Curr. Top. Lact. Acid Bact. Probiotics 2023;9(2):45-57
https://doi.org/10.35732/ctlabp.2023.9.2.45
ISSN 2287-853X

Review Article

Integrative Insights into the Gut-Muscle Axis: Unraveling Its Role in Sarcopenia Pathogenesis and Therapeutic Approaches

Seoyeon Chae and Sunhye Lee*

Department of Food Science, Sun Moon University, Asan, Chungchengnam-do 31460, Korea

Received: Nov. 19, 2023
Revised: Dec. 20, 2023
Accepted: Dec. 20, 2023

*Corresponding author :
Sunhye Lee
Department of Food Science, Sun Moon University, Asan, Chungchengnam-do 31460, Korea.
Tel: +82-41-530-2257,
Fax: +82-41-541-7424
E-mail: lsh71300@sunmoon.ac.kr

ORCID
Seoyeon Chae
https://orcid.org/0009-0007-3722-1041
Sunhye Lee
https://orcid.org/0000-0002-4825-745X

Abstract

Sarcopenia, characterized by the progressive loss of skeletal muscle mass and function, poses a growing public health concern, predominantly affecting the elderly. Recent research has illuminated the pivotal role of the gut-muscle axis in sarcopenia's pathogenesis, suggesting a complex interplay between gut microbiota, metabolic pathways, and muscle health. This review offers a comprehensive examination of the emerging evidence on the gut-muscle axis, delineating its impact on muscle physiology and the onset of sarcopenia. We explore the bidirectional communication between the gut microbiota and skeletal muscles, emphasizing how alterations in gut microbiota composition and functionality can influence muscle metabolism, inflammation, and protein synthesis. Furthermore, the review highlights the mechanistic pathways, including microbial metabolites and gut-derived signals, that modulate muscle homeostasis. We also discuss the age-related changes in the gut microbiota and their corresponding effects on muscle biology. In addition, this review critically evaluates current and potential therapeutic strategies targeting the gut-muscle axis. These include dietary interventions, probiotics, prebiotics, and fecal microbiota transplantation, focusing on their efficacy in modulating the gut microbiota composition and ameliorating sarcopenia symptoms. By integrating insights from various studies, this review underscores the gut-muscle axis as a novel and promising target for therapeutic interventions in sarcopenia, paving the way for future research and clinical applications in managing its age-related conditions.

Keywords

sarcopenia, aging, gut microbiota, gut-muscle axis

Introduction

Advancements in applied sciences and healthcare technologies, along with socioeconomic improvements, have contributed to the prolongation of human life expectancy. Recent estimates, as of 2019, indicate that the global population of individuals over the age of 65 stood at around 703 million. This number is expected to rise significantly, reaching approximately 1.5 billion by 2050 (UN DESA, 2020). Globally, life expectancy has seen an increase, with this trend being particularly marked in the elderly population (UN DESA, 2020). Concurrently there is a growing prevalence of age-related diseases (Carmona and

Michan, 2016), indicating that longer lifespans contribute to an increased global incidence of diseases in later life (Partridge *et al.*, 2018). Recent research increasingly points to a significant and inevitable decline in muscle mass and function with aging (Blau *et al.*, 2015; Brook *et al.*, 2016; Cartee *et al.*, 2016; Curtis *et al.*, 2015; Francis *et al.*, 2017; Giallauria *et al.*, 2015; Larsson *et al.*, 2019). Defined specifically as an age-related syndrome, sarcopenia involves a progressive and widespread reduction in skeletal muscle mass and strength. While a gradual decrease in muscle mass and strength is a recognized aspect of aging, individuals with sarcopenia exhibit a more rapid decline in muscle functionality (Cruz-Jentoft *et al.*, 2019). This condition may lead to a diminished quality of life in the elderly, heightened risk of movement-related disorders (including falls, bone fractures, and metabolic diseases), and an elevated rate of early mortality in the older population (Curtis *et al.*, 2015; Larsson *et al.*, 2019; Shaw *et al.*, 2017). Numerous physiological factors are suggested as potential contributors to the development of sarcopenia. These factors encompass a wide range of influences, including but not confined to alterations in hormonal balance associated with aging, modifications in gut physiology, the presence of persistent low-level inflammation, DNA damage, heightened oxidative stress, and impaired mitochondrial function (Azzolino *et al.*, 2019; Beyer *et al.*, 2012; Jackson and McArdle, 2016; Sakuma and Yamaguchi, 2012).

Interestingly, an increasing body of research suggests a strong link between gut microbiota and sarcopenia in the elderly (Ticinesi, Nouvenne, *et al.*, 2019). The growing recognition of the connection between gut microbiota and human health is evident, with the understanding that gut microbiota plays a role in various interactions affecting health throughout a host's life. The gut microbiota seems crucial for the musculoskeletal system, influencing intestinal permeability, energy metabolism, hormone secretion, systemic inflammation, and immune response (Locantore *et al.*, 2020). However, imbalances in microbial composition may contribute to aging muscle and sarcopenia development (Picca *et al.*, 2018). In fact, significant decreases in gut microbial diversity have been observed in sarcopenia patients (Kang *et al.*, 2021; Ticinesi *et al.*, 2020). Therefore, modulating the composition of the gut microbiota could be a viable approach to treating musculoskeletal disorders. Understanding the relationship and causality between gut microbiota and sarcopenia is key for its therapeutic potential. Identifying specific bacterial markers that enhance muscle function and can be developed into next-generation probiotics is essential. Advanced research using multi-omics approaches on gut microbiota could open new possibilities for assessing and treating sarcopenia (J.-C. Liu *et al.*, 2022). Hence, this review intends to compile and analyze the correlation between gut microbiota and age-related sarcopenia, the possible mechanism of gut microbiota in treating sarcopenia, and the causal effects of gut microbiota on age-related sarcopenia.

Introduction to sarcopenia

Sarcopenia, often referred to as a "Geriatric Giant," is a progressive disorder of the skeletal muscles characterized by a decrease in muscle mass and function (Cruz-Jentoft and Sayer, 2019). This condition is linked to several negative outcomes, including a heightened risk of falls, functional decline, frailty, and increased mortality in older populations (Cesari *et al.*, 2014; Cruz-Jentoft *et al.*, 2019; Landi *et al.*, 2012). The European Working Group on Sarcopenia in Older People (EWGSOP) outlines that the diagnosis of sarcopenia necessitates measuring muscle mass (through methods like mid-arm muscle circumference, dual energy X-ray absorptiometry, or bioelectrical impedance analysis), muscle strength (evaluated via hand grip), and physical performance (assessing mobility and balance). These measures help in determining the severity of the disease using established cut-off values (Cruz-Jentoft *et al.*, 2019).

In the context of the underlying mechanisms of muscle wasting, chronic low-grade inflammation has been associated with the onset of sarcopenia, as it can initiate

pathways that result in muscle wasting and decrease the synthesis of muscle protein (Marcell, 2003). Furthermore, Oxidative stress plays a role by damaging muscle cells and disrupting the equilibrium between muscle protein synthesis and breakdown (Marcell, 2003). Insulin resistance is another contributing factor, as it can diminish muscle protein synthesis and enhance muscle protein degradation, thus promoting muscle wasting (Cruz-Jentoft and Sayer, 2019; Marcell, 2003). Hormonal changes also influence sarcopenia, with older men experiencing reduced testosterone levels and older women experiencing decreased estrogen levels, both of which can lead to a reduction in muscle protein synthesis and an increase in muscle protein degradation (Marcell, 2003). Additionally, as aging progresses, the activation of muscle satellite cells becomes less efficient, which leads to a reduction in muscle repair and an escalation in muscle wasting. (Cruz-Jentoft and Sayer, 2019; Marcell, 2003).

The decline in human skeletal muscle mass with age, a key factor leading to sarcopenia, is attributed to a reduction in both the size and number of myofibers, including both fast and slow type myofibers. Notably, the loss of fast myofibers, which rely on glycolytic metabolism, typically begins earlier (Lexell *et al.*, 1983). The nervous system, crucial for muscle strength, also deteriorates with age. This deterioration is due to factors like the loss of motoneurons, the demyelination of axons, and the retraction of nerve terminals from neuromuscular junctions (Chai *et al.*, 2011; Ham *et al.*, 2020). Furthermore, an important aspect of sarcopenia is the anabolic resistance of older skeletal muscle to protein nutrition. This resistance can be mitigated through resistance exercise and dietary supplementation (Farnfield *et al.*, 2012; Narici and Maffulli, 2010).

Introduction to microbiota

There has been a growing body of research indicating a relationship between gut microbes and skeletal muscle metabolism. The condition of the gut microbiome may influence both the composition and functionality of skeletal muscle. Disorders in the intestinal microbiota can lead to health deterioration in patients and the elderly, impacting their quality of life. Consequently, it is imperative to identify effective intervention strategies by understanding the role of gut microbiota in skeletal muscle metabolism.

Recent pre-clinical studies have shown a significant correlation between the composition of the intestinal microbiome and the structure and metabolic indicators of skeletal muscle (Lahiri *et al.*, 2019; Manickam *et al.*, 2018). Experiments involving the transplantation of intestinal flora for skeletal muscle enhancement have been conducted. Certain gut microbiomes can produce metabolites that foster skeletal muscle anabolism. For instance, an optimally functioning gastrointestinal microbiome featuring microbiota like *Propionibacteria* and *Lactobacillus reuteri* has the capacity to generate substantial quantities of folate and vitamin B_{12}. These bioactive compounds are implicated in enhancing muscle anabolism and mitigating the adverse effects of hyperhomocysteinemia-induced oxidative stress and endothelial damage. Consequently, this could lead to an amelioration in muscle functionality (Kuo *et al.*, 2007). Furthermore, the gut microbiota such as by *Bacillus subtilis* possesses the capability to biosynthesize specific amino acids, such as tryptophan, which serve as essential substrates for facilitating muscle protein anabolism (Lin *et al.*, 2017). Further, short-chain fatty acids (SCFAs), produced by the intestinal microbiota, including *Faecalibacterium*, *Succinivibrio*, and *Butyricimonas*, can enter the systemic circulation and become assimilated by skeletal muscle cells. Within these cells, SCFA serve as ligands for free fatty acid receptors 2 and 3, which are recognized for their pivotal role in regulating glucose uptake and metabolism, as well as enhancing insulin sensitivity. (Kimura *et al.*, 2014). Notably, experiments involving the transplantation of fecal material from malnourished children into mice resulted in altered growth patterns in the recipient mice. Conversely, transplantation of fecal microbiota from well-nourished children into mice did not exert any significant impact on growth. This underscores the concept that a healthy gut microbiota

promotes anabolic processes, while a dysbiotic microbiota is linked to anabolic resistance or, in some cases, catabolism (Ticinesi *et al.*, 2017). Mice made germ-free (GF) and then transplanted with feces from elderly individuals exhibited varying functions, with some showing increased lean mass and reduced fat mass (Fielding *et al.*, 2019). In another study, the mice transplanted with feces from the physically high-functioning elderly demonstrated greater grip strength and a higher proportion of beneficial microbiota such as *Prevotella* and *Barnesiella* at the genus level (Ticinesi *et al.*, 2017). GF mice typically had lower muscle mass and fewer muscle fibers, with increased markers of muscle atrophy, compared to pathogen-free mice. Remarkably, these effects were largely reversed following fecal transplantation and treatment with SCFA (Lahiri *et al.*, 2019). Studies in animal models consistently reveal that alterations in gut microbiome composition can regulate the metabolic functions of skeletal muscle. Thus, understanding the intricate relationship between the gut microbiome and host physiology is crucial for developing lifestyle, nutritional, and pharmaceutical interventions to preserve and enhance skeletal muscle health.

Studies in humans have also identified a link between the composition of the gut microbiome in the elderly and skeletal muscle function. Alterations in the gut microbiome, often observed when older adults move to long-term care facilities, can impact bone and body composition. This transition seems largely attributable to dietary modifications, shifting from a fiber-rich, predominantly plant-based diet at home to one with lower fiber, increased fat, and greater sucrose levels in the facilities. Furthermore, elderly adults in these institutions frequently undergo prolonged antibiotic therapy and have coexisting medical conditions. They also live alongside other seniors, factors which collectively impact gut microbiota. Such changes can potentially contribute to conditions such as sarcopenia, osteoporosis, and obesity, consequently heightening fracture risks (Inglis and Ilich, 2015).

Correlation between gut microbiota and age-related sarcopenia via gut-muscle axis

Currently, the role of the gut-muscle axis in maintaining muscle health during aging is supported by evidence from animal studies and human research. Nonetheless, the precise mechanisms at play are not fully elucidated. This study intends to thoroughly investigate the possible underlying mechanisms. These encompass factors such as protein metabolism, systemic chronic inflammation, metabolic resistance, mitochondrial dysfunction, and their impact on the expression of host genes. In older adults, the gut microbiota may impact their health by affecting aging-related sarcopenia. The reduction in muscle mass and strength observed in the elderly could be linked to changes in their gut microbiota. Studies have shown that individuals with sarcopenia, or those at risk of sarcopenia, exhibit notably lower microbial diversity compared to healthy controls. These individuals tend to have higher levels of Lactobacillus and lower levels of *Lachnospira*, *Fusicantenibacter*, *Roseburia*, *Eubacterium*, and *Lachnoclostridium* (Kang *et al.*, 2021). In elderly patients with sarcopenic cirrhosis, there has been a significant increase in potentially pathogenic bacteria like *Klebsiella* and *Eggerthella*, while beneficial bacteria such as Akkermania and Prevotella have decreased, fostering a pro-inflammatory environment (Ponziani *et al.*, 2021). Furthermore, Ticinesi *et al.* found that elderly sarcopenic patients, compared to non-sarcopenic controls, had a lower abundance of bacteria that produce SCFAs such as *Faecalibacterium prausnitzii* and *Roseburia inulinivorans* (Ticinesi *et al.*, 2020). Analysis of the fecal metagenome in these individuals revealed a reduced representation of genes responsible for the synthesis of SCFAs, along with genes involved in the biotransformation of carotenoids and isoflavones, and those facilitating the interconversion of amino acids. These observations emphasize the significant relationship between the gut microbiota's composition and the development of sarcopenia.

Several animal studies have investigated the link between intestinal microbiota and age-related sarcopenia in older mice and rats. Research by Siddharth *et al.* demonstrated

that aging can modify the intestinal microbial composition in aged male rats, exemplified by changes in the ratio of *Sutterella* to *Barneseilla*, and the metabolic capabilities of the gut microbiota (Siddharth *et al.*, 2017). Furthermore, GF mice, which lack intestinal microbiota, exhibited skeletal muscle atrophy, decreased levels of insulin-like growth factor-1, and lowered expression of genes related to the neuromuscular junction, specifically those encoding Rapsyn and Lrp4, in comparison to pathogen-free mice (Lahiri *et al.*, 2019). These findings suggest that age-related alterations in intestinal microbiota may contribute to the deterioration of muscle function in older mice or rats.

Overall, the aforementioned studies provide initial evidence of a link between intestinal microbiota and muscle metabolism. However, further research is necessary to validate these initial findings. Future investigations should also focus on identifying specific bacterial markers associated with the development of sarcopenia, which could offer novel targets for therapeutic intervention.

Mechanism of gut-muscle axis in age-related sarcopenia

A range of human studies and animal model research has delved into the potential mechanisms by which gut microbiota contributes to muscle loss. These studies have focused on various aspects, including protein anabolism, mitochondrial dysfunction, chronic inflammation and immune responses, as well as imbalanced metabolism.

Protein anabolism

Skeletal muscle quality is influenced by the balance between muscle protein synthesis (MPS) and muscle protein breakdown. Gut microbiota are capable of synthesizing certain essential amino acids, such as tryptophan, which are fundamental for MPS and metabolism (Lin *et al.*, 2017). Tryptophan which can be synthesized by *Bacillus subtilis* plays a crucial role in stimulating the IGF-1/p70s6k/mTOR signaling pathway in muscle cells, which is essential for myofibril synthesis (Dukes *et al.*, 2015; Lin *et al.*, 2017). Conversely, gut microbiota imbalances, known as dysbiosis, are marked by reduced diversity, an increased presence of pathogenic bacteria, and compromised integrity of epithelial tight junctions, which may enhance intestinal permeability. This condition could enable the migration of microbial derivatives like lipopolysaccharide (LPS) into the bloodstream and diminish SCFA levels, leading to impaired protein metabolism and a decrease in MPS (Mesinovic *et al.*, 2019; Ni Lochlainn *et al.*, 2018). Therefore, an imbalanced gut microbiome can lead to lower protein absorption and availability, contributing to anabolic resistance and potentially causing sarcopenia. Investigating the role of gut microbiota in contributing to anabolic resistance and identifying ways to improve MPS are critical areas for future research.

Mitochondrial dysfunction

In skeletal muscle, primary aging leads to mitochondrial energetics deficiency and muscle mass reduction (Cartee *et al.*, 2016). It is suggested that ultrastructural modifications in the number and functionality of mitochondria caused reduced muscle protein synthesis (Marzetti *et al.*, 2013, 2016; St-Jean-Pelletier *et al.*, 2017). Interestingly, research has revealed a reciprocal interaction between gut microbiota and mitochondria. This exchange primarily occurs through signals sent from the gut microbiota to mitochondria and back, facilitated by endocrine, immune, and humoral connections (Mottawea *et al.*, 2016). Key insights into the mitochondrial-microbiota relationship have emerged from studies focusing on mitochondrial functions and the tactics bacterial pathogens use to interfere with calcium homeostasis, redox state maintenance, and mitochondrial structure (Lobet *et al.*, 2015). Additionally, recent investigations have shown that metabolites produced by the commensal gut microbiota, such as SCFAs and secondary bile acids, can impact mitochondrial activities related to energy generation, mitochondrial formation, redox equilibrium, and inflammatory pathways, suggesting their potential role in enhancing endurance (Circu and Aw, 2012; Den Besten *et al.*, 2013; Mottawea *et al.*, 2016).

For instance, gut commensal microbiota reduce ROS production via SCFA such as N-butyrate (Mottawea *et al.*, 2016). Therefore, a disruption of the relationship leads to dysfunctional mitochondria. It is worth noting that mitochondrial dysfunction may play a vital role to link the relation between chronic inflammation and age-related sarcopenia, and the gut microbiota dysbiosis may be a key role in the gut–muscle crosstalk (Picca *et al.*, 2018). Consequently, any disruption of this intricate relationship can precipitate mitochondrial dysfunction.(Ni Lochlainn *et al.*, 2018).

Systemic chronic inflammation and metabolic resistance

Sarcopenia's progression is intimately linked to age-related systemic chronic inflammation (Grosicki *et al.*, 2018; Ni Lochlainn *et al.*, 2018). Disruptions in gut microbiota can compromise the integrity of the host's intestinal barrier and disturb the balance between pro-inflammatory and anti-inflammatory cytokines, which in turn can lead to the development of sarcopenia (Ni Lochlainn *et al.*, 2018; Picca *et al.*, 2018). Beyond changes in microbial composition, microbial by-products like LPS can also contribute to sarcopenia by inducing systemic chronic inflammation and insulin resistance. Therefore, inflammaging – the chronic, low-grade inflammation associated with aging – plays a crucial role in both the development and persistence of sarcopenia (Livshits and Kalinkovich, 2019).

SCFA production

SCFAs, key by-products of the gut microbiota, play a significant role in altering muscle biology (Lahiri *et al.*, 2019). SCFAs are known to aid in increasing muscle mass and enhancing physical function by boosting muscle glycogen levels (Fushimi and Sato, 2005; Lahiri *et al.*, 2019). They also enhance the metabolic efficiency of muscle fibers by increasing ATP production (Leonel and Alvarez-Leite, 2012), and can improve lean muscle mass and cross-sectional area by inhibiting histone deacetylase activity (Walsh *et al.*, 2015). As individuals age, changes in the microbiota are characterized by a reduction in microbial diversity and a rise in pathogenic bacteria, particularly Proteobacteria, along with a relative decline in advantageous bacteria like *Bifidobacterium*. In addition to shifts in microbial diversity, there is a significant decrease in the production of beneficial microbial metabolites, such as SCFAs which might be associated with the process of aging (Chen *et al.*, 2019; Rampelli *et al.*, 2013). In fact, a decrease in gut microbiota-derived SCFAs has been linked to subclinical chronic inflammation, which can lead to sarcopenia (Ticinesi *et al.*, 2017). These findings underscore a strong correlation between gut microbiota, through its SCFA metabolites, and muscle mass.

Modulation of host gene expression with microbial metabolites

Imbalances in gut microbiota can lead to the production of certain detrimental bacterial metabolites. For example, indoxyl sulfate, a metabolite of tryptophan derived from the gut microbiome and classified as a uremic toxin, is generated by certain gut bacteria including *Escherichia coli*, *Clostridium* species, and *Bacteroides* species. It has been demonstrated to stimulate increased activity in the pentose phosphate pathway and enhance glycolysis in C2C12 myoblasts. These metabolic processes are associated with the onset of sarcopenia. (Grosicki *et al.*, 2018; Sato *et al.*, 2016; Wikoff *et al.*, 2009). Additionally, an increase in LPS levels as a by-product of gram-negative bacteria, resulting from a consequence of dysbiosis, can disrupt retinoic acid signaling. This disruption occurs through the generation of reactive oxygen species and affects antioxidant genes like Nrf2 and AKR1B10, thereby hindering the development of muscle progenitor cells (Song *et al.*, 2020).

Collectively, a dysregulated gut microbiota can affect muscle mass and function through various mechanisms, such as inflammation, immune responses, protein metabolism, metabolism of SCFAs, and mitochondrial dysfunction. These interactions, whether direct or indirect, establish a connection with sarcopenia via the gut-muscle axis, thereby significantly impacting the

physiological functions of the host.

Therapeutic interventions targeting gut-muscle axis for sarcopenia

Based on the understanding of the gut-muscle axis, numerous studies have proposed that modifying gut microbiota could be a potential therapeutic approach for managing age-related sarcopenia. There is a growing body of preclinical and human research that either directly or indirectly establishes a connection between gut microbiota and muscle mass/function. Several interventions targeting gut microbiota have been suggested, including the use of probiotics and/or prebiotics, SCFAs, dietary supplementation, and exercise, all of which have shown effectiveness in improving muscle mass and overall host function. The composition of the gut microbiota is influenced by dietary habits, which can lead to microbiota changes critical for organism function (Singh *et al.*, 2017). Supplementing with prebiotics and/or probiotics has shown to be beneficial in improving intestinal homeostasis and enhancing skeletal muscle metabolism and synthesis (Salazar *et al.*, 2017). Furthermore, exercise or physical activity also contributes to regulating the gut microbiota, showcasing its role in gut health and overall physiological function (Franko *et al.*, 2016).

High-protein diets

Protein supplementation is a commonly utilized approach for preventing and managing sarcopenia. It is well-established that increasing dietary protein intake can have a positive impact on both skeletal muscle mass and function. Furthermore, there is empirical evidence to suggest that adhering to a high-protein diet in accordance with recommended macronutrient distribution guidelines can be effective in alleviating the consequences of sarcopenia. (Ford *et al.*, 2018). A study has demonstrated a positive correlation between protein intake and the diversity of gut microbiota (Singh *et al.*, 2017). It appears that the source of protein may also play a role in this relationship. Additionally, research indicates that the supplementation of whey protein and leucine has the potential to enhance muscle mass and function (Bechshøft *et al.*, 2016; Kobayashi, 2018). However, further investigation is required to establish a connection between the improvement in muscle mass and function achieved through high-protein diets and the modulation of gut microbiota.

Prebiotics and probiotics

An increasing number of both animal and human studies suggest that the use of prebiotics and/or probiotics can have beneficial effects on skeletal muscle. Prebiotics, which are non-digestible carbohydrates fermented in the lower part of the gut and selectively stimulate the growth and/or activity of specific bacteria, have been shown to have positive effects on the host (Delzenne and Cani, 2011). Some studies have explored the impact of prebiotics on skeletal muscle mass and strength by altering gut microbiota (Bindels and Delzenne, 2013). In one study involving elderly human subjects, a prebiotic supplement containing inulin and fructooligosaccharide, expected to promote a healthy microbiome, was administered. The subjects who consumed the prebiotic supplement exhibited greater hand strength and endurance compared to control subjects, although the effects on the microbiome were not reported (Y. Liu *et al.*, 2016; Ni Lochlainn *et al.*, 2021). Additionally, research by Cani *et al.* demonstrated the beneficial effects of prebiotic supplementation on the skeletal muscle of mice (Cani *et al.*, 2009). Prebiotic intake modulated bacteria that produce SCFAs, which in turn altered skeletal muscle mass and function. SCFAs promoted the release of insulin-like growth factor-1 from the host, acting as an anabolic hormone to enhance skeletal muscle and reduce inflammation (Schroeder and Bäckhed, 2016; Ticinesi *et al.*, 2017). Probiotics are live microorganisms that provide health benefits to the host when administered in adequate amounts (Delzenne and Cani, 2011). In a mouse model of acute leukemia, sarcopenia was attenuated through oral supplementation with specific *Lactobacillus* species as one of representative probiotics (Bindels *et al.*, 2012).

Furthermore, supplementation with *Lactobacillus plantarum* resulted in increased muscle mass and function In young adults, the consumption of TWK10 for a duration of six weeks resulted in improved endurance performance in a maximal treadmill running test (Huang *et al.*, 2018). Furthermore, the intake of heat-killed *Bifidobacterium breve* B-3 had a significant positive impact on skeletal muscle mass and function. This effect was accompanied by enhanced mitochondrial biogenesis, indicated by increased phosphorylation of AMP-activated protein kinase, activation of peroxisome proliferator-activated receptor gamma coactivator 1-alpha, and elevated cytochrome c oxidase activity in the rat soleus muscle (Toda *et al.*, 2020).

Fecal microbiota transplantation

Fecal microbiota transplantation (FMT) involves the introduction of a donor feces solution into patients (Van Nood *et al.*, 2013). Several studies have suggested that FMT may have the potential to enhance skeletal muscle mass and function. For example, Yan *et al.* conducted an experiment in which they transferred gut microbiota from obese pigs to GF mice. Several studies have suggested that FMT may have the potential to enhance skeletal muscle mass and function. For example, Yan *et al.* conducted an experiment in which they transferred gut microbiota from obese pigs to germ-free (Yan *et al.*, 2016). Similarly, a recent study investigated the role of intestinal microbial imbalances in sarcopenia in mice with chronic kidney disease (CKD) (Uchiyama *et al.*, 2020). When the cecal bacteria from CKD mice were transplanted into GF mice, the GF mice developed features of sarcopenia observed in the CKD mice. However, their muscle function improved, and disease symptoms were alleviated, highlighting the potential of FMT in this context.

Exercise

Exercise training, especially resistance training, has long been recognized as a highly promising method for enhancing muscle mass and strength in older individuals The majority of clinical trials have consistently demonstrated the positive impact of exercise in the prevention of sarcopenia (Beaudart *et al.*, 2017). Exercise exerts a significant influence on the intestinal microbiome, with some studies indicating that it is associated with increased microbial diversity and the presence of taxa that offer beneficial metabolic functions (Bressa *et al.*, 2017; Clarke *et al.*, 2014; Ticinesi, Lauretani, *et al.*, 2019). A reciprocal relationship between skeletal muscle and the gut microbiome has been postulated (Ni Lochlainn *et al.*, 2018). a significant body of research indicates a synergistic effect in improving muscle performance when exercise is combined with protein supplementation (Bechshøft *et al.*, 2016; Kobayashi, 2018; Ni Lochlainn *et al.*, 2018). However, the results of implementing a combined approach that includes exercise and dietary protein supplements have displayed variations among different population groups, emphasizing the necessity for additional investigations (Dhillon and Hasni, 2017).

Conclusions and Perspectives

The gut microbiota-muscle axis plays a pivotal role in both humans and animals. It involves interactions between the gut microbiota and skeletal muscle through mechanisms such as inflammatory immunity, autophagy, protein anabolism, energy regulation, oxidative stress, mitochondrial function, and endocrine and insulin resistance. These interactions collectively influence the physiological functions of the body.

Dietary supplementation, probiotics, prebiotics, SCFAs, and exercise have the potential to impact the composition of the gut microbiota, leading to improvements in skeletal muscle mass and function. While there is a substantial body of research highlighting the strong connection and communication between gut microbiota and muscle tissue, there is currently a lack of clear experiments that pinpoint the specific types of probiotics, prebiotics, or SCFAs that promote muscle growth and development. Additionally, there is a scarcity of research quantifying the optimal dosage of these supplements for muscle-related

benefits. Further investigation is needed in these areas. To substantiate the impact of the aforementioned influencing factors and elucidate the underlying mechanisms, a considerable number of rigorous interventional experimental studies are required. These studies should aim to demonstrate the precise ways in which dietary supplementation, probiotics, prebiotics, SCFAs, and exercise modulate the gut microbiota. As research methodologies continue to advance, our comprehension of the gut microbiota-muscle axis is expected to become more sophisticated. By effectively regulating the gut microbiota, individuals may have the potential to ameliorate various conditions stemming from diminished skeletal muscle mass and function.

Author Contribution

The final manuscript was read by all authors and approved.

Conflicts of Interest

The authors declare no conflict of interest.

Acknowledgments

This work was supported by the National Research Foundation of Korea(NRF) grant funded by the Korea government(MSIT) (No. 202201200002).

References

1. Azzolino D, Passarelli PC, De Angelis P, Piccirillo GB, D'Addona A and Cesari M (2019) Poor oral health as a determinant of malnutrition and sarcopenia. *Nutrients*, **11**(12), 2898.
2. Beaudart C, Dawson A, Shaw SC, Harvey NC, Kanis JA, Binkley N, Reginster JY, Chapurlat R, Chan DC and Bruyère O (2017) Nutrition and physical activity in the prevention and treatment of sarcopenia: Systematic review. *Osteoporos. Int.* **28**, 1817-1833.
3. Bechshøft RL, Reitelseder S, Højfeldt G, Castro-Mejía JL, Khakimov B, Ahmad HF Bin, Kjær M, Engelsen SB, Johansen SMB and Rasmussen MA (2016) Counteracting age-related loss of skeletal muscle mass: A clinical and ethnological trial on the role of protein supplementation and training load (CALM Intervention Study): Study protocol for a randomized controlled trial. *Trials*, **17**(1), 1-17.
4. Beyer I, Mets T and Bautmans I (2012) Chronic low-grade inflammation and age-related sarcopenia. *Curr. Opin. Clin. Nutr. Metab. Care*, **15**(1), 12-22.
5. Bindels LB, Beck R, Schakman O, Martin JC, De Backer F, Sohet FM, Dewulf EM, Pachikian BD, Neyrinck AM and Thissen J-P (2012) Restoring specific lactobacilli levels decreases inflammation and muscle atrophy markers in an acute leukemia mouse model. *PLoS One*, **7**(6), e37971.
6. Bindels LB and Delzenne NM (2013) Muscle wasting: The gut microbiota as a new therapeutic target? Int. J. Biochem. *Cell Biol.* **45**(10), 2186-2190.
7. Blau HM, Cosgrove BD and Ho AT V (2015) The central role of muscle stem cells in regenerative failure with aging. *Nat. Med.* **21**(8), 854-862.
8. Bressa C, Bailén-Andrino M, Pérez-Santiago J, González-Soltero R, Pérez M, Montalvo-Lominchar MG, Maté-Muñoz JL, Domínguez R, Moreno D and Larrosa M (2017) Differences in gut microbiota profile between women with active lifestyle and sedentary women. *PLoS One*, **12**(2), e0171352.
9. Brook MS, Wilkinson DJ, Phillips BE, Perez-Schindler J, Philp A, Smith K and Atherton PJ (2016) Skeletal muscle homeostasis and plasticity in youth and ageing: impact of nutrition and exercise. *Acta Physiol.* **216**(1), 15-41.
10. Cani PD, Possemiers S, Van de Wiele T, Guiot Y, Everard A, Rottier O, Geurts L, Naslain D, Neyrinck A and Lambert DM (2009) Changes in gut microbiota control inflammation in obese mice through a mechanism involving GLP-2-driven improvement of gut permeability. *Gut*, **58**(8), 1091-1103.
11. Carmona JJ and Michan S (2016) Biology of healthy

aging and longevity. Rev. *Investig. Clin.* **68**(1), 7-16.
12. Cartee GD, Hepple RT, Bamman MM and Zierath JR (2016) Exercise promotes healthy aging of skeletal muscle. *Cell Metab.* **23**(6), 1034-1047.
13. Cesari M, Landi F, Vellas B, Bernabei R and Marzetti E (2014) Sarcopenia and physical frailty: two sides of the same coin. *Front. Aging Neurosci.* **6**, 192.
14. Chai RJ, Vukovic J, Dunlop S, Grounds MD and Shavlakadze T (2011) Striking denervation of neuromuscular junctions without lumbar motoneuron loss in geriatric mouse muscle. *PLoS One*, **6**(12), e28090.
15. Chen R, Xu Y, Wu P, Zhou H, Lasanajak Y, Fang Y, Tang L, Ye L, Li X and Cai Z (2019) Transplantation of fecal microbiota rich in short chain fatty acids and butyric acid treat cerebral ischemic stroke by regulating gut microbiota. *Pharmacol. Res.* **148**, 104403.
16. Circu ML and Aw TY (2012) Intestinal redox biology and oxidative stress. *Semin. Cell Dev. Biol.* **23**(7), 729-737.
17. Clarke SF, Murphy EF, O'Sullivan O, Lucey AJ, Humphreys M, Hogan A, Hayes P, O'Reilly M, Jeffery IB and Wood-Martin R (2014) Exercise and associated dietary extremes impact on gut microbial diversity. *Gut*, **63**(12), 1913-1920.
18. Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyère O, Cederholm T, Cooper C, Landi F, Rolland Y and Sayer AA (2019) Sarcopenia: Revised European consensus on definition and diagnosis. *Age Ageing*, **48**(1), 16-31.
19. Cruz-Jentoft AJ and Sayer AA (2019) Sarcopenia. *Lancet*, **393**(10191), 2636-2646.
20. Curtis E, Litwic A, Cooper C, and Dennison E (2015) Determinants of muscle and bone aging. *J. Cell. Physiol.* **230**(11), 2618-2625.
21. Delzenne NM, and Cani PD (2011) Interaction between obesity and the gut microbiota: relevance in nutrition. *Annu. Rev. Nutr.* **31**, 15-31.
22. Den Besten G, Van Eunen K, Groen AK, Venema K, Reijngoud D-J and Bakker BM (2013) The role of short-chain fatty acids in the interplay between diet, gut microbiota, and host energy metabolism. *J. Lipid Res.* **54**(9), 2325-2340.
23. Dhillon RJS and Hasni S (2017) Pathogenesis and management of sarcopenia. *Clin. Geriatr. Med.* **33**(1), 17-26.
24. Dukes A, Davis C, El Refaey M, Upadhyay S, Mork S, Arounleut P, Johnson MH, Hill WD, Isales CM, and Hamrick MW (2015) The aromatic amino acid tryptophan stimulates skeletal muscle IGF1/p70s6k/mTor signaling in vivo and the expression of myogenic genes *in vitro*. *Nutrition*, **31**(7-8), 1018-1024.
25. Farnfield MM, Breen L, Carey KA, Garnham A and Cameron-Smith D (2012) Activation of mTOR signalling in young and old human skeletal muscle in response to combined resistance exercise and whey protein ingestion. *Appl. Physiol. Nutr. Metab.* **37**(1), 21-30.
26. Fielding RA, Reeves AR, Jasuja R, Liu C, Barrett BB and Lustgarten MS (2019) Muscle strength is increased in mice that are colonized with microbiota from high-functioning older adults. *Exp. Gerontol.* **127**, 110722.
27. Ford AC, Harris LA, Lacy BE, Quigley EMM and Moayyedi P (2018) Systematic review with meta-analysis: the efficacy of prebiotics, probiotics, synbiotics and antibiotics in irritable bowel syndrome. *Aliment. Pharmacol. Ther.* **48**(10), 1044-1060.
28. Francis P, Lyons M, Piasecki M, Mc Phee J, Hind K, and Jakeman P (2017) Measurement of muscle health in aging. *Biogerontology*, **18**, 901-911.
29. Franko A, Huypens P, Neschen S, Irmler M, Rozman J, Rathkolb B, Neff F, Prehn C, Dubois G and Baumann M (2016) Bezafibrate improves insulin sensitivity and metabolic flexibility in STZ-induced diabetic mice. *Diabetes*, **65**(9), 2540-2552.
30. Fushimi T and Sato Y (2005) Effect of acetic acid feeding on the circadian changes in glycogen and metabolites of glucose and lipid in liver and skeletal muscle of rats. *Br. J. Nutr.* **94**(5), 714-719.
31. Giallauria F, Cittadini A, Smart NA and Vigorito C (2015) Resistance training and sarcopenia. *Monaldi*

Arch. Chest Dis. **84**(1-2).
32. Grosicki GJ, Fielding RA and Lustgarten MS (2018) Gut microbiota contribute to age-related changes in skeletal muscle size, composition, and function: biological basis for a gut-muscle axis. *Calcif. Tissue Int.* **102**, 433-442.
33. Ham DJ, Börsch A, Lin S, Thürkauf M, Weihrauch M, Reinhard JR, Delezie J, Battilana F, Wang X and Kaiser MS (2020) The neuromuscular junction is a focal point of mTORC1 signaling in sarcopenia. *Nat. Commun.* **11**(1), 4510.
34. Huang W-C, Hsu Y-J, Li H, Kan N-W, Chen Y-M, Lin J-S, Hsu T-K, Tsai T-Y, Chiu Y-S and Huang C-C (2018) Effect of *Lactobacillus plantarum* TWK10 on improving endurance performance in humans. *Chin. J. Physiol.* **61**(3), 163-170.
35. Inglis JE and Ilich JZ (2015) The microbiome and osteosarcopenic obesity in older individuals in long-term care facilities. *Curr. Osteoporos. Rep.* **13**, 358-362.
36. Jackson MJ and McArdle A (2016) Role of reactive oxygen species in age-related neuromuscular deficits. *J. Physiol.* **594**(8), 1979-1988.
37. Kang L, Li P, Wang D, Wang T, Hao D and Qu X (2021) Alterations in intestinal microbiota diversity, composition, and function in patients with sarcopenia. *Sci. Rep.* **11**(1), 4628.
38. Kimura I, Inoue D, Hirano K and Tsujimoto G (2014) The SCFA receptor GPR43 and energy metabolism. *Front. Endocrinol.* **5**, 85.
39. Kobayashi H (2018) Amino acid nutrition in the prevention and treatment of sarcopenia. *Yakugaku Zasshi J. Pharm. Soc. Japan* **138**(10), 1277-1283.
40. Kuo H-K, Liao K-C, Leveille SG, Bean JF, Yen C-J, Chen J-H, Yu Y-H and Tai T-Y (2007) Relationship of homocysteine levels to quadriceps strength, gait speed, and late-life disability in older adults. *Journals Gerontol. Ser. A Biol. Sci. Med. Sci.* **62**(4), 434-439.
41. Lahiri S, Kim H, Garcia-Perez I, Reza MM, Martin KA, Kundu P, Cox LM, Selkrig J, Posma JM and Zhang H (2019) The gut microbiota influences skeletal muscle mass and function in mice. *Sci. Transl. Med.* **11**(502), eaan5662.
42. Landi F, Liperoti R, Russo A, Giovannini S, Tosato M, Capoluongo E, Bernabei R and Onder G (2012) Sarcopenia as a risk factor for falls in elderly individuals: results from the ilSIRENTE study. *Clin. Nutr.* **31**(5), 652-658.
43. Larsson L, Degens H, Li M, Salviati L, Lee Y Il, Thompson W, Kirkland JL and Sandri M (2019) Sarcopenia: aging-related loss of muscle mass and function. *Physiol. Rev.* 99(1) 427-511.
44. Leonel AJ and Alvarez-Leite JI (2012) Butyrate: Implications for intestinal function. *Curr. Opin. Clin. Nutr. Metab. Care*, **15**(5), 474-479.
45. Lexell J, Henriksson-Larsén K, Winblad B and Sjöström M (1983) Distribution of different fiber types in human skeletal muscles: Effects of aging studied in whole muscle cross sections. *Muscle Nerve Off. J. Am. Assoc. Electrodiagn. Med.* **6**(8), 588-595.
46. Lin R, Liu W, Piao M, and Zhu H (2017) A review of the relationship between the gut microbiota and amino acid metabolism. *Amino Acids*, **49**, 2083-2090.
47. Liu J-C, Dong S-S, Shen H, Yang D-Y, Chen B-B, Ma X-Y, Peng Y-R, Xiao H-M and Deng H-W (2022) Multi-omics research in sarcopenia: Current progress and future prospects. *Ageing Res. Rev.* **76**, 101576.
48. Liu Y, Gibson GR and Walton GE (2016) An in vitro approach to study effects of prebiotics and probiotics on the faecal microbiota and selected immune parameters relevant to the elderly. *PLoS One*, **11**(9), e0162604.
49. Livshits G and Kalinkovich A (2019) Inflammaging as a common ground for the development and maintenance of sarcopenia, obesity, cardiomyopathy and dysbiosis. *Ageing Res. Rev.* **56**, 100980.
50. Lobet E, Letesson J-J and Arnould T (2015) Mitochondria: a target for bacteria. *Biochem. Pharmacol.* **94**(3), 173-185.
51. Locantore P, Del Gatto V, Gelli S, Paragliola RM and Pontecorvi A (2020) The interplay between immune system and microbiota in osteoporosis. *Mediators*

Inflamm. **2020**.

52. Lubben J and Damron-Rodriguez J (2010) World Population Aging. In *Handbook of Social Work in Health and Aging United Nations*.
53. Manickam R, Oh HYP, Tan CK, Paramalingam E and Wahli W (2018) Metronidazole causes skeletal muscle atrophy and modulates muscle chronometabolism. *Int. J. Mol. Sci.* **19**(8), 2418.
54. Marcell TJ (2003) Sarcopenia: causes, consequences, and preventions. *Journals Gerontol. Ser. A Biol. Sci. Med. Sci.* **58**(10), M911–M916.
55. Marzetti E, Calvani R, Cesari M, Buford TW, Lorenzi M, Behnke BJ and Leeuwenburgh C (2013) Mitochondrial dysfunction and sarcopenia of aging: From signaling pathways to clinical trials. *Int. J. Biochem. Cell Biol.* **45**(10), 2288–2301.
56. Marzetti E, Calvani R, Lorenzi M, Tanganelli F, Picca A, Bossola M, Menghi A, Bernabei R and Landi F (2016) Association between myocyte quality control signaling and sarcopenia in old hip-fractured patients: Results from the Sarcopenia in HIp FracTure (SHIFT) exploratory study. *Exp. Gerontol.* **80**, 1–5.
57. Mesinovic J, Zengin A, De Courten B, Ebeling PR and Scott D (2019) Sarcopenia and type 2 diabetes mellitus: a bidirectional relationship. *Diabetes, Metab. Syndr. Obes. Targets Ther.* 1057–1072.
58. Mottawea W, Chiang C-K, Mühlbauer M, Starr AE, Butcher J, Abujamel T, Deeke SA, Brandel A, Zhou H and Shokralla S (2016) Altered intestinal microbiota–host mitochondria crosstalk in new onset Crohn's disease. *Nat. Commun.* **7**(1), 13419.
59. Narici M V, and Maffulli N (2010) Sarcopenia: Characteristics, mechanisms and functional significance. *Br. Med. Bull.* **95**(1), 139–159.
60. Ni Lochlainn M, Bowyer RCE and Steves CJ (2018) Dietary protein and muscle in aging people: The potential role of the gut microbiome. *Nutrients*, **10**(7), 929.
61. Ni Lochlainn M, Nessa A, Sheedy A, Horsfall R, García MP, Hart D, Akdag G, Yarand D, Wadge S and Baleanu A-F (2021) The PROMOTe study: Targeting the gut microbiome with prebiotics to overcome age-related anabolic resistance: protocol for a double-blinded, randomised, placebo-controlled trial. *BMC Geriatr.* **21**, 1–10.
62. Partridge L, Deelen J and Slagboom PE (2018) Facing up to the global challenges of ageing. *Nature*, **561**(7721), 45–56.
63. Picca A, Fanelli F, Calvani R, Mulè G, Pesce V, Sisto A, Pantanelli C, Bernabei R, Landi F and Marzetti E (2018) Gut dysbiosis and muscle aging: Searching for novel targets against sarcopenia. *Mediators Inflamm.* 2018.
64. Ponziani FR, Picca A, Marzetti E, Calvani R, Conta G, Del Chierico F, Capuani G, Faccia M, Fianchi F and Funaro B (2021) Characterization of the gut-liver-muscle axis in cirrhotic patients with sarcopenia. *Liver Int.* **41**(6), 1320–1334.
65. Rampelli S, Candela M, Turroni S, Biagi E, Collino S, Franceschi C, O'Toole PW and Brigidi P (2013) Functional metagenomic profiling of intestinal microbiome in extreme ageing. *Aging* (Albany NY), **5**(12), 902.
66. Sakuma K and Yamaguchi A (2012) Sarcopenia and age-related endocrine function. *Int. J. Endocrinol.* 2012.
67. Salazar N, Valdés-Varela L, González S, Gueimonde M and De Los Reyes-Gavilán CG (2017) Nutrition and the gut microbiome in the elderly. *Gut Microbes*, **8**(2), 82–97.
68. Sato E, Mori T, Mishima E, Suzuki A, Sugawara S, Kurasawa N, Saigusa D, Miura D, Morikawa-Ichinose T and Saito R (2016) Metabolic alterations by indoxyl sulfate in skeletal muscle induce uremic sarcopenia in chronic kidney disease. *Sci. Rep.* **6**(1), 36618.
69. Schroeder BO and Bäckhed F (2016) Signals from the gut microbiota to distant organs in physiology and disease. *Nat. Med.* **22**(10), 1079–1089.
70. Shaw SC, Dennison EM and Cooper C (2017) Epidemiology of sarcopenia: Determinants throughout the lifecourse. *Calcif. Tissue Int.* **101**(3), 229–247.
71. Siddharth J, Chakrabarti A, Pannerec A, Karaz S,

Morin-Rivron D, Masoodi M, Feige JN and Parkinson SJ (2017) Aging and sarcopenia associate with specific interactions between gut microbes, serum biomarkers and host physiology in rats. *Aging* (Albany NY), **9**(7), 1698.

72. Singh RK, Chang H-W, Yan DI, Lee KM, Ucmak D, Wong K, Abrouk M, Farahnik B, Nakamura M and Zhu TH (2017) Influence of diet on the gut microbiome and implications for human health. *J. Transl. Med.* **15**(1), 1-17.
73. Song J, Wang C, Long D, Li Z, You L, Brand-Saberi B, Wang G and Yang X (2020) Dysbacteriosis-induced LPS elevation disturbs the development of muscle progenitor cells by interfering with retinoic acid signaling. *FASEB J.* **34**(5), 6837-6853.
74. St-Jean-Pelletier F, Pion CH, Leduc-Gaudet J, Sgarioto N, Zovilé I, Barbat-Artigas S, Reynaud O, Alkaterji F, Lemieux FC and Grenon A (2017) The impact of ageing, physical activity, and pre-frailty on skeletal muscle phenotype, mitochondrial content, and intramyocellular lipids in men. *J. Cachexia. Sarcopenia Muscle*, **8**(2), 213-228.
75. Ticinesi A, Lauretani F, Milani C, Nouvenne A, Tana C, Del Rio D, Maggio M, Ventura M and Meschi T (2017) Aging gut microbiota at the cross-road between nutrition, physical frailty, and sarcopenia: is there a gut-muscle axis? *Nutrients*, **9**(12), 1303.
76. Ticinesi A, Lauretani F, Tana C, Nouvenne A, Ridolo E and Meschi T (2019) Exercise and immune system as modulators of intestinal microbiome: Implications for the gut-muscle axis hypothesis. *Exerc. Immunol. Rev.* 25.
77. Ticinesi A, Mancabelli L, Tagliaferri S, Nouvenne A, Milani C, Del Rio D, Lauretani F, Maggio MG, Ventura M and Meschi T (2020) The gut-muscle axis in older subjects with low muscle mass and performance: A proof of concept study exploring fecal microbiota composition and function with shotgun metagenomics sequencing. *Int. J. Mol. Sci.* **21**(23), 8946.
78. Ticinesi A, Nouvenne A, Cerundolo N, Catania P, Prati B, Tana C and Meschi T (2019) Gut microbiota, muscle mass and function in aging: A focus on physical frailty and sarcopenia. *Nutrients*, **11**(7), 1633.
79. Toda K, Yamauchi Y, Tanaka A, Kuhara T, Odamaki T, Yoshimoto S and Xiao J (2020) Heat-killed Bifidobacterium breve B-3 enhances muscle functions: Possible involvement of increases in muscle mass and mitochondrial biogenesis. *Nutrients*, **12**(1), 219.
80. Uchiyama K, Wakino S, Irie J, Miyamoto J, Matsui A, Tajima T, Itoh T, Oshima Y, Yoshifuji A and Kimura I (2020) Contribution of uremic dysbiosis to insulin resistance and sarcopenia. *Nephrol. Dial. Transplant.* **35**(9), 1501-1517.
81. Van Nood E, Vrieze A, Nieuwdorp M, Fuentes S, Zoetendal EG, de Vos WM, Visser CE, Kuijper EJ, Bartelsman JFWM and Tijssen JGP (2013) Duodenal infusion of donor feces for recurrent *Clostridium difficile*. *N. Engl. J. Med.* **368**(5), 407-415.
82. Walsh ME, Bhattacharya A, Sataranatarajan K, Qaisar R, Sloane L, Rahman MM, Kinter M and Van Remmen H (2015) The histone deacetylase inhibitor butyrate improves metabolism and reduces muscle atrophy during aging. *Aging Cell*, **14**(6), 957-970.
83. Wikoff WR, Anfora AT, Liu J, Schultz PG, Lesley SA, Peters EC and Siuzdak G (2009) Metabolomics analysis reveals large effects of gut microflora on mammalian blood metabolites. *Proc. Natl. Acad. Sci.* **106**(10), 3698-3703.
84. Yan H, Diao H, Xiao Y, Li W, Yu B, He J, Yu J, Zheng P, Mao X and Luo Y (2016) Gut microbiota can transfer fiber characteristics and lipid metabolic profiles of skeletal muscle from pigs to germ-free mice. *Sci. Rep.* **6**(1), 31786.