Interactions between gut microbiota and skeletal muscle

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ABSTRACT: The gut microbiota is now recognized as a major contributor to the host's nutrition, metabolism, immunity, and neurological functions. Imbalanced microbiota (ie, dysbiosis) is linked to undernutrition-induced stunting, inflammatory and metabolic diseases, and cancers. Skeletal muscle also takes part in the interorgan crosstalk regulating substrate metabolism, immunity, and health. Here, we review the reciprocal influence of gut microbiota and skeletal muscle in relation to juvenile growth, performance, aging, and chronic diseases. Several routes involving the vascular system and organs such as the liver and adipose tissue connect the gut microbiota and skeletal muscle, with effects on fitness and health. Therapeutic perspectives arise from the health benefits observed with changes in gut microbiota and muscle activity, further encouraging multimodal therapeutic strategies.

KEYWORDS: Gut microbiota, Skeletal muscle, Metabolic and inflammatory disorders, Aging, Exercice, Nutrition, Biotics, Fitness, Performance, Muscle weakness

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Introduction

The relation between health evolution over lifespan and the metabolic and immune functions of both gut microbiota (GM) and skeletal muscle is now well documented.

A healthy microbiota is ensured by a diverse microbiome with activities contributing to immune and metabolic homeostasis, notably through reinforcing the intestinal barrier.[1] Promotion of this barrier involves competition phenomena, modulation of gut inflammation, and maintenance of the mucus layer. In this process, Akkermansia muciniphila (*A. muciniphila*), whose levels depend on diet,[2,3] has been especially characterized for its protective effects on intestinal permeability, obesity and insulin resistance (reviewed by Rastelli et al[1] and Cani[4]).

Conversely, dysbiosis, characterized by microbial imbalance with loss of microbial diversity, alters the integrity of the intestinal barrier, facilitating the passage of endotoxins (ie, lipopolysaccharides (LPS)) and other microbial products (eg, the tryptophan derivative indoxyl sulfate) in the circulation. These microbial factors trigger innate immunity, leading to low-grade systemic inflammation and, as a consequence, to metabolic and muscular disorders (reviewed by Grosicki et al[5]). In particular, the expression of tumor necrosis factor α (TNFα) and interleukin 6 (IL-6) is stimulated by LPS and indoxyl sulfate in immune tissues and myoblast.[5] Depending on host genotype, diet, environment, and age, GM dysbiosis thus contributes to chronic diseases such as high-fat diet-induced obesity, type 2 diabetes mellitus, cancer, and cardiovascular, liver or kidney diseases, and ulcerative colitis[1,5,6] (Figure 1).

Whereas muscle loss and weakness are linked to increased morbidity and mortality, they recently appeared to be related to GM dysbiosis and systemic inflammation (Figure 1). Of note, higher circulating levels of TNFα and IL-6 in the elderly and persons with inflammatory diseases (such as heart failure, sepsis, and cancer) have been associated with a reduction in muscle mass and strength.[5]

Healthy diets (defined as high in fiber and low in fat) and some specific biotics have been shown to display benefits on intestinal, inflammatory and metabolic parameters.[5,7] Potentially beneficial bacteria include species contained in the probiotic mixture VSL#3, that is, *Lactobacillus, Bifidobacterium*, and *Streptococcus*.[8] Promising probiotic-derived products (ie, postbiotics) include pasteurized *A. muciniphila*[7] and short-chain fatty acids (SCFAs, particularly butyrate), which are synthetized by bacteria and may improve epithelial barrier function and gut permeability by modulating the expression of tight junction proteins and mucins (reviewed by Canfora et al[9]).

GM also has direct effects beyond the gastrointestinal tract, notably on organs interdependent on the levels of glycemia including brain, liver, adipose tissue, and skeletal muscle. Thus, insulin-sensitive skeletal muscle participates de facto in the body-wide interplay regulating substrate metabolism and energy, which conversely affects its function.[1,9]

In this review, we recapitulate the reported relation between the GM and skeletal muscle in normal—including old age—and pathophysiologic states, and the therapeutic perspectives arising from this relation. Studies discussed below using rederivation in germ-free (GF) or gnotobiotic mice, antibiotics, probiotics or fecal microbiota transplants have highlighted the influence of GM on muscle metabolism in healthy or inflammatory states, with an impact on the

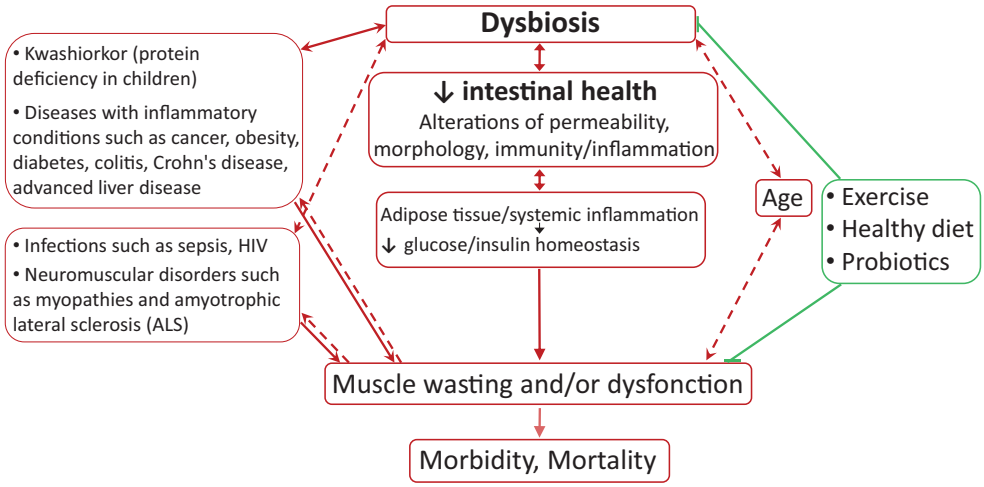

Figure 1. Influence of gut microbiota on health in relation to age and physical activity. Summarized in this schematic representation are causality and reciprocal links between pathologies, aging or exercise and muscle function, which involve unbalanced gut microbiota and decreased intestinal health. Solid arrow lines illustrate well-documented links, whereas dotted arrow lines show links that remain to be confirmed by further studies.

proportion of lean and fat masses, muscular typology and force. These effects are linked to the regulation of metabolism and inflammation in skeletal muscle, serum, and organs such as intestine, liver, and adipose tissue.

Survey Methodology

The literature search aimed to collect published data on the relation between GM and skeletal muscle with reciprocal influences potentially contributing to muscle mass and strength, and as such healthier states. We searched literature relevant to the topic using PubMed, Google, and a book.[10] Key words such as skeletal muscle and gut microbiota, lean body mass, nutrition, prebiotics, probiotics, dairy foods and supplements, chronic inflammatory diseases, cancer, aging, sarcopenia, frailty, muscular dystrophies linked to metabolic and inflammatory disorders, physical activity, exercise, fitness, performance were used to perform the searches.

Influence of Gut Microbiota Products and Metabolites on Skeletal Muscle Function

GM metabolizes organic substrates, either foodborne and not digested by human enzymes in the digestive tract, or from endogenous secretions (mucopolysaccharides, cell debris. . .).

It synthesizes and regulates the synthesis (in the host tissues) of molecules known as neurotransmitters, that is, histamine, serotonin, γ-aminobutyric acid (GABA), catecholamines, and the gases nitric oxide and hydrogen sulfide (H_2S). The production of such molecules elicited by the microbiota impacts bacterial interactions (via a "quorum" sensing mechanism) and intestinal immunity, and has also been linked to specific intestinal, metabolic and neurophysiological features.[1,11] These may implicate different signaling pathways, that is, neuroendocrine circuitry including enteric neurons and/or vagal nerves, and modulation of systemic metabolites and inflammatory profiles.

Some other GM byproducts, such as SCFAs, phenolic products, bile acids derived from intestinal bacteria and conjugated linoleic acid, can improve muscle glucose homeostasis, energy expenditure, protein synthesis and physical performance via the regulation of intestinal permeability, interorgan cross-talks and/or direct targeting of skeletal muscle (Table 1).

The specific benefits of major GM SCFA metabolites—acetate, propionate and butyrate—on blood glucose, insulin responses, and skeletal muscle function have been described in numerous studies. Recently, administering a mixture of these SCFAs to GF mice was shown to partly reverse skeletal muscle impairment caused by GM deficiency, notably through the improvement of muscle strength[12] (Table 2). Moreover, acetate infusion restored exercise tolerance in antibiotic-treated mice.[13] By targeting intestine, adipose tissue and skeletal muscle, they affect muscle metabolism via several ways.[9] In enteroendocrine L-cells, their binding to G-protein coupled receptors—Free Fatty Acid Receptor (FFAR)1 and FFAR3—promotes the production of the anorexigenic peptide YY (PYY) and of glucagon-like peptide-1 (GLP-1), an anti-diabetic hormone acting as incretin and insulin sensitizer. Butyrate, propionate, and succinate (precursor of propionate) also activate gluconeogenesis in enterocytes, which improves insulin sensitivity and metabolism through signaling to the gastrointestinal nerves and brain.[14,15] As mentioned above, SCFAs (especially butyrate) may also improve epithelial barrier function and gut permeability by modulating the expression of tight junction proteins and mucins, thus preventing endotoxemia.[9] Beside the intestine, small amounts of propionate and butyrate and high amounts of acetate reach the circulation and may directly affect peripheral cells and tissues.[9,16] Butyrate in particular may prevent low-grade inflammation with an impact on skeletal muscle by upregulating anti-inflammatory Regulatory T Cells and directly decreasing the secretion of adipose tissue-derived proinflammatory cytokines and chemokines.[9] In addition, SCFAs may favor

Table 1. The possible impacts of bacterial metabolites on human skeletal muscle health.

GM PRODUCTS	MAIN SUBSTRATES	MAIN BACTERIA TAXA INVOLVED	OTHER DIETARY SOURCES	POTENTIAL MAIN IMPACTS ON MUSCLES
Lactate	Complex carbohydrates (dietary fibers)	Fibrolytic bacteria, bifidobacteriales, lactic acid bacteria	Fermented milk products, wine, akebia fruit	Energy substrate[28]
Succinate	Complex carbohydrates (dietary fibers)	Bacteroidetes, for example, *P. copri*	Food additives and dietary supplements	↑ Insulin sensitivity and metabolism[15,29]
Imidazole propionate	Histidine	Bacteria with urocanate reductase activity, for example, *Streptococcus mutans* and *Eggerthella lenta*	/	Related to impairment of insulin signaling and glucose tolerance[27]
Short chain fatty acids (SCFAs)	Complex carbohydrates (dietary fibers) and proteins	Most bacteria, fibrolytic, glycolytic, and/or proteolytic	/	↓ Systemic insulin resistance and inflammation and appetite,[1] ↑ muscle insulin sensitivity, ↓ muscle atrophy, ↑ muscle strength and exercise capacity[16]
Branched-chain fatty acids	Branched-chain amino acids (BCAA)	Most bacteria, displaying a proteolytic activity	/	Related to insulin resistance[30,31]
Phenolic metabolites, in particular isovanillic acid 3-O-sulfate	Dietary phenolics (eg, from cereal brans and berry fruits)[19]	Butyrate-producing bacteria	/	↑ Glucose uptake and metabolism in the differentiated human skeletal muscle myoblast line[19]
Conjugated linoleic acid	Linoleic acid	*Bifidobacteria*[32]	Dairy products and meat	↑ Body mass and physical performance[20]
Secondary and tertiary bile acids (deoxycholic, lithocholic, and ursodeoxycholic acids)	Primary bile acids	*Clostridium*	/	↑ Systemic glucose homeostasis and energy expenditure[18]
Trimethylamine (TMA), oxidized in the liver into TMA N-oxide (TMAO)	Choline from phosphatidyl-choline (found in meat, eggs, fish, and crustaceans) and L-carnitine (found in red meat)	Taxa of several distinct phyla, involved according to the diet and the host phylogeny[33]	/	TMAO associated with cardiometabolic disorders,[22] ↓ TMA/total creatine correlates with ↓ muscle function[24]
Vitamins				
Vitamin B8 (biotin, BH, B7)	Alanine and pimeloyl-CoA	Notably bifidobacteriales and lactic acid bacteria[34]	Large range of aliments (eg, offal, milk, and eggs), at low concentration	Energy production and storage[35]
Vitamin B12 (cobalamin)	δ-Aminolevulinate[36]	Few archea and bacteria, including *Streptococcus*, bifidobacteriales, lactic acid bacteria[34]	Animal derived food (eg, raw liver of beef, pork, or chicken, fish, and shellfish); plant derived food[37]	Deficiency related to muscle and neurological dysfunctions, ↓ energy and exercise tolerance[35,38,39]
Vitamin K2 (menaquinones)	Vitamin K1, iself synthetized from chorismic acid in plants and microorganisms	*Bacteroides* and bifidobacteriales[40]	Fermented food (cheese, nattō)	↑ Muscle-bone interactions[41]

fatty acid oxidation by binding directly to their receptors—FFAR1 and FFAR3—in human skeletal muscle.[16]

Tryptophan products such as indoles and derivatives, and secondary bile acids (eg, deoxycholic acid and lithocholic acid) share SCFAs' ability to increase the production of GLP-1 and PYY in L-cells through distinct mechanisms.[1,17] Secondary bile acids act through G-protein coupled bile acid receptor 1 (GPBAR-1, also known as TGR5), which is

Table 2. Effects of GM modulation on skeletal muscle, inflammation, and metabolism in unaged models.

MODELS OF HEALTHY OR STANDARD DIETS		
MODELS OF GM MODULATION, DIET, DAMAGE TYPE REFERENCES	EFFECTS OF GM ON MUSCLE MASS, PHENOTYPE, AND/OR FUNCTION	OTHER RELATED EFFECTS
Male GF and PF C57BL/6J male mice (6-8 wk old)[12]	Effects of GM depletion:	
Standard chow diet (R36 Lactamin, Stockholm, Sweden): 3.5% cellulose (%weight), 22.9% protein (%energy), 67.1% carbohydrate, and 9.6% fat	↓ Muscle weight, ↓ locomotion and grip strength	↑ Serum corticosterone
	↑ FoxO3/pAMPK degradation pathway with:	Alteration of metabolism, notably related to amino acids glycine and alanine, bile acids and choline in liver and serum
	↑ Atrogin-1 and MuRF1 atrophic markers	
	↑ Transcription of genes inducing BCAA catabolism, ↓ oxidative capacity, ↑ amino acids such as glycine and alanine, ↓ transcription of genes involved in NMJ function and troponin	
	At least partly normalized in GF mice transplanted with GM from PF mice, or treated with SCFAs acetate, propionate, and butyrate	
GF or SPF C57Bl/6J male mice (2 mo or 6-7 mo old, respectively) treated or not with metronidazole for 4 wk[65]	Effect of the antibiotic metronidazole: In SPF mice	
Standard chow diet	↓ Weight of hind limb muscles	↑ Fecal proteobacteria
	↓ Myofiber surface area in the tibialis anterior	
	↑ In the gastrocnemius of factors involved in:	
	Protein breakdown, that is, *FoxO3, Hdac4, myogenin, MuRF1, atrogin-1*	
	Circadian clock and metabolism, that is, *Cry2, Ror-β, E4BP4, Per2, FOX01, PPARγ*, and *adiponectin*	
	In GF mice	
	↓ Weight of hind limb muscles	↓ Body weight
	↓ *FOX01* and *Pdk4,* ↑ clock gene *Bmal1,* ↓ *Per2*	
Male C57BL/6 mice treated or not at 14 wk by treatment with a broad-spectrum antibiotics cocktail (ampicillin, streptomycin, colistin, and vancomycin)	Effects of the broad-spectrum antibiotics cocktail: ↓ Endurance	↓ Transporters *FFAR3* (*Gpr41*) and sodium/glucose cotransporter 1 *Sglt1* in ileum
	↓ Extensor digitorum longus (EDL) muscle fatigue index in an ex vivo contractile test	
For 21 d	↓ Muscle glycogen levels	
Or for 10 d followed by a 11 d natural recolonization (NAT group)[66]		
69.2% of cereals, 20.2% of vegetal proteins, 6.0% of animal proteins, and 4.6% of mineral and vitamin cocktail (SAFE A03)	Normalized following natural reseeding (NAT group)	
Male Institute of Cancer Research (ICR) mice supplemented or not for 6 wk with *L. plantarum* TWK10[60]	Effect of *L. plantarum* TWK10 (one or both doses): ↑ Relative muscle weight (%)	↓ Body weight and epididymal fat pad

(Continued)

Table 2. (Continued)

MODELS OF HEALTHY OR STANDARD DIETS		
MODELS OF GM MODULATION, DIET OR DAMAGE TYPE REFERENCES	EFFECTS OF GM ON MUSCLE MASS, PHENOTYPE, AND/OR FUNCTION	OTHER RELATED EFFECTS
Standard diet (No. 5001; PMI Nutrition International, USA)	↑ Grip strength ↑ Endurance in an exhaustive swimming test ↑ Type I fibers (slow muscle) in gastrocnemius	↑ Relative weight of kidney and heart ↑ Food and water intake ↓ Serum albumin, blood urea nitrogen, creatinine, and triacylglycerol ↓ Serum lactate, ammonia, CK, glucose after acute exercise challenge
7 wk old GF male C57BL/6JNarl mice inoculated or not with either *L. plantarum* TWK10, *Eubacterium rectale* (*E. rectale*), or *Clostridium coccoides* (*C. coccoides*) for 6 wk[61]	Effect of *E. rectale* compared to either GF, *L. plantarum* TWK10, or *C. coccoides* gnotobiotic mice after training:	
Subjected to swimming endurance training in the last 4 wk Standard diet (#5010, PMI Nutrition International, USA)	↑ Endurance in an exhaustive swimming test	↑ Liver glycogen content
6 wk old ICR mice receiving or not a treadmill exercise and/or supplementation with *B. longum* subsp. *Longum* OLP-01 (*B. longum* OLP-01) isolated from an elite weightlifting Olympic gold medalist for 6 wk[62]	Effect of *B. longum* OLP-01 supplementation after training:	
Sufficient chow diet (No. 5001; PMI Nutrition International, USA)	↑ Grip strength and endurance in an exhaustive swimming test	↓ Fatigue-associated indexes: lactate, ammonia, CK, lactate dehydrogenase in sera, and glycogen content in liver, gastrocnemius, and soleus ↓ Inflammation and injury indexes: platelet/lymphocyte ratio, aspartate aminotransferase, and CK
GF male and female C57BL/6J mice colonized at 8 to 9 wk with GM from sedentary old human (70-85 y) with high or low functioning, defined with the SPPB test[107]	Effects of GM colonization from high-functioning compared to low-functioning old adults (assessed 1 mo after gavage)	
Standard LabDiet 5021 (LabDiet)	↑ Grip strength No difference in treadmill endurance capacity	No difference in whole body mass
Recreationally-trained male human subjects supplemented during breakfast with casein (2 wk), or with casein + *B. coagulans GBI-30, 6086* (2 wk) in a cross-over trial[63]	Effect of *B. coagulans* GBI-30, 6086 on the outcome of muscle damage:	
Diet-controlled exercise bout: muscle damaging one-legged exercise at the conclusion of the supplementation periods	↑ Athletic performance	↑ Perceived recovery ↓ Soreness

(Continued)

Table 2. (Continued)

MODELS OF MALNUTRITION AND/OR OBESITY		
MODELS OF GM MODULATION, DIET OR DAMAGE TYPE REFERENCES	EFFECTS OF GM ON MUSCLE MASS, PHENOTYPE, AND/OR FUNCTION	OTHER RELATED EFFECTS
GF or WT BALB/c infant mice[47]	Effect of GM depletion:	
GF mice monocolonized or not with *L. plantarum*^{WJL} or *L. plantarum*^{NIZO2877} (done by gavage of 8 wk old GF mice, mating 20 d after colonization, and natural colonization of infants from the dams)	↓ Somatotrophic axis: ↓ GHR/IGF-1/IGFBP3 signaling in liver, sera, and quadriceps	
Pups bred with mothers on a standard breeding diet (25% proteins, 9% fats) until weaning at day 21		On breeding diet: ↓ weight (total, liver, kidney, spleen, heart), and ↓ body and femur length (at day 56, effects dependent of IGF-1)
Then still maintained on the standard breeding diet from 21 to 56 d old		On depleted diet: stunting
Or switched to a model of chronic undernutrition with a nutritionally depleted diet low in proteins (8.6%), fats (2.4%), and vitamins	Effect of *L. Plantarum*^{WJL} compared to GF mice (strain-specific effect):	
		On both diets: ↑ body weight, ↑ body and femur lengths
		On depleted diet: ↓ chronic undernutrition-induced GH resistance with ↑ organs' weight (liver, kidney, spleen, heart)
Male C57BL/6J colonized or not at 6 to 10 wk with fecal content harvested from an adult conventionally raised mouse[52]	Effects of GM depletion:	
Western diet (WD, 41% lipids, 41% simple carbohydrates, 18% proteins, 4.8 kcal/g) 2 to 3 wk after conventionalization or maintenance on low-fat polysaccharide-rich chow diet (5% lipids, 4.1 kcal/g)	↑ Locomotor activity (on both diets)	↑ LPL inhibitor FIAF in the intestine (on both diets)
	↑ ACC, AMPK-P in the gastrocnemius muscle (on Western diet)	↑ AMPK-P and ↓ glycogen synthesis in the liver (on Western diet)
At birth, colonization of GF BALB/C mice with the fecal suspensions prepared from lean Yorkshire pigs (YP) and Obese Rongchang pigs (RP)[53]	Effects of GM colonization from RP compared to YP:	
	↑ Slow-contracting fiber proportion	↑ Body fat
Ad libitum chow diet	↓ Fiber size and fast IIb fiber percentage	↑ Firmicutes/Bacteroidetes
	↑ Lipogenesis in the gastrocnemius muscle	
	Reproduction of the skeletal muscle phenotypes and lipid metabolic profiles	
MODELS OF INFECTIOUS, INFLAMMATORY, AND/OR IMMUNE DISORDERS		
MODELS OF GM MODULATION, DIET OR DAMAGE TYPE REFERENCES	EFFECTS OF GM ON MUSCULAR MASS, PHENOTYPE, AND/OR FUNCTION	OTHER RELATED EFFECTS
C57Bl/6 mice from Jackson Laboratories or from UC Berkeley colony treated or not at 5 wk with the broad-spectrum AVNM antibiotics cocktail (ampicillin, neomycin, metronidazole, vancomycin) for 5 d[57]	Effects of *E. Coli* O21:H+ in challenged mice:	
	↓ Muscle wasting	Activation of the NLR family CARD domain containing 4 (NLRC4) inflammasome in the white adipose tissue
	↓ *Atrogin-1* and *MuRF1* induction	

(Continued)

Table 2. (Continued)

MODELS OF INFECTIOUS, INFLAMMATORY, AND/OR IMMUNE DISORDERS			
MODELS OF GM MODULATION, DIET OR DAMAGE TYPE REFERENCES	EFFECTS OF GM ON MUSCULAR MASS, PHENOTYPE, AND/OR FUNCTION	OTHER RELATED EFFECTS	
GF or gnotobiotic Swiss Webster mice 8 to 10 wk old Colonized or not with heat-killed or live *E. Coli* O21:H+ (resistant to antibiotic AVNM cocktail), or *E. Coli* MG1655 Ad libitum standard mouse chow diet Intestinal damage with 5% DSS in drinking water for 7 d or infection with *Salmonella* Typhimurium, or pneumonic infection with *Burkholderia thailandensis*	↑ IGF-1/PI3K/P-AKT signaling in skeletal muscle	> ↑IGF-I in the white adipose tissue and serum	
BaF3 mouse model of leukemia BaF3 and controls female BALB/c mice orally supplemented or not with *Lactobacillus* species *L. reuteri* 100-23 and *L. gasseri* 311476, or *L. acidophilus* NCFM at 6 wk, the first day after BaF3 inoculation[55]	Specific effects of *L. reuteri* 100-23 and *L. gasseri* 311476:		
Chow diet	↓ Atrophy markers *atrogin-1, MuRF1, LC3, Cathepsin L* in the gastrocnemius and in the tibialis	Restoration of lactobacilli levels ↓ Serum inflammatory cytokines	
$Apc^{Min/+}$ C57BL/6J mice, model predisposed to cancer cachexia and wildtype littermates[56]	Effects of *L. reuteri*:		
CD-1 Swiss stock mice for aging studies (no transgenic predilections to cancer) Athymic homozygous nude mice Crl:NU(NCr)-$Foxn1^{nu}$ Ad libitum standard mouse chow diet Orally supplemented or not with *L. reuteri* at 8 wk	↑ Muscle weight/body weight, muscle fiber size, minimal feret's diameter (dependent of thymus FoxN1) of the gastrocnemius muscle	↓ Blood neutrophils (dependent of thymus FoxN1)	*$Apc^{Min/+}$ mouse model*: ↓ thymus weight/body weight, intestinal polyps *CD-1 mice:* ↑ thymus weight/body weight, growth hormone, survival

Abbreviations: ACC, acetyl-CoA carboxylase; CK, creatine kinase; DSS, dextran sulfate sodium; GHR, growth hormone receptor; Gpr41, G protein-coupled receptor 41 (also called FFAR3); IGFBP3, IGF-1 binding protein-3; NMJs, neuromuscular junctions; Sglt1, sodium/glucose cotransporter 1; (S)PF, (specific) pathogen-free. Only significant differences are indicated.

inhibited by H_2S (derived from sulfate or sulfur amino acids) (Table 1).[17]

Importantly, secondary and tertiary bile acids (eg, ursodeoxycholic acid) may also stimulate energy expenditure by activating TGR5 expressed in skeletal muscle, thus locally activating the type II iodothyronine deiodinase (DIO2). DIO2 generates or transforms the inactive thyroxine (T4) to active T3 thyroid hormone, a key mediator of metabolism and energy homeostasis.[18]

Isovanillic acid 3-o-sulfate, a phenolic product, was shown to promote muscle glucose uptake dose-dependently in differentiated human myoblasts, suggesting that they may also directly stimulate glucose uptake and metabolism.[19]

In addition to conjugated linoleic acid provided by meat and dairy products from ruminants, conjugated linoleic acid isomers produced by human intestinal bacteria may also display insulin-dependent positive effects on lean body mass and physical performance.[20]

Moreover, trimethylamine (TMA) is produced by bacteria from meat and from other products containing either phosphatidylcholine or L-carnitine including eggs, fish, and crustaceans. It is converted into TMA N-oxide (TMAO) which is associated with inflammatory, cardiometabolic, and renal disorders (described by Lamb and Gizard[21] and Yang et al[22]). TMA and TMAO are involved in lipid

metabolism[22] and absorbed in skeletal muscle.[23] The ratio of TMA versus total creatine—the energy substrate used for muscle contraction—has been reported to correlate with muscle function and to be decreased in patients with Duchenne Muscular Dystrophy (DMD)[24] suggesting specific roles for TMA in muscle.

Potentially harmful circulating levels of branched-chain amino acids (BCAAs) and related metabolites were identified in obese human subjects and in the gastrocnemius muscles of rats on high-fat diet as a novel metabolic "signature," associated with insulin resistance and incomplete lipid oxidation.[25] More recently, the positive correlation between serum GM-derived BCAA levels and insulin resistance was also shown in mice and humans.[26] Furthermore, increased expression of genes involved in BCAA metabolism in the tibialis anterior muscle accompanied the loss of muscle weight, hindlimb grip strength, and spontaneous activity of mice[12] (Table 2).

Imidazole propionate—which is produced by bacteria from histidine—may also be linked to insulin resistance. In a gut simulator, it was more abundant in fecal microbiota from human subjects with type 2 diabetes compared to subjects without. Moreover, its administration to mice resulted in impaired insulin signaling and glucose tolerance.[27]

Based on this knowledge, deeper molecular investigations are warranted to evaluate the actions of GM metabolites on skeletal muscle at the individual level and in association (Table 1).

Influence of Diet-Modulated Gut Microbiota on Muscle Growth and Function

Impact of the gut microbiota in protein undernutrition during juvenile growth

The pathophysiological influence of GM following undernutrition—notably insufficient protein consumption—has been studied mainly in children. Protein malnutrition—notably characterized by muscle wasting—has been associated with GM immaturity and dysbiosis in children from Malawi,[42] Bangladesh,[43] and India[44] (Figure 1).

Smith et al[42] showed that GM composition was different in Malawian twin pairs discordant for kwashiorkor. GM maturation following dietary intervention with ready-to-use therapeutic food (RUTF) was also altered in kwashiorkor compared to healthy cotwins. Furthermore, GM transplantation from kwashiorkor cotwins in GF mice fed with a "Malawian" diet was associated with a greater weight loss than those transplanted with their healthy sibling's microbiota, a difference minimized by 2 weeks feeding with RUTF. In line with this, RUTF-associated levels of SFCAs, including acetate, propionate, butyrate, and their lactate precursor, were higher in mice transplanted with the healthy co-twin's microbiota.

Likewise, transplanting microbiota from 6- and 18-month-old healthy or undernourished Malawian donors into young GF mice fed a Malawian diet revealed that immature microbiota from undernourished infants/children transmit impaired growth phenotypes.[45] Growth of mice having received microbiota from severely stunted and underweight infants was improved following either co-housing with mice having received healthy infants' microbiota, or the addition of *Ruminococcus gnavus* and *Clostridium symbiosum* to their microbiota.[45]

Nutritional intervention alone failed to restore optimal microbiome function and growth dynamics.[42,43,46] In the study by Smith et al,[42] the RUTF-induced transient maturation of microbiome metabolic function in children with kwashiorkor regressed when RUTF was stopped. Weight gain induced by RUTF was also only transitory in kwashiorkor co-twins mice, which lost weight when returning to the Malawian diet. Further to this, in the study by Subramanian et al[43] dietary intervention programs such as RUTF or Khichuri-Halwa in malnourished Bangladeshi children failed to completely restore a healthy GM and nutritional status.

Among the considered complementary intervention strategies, studies in *Drosophila melanogaster* and mouse host models have highlighted that *Lactoplantibacillus* (formerly *Lactobacillus*) *plantarum* (*L. plantarum*) promotes linear growth.[47,48] In the *Drosophila* model, such beneficial outcome results, at least in part, from the capacity of *L. plantarum* to promote the expression of intestinal peptidases and from the consequent increase of dietary protein assimilation and sustained host TOR (target of rapamycin) signaling pathway.[49]

These data highlight that in the context of insufficient protein consumption, GM composition and activities are related to the nutritional status. They call for further elucidation of the molecular mechanisms promoting host-microbiome interaction to favor long-term growth recovery with gain of muscle mass in response to intervention. They will notably involve the evaluation of the effects of microbiota targeting, for example, with *L. plantarum*, on colon health and butyrate production. Indeed, butyrate promotes intestinal epithelial cell health and exerts anti-inflammatory and pro-anabolic effects (for review see Cani,[4] Canfora et al,[9] and Ticinesi et al[50]).

Influence of the gut microbiota on muscle function in inflammation-associated chronic diseases

Chronic diseases, generally associated with a proinflammatory state and with lack of physical activity, lead to a reduction in muscle mass and strength—a comorbidity increasing the risk of mortality.[50,51] Regardless of the well-recognized impact of GM on chronic diseases, it also appears that GM influences the course of muscle fate in the context of these diseases, and as such their outcomes (Table 2).

As an initial proof of concept, Bäckhed et al[52] showed that resistance of GF mice to obesity induced by a high-fat, high-sugar Western diet for 5 to 8 weeks, was related to reduced hepatic glycogenesis, increased fatty acid oxidation in the gastrocnemius muscle, and increased locomotor activity. Higher

AMPK (AMP-activated protein kinase) and ACC (Acetyl-CoA carboxylase) phosphorylation, and carnitine palmitoyltransferase activity in the muscle was linked to higher intestinal production of the LPL (lipoprotein lipase) inhibitor FIAF (fasting-inducible adipose factor), and higher serum triglyceride levels. Highlighting the cooperation of organs in the GM/muscle axis, these results invite to further characterize the relations between GM and intestinal FIAF-dependent signaling.

More recently, in the context of obesity, transplantation of GM from obese and normal pigs was able to transfer the fiber characteristics and lipid metabolic profiles of skeletal muscle to GF mice.[53]

Besides diet-induced obesity, few studies suggest that targeting GM with specific food or biotics could represent an interesting strategy to restore muscle function during chronic diseases such as cancer, diabetes, or advanced liver diseases.

A recent case-control study indicated that soy-whey blended protein improved muscle function through GM in a subset of patients with hematological malignancies, who have failed to enhance muscle function after hematopoietic stem cell transplantation.[54] Improvement was associated with changes in fecal abundance of *Streptococcus, Ruminococcus*, and *Veillonella* and prediction of increased microbial activities in the pentose phosphate pathway and amino acid biosynthesis—with a putative impact on muscle protein anabolism.

In mouse models of acute leukemia and cachexia, GM restoration with specific strains (ie, *L. reuteri* 100-23 and *L. gasseri* 311476) decreased systemic inflammation and muscle atrophy markers in the gastrocnemius and tibialis in a strain- and species-specific manner.[55] *L. reuteri* was further shown to lower systemic indices of inflammation and inhibit cachexia linked to age.[56]

Alteration of intestinal permeability in response to dysbiosis was shown to take part in chronic metabolic and inflammatory disorders and may contribute to muscle pathophysiology.[5,50,51] In line with this, Schieber et al[57] used mouse models of intestinal physical damage or infection to demonstrate that a specific strain of *Escherichia coli* prevents muscle atrophy. This effect is mediated by the production of the insulin-like growth factor-1 (IGF-1) in white adipose tissue via a mechanism dependent on the NLRC4 inflammasome, and the consequent activation of phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) pathway in skeletal muscle.[57]

At the level of the organism, further studies are expected to establish the beneficial effects of nutrients and probiotics on the intestine-muscle axis and the regulatory pathways involved in such effects.

Influence of the gut microbiota on skeletal muscle strength and fitness in young, healthy subjects

Recent randomized studies on healthy humans and animals have indicated that probiotics and dairy fermented milk elicit metabolic and weight benefits.[58,59] By modifying microbiome function, they increase notably the percentage of lean body mass. Few studies evaluating probiotics potential on muscle capacities have provided scattered but encouraging results. In murine models, supplementation with a strain of *L. plantarum* increased muscle mass, increased the slow and oxidative muscle phenotype associated with muscle endurance in an exhaustive swimming test, and decreased oxidative lesions[60] (Table 2). However, it failed to increase endurance when inoculated in GF mice, suggesting that its effects on muscle capacities require cooperation with other bacteria.[61] Furthermore, supplementation during training with *Bifidobacterium longum* subsp. *Longum* OLP-01 (*B. longum* OLP-01), a strain isolated from an elite weightlifting Olympic gold medalist, increased grip strength and endurance.[62] In human studies, a strain of *Bacillus coagulans* (*B. coagulans*) increased performance and recovery following a damaging exercise bout in adult male subjects doing recreational training for at least 3 months.[63] In addition, *L. plantarum* PS128 improved endurance running performance in triathletes, an effect which was associated with changes in the microbiota composition and higher levels of SCFAs acetate, propionate, and butyrate.[64] In line with this, depletion of GM using antibiotics was recently associated with decreased muscle capacity, notably in link with an alteration of glucose homeostasis regulatory pathways[65,66] (Table 2).

Several studies also point to a positive relation between fitness and eubiosis. Notably, in healthy humans between 18 and 35 years old, peak oxygen uptake was assessed in a ramp maximal exercise test, and correlated with increased GM diversity independently from diet.[67] GM diversity was also associated with increased production of fecal butyrate and high levels of key butyrate-producing taxa (Clostridiales, *Roseburia*, *Lachnospiraceae*, and *Erysipelotrichaceae*).

While these results encourage further research to better identify beneficial nutrients and dietary supplements for different types of populations, increasing evidence suggests that exercise itself also exerts a positive influence on GM composition (discussed below).

Modulation of the Gut Microbiota by Exercise

Metabolic and inflammatory states, muscle function and GM are interdependent. Intervention studies in human and animal models show that GM composition and activity are not only influenced by diet[68-70] (and above), but also by physical activity such as fitness (Mach and Fuster-Botella[71] and Shin et al[72] and references therein). Globally, exercise promotes microbial diversity with species potentially beneficial to host health.[71]

In relation to a human study by Estaki et al,[67] higher levels of butyrate or butyrate-producing taxa were reported in mice voluntary running on a free wheel[73] and in voluntary running rats fed with a 25% casein-sucrose diet.[74] In addition, improvements in GM composition and physical functioning elicited by 6 weeks of aerobic exercise training were observed in conjunction with increased SCFA-producing capacity and main fecal

SCFAs (acetate, propionate, and butyrate) in young lean adult humans, at a much higher extent than in obese participants.[75] These conclusions warrant similar studies in older adults.

Exercise favors the butyrate-producing species *Faecalibacterium prausnitzii* (*F. prausnitzii*, Clostridiales order),[71,73,76] whose decrease may be associated with high frailty (referenced in Ticinesi et al[50] and Saraswati and Sitaraman[77]). In addition to the benefits brought by butyrate, *F. prausnitzii* promotes oxygen detoxification and lowers the oxygen tension in the lumen.[73] Importantly, in mice either fed a normal diet (lean) or a high-fat diet (obese) for 12 weeks, *F. prausnitzii* was only detected in mice exercising on a free running wheel.[73]

Running distance on wheel of mice and time spent in brisk walking of elderly women were also associated with an increased abundance of intestinal *Bacteroides* spp.[78,79] *Bacteroides* spp. have been shown to be reduced in aging[80] and inversely related to obesity linked to high-fat and high-carbohydrate diets.[81] In line with this, in mice fed a low fat or an high-fat diet, a modest inverse relationship was found between the ΔCt Bacteroidetes: ΔCt Firmicutes ratio and the recorded voluntary distance on wheel.[78]

Lactobacillus (Firmicutes phylum, Lactobacilliales order), *Streptococcus* (Firmicutes phylum, Lactobacilliales), *Bifidobacterium* (Actinobacteria phylum, Bifidobacteriales order), which are components of probiotic yogurts and commercial dietary supplements, produce lactic acid—a major GM metabolite precursor of SCFAs.[10,71]

Some species/strains of *Lactobacillus* or *Bifidobacterium* have been shown to favor the integrity of the intestinal barrier by increasing the expression of tight junction proteins[71] and to increase muscle weight and muscle fiber size[56] (see above). Interestingly, fecal abundances of *Lactobacillus* and/or *Bifidobacterium* genus were increased in rats fed ad libitum and freely running on a wheel compared to the other groups (food restricted groups and ad libitum fed group without wheel access),[82] as well as in normal mice or obese rats exercising moderately on a treadmill.[83,84]

In this latter model, *Streptococcus*, of which certain species are pathogenic, was decreased after moderate exercise in non-obese Wistar rats.[83] Besides, *Ruminococcus*, a dominant genus in human enterotype 3, was significantly correlated with blood lactate concentration.[83] Lactate may represent a biomarker for frailty.[85] However, the relations between frailty and a set of parameters including diet, exercise, aging, and the abundance of specific genus are not clearly defined yet.[50,86]

Growth of the genus *Prevotella* (Bacteroidetes phylum), a mucin degrader enriched in human enterotype 2, has been reported to be favored (in association or not with *Bacteroides*) with a bacterial network (including possibly *F. prausnitzii*) by a regime rich in vegetable fibers, prebiotics which favor de facto the microbial diversity and a lesser inflammatory profile.[29,87,88] However, 6 weeks of low-intensity treadmill running lowered slightly the *Bacteroides*/*Prevotella* spp genus cecal microbiota in db/db mice compared to sedentary controls.[84]

Reduction in the *Bacteroides*/*Prevotella* group has been observed in elderly individuals following hospitalization and in a small cohort with high frailty scores (reviewed by Saraswati and Sitaraman[77]), and *Prevotella* (as *Ruminococcus*) was reported to be less abundant amongst frail long-term care residents compared to community-dwelling elderly individuals.[89] However, calling for further analyses, the average relative abundance of some taxa including *Prevotella* in the fecal microbiota from inpatients aged 83 ±8 years was significantly correlated with the number of drugs and an index of frailty/disability.[90]

Taken together, these data encourage extensive studies to define the virtuous feedback between exercise and GM, with benefits on intestinal inflammation and metabolic state, and on muscle homeostasis and function. Such studies may further explore the relation with the risk of infection from opportunistic pathogens, for example, *Enterobacter*, which has been associated with comorbidity in hospitalized patients.[90] Furthermore, they may target specifically low taxonomic ranks, such as the species *A. muciniphila*, which is known for its benefits against the metabolic syndrome and may be modulated by physical activity.[71]

Finally, as these data suggest a causal influence of muscle maintenance and development on GM, they also encourage studies on the impact of loss of muscle function on GM. Providing an additional line of evidence for this causal relationship, 22 days of hindlimb unloading in mice was recently shown to induce GM dysbiosis, an effect which was alleviated by VSL≠3.[91] Further analyses should lead to identify strategies against dysbiosis, especially for sedentary people.

Perspectives: Balancing the Gut Microbiota to Prevent or Treat Muscle Loss Occurring During Aging or Neuromuscular Diseases

Treatment of sarcopenia linked to aging

Primary sarcopenia (ie, loss of muscle mass and function related to aging alone) usually precedes frailty. Both primary sarcopenia and frailty are strong predictors of morbidity, disability, and death in older people.[92] A recent meta-analysis indicated that bone health and calcium homeostasis are critically associated with the onset of sarcopenia and physical frailty.[93]

To counteract sarcopenia, vitamin D supplementation is recommended in addition to calcium for men and women 60 and over to "reduce the risk of falling associated with postural instability and muscle weakness" (EFSA claim). Supporting this claim, vitamin D supplementation to elderly persons in long-stay geriatric care units or community-dwelling displayed additional benefits to calcium alone in improving musculoskeletal function (including muscle strength) and risk of falling.[94,95] A recent meta-analysis lacked evidence of the effect of vitamin D on muscle strength, but it was based on few studies with or

without calcium supplementation, in which most had a small number of participants.[96] There is therefore a need for further analyses to establish a relation between GM, calcium absorption and bone mineralization. Probiotics supplements—notably with *L. reuteri* strain—have already been shown to effectively reduce vitamin D deficiency,[97] while prebiotics supplements are increasing biosynthesis of provitamin D3 (7-dehydrocholesterol).[98]

Additional nutritional, pharmacological, and/or multimodal strategies are to be considered. Among them, protein pulse feeding, or L-citrulline combined with exercise have been shown to be efficient for sets of seniors.[99,100] The drug candidate Sarconeos (BIO101), an activator in muscle cells of the angiotensin receptor type MAS-R, is currently being tested in Phase 2b clinical trial (SARA-INT) (https://www.biophytis.com/en/).

As a potentially interesting supplement in relation with the GM, N-acetyl-L-cysteine, a precursor of the biologic antioxidant glutathione, was shown to inhibit muscle fatigue in humans[101] and to display male-specific effects on *Drosophila* lifespan, stress-resistance and locomotor activity.[102] Interestingly, the benefits of N-acetyl-L-cysteine against dysbiosis and glucose metabolic disorders were recently shown in high-fat diet-fed mice.[103]

In addition, apelin was identified as a diagnostic tool of early sarcopenia and a potential target to prevent muscle weakness in a study using mouse models and participants of Multidomain Alzheimer Prevention Trial (MAPT study) and Life-P.[104] Production of the peptide is induced by muscle contraction in an age-dependent manner and increases muscle strength. Pleading for further investigation on the GM/apelin pathway, the GM-derived compound LPS was reported to interact with the endocannabinoid system to regulate inflammation and apelin signaling in adipose tissue.[105]

Finally, the SPRINTT consortium is identifying subjects with physical frailty and sarcopenia and testing the efficacy of multicomponent interventions—with physical exercise, proper nutrition, and technological tools—in the prevention of physical frailty and mobility.[106]

Further research examining the contribution of GM to the musculoskeletal benefits offered by these strategies and the potential benefits of biotic supplements is expected. These studies will require a better knowledge on the relation between GM dysbiosis and sarcopenia, a knowledge still extremely limited.[50] Recently, a comparison study between sedentary older adults (70-85 years) assessed with the short physical performance battery (SPPB) test, revealed higher levels of *Prevotellaceae*, *Prevotella, Barnesiella*, and *Barnesiella intestinihominis* in people with higher muscle strength, compared to adults with lesser muscle strength (defined as low-functioning).[107] The GM causal effect translated in mice as grip strength was significantly higher in mice colonized with microbiota from high-functioning, when compared with low-functioning adults (Table 2). The effects may notably account from the production of SCFAs acetate, propionate, and butyrate encoded by genes contained in *Barnesiella* and Prevotellaceae.[107] In line with this, in the study of Walsh et al[108] butyrate treatment protected C57Bl/6 female mice from aged-linked atrophy in hindlimb muscle. This effect was linked to higher glucose tolerance and oxygen consumption, and improved markers of mitochondrial biogenesis, oxidative stress, and apoptosis in muscle. Interestingly, ubiquitin-mediated proteasomal degradation was not affected.

In another study with mice, 12 weeks of probiotic supplementation in aged mice with either *L. casei* LC122 or *Bifidobacterium longum* increased both muscle function (evaluated using grip strength and forced swimming tests) and cognitive ability.[109] This was related to fecal microbial changes, as well as improved gut barrier permeability, liver lipid metabolism, and oxidative and inflammatory profiles.

As further support to the strategy of GM targeting, cross-sectional studies have positively associated dietary fiber intake with handgrip strength and physical functioning in old adult humans.[110,111] Furthermore, in a randomized controlled trial performed on nursing home residents, prebiotics containing inulin and fructo-oligosaccharides significantly improved hand-grip strength compared to placebo.[112] Fecal GM was not assessed in this study, however, these prebiotics are known to exert beneficial effects on GM, notably through the increased production of SCFAs.[50]

In these avenues of research, studies examining the direct relation between GM and muscle fitness in healthy subjects will help to improve the general scheme of nutritional and lifestyle influences and recommendations.

Targeting the gut microbiota to prevent muscle atrophy in myopathies and amyotrophic lateral sclerosis (ALS)

Genetic myopathies such as DMD, Becker muscular dystrophy (BMD), limb-girdle muscular dystrophy (LGMD), and Steinert disease (myotonic dystrophy type 1 or MD1) are linked to metabolic and inflammatory alterations. In DMD and LGMD patients, drastic decreased protein assimilation and increased protein catabolism were also reported,[113] from which BMD patients would be preserved.[114] Insulin resistance in MD1 eventually leads to dys-regulation of protein metabolism.[115] Alterations of lipid and muscle metabolisms also feature these pathologies.[116-118] Notably, mitochondrial dysfunction, reduced adenosine triphosphate (ATP) levels, increased oxidative stress, and basal metabolic rate have been described in skeletal muscles of DMD and BMD patients.[113,118] Alterations of systemic inflammation also characterize these diseases, with notably increased levels of TNFα in muscle biopsies of DMD patients compared to healthy subjects. Strikingly, higher levels are related to better muscle function,

pointing out the complexity of inflammation processes evolving along with the disease.[119] Endocrine disturbances such as hypogonadism, low levels of testosterone, and elevated levels of luteinizing hormone have also been reported in DMD, BMD, and MD1 patients (reviewed by Cruz Guzmán et al[120]). Nonsteroidal anti-inflammatory medications can prevent pain in MD1 patients,[115] and corticosteroids are used to stabilize motor functions of patients with DMD and BMD.[121]

Given the impact of GM on inflammatory, endocrine, and metabolic functions, there is a need for further experimental research and computer modeling aiming to identify novel personalized tools targeting GM for the maintenance of skeletal muscle in the context of these genetic diseases.

Further studies are also expected to evaluate the influence of GM on amyotrophic lateral sclerosis (ALS), as indicated by the recent published data on GM alteration in ALS patients.[122] This disease is characterized by high levels of systemic TNFα and IL-6,[123] which have been associated with GM-dependent metabolic syndrome and aging. Second, animal models of ALS have demonstrated a spatiotemporal alteration of glial cells and macrophages, which generate a local chronic inflammatory state deleterious for surrounding neurons.[124] GM modulation also impacts lymphocytes and glial cells in multiple sclerosis,[11] and the reactivation of the immune system related to relapsing events (clinicals trials reviewed by Schepici et al[125]). Thus, strategies targeting GM to counteract these alterations are promising as therapeutic interventions to treat these diseases.

Conclusion and Perspectives

Further studies in healthy and diseased subjects will help to better understand the microbiota-skeletal muscle axis, its underlying mechanisms (at metabolic, immune, inflammatory, hormonal, and neuro-transmission levels) and pathophysiological outcomes.

It will further characterize the regulatory effects exerted by specific bacteria on muscle protein synthesis and degradation processes. As mentioned above, counter-influence of microbiota on muscle loss has been associated with increased gene expression of atrophy markers, in particular the muscle-specific E3 ubiquitin ligases, muscle ring finger 1 (*MuRF1*) and *atrogin-1*.[12,57,65] Playing a crucial role in skeletal muscle atrophy,[126] their expression is downregulated by the GM-dependent IGF-1/PI3K/AKT pathway.[47,57] Interestingly, while MurF1 has been involved in the breakdown of myofibrillar proteins (actin, myosin heavy chain),[127,128] the IGF-1/PI3K/AKT pathway and atrogin-1 have been shown to control protein synthesis.[129,130] Further, as aging and butyrate may affect hindlimb muscle atrophy without regulating *MuRF1* and *atrogin-1*,[108] it would also be of interest to examine alternative pathways involved in muscle maintenance.

For this axis and related others (eg, GM-metabolism per se or GM-nervous system), it will be important to evaluate the possible "double-edged sword" feature of specific bacteria and their networks, which depend on the context. As discussed by Cani,[4] some bacteria such as *Prevotella copri* (*P. copri)* and *A. muciniphila* have been associated with either good or bad metabolic outcomes. *P. copri* has been both positively and negatively related to glucose tolerance and insulin sensitivity. Moreover, although *A. muciniphila* levels are generally considered to be inversely related to metabolic disorders in genetically obese and diabetic mice and diet-induced obese mice, few studies have reported their increased abundance in mice fed a high-fat high-sucrose diet.[4] Microbiota-based intervention studies and in silico or mathematical modeling—taking into account bacterial cross-talks—should improve personalized counseling in terms of nutrients, supplements, and/or physical activity against muscle weakness. Finally, current and future strategies depend certainly, to a large extent, on the gut microbiota.

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