteriaceae*, *Coriobacteriaceae*, *Leuconostocaceae*, and *Flavobacteriaceae* were found to be decreased, while *Acidaminococcaceae*, *Desulfovibrionaceae*, and *Pasteurellaceae* were increased.[22] At the phylum level, MG patients had higher levels of *Bacteroidetes* and lower levels of *Actinobacteria* and *Verrucomicrobia*.[31] In addition, Firmicutes have been found in MG and HCs[29] and tested to be increased and decreased in patients with MG compared with HCs.[23] This is due to the large percentage of Firmicutes in the intestinal bacteria (65%–79.4%) and is the domain of fecal microbiota in MG and HC participants,[29] and different subtypes of Firmicutes can be upregulated or downregulated at the same time. In addition, two clinical studies have shown that the level of SCFAs is lower in patients with MG compared with HCs,[28,30] while another study analyzed the level of SCFAs in stool samples and found no difference between the MG group and HCs.[29] In blood tests, microbial dysbiosis was found to be closely related to inflammatory biomarkers, which may be due to the fact that dysbiosis can promote chronic inflammation and impairs systemic immune responses.[28] Only one clinical intervention has demonstrated efficacy compared with no treatment; patients with MG administered fufang guangqi decoction achieve significant symptom relief.[24] Patients with MG who are medicated have different microbial communities than control patients; they tend to have lower levels of *Blautia* and *Bacteroides* and higher levels of *Bifidobacterium* and *Lactobacillus* at the genus level.[24]

For pre-clinical studies, female Lewis rats were used as an MG model,[25] and GF mice were colonized with the gut microbiota of MG patients.[31] The first study confirmed that administration of therapeutic probiotics (*Lactobacillus crispatus* LMG P-23257, *Lactobacillus rhamnosus* ATCC 53103, *Bifidobacterium animalis* subsp. *lactis* BB12, and *B. animalis* subsp. *lactis* LMG S-28195) is beneficial for alleviating MG symptoms. The latter study examined how the gut-microbiota-brain axis was affected by the microbiome.[31] GF mice were colonized with fecal microbiota from MG patients (MMb) or healthy people (HMb) or co-colonized with samples from patients and healthy people (CMb). Metabolic characterization revealed that gut-brain communication differed significantly between the MMb and HMb groups. However, the anxiety-like behavior of the MMb group was reversed in the CMb group. A total of 71 metabolites differed between the MMb and HMb groups, which was reversed by co-colonization in the CMb group. In addition, co-colonization reversed the gut microbiota, which consisted mainly of *Bacteroides* and *Firmicutes* and correlated strongly with reversed metabolites along the MGB axis.

As mentioned above, the composition of the gut microbiota and metabolites is altered in patients with MG and is associated with its onset and progression. In the future, modulation of the gut microbiota could be an effective approach to prevent and treat MG. More details regarding the changes in the gut microbiota of MG patients are summarized in Table (A).

Inflammatory myopathies

Idiopathic inflammatory myopathies (IIMs) are acquired immune-mediated disorders that primarily affect striated muscle but can also involve other organs, such as the skin, joints, lungs, heart, and gastrointestinal tract.[32,33] Subtypes of IIMs include dermatomyositis, polymyositis, overlap myositis, sporadic inclusion body myositis, and necrotizing autoimmune myopathy.[32,33] The pathophysiology of IIMs is not fully understood.[32,33] IIMs are always accompanied by proximal muscle weakness, elevated muscle enzyme levels, myopathic changes on electromyography, and abnormal muscle biopsy.[32,33] Various myositis-specific antibodies have demonstrated associations with distinct phenotypes as well as increased risks for neoplastic diseases and systemic complications.[32,33] The prognosis, response to treatment, and manifestations in different subgroups vary significantly.[32,33] Immunosuppression is the routine treatment for dermatomyositis, polymyositis, and immune-mediated necrotizing myopathy, while symptomatic therapies are used in the treatment of body myositis.[32,33] In recent years, research has shown that the gut microbiome may be one of the most important factors in the pathophysiology of IIMs (Figure 2). In one of these studies, the impact of interleukin-2 (IL-2) as a therapeutic approach for IIMs on the gut microbiota was analyzed in humans and animals.[34] A correlation analysis was performed between the gut microbiota and clinical markers of the etiology of IIMs. A previous study found that low-dose IL-2 could regulate cellular immunity, promote immunity, and be effective in curing IIMs.[35,36] One study analyzed the influence of administration of IL-2 as a therapeutic approach for IIMs on gut microbiota in humans and non-obese diabetic (NOD) mice (a model for autoimmune diseases).[34] Thirteen patients with active IIMs were enrolled in the study and received 1×10^6 IU of IL-2 administered subcutaneously every other day for 12 weeks in addition to conventional therapy. Stool samples were collected for 16S rRNA gene sequencing to assess structural and functional changes in the fecal microbiota and investigate their association with clinical and immunological features. These findings revealed that the diversity of the microbiota in patients with IIM was significantly lower than that in HCs. Prevotellaceae, a family of inflammation-related bacteria, had elevated levels, while the levels of the butyrate-producing bacteria *Pseudobutyrivibrio*, *Lachnospiraceae*, *Roseburia*, and *Blautia* had decreased dramatically. In addition, butyrate-producing bacteria (i.e., *Lachnospiraceae* and *Pseudobutyrivibrio*), were associated with an increase in L-leucine and asparagine.[34] Female NOD mice were injected subcutaneously with a low dose of IL-2 at 30,000 IU daily for 60 days.[34] The results suggest that IL-2 injection can alter the bacterial ecology in animals prone to autoimmune diseases by suppressing inflammation and promoting immune system plasticity.

Fabry disease

Fabry disease is a rare X-linked lysosomal storage disease caused by a deficiency in α-galactosidase A activity, resulting in accumulation of glycosphingolipids such as globotriaosylsphingosine (lyso-Gb3).[37] Patients have a significantly shorter life expectancy because of the progressive, fatal, and destructive nature of Fabry disease.[39] Symptoms include acroparesthesia, irregular sweating, corneal verticillata, angiokeratomas, and conditions affecting the heart, blood vessels, and kidneys (e.g., cardiomyopathy, arrhythmia, stroke, and proteinuria).[40] These symptoms usually appear between the ages of 40 and 60. Replacement of the enzyme with recombinant human galactosidase A is a specific treatment for Fabry disease.[39]

A study from Spain investigated the effect of a clinically relevant concentration of lyso-Gb3 on the composition of the gut microbiota and mono- or multispecies bacterial biofilm formation (Figure 3).[37] The results demonstrated that lyso-Gb3 promotes the bacterial capacity to form biofilms and dramatically increase the growth of *Bacteroides fragilis* in multispecies biofilms.

During lyso-Gb3 treatment, there was an increase in certain bacteria, including Enterobacteriaceae, *Enterococcus*, and *Prevotella*. However, the levels of *Akkermansia*, *Bacteroides*, *Bifidobacterium*, *Clostridium leptum*, *Blautia coccoides, Eubacterium rectale*, and *Lactobacillus* were significantly lower after lyso-Gb3 treatment. The treatment also altered the composition of bacteria in a suspension of human colon microbiota, increased the amount of *B. fragilis*, and modified the synthesis of SCFAs, resulting in a decrease in the level of butyrate.

Glycogen storage disease

Glycogen storage disease (GSD) is a metabolic disorder caused by inactivity of glycogen-metabolizing enzymes.[44] It is categorized into more than 12 subgroups, based on which tissue is affected and the absence of enzymes.[45] The most prevalent subtypes of GSD are GSD I, GSD III, and GSD IX.[44] Because the bulk of glycogen is stored in the muscles and liver, glycogen breakdown disorders often affect these two organs. The liver, muscle, heart, kidneys, and brain may all be affected depending on the type of GSD.[38,45,46] The symptoms and treatments vary depending on the subtypes and enzymes affected.[46] In recent years, evidence of the interaction between gut commensal bacteria and hereditary metabolic diseases has expanded dramatically (Figure 3).

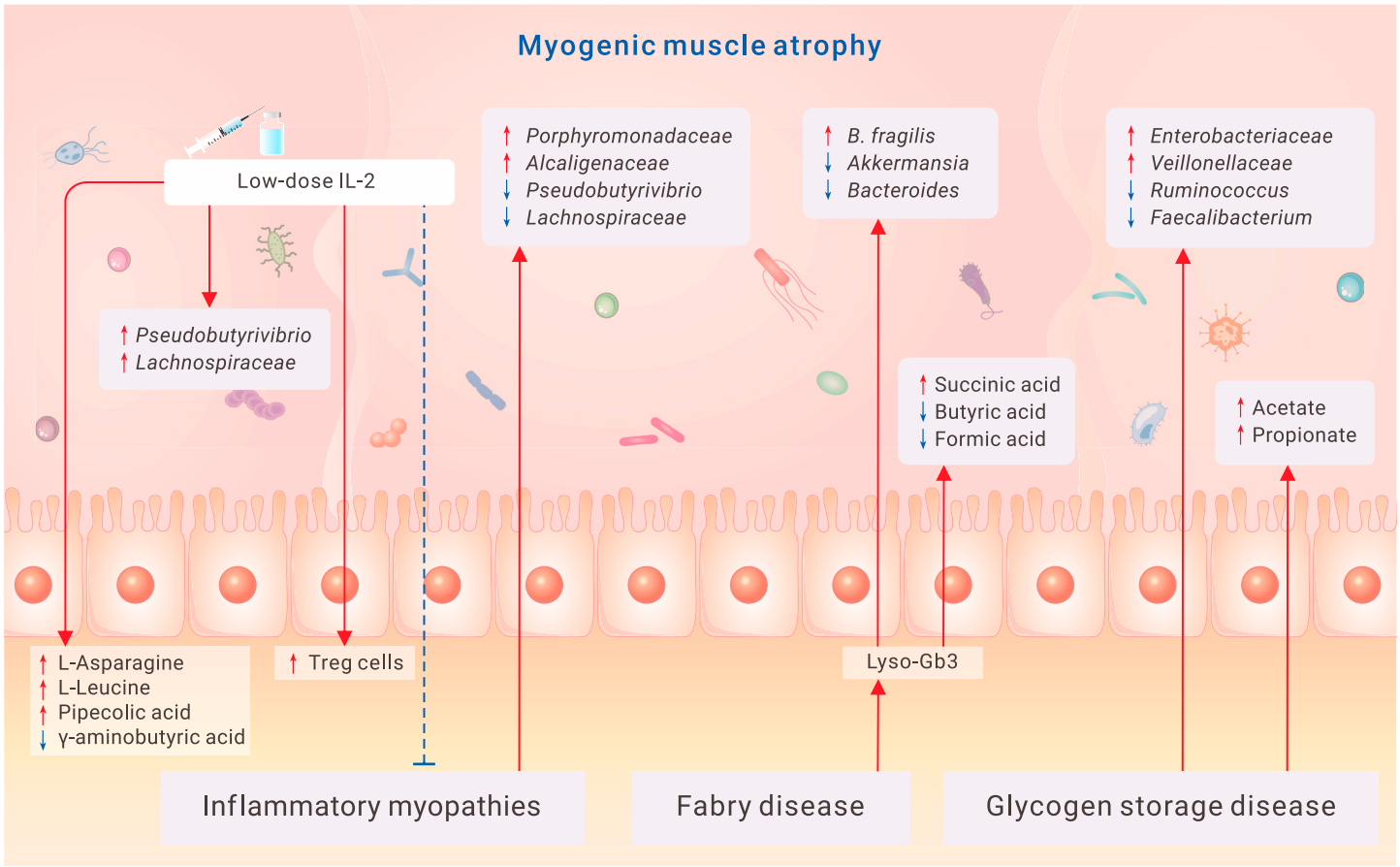

Figure 2. According to microbiota analysis, several butyrate-producing bacteria, including *Pseudobutyrivibrio*, Lachnospiraceae, *Roseburia*, and *Blautia*, drastically decreased in patients with idiopathic inflammatory myopathies (IIMs) Low-dose IL-2 was effective in active IIMs with a large increase in the proportion of Regulatory T-cells (Treg) cells and certain butyrate-producing bacteria, such as Lachnospiraceae, *Pseudobutyrivibrio*, etc., which are linked to an increase in L-asparagine and L-leucine.[34] Fabry disease can lead to accumulation of glycosphingolipids, such as globotriaosylsphingosine (lyso-Gb3). Lyso-Gb3 can change the biofilm formation capacity of several individual bacteria, including *B. fragilis*, and modify formation of SCFAs.[37] Stark variations in the gut microbiota between patients with glycogen storage disease (GSD) and HCs were revealed. Fecal acetate and propionate increased significantly in GSD patients.[38] Blue arrows represent promotion effects. Red arrows represent inhibition effects.

Because food intake is one of the major determinants of the composition of the gut microbiota, the connection between GSD and gut microbiota variation is probably associated with diet in the treatment of patients and the generation of microbial metabolites.[38] The main goals of food therapy are preventing hypoglycemia, achieving optimal adequate metabolic control, limiting secondary metabolic disturbances, and minimizing long-term consequences.[38] Two studies have assessed the impacts of diet on the intestinal ecosystem of GSD patients and found that GSD patients have low gut microbiota diversity compared with HCs. A study from Italy compared the gut microbiota of 9 patients with GSD with that of 12 HCs and discovered that diet has the potential to significantly influence gut microbiota over their lifespan.[38] In patients with GSD, the relative abundances of *Faecalibacterium* and *Oscillospira* were markedly diminished, whereas the relative abundance of *Enterobacteriaceae* and *Veillonellaceae* increased.[38] Because of unbalanced bacterial interactions, fecal acetate and propionate levels in patients with GSD were considerably elevated, but their positive effects were likely lowered. In addition, the nutritional value of the different bacterial species differed considerably between the experimental groups. A Brazilian study evaluated the fecal microbiota of 24 patients with GSD (Ia = 15, Ib = 5, III = 1, Ixα = 3) treated with uncooked cornstarch and HCs. The study showed that those with GSD exhibited lower fecal bacterial diversity and intestinal dysbiosis. The abundance of bacteria was significantly affected by the amount of sugar, total carbohydrates, and pH of the feces, with evidence from patients showing significantly high levels of *Lactobacillus* and *Escherichia/Shigella*, demonstrating their biological significance in GSD. However, *Lactobacillus*, which has been found previously to be more abundant in patients with GSD, was not identified after excluding all patients with inflammatory bowel disease (IBD)-like symptoms. In addition to dietary interventions, the effect of probiotic therapy on the etiology of GSD has also been investigated. A case study from Spain examined the effects of probiotics on a 36-year-old male patient with GSD Ia and IBD-like symptoms. The patient was administered a commercial probiotic (VSL#3) as a nutritional supplement because of its high microbial species and strain value.[47] The authors concluded that probiotics might enhance the nutritional utilization and quality of life of GSD Ia patients by reducing the frequency of bowel episodes of diarrhea and abdominal discomfort. More details regarding the changes in the gut microbiota of GSD patients are summarized in Table (B).

THE GUT MICROBIOTA AND NEUROGENIC MUSCLE ATROPHY

Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is a complicated neurodegenerative disease characterized by progressive degeneration of motor neurons and muscle atrophy.[48] Patients with spinal-onset ALS (sALS) have symptoms that begin in the limbs; in contrast, those with bulbar-onset ALS (bALS) have symptoms beginning in the head and neck.[49] ALS is also correlated with mitochondrial dysfunction[50] and altered immunological conditions.[51,52] Patients have limited clinical treatment choices, and the typical survival time is 2–5 years, frequently because of respiratory muscle failure.[53]

Since 2017, many studies on the gut microbiota of ALS populations have been conducted. To date, there is contradictory evidence regarding whether the gut microbiota of patients with ALS varies from that of HCs (Figure 3). A German analysis found that the diversity and abundance of the bacterial species were basically the same across all taxonomic levels in patients with ALS and HCs.[54] While some research revealed no changes between ALS patients and HCs in α diversity and community structure of the gut microbiota,[55,56] others discovered contrary findings.[41,57–59] According to a recent study, different microbiological mechanisms contribute to the development of two previously classified ALS subgroups (sALS vs. bALS).[60] Patients with sALS and bALS experience expanding dysbiosis in either the gut or oral cavity. However, both sALS and bALS patients

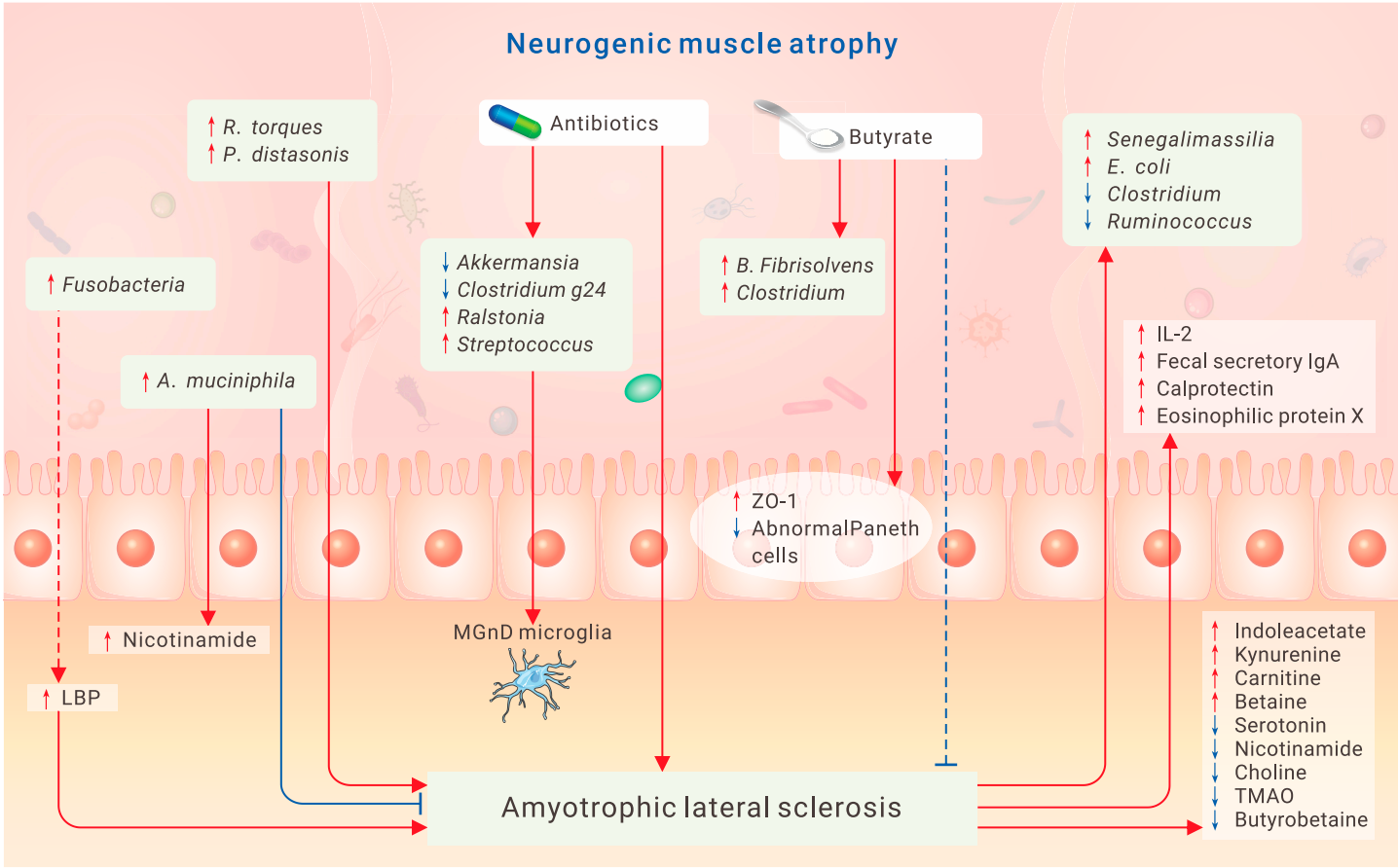

Figure 3. In spinal-onset amyotrophic lateral sclerosis (sALS), high fecal *Fusobacterium* abundance is favorably connected with microbial translocation, whereas bALS is positively correlated with high oral *Fusobacterium* abundance Serum metabolites, the gut microbiota, and intestinal immune factors are significantly altered in ALS patients. In antibiotic-treated Sod1-Transgenic (Tg) mice, *R. torques* and *P. distasonis* worsen ALS symptoms, while *A. muciniphila* ameliorates them.[41] In the SOD1 mice, low-dose antibiotic therapy worsened motor function and decreased the survival rate; alterations in microglia came before changes in motor performance.[42] The intestinal microbial homeostasis, gut integrity, and lifespan of the ALS mice are improved by feeding them butyrate, which is accompanied by a dramatically reduced number of aberrant Paneth cells.[43] Blue arrows represent promotive effects. Red arrows represent inhibitory effects.

had considerably higher levels of blood lipopolysaccharide-binding proteins (LBPs), suggesting greater microbial translocation to the blood. Furthermore, the Firmicutes/Bacteroidetes (F/B) ratio may decrease[55,59,61] or show no discernible change.[54] Kim et al.[60] discovered that patients with bALS had a decreased oral F/B ratio, while those with sALS had an increased fecal F/B ratio. These studies also pinpointed specific beneficial bacteria that differed significantly in patients with ALS and HCs; for example, decreased *Ruminococcus*,[61,62] *Prevotella*,[57] Erysipelotrichaceae,[55] *Fusicatenibacter*[55], *Roseburia intestinalis*, and *E. rectale*[56] in ALS patients. Additionally, gut inflammation in patients with ALS was also studied. They had higher levels of immunoglobulin A (IgA), calprotectin, and eosinophilic protein X in feces.[61] IL-2 levels were also greater in patients with ALS.[55] Patients with ALS who experienced rapid disease progression had lower levels of IL-21 than those who experienced slow or moderate disease progression.[55] High Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase 2 activity may be related to the neuroinflammatory process.[63]

In addition to alteration of the gut microbiota and host inflammatory response, a plethora of studies have reported the impact of regulatory mechanisms of bacterium-derived metabolites on ALS pathogenesis. Lower levels of carbon metabolism, particularly butanoate metabolic pathway enzymes, have been observed in the expected functional profile of microbiomes in patients with ALS.[57] However, fecal SCFAs levels varied among analyses, with some demonstrating higher levels in the ALS group[58] while others revealed no appreciable difference.[55] In any event, those with ALS who consumed more fiber had greater survival rates. Moreover, eating more vegetable fiber has been linked to reduced levels of pro-inflammatory cytokines in the cerebrospinal fluid.[64] Additionally, repeated antibiotic usage may be associated with a higher subsequent risk of ALS.[65] These findings demonstrate that alterations in the metabolic function of the gut microbiota, especially the levels of SCFAs, may have a negative impact on the clinical outcomes of patients with ALS. Several additional intervention studies on Italian patients with ALS have also demonstrated that administration of probiotics for 6 months altered the composition of the gut microbiota, but disease progression was not detected.[62,66] Furthermore, the effects of fecal microbiota transplantation (FMT)[67] or a ketogenic diet[68] have not been documented.

The relationship between the gut microbiota and ALS progression has been examined in pre-clinical investigations using ALS animal models. In a mutant superoxide dismutase 1 ($SOD1^{G93A}$) familial ALS mouse model, gut dysbiosis in early infancy was followed by motor impairment, muscle atrophy, and immune cell proliferation and activation.[69] At 60 days of age, $SOD1^{G93A}$ and WT mice had different microbial structures. The relative abundance of *Acetatifactor muris* and *Bacteriodes vulgatus* was reduced in $SOD1^{G93A}$ mice, whereas *Akkermansia muciniphila* and *Bacteroides caccae* were more common in the colon of wild-type (WT) mice. Finally, they determined the correlations between disease processes and phenotypic parameters. For instance, there were favorable relationships between gut colonization, muscular power, and motor neuron density. The size, thickness, and length of the tibialis anterior muscle are positively correlated with the presence of certain bacteria in the digestive tract. Although the vagus nerve is believed to serve as a direct line of communication between the gastrointestinal tract and the brain, vagal nerve stimulation had no effect on the composition of the gut microbiota.[70] *C9orf72* has been identified as preventing the microbiota from inducing a pathological inflammatory response.[71] Study results suggested that the environment in which animals are raised might be a major predictor of survival. In *C9orf72* mutant mice, a broad-spectrum antibiotic used to remove gut bacteria or transplant gut microflora from a protective environment attenuates inflammatory phenotypes. Antibiotic-treated $SOD1^{G93A}$ mice also exhibit enhanced enteric neuromuscular function.[72] In other studies, GF or

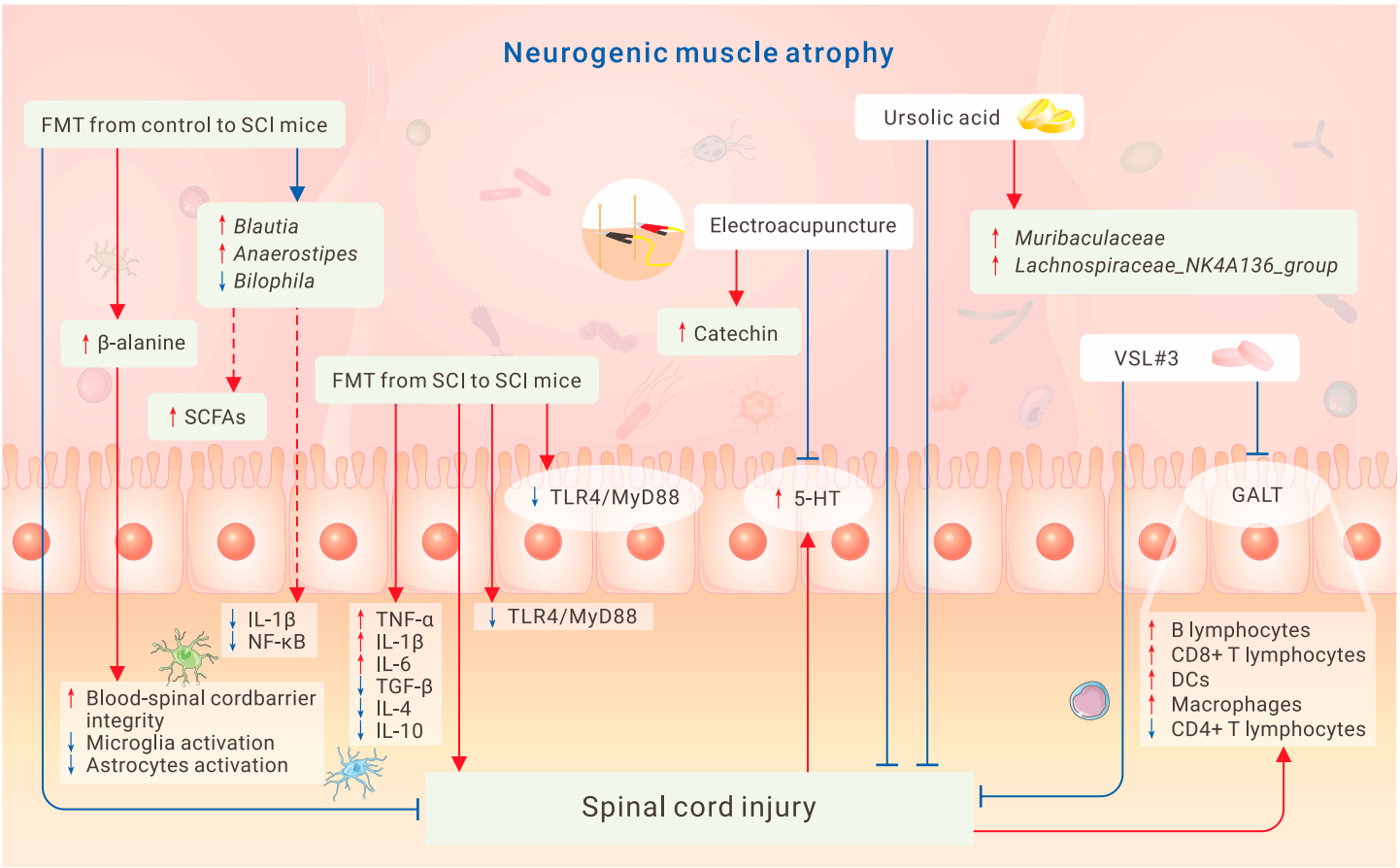

Figure 4. FMT enhances gastrointestinal and locomotor functions in spinal cord injury (SCI) mice, perhaps via the anti-inflammatory properties of short-chain fatty acids (SCFAs)[87] After fecal transplantation from SCI mice, inflammation in the SCI group increased, and SCI was more severe. Dysregulation of the gut microbiota can worsen SCI by triggering the TLR4/MyD88 signaling pathway.[88] The microenvironment, which includes the blood-spinal cord barrier, immune cell activation, and production of neurotrophic factors, is significantly impacted by FMT treatment. β-Alanine supplementation dramatically increases neuronal survival in SCI mice and maintained blood-spinal cord barrier integrity at the location of the lesion.[89] Rats with SCI had abnormal metabolic circumstances, and when compared with SCI rats, the electroacupuncture (EA) and FMT group displayed higher catechin levels. The effects of SCI on 5-hydroxytryptamine (5-HT) system expression in the colon were considerably reversed by treatment with EA and FMT.[90] Ursolic acid treatment can increase the body weight and soleus muscle weight of SCI mice by improving the gut environment.[91] SCI changes immune cell activation in gut-associated lymphoid tissues (GALTs). Giving commercial probiotics (VSL#3) to SCI mice causes a protective immune response and imparts neuroprotection with enhanced locomotor recovery.[92] Blue arrows represent promotion effects. Red arrows represent inhibition effects.

broad-spectrum antibiotic conditions accelerated disease progression in Sod1-Tg mice.[41,42] *A. muciniphila* and its associated nicotinamide may protect the central nervous system by inhibiting neurodegeneration of microglia, whereas *Ruminococcus torques* and *Parabacteroides distasonis* may exacerbate the symptoms of ALS. Feeding $SOD1^{G93A}$ mice with butyrate[72,43] or inhibiting carnitine palmitoyl transferase 1 lipid metabolism[73,74] restores intestinal microbial homeostasis and reverses or slows disease progression. These results indicate that the gut microbiota is crucial for development of ALS. More details regarding the altered gut microbiota in patients with ALS are summarized in Table (C).

Spinal cord injury

Spinal cord injury (SCI) is a common form of damage to the central nervous system that causes permanent impairment and functional loss below the injury site. SCI can be divided into cervical, thoracic, lumbar, and sacral SCIs based on the site of injury. Because of limited therapeutic options, SCI is a neurological disorder requiring lifelong care.[75] Patients with SCI frequently experience neurogenic bowel dysfunction (NBD) because of loss of regulation of the gastrointestinal system by the CNS. There are two distinct types of intestinal problems, lower motor neuron (LNN) and upper motor neuron (UMN), in SCI bowel disorder.[76] More research is underway to investigate the role of the gut microbiota as a disease-modifying factor.

The relationship between the gut microbiota and SCI was investigated by recruiting patients with SCI (15 UMN and 15 LNN) and 10 HCs for 16S rRNA sequencing.[77] The study indicated that the butyrate-producing bacterium *Pseudobutyrivibrio* was significantly reduced in UMN. In addition, LMN patients with bowel dysfunction had considerably decreased levels of the *Roseburia*, *Pseudobutyrivibrio*, and *Megamonas* genera.[77] Another study distinguished between paraplegia and quadriplegia and found that patients with SCI and quadriplegia exhibited more severe NBD symptoms. Moreover, the gut microbial community in patients with SCI was associated with blood biomarkers (Glucose [GLU], high-density lipoprotein [HDL], Creatinine [CR], and C-reactive protein [CRP]) and symptoms of NBD.[78] The structure of the gut microbiota differed significantly between patients with SCI and HCs.[79] The α diversity decreased in patients with SCI. As the degree of injury increased, NBD scores decreased, and the microbiota structure also deviated more from that of the healthy group.[80,81] It has been reported that the gut microbiota of patients varies depending on the injury site. However, it cannot be distinguished by post-injury repair time, age, BMI, nutritional type, Bristol stool classification, sex, or etiology (traumatic or non-traumatic) in patients with SCI. Another study distinguished between patients with acute and chronic SCI and found differences in their gut microbiota.[82] The different outcomes of these two studies may be due to patient selection at different time points post injury. Administration of antibiotics is another confounding factor that affects the gut microbiota of patients with SCI.[80] Furthermore, the gut microbiota and metabolites differed between patients with SCI with normal and abnormal glucose tolerance.[83] Particularly, patients with pre-diabetes/type 2 diabetes had a lower abundance of *Clostridium* and a higher abundance of *Akkermansia*, along with higher serum levels of gut microbiota-derived metabolites; e.g., as indole sulfate (breakdown of tryptophan by gut microbes[84]) and phenylacetylglutamamide (microbial conversion of phenylalanine[85,86]). The differences in the gut microbiota in patients with different degrees of injury and

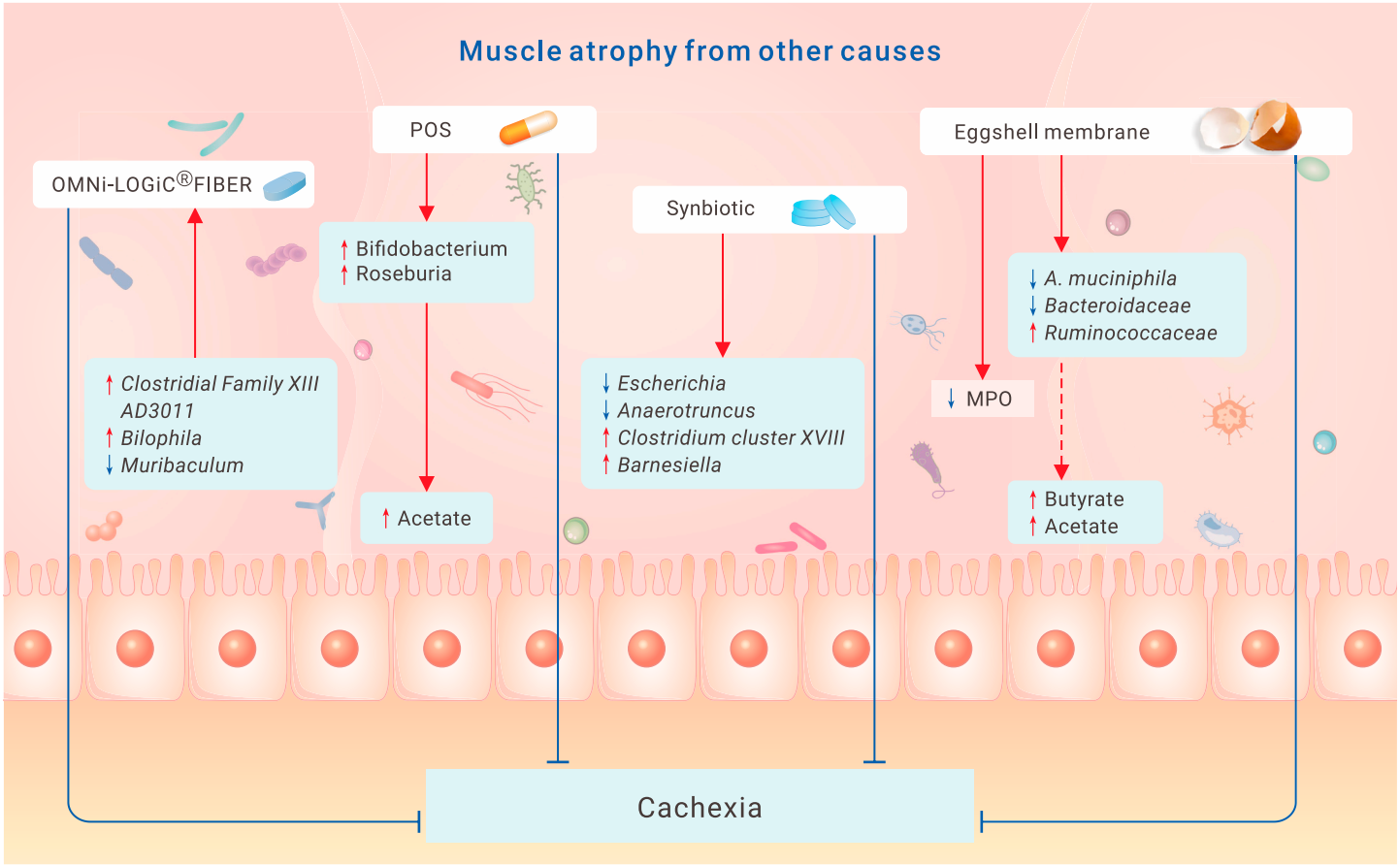

Figure 5. Tumor-associated cachexia (TAC) brought on by neuroblastoma increases gut permeability and modifies the gut microbiota The fecal microbiome appeared to change after taking prebiotics like OMNi-LOGiC FIBRE.[106] Gut microbiota analysis showed that pectic oligosaccharides (POSs) increased the abundance of *Bifidobacterium* spp., *Roseburia* spp., and *Bacteroides* spp. in mice with leukemia and increased acetate in the fecal content, which altered the fatty acid composition of adipose tissue and blocked the induction of markers controlling β-oxidation, which prevented fat mass loss.[107] Giving leukemic mice a symbiotic containing live *L. reuteri* 100-23 and inulin-type fructans restored the *Lactobacillus* population and decreased the levels of Enterobacteriaceae. Additionally, it decreased muscular atrophy and morbidity and increased survival.[108] Eggshell membrane (ESM) supplementation improved anorexia, lean fat tissue mass, and skeletal muscle atrophy and decreased physical function, Myeloperoxidase (MPO) activity, and microbial dysbiosis of cachexia.[108] Blue arrows represent promotion effects. Red arrows represent inhibitory effects.

complications suggest the possibility of the gut microbiota as an intervention target in patients with SCI (Figure 4).

Pre-clinical research has reinforced the connection between the gut microbiota and SCI. SCI animal models have increased intestinal permeability, resulting in bacterial ectopy in some vital organs.[92] Metagenomic analysis revealed a decrease in *Lactobacillus johnsonii* and *CAG-1031*, but *Weissella cibaria*, *Lactococcus lactis A*, and *Bacteroides thetaiota* were increased.[93] Additionally, microbial genes encoding tryptophan, vitamin B proteins, folate biosynthesis, and essential pathways of central nervous system function were also decreased in an SCI animal model.[93] These findings reveal the significance of these microbial strains and their metabolic pathways in the pathogenesis of SCI. Moreover, probiotic interventions can alleviate pathogenic symptoms. In a pre-clinical animal model, antibiotic-induced gut dysbiosis can exacerbate neurological impairment of SCI, while a commercial probiotic product (VSL#3) triggers protective immune responses in gut-associated lymphoid tissue and promotes motor recovery in mice with SCI.[92] Electroacupuncture can ameliorate SCI by improving intestinal morphology and function, followed by increased levels of the intestinal microbial metabolite catechin and a decrease in colonic 5-HT concentration.[90] Ursolic acid has anti-inflammatory properties and can promote synaptic regeneration, thereby slowing the progression of SCI. These favorable effects on patients with SCI reflect the improvement in the intestinal microenvironment with modified glutamine metabolic signaling pathways, followed by an increase in body and soleus muscle mass.[91] β-Alanine, a metabolite in feces, increases neuronal survival and integrity of the blood-spinal cord barrier at the lesion site in SCI mice.[88] These findings imply that physical and dietary interventions may have a positive impact on the gut microenvironment and assist with recovery of SCI patients. Transplantation of fecal microbiota from uninjured mice to those with SCI improves their motor function recovery[86,87] and spinal cord microenvironment (i.e., microcirculation, blood-spinal cord barrier, activation of immune cells, and secretion of neurotrophic factors).[89] Transplanted feces from mice with SCI aggravates SCI in other mice.[88] These studies suggest the feasibility of the gut microbiota as an intervention in treating SCI. Fecal transplantation can restore dysbiosis caused by SCI and development of anxiety-like behavior.[94] The physical and mental state of the donor is an essential factor in the efficacy of fecal microbiota transplantation (FMT) after SCI.[95] These findings underlies the significance of microbial composition and gut bacteria-derived metabolites during SCI progression. New intervention strategies can be created to treat SCI in clinical practice by identifying important bacterial taxa and chemicals generated by bacteria. Further details regarding the changes in the gut microbiota of patients with SCI are summarized in Table (D).

Cachexia

Cachexia is a multifactorial syndrome that causes skeletal muscle loss. Patients usually present with symptoms such as loss of weight, fat, and appetite as well as systemic inflammatory responses. All of these symptoms reduce the patients' quality of life and the survival possibility.[96–98] It can be partially but not completely reversed by conventional nutritional support. Patients with cancers and chronic diseases, such as tumors, chronic obstructive pulmonary disease, AIDS, sepsis, and chronic kidney disease, are more susceptible to cachexia.[99] Among these, approximately 50%–70% of cancer patients experience varying degrees of cachexia, which may account for 20% of cancer-related deaths.[100–102]

The gut microbiome is vital for regulation of several aspects of cancer cachexia (Figure 5). Studies have shown that the gut microbiota is critical for

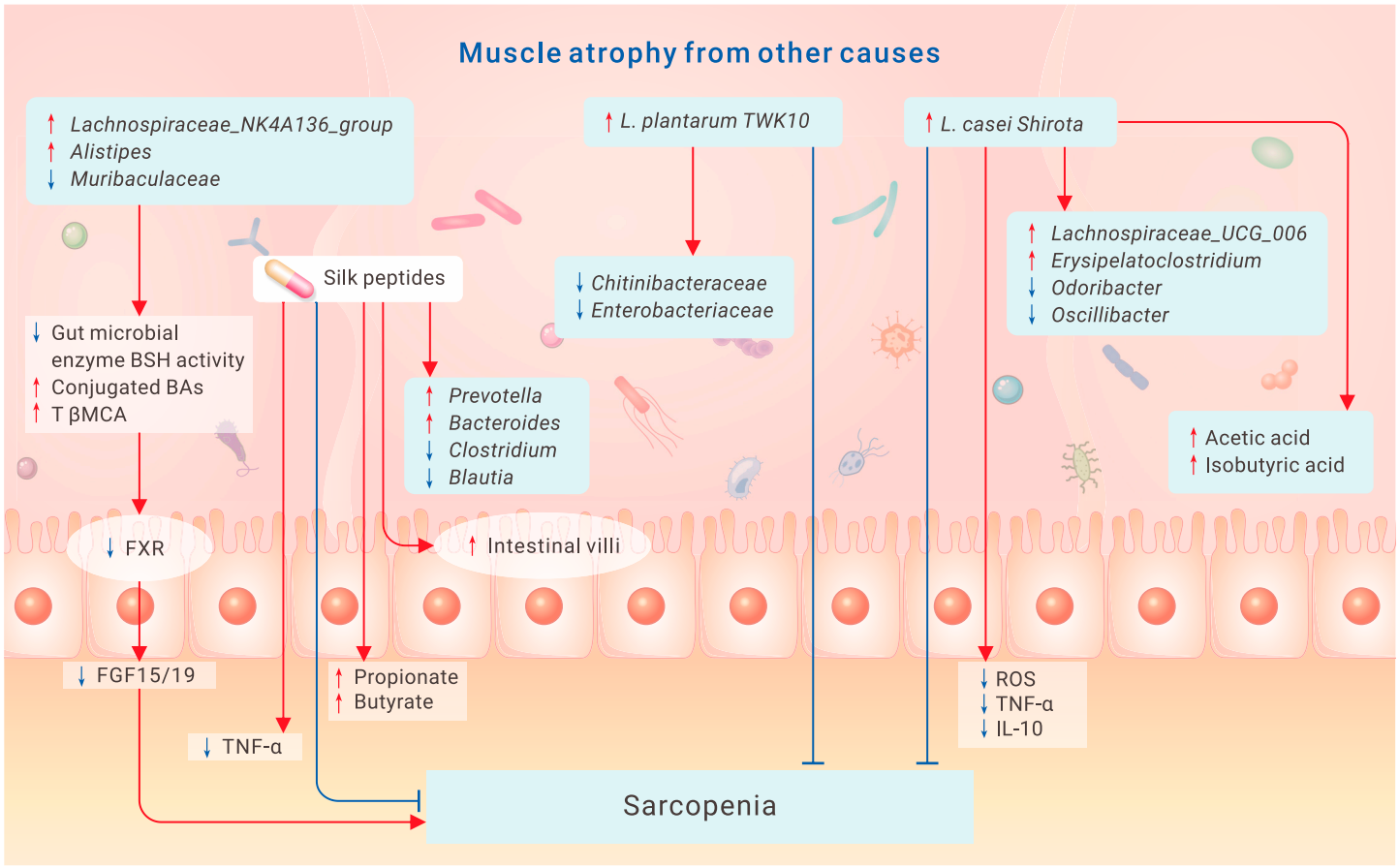

Figure 6. Because of alterations in the gut microbiota and microbial bile acid metabolism with aging, ileal FXR-FGF15/19 signaling is downregulated in older men and aged male mice Ileal Farnesoid X receptor (FXR) activation increased skeletal muscle protein synthesis in a FGF15/19-dependent way.[117] Silk peptide (SP) intake prevents middle-aged female rats from losing grip strength and lean body mass. After consuming SP, higher serum levels of total amino acids were maintainedthrough the modification of the gut flora.[132] TWK10 improved muscle strength in young mice and reduced the aging-related decrease of muscle strength in old mice, maybe via modifying the imbalance of the gut microbiota.[133] Age-related reductions in muscle mass, strength, and mitochondrial function were lessened by *L. casei Shirota* (LcS) supplementation. In older mice, LcS could restore the content of SCFAs (acetic, isobutyric, butyric, and hexanoic acid); it also reduced age-related increases in inflammation and reactive oxygen species.[134] Blue arrows represent promotive effects. Red arrows represent inhibitory effects.

digestion and absorption of host nutrients, control of muscle mass and systemic inflammation, improvement of gut barrier function and insulin sensitivity,[97,103] and occurrence of associated metabolic disorders in patients with cachexia.[104] In clinical studies, patients with cachexia have more *Proteobacteria* and *Enterobacteriaceae* than HCs or patients with cancer without cachexia.[100] The amount of *Veillonella* is also decreased in patients with cachexia. In contrast, *Lactobacillus* spp. are less abundant in the population with cachexia. More importantly, *Enterobacteriaceae* are positively correlated with weight loss, indicating that the phenotype of cancer cachexia is related to the increase in *Enterobacteriaceae*.[100] Another clinical study identified that a major representative of the *Enterobacteriaceae* family, *Klebsiella oxytoca*, is increased in patients with cachexia.[98] To modulate the gut microbiota in patients with cachexia, FMT could be an optional treatment. Fecal microbiotas from healthy obese individuals were transplanted into patients with gastroesophageal cancer. Although the characteristics of cachexia did not change after transplantation, the survival time of patients was prolonged, indicating that interventions based on gut microbiota may be beneficial.[105]

In addition to these clinical trials, several pre-clinical studies have suggested that the gut microbiota may be significantly involved in the etiology of cancer cachexia. The composition of the gut microbiota differs dramatically between animals with colon cancer and those with leukemic cachexia. More specifically, the relative abundance of *Lactobacillus* decreased, followed by a significant decline in muscle mass.[109] In addition to the decline in the abundance of *Lactobacillus*, the expansion of Enterobacteriaceae may potentially contribute to development of cachexia.[110,111] Further research into the impact on the development of cachexia revealed that *K. oxytoca* is one of the key species of *Enterobacteriaceae* that was increased in a colon cancer mouse model,[112] which is in line with clinical data.[98]

In addition, pectin oligosaccharides or inulin can change the gut microbiota and control the progression of leukemia and other associated metabolic disorders.[107] Therefore, administration of a symbiotic regimen consisting of inulin-type fructans and *Lactobacillus reuteri* could reverse dysbiosis of the gut microbiota caused by cachexia based on the beneficial effects of pre- and probiotics. This alleviates cancer progression, reduces morbidity, prevents muscle mass loss, and increases the survival rates of leukemia cachexia mice.[108] Prebiotic fiber-rich carbohydrates may be another novel dietary strategy for regulating the gut microbiota, with potential benefits for cachexia and cancer progression.[106] In addition to prebiotic supplementation, eggshell membrane (ESM) can improve gut microbial dysbiosis and alleviate cachexia symptoms such as anorexia, skeletal muscle atrophy, and impaired body function.[113] More details regarding the changes in the gut microbiota of cachexia mice are summarized in Table (E).

GUT MICROBIOTA AND MUSCLE ATROPHY FROM OTHER CAUSES

Sarcopenia

Sarcopenia, aging-related progressive loss of skeletal muscle mass and function, increases the risk of disability, frailty, and mortality.[114] To date, there is no consensus on the mechanism of sarcopenia. Nevertheless, a number of pathophysiological and environmental variables, such as genetic predisposition, immobility, malnutrition, endocrine dysfunction, and inflammation, have been associated with age-related skeletal muscle loss.[115] Beyond age 30, muscle mass declines by 3%–8% annually, and the rate of decline increases after age 60. In the absence of effective clinical treatment, sarcopenia in older adults threatens their health and increases the risk of fractures, falls, and even death, leading to a lower quality of life and physical disability.[116]

In older males and old male mice, FXR-FGF15/19 signaling is negatively regulated in the ileum, along with alterations in gut microbiota composition and bile

acid metabolism (Figure 6). These new findings suggest that targeting the FXR-FGF15/19-Extracellular signal-regulated kinase (ERK) pathway to improve skeletal muscle mass and function may serve as an alternative.[117] Furthermore, shotgun metagenomics sequencing revealed that the composition and function of the fecal microbiota are different in HCs and seniors with sarcopenia.[114] Compared with HCs, the levels of SCFAs, carotenoids, and isoflavones were lower in sarcopenia subjects, who also had a considerably lower conversion rate of amino acids.[114] Similar research from Italy investigated the gut microbial taxa, systemic inflammation, and metabolic traits in the elderly with or without physical frailty and sarcopenia (PF&S).[118] Participants were divided into PF&S and non-PF&S groups using the sequential and orthogonalized covariance selection technique. Participants in the PF&S group exhibited higher levels of *Oscillospira* and *Ruminococcus* and lower levels of Barnesiellaceae and Christensenellaceae. Serum aspartic acid levels were high, whereas circulating levels of threonine and macrophage inflammatory protein 1α were low. In the gut-liver-muscle axis study, cirrhosis patients with sarcopenia had lower diversity and composition than nonsarcopenic cirrhotic patients and nonsarcopenic control groups.[119] Specifically, the relative abundance of *Methanobacteriaceae*, *Prevotellaceae*, *Verrucomicrobiaceae*, *Prevotella*, and *Akkermansia* was reduced, whereas *Eggerthella* was increased in cirrhosis patients with sarcopenia. Previous research has demonstrated that Methanobacteriaceae might increase polysaccharide digestion by bacteria and fungi, which would then improve lean body mass and support physical function.[119–121] A decrease in *Prevotella*, another known sign of frailty, has been observed in patients with sarcopenic cirrhosis.[122–124] In contrast, an increase in *Eggerthella* is often linked to physical frailty.[125,126] Another pilot study examined the association between sarcopenia and biomarkers of cirrhosis (chronic inflammation and bacterial translocation). The incidence of bacterial translocation, status of systemic inflammatory syndrome, initial model for Model For End-Stage Liver Disease (MELD) scores, caloric intake, resting energy expenditure, increased hospital admission, and mortality did not differ appreciably between sarcopenic and nonsarcopenic participants.[127] A study from China compared the composition of the gut microbiota of sarcopenic (Case) and possible sarcopenic individuals (preCase). Researchers observed that microbial diversity decreased in Case and preCase individuals compared with HCs.[128] They also found that, at the genus level, sarcopenic and possibly sarcopenic samples tended to have lower levels of *Lachnospira*, *Fusicantenibacter*, *Roseburia*, *Eubacterium*, and *Lachnoclostridium*, which are butyrate producers, but higher levels of *Lactobacillus*. A British study examined the gut microbiota in patients with sarcopenia with good and poor appetite.[129] They discovered that patients with poor appetite tended to have lower muscle strength than those with good appetite. However, no significant difference in muscle mass was observed between the two groups. Compared with groups with good appetite, those with poor appetite were associated with reduced content of *Lachnospira*, which was linked to higher levels of butyrate and an improvement in muscle strength. For those with chronic kidney disease (CKD), patients with sarcopenia had a different gut microbiota composition compared with nonsarcopenic patients.[130] At the family level, *Micrococcaceae* and *Verrucomicrobiaceae* were increased, whereas *Gemellaceae* and *Veillonellaceae* were decreased in sarcopenic patients. At the genus level, *Megasphaera*, *Rothia*, *Veillonella*, *Akkermansia*, and *Coprobacillus* increased, whereas *Acidaminococcus* and *Gemella* decreased in patients with sarcopenia. An investigation examining the relationship between sarcopenia and *Helicobacter pylori* infection involved 3,453 participants from the US.[131] In addition, patients with sarcopenia and active *H. pylori* infection may benefit from *H. pylori* eradication therapy because *H. pylori* infection may decrease muscle mass.[131]

Prebiotic and probiotic treatments have been shown to improve muscle mass and function in elderly patients with sarcopenia. Administration of 1-kestose increased the relative abundance of *Bifidobacterium longum* in the intestine, followed by a substantial increase in skeletal muscle mass index and a remarkable drop in body fat percentage.[135] Administration of acylated and unacylated ghrelin could determine the essential role of ghrelin signaling in preserving muscular condition in elderly mice.[115] This may be achieved by acylated and unacylated ghrelin-mediated enhanced anabolism and inhibition of catabolism during muscle atrophy.[115] Silk peptide is widely utilized in China and Korea for hair and skin goods because of its hydroxyl-amino acid components. According to a Korean study, silk peptides may be able to stop middle-aged female mice with sarcopenia from losing muscular mass and strength.[132] Along with improved muscular parameters, silk peptides increased the levels of *Bacteroides* and *Prevotella*, whereas they decreased *Blautia* and *Clostridium* in feces, along with elevated levels of propionate and butyrate in serum. The protective effect of the silk peptide is due to its significance in maintaining a high level of total amino acids in the serum and improving systemic insulin resistance and serum inflammation by modifying the gut flora.

In a double-blind study, *Lactobacillus plantarum* TWK10 (TWK10), a probiotic isolated from sauerkraut, increased left-hand and lower-limb muscle mass and strength after the sixth week of administration.[136] Prolonged supplementation until the 18th week resulted in greater benefits.[136] In another clinical trial, TWK10 supplementation was also linked to elevated muscle mass and strength at a particular muscle location. TWK10 administration for 8 weeks had a beneficial impact on the microbiome by increasing SCFA-producing bacteria, along with elevated levels of SCFAs. This beneficial effect may be due to the suppressed growth of age-related pathogenic bacteria.[133] *Lactobacillus casei Shirota* (LcS) also has a positive impact on preventing age-related decline in muscle mass, strength, and mitochondrial function.[134] In aged mice, LcS can alter the composition of gut bacteria, elevate the level of SCFAs (acetic, isobutyric, butyric, penic, and hexanoic acid), and reduce aging-induced inflammation. Genera that decreased upon LcS intervention were *Oscillibacter* and *Alistipes*, which were found to be high in the aged group and negatively correlated with healthy muscle conditions. *L. plantarum HY7715*, commonly present in kimchi, is a lactic acid bacterium that can slow the progression of sarcopenia while increasing skeletal muscle mass and physical activity in aged mice.[116]

In an FMT study, fecal samples from elderly donors were transplanted into GF mice in two groups according to their levels of physical functioning (high- and low-functioning groups).[20] The study demonstrated that the two elderly donor groups had substantial differences in running endurance and whole-body lean mass, while such differences appeared to be neutralized in matched mice that received transplants. In contrast to low-functioning colonized mice, high-functioning colonized mice exhibited a higher abundance of the *Prevotellaceae* family, *Prevotella* and *Barnesiella* genera, and *Barnesiella intestinihominis*. After a 1-month follow-up, high-functioning colonized mice had a dramatically better grip strength, which was 6.4% greater than that of low-functioning colonized mice. Another study further supported the negative impact of aging on gut microbiota composition, particularly by altering the bacterial metabolic potential in the intestine and the percentage of *Sutterella* to *Barneseilla*.[137] More details regarding the altered gut microbiota in sarcopenia are summarized in Table (F).

STRENGTHS AND LIMITATIONS

This systematic review represents the most recent and comprehensive analysis of the gut-muscle axis, specifically focusing on the role of beneficial and pathogenic bacteria in muscular physiology and pathophysiology of muscular atrophy. This encompasses various factors that contribute to muscle atrophy, including myogenic, neurogenic, and other related conditions. By incorporating clinical and pre-clinical studies, this review provides a comprehensive examination of the relationship between the gut microbiota and the development, progression, and treatment of muscular atrophy. Here, we identified and analyzed key bacteria and metabolites based on the current literature, highlighting their significance in clinical and pre-clinical investigations. A summary table outlining the key bacteria and metabolites associated with different muscular atrophy-related diseases is provided. Furthermore, we explored the potential regulatory mechanisms underlying these interactions. Despite its comprehensive approach, this study had certain limitations. Because of the limited number of eligible studies on inflammatory myopathies, fabry disease, and glycogen storage diseases, additional clinical investigations are needed to further explore the role of the gut microbiota in these conditions. Moreover, further pre-clinical mechanistic studies are warranted to deepen our understanding of the emergence and progression of muscular atrophy; this knowledge is crucial for the development of innovative therapeutic strategies for clinical treatment.

CONCLUSION AND PERSPECTIVE

The causes of muscle atrophy-related disease are complex, and effective treatment options are currently lacking, making many of these lifelong disorders. Reducing or even reversing muscle atrophy and promoting rehabilitation remain high priorities in clinical settings. The role of the microbiota in these

diseases may be mediated by bacterium-related metabolites or inflammatory signals. Interventions targeting the microbiota have shown promising results in alleviating disease development and progression. However, understanding the involvement of the microbiota in diseases associated with muscular wasting poses challenges because of variations in the critical targets identified in different studies. These variations may arise from differences in study populations, geographic locations, modeling techniques, and intervention modalities. Despite these challenges, recent studies have shed light on the vagus nerve-mediated bidirectional communication between the gut and brain, which has a significant impact on various functions, such as mood, stress, memory, and metabolism. Research has demonstrated that the vagus nerve plays a crucial role in conveying information about the gut to the brain, thereby influencing behavior and physiology. This communication channel appears to play a crucial role in mood and metabolic diseases. For instance, alterations in the gut microbiota have been shown to affect the plasticity of the hippocampus and induce depression-like behaviors in mice, which are dependent on the vagus nerve and production of neurotransmitters, such as serotonin.[138] Additionally, specific probiotics have been found to improve social behaviors in mice through the oxytocin pathway and the vagus nerve, highlighting the complex relationship between the gut microbiota and brain function.[139] Furthermore, the vagus nerve modulates eating behavior by regulating appetite and learning nutritional preferences. This suggests that gut microorganisms can influence host feeding behavior and metabolic control under physiological and pathological conditions.[140] Therefore, to gain a more objective, comprehensive, and reliable understanding of microbial involvement in diseases associated with muscle atrophy, it is necessary to analyze trends across related studies and conduct broader and more in-depth investigations of the microbiota in the context of muscular atrophy. In summary, although the underlying mechanisms of diseases associated with muscle atrophy are complex, exploring the role of the microbiota and its interaction with the vagus nerve provides valuable insights into potential therapeutic strategies. By unraveling the intricate connections between the gut microbiota, brain function, and systemic physiology, researchers can pave the way for more effective interventions and management of these debilitating conditions.

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AUTHOR CONTRIBUTIONS

S.C., P.Z., and H.D. wrote the manuscript. Y.Q. participated in manuscript revision, proofreading, and graphical abstraction generation. Y.Y., D.W., and L.X. edited the manuscript. P.Z., S.C., H.D., and J.W. participated in discussions, language editing, and manuscript revision.

DECLARATION OF INTERESTS

The authors declare no competing interests.

SUPPLEMENTAL INFORMATION

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