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Role of the Gut Microbiome in Skeletal Muscle Physiology and Pathophysiology

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Abstract

Purpose of Review This review aims to summarize the recent findings about the contribution of the gut microbiome to muscle pathophysiology and discuss molecular pathways that may be involved in such process. Related findings in the context of cancer cachexia are outlined.

Recent Findings Many bacterial metabolites have been reported to exert a beneficial or detrimental impact on muscle physiology. Most of the evidence concentrates on short-chain fatty acids (SCFAs), with an emerging role for bile acids, bacterial amino acid metabolites (bAAms), and bacterial polyphenol metabolites. Other molecular players worth considering include cytokines, hormones, lipopolysaccharides, and quorum sensing molecules.

Summary The current literature clearly establishes the ability for the gut microbiome to modulate muscle function and mass. The understanding of the mechanisms underlying this gut-muscle axis may lead to the delivery of novel therapeutic tools to tackle muscle wasting in cancer cachexia, chronic kidney disease, liver fibrosis, and age-related sarcopenia.

Keywords Fibroblast growth factor 19 · Takeda G protein–coupled receptor 5 · P-cresol sulfate · Indoxyl sulfate · Kynurenine · Urolithin

Introduction

The skeletal muscle is a tissue that represents 30–40% of total body mass in healthy humans. Striated skeletal muscles are primarily composed of myofibers, whose number and size determine the muscle mass. The size of the myofiber results from the balance between protein synthesis, protein degradation, and regeneration processes [1]. The past few years have seen increasing awareness of the prognostic value of changes in the skeletal muscle compartment in various chronic diseases, including cancer and liver fibrosis [2•, 3, 4]. The best option to treat muscle loss seems to be a multimodal approach, which would consist of nutritional support, physical exercise, and pharmacological agents [5, 6]. However, the nature of these pharmacological and nutritional tools remains largely undefined [4, 7]. In this context, the gut microbiota appears as a new and promising target [8–11].

The terms "microbiota" and "microbiome" are overlapping but not similar. The microbiota comprises all living members forming the microbiome. This includes bacteria, archaea, fungi, algae, and small protists [12]. The term "microbiome" combines both the microbiota (community of microorganisms) and their "theatre of activity", involving the whole spectrum of molecules produced by the microorganisms, including their structural elements (nucleic acids, proteins, lipids, polysaccharides), metabolites (signaling molecules, toxins, and organic and inorganic molecules), and molecules produced by coexisting hosts and structured by the surrounding environmental conditions [12].

The gut microbiota, localized in the gastrointestinal tract of mammals, - the main site of the human microbiota - is a key regulator of host metabolism and immunity [13, 14]. The essential role of the gut microbiota in health and disease has generated massive interest in modulating its composition and metabolic function, using mainly prebiotics, probiotics, and antibiotics [8, 15•]. Prebiotics are now defined as substrates selectively utilized by host microorganisms, conferring a health benefit [16], whereas probiotics are defined as live

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microorganisms which, when administered in adequate amounts, confer a health benefit on the host [17]. The appreciation that the gut microbiota influences health has also prompted tremendous interest in the mechanisms underlying this crosstalk and the therapeutic opportunities that may ensue from them. Many of the effects that microbes exert on host physiology are mediated by metabolites that are either produced by the microbes or derived from the transformation of environmental (e.g., dietary) or host molecules [18, 19•, 20].

In this review, we first introduce key evidence for a gut microbiota–muscle axis in mice and humans. We then elaborate on the mechanisms underlying such crosstalk, focusing on bacterial metabolites. Finally, the gut microbiota–muscle axis is discussed in the context of cancer-associated muscle atrophy, often referred to as cancer cachexia.

Proof-of-Concept of a Gut Microbiota–Muscle Axis in Mice and Humans

One of the first pieces of evidence that the gut microbiota influences muscle physiology comes from a seminal paper from the Gordon group [21]. In this publication, the authors reported that the conventionalization of C57BL/6 germ-free mice (i.e., administration of a whole complex microbiota to mice devoid of any microbes) induces a 7% decrease in lean body mass. Gut microbiota depletion (using C57BL/6 germ-free mice [22••]) or gut microbiota dampening (through broad spectrum antibiotic treatment [23••]) was later on also associated with alteration of muscle function (muscle atrophy [22••], higher fatigability [23••], lower running endurance [23••]) and muscle metabolism (reduction in glycogen content in one study [23••] and increase in glycogen content in the other [22••]). Such changes in muscle mass may be mouse strain specific, as no difference in muscle mass was found in C3H conventionalized mice compared to germ-free littermates [24], and/or antibiotic cocktail dependent, as administration of a different cocktail did not change the lean mass in mice [25]. Interestingly, mono-colonization of germ-free mice with different bacterial strains revealed a strain-specific ability to improve exercise endurance [26] while several probiotics improved muscle mass, muscle strength, endurance performance, and/or glycogen storage in conventional mice [27, 28, 29, 30, 31, 32•].

In humans, several reports also support the existence of such a gut-muscle axis. Among others, transfer of fecal microbiota from high-functioning older adults to germ-free mice increased the muscle strength of these mice compared to mice colonized with the fecal material of low-functioning adults [33]. However, this transfer did not impact the whole-body lean mass and the treadmill endurance capacity. Furthermore, Buigues and colleagues reported that administration of prebiotics, including inulin and fructo-oligosaccharides, improves handgrip strength in elderly people with frailty [34]. In a pilot study including 8 recreational runners, administration of *Lactobacillus plantarum* PS128 for 4 weeks before a half-marathon reduced muscle damage and oxidative stress associated to the half-marathon, without impacting exercise capacity [35]. Other probiotics with muscle- and exercise-enhancing properties have also been reported [31, 32•].

Of note, some reports found no impact of a gut microbiota modulation on muscle parameters in humans. For instance, short-term antibiotic treatment had no effects on fasting and postprandial forearm substrate metabolism and blood flow in obese men with impaired glucose metabolism, suggesting that the gut microbiota does not impinge on these processes, at least in a short timeframe [36]. In another study, inulin was administered to 12 prediabetic patients for 6 weeks. Although inulin administration reduced markers of insulin resistance as compared to the placebo, it did not affect glucose oxidation, fat oxidation, pyruvate oxidation, or substrate preference measured ex vivo in muscle biopsies [37]. Lack of effects has also been reported for several probiotics [32•].

Mechanisms Underlying the Contribution of the Gut Microbiota to Muscle Physiology

At the molecular level, Bäckhed and colleagues reported that muscles of germ-free mice fed a diet high in fat and sucrose are characterized by an increase in AMP-activated protein kinase (AMPK) activity, carnitine-palmitoyl transferase (CPT1) activity, and medium-chain acyl-CoA dehydrogenase (*Mcad*) expression [38]. CPT1 catalyzes the rate-limiting step for entry of long-chain fatty acyl-CoA into mitochondria while MCAD is a mitochondrial enzyme that catalyzes the initial step of the β-oxidation of medium-chain fatty acids. Such changes suggest that the absence of gut microbiota promotes fatty acid catabolism. Twelve years later, Lahiri and colleagues reported similar changes in AMPK activity but only trends towards a reduced expression of *Cpt1b* and *Mcad*, in the muscle of germ-free mice fed a standard chow, as compared to pathogen-free mice [22••]. They also reported in the muscle of germ-free mice (i) a reduction in the expression of insulin-like growth factor 1 (*Igf1*), (ii) an increase in atrogenes (*muscle-specific RING finger protein 1* (*Murf-1*), *Atrogin-1*), (iii) a reduction in the expression of genes involved in differentiation (*myogenic differentiation 1* (*MyoD1*), *myogenin*), (iv) signs of an altered mitochondrial function (reduced activity of the succinate dehydrogenase, SDH; reduced levels of mitochondrial DNA; reduced expression of the mitochondrial transcription factor A *Tfam*)-such changes were not observed upon antibiotics treatment [23••]-z, (v) a reduction in the expression of *Rapsyn* and *LDL receptor–related protein 4* (*Lrp4*), two proteins important for neuromuscular junction assembly and

function, and (vi) signs of an activation of the branched-chain amino acid catabolic pathway. Metabolite profiling using proton nuclear magnetic resonance revealed higher levels of alanine and glycine in the skeletal muscle of germ-free mice compared to pathogen-free mice [22••]. The metabolic origin of these amino acids (AAs) and their contribution to the muscle alterations observed in germ-free mice remain unclear at this stage.

By which mechanisms the gut microbiota is modulating muscle physiology is a recent research area. The main metabolites studied in this context are short-chain fatty acids. Other bacterial metabolites that may play a role in muscle physiology are emerging, including bile acids, bacterial amino acid metabolites, and metabolites originating from the bacterial transformation of polyphenols (Fig. 1). Additional molecular players beyond bacterial metabolites can also be envisioned and are discussed below. Lastly, we can envision that the gut microbiome impacts muscle physiology indirectly, through a modulation of third-party tissues, such as the adipose tissues [39].

Short-Chain Fatty Acids (SCFAs) SCFAs are produced by bacterial fermentation of carbohydrates and, to a lower extent, of proteins. The main SCFAs are acetate, propionate, and butyrate, which exert pleiotropic effects on host metabolism and immunity [40–42]. How SCFAs can impact muscle physiology has been recently extensively reviewed [43••]. In summary, SCFAs have been shown to influence lipid, carbohydrate,

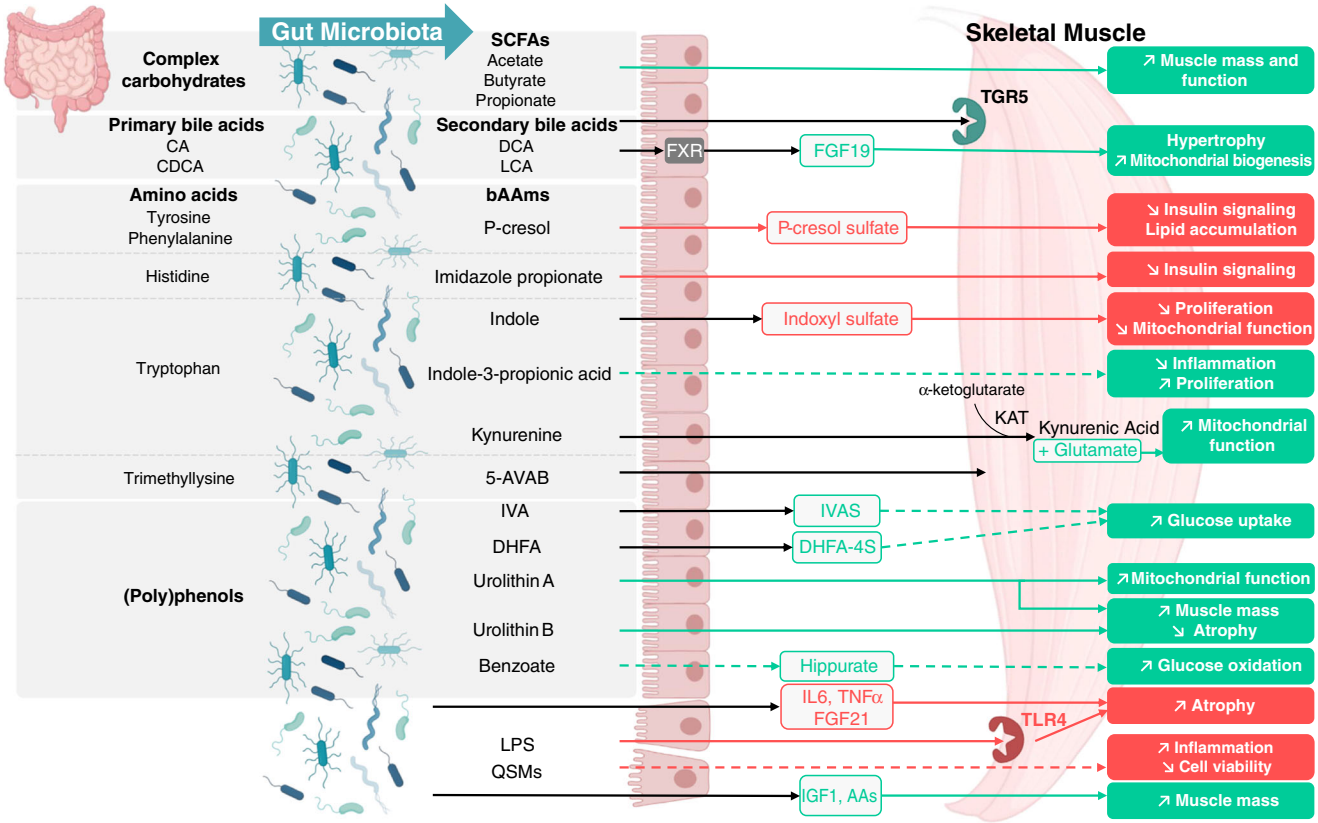

Fig. 1 Mechanisms underlying the contribution of the gut microbiota to muscle physiology. Nutrients are transformed through gut microbiota catabolism into metabolites. These metabolites cross the gut barrier, and can, directly or via their transformation into co-metabolites by the host, act on skeletal muscle metabolism. Bile acids can also act indirectly by activating FXR in intestinal cells which leads to the release of FGF19. Gut microbiota modulation can also impact the production of pro-inflammatory cytokines such as IL6 and TNFα involved in muscle regulation. LPS, a bacterial wall component, can pass the gut barrier and its translocation is fostered when the gut permeability is altered, as it is the case in several pathological conditions. TLR4 activation by LPS induces muscle atrophy. QSMs mediate the intra-bacterial communication and are released by bacteria upon stress conditions. Some of these QSMs can reach the systemic circulations and impair muscle function in vitro. Levels of amino acids and growth factors such as IGF1 and FGF21 have been shown to be modulated by the gut microbiota and are known to modulate the muscle functions. Green, red, and black arrows indicate respectively the pathways associated with beneficial effects, detrimental effects, and contradictory or unknown effect on muscle. Dotted arrows are used for effects reported exclusively through in vitro studies. SCFAs, short-chain fatty acids; CA, cholic acid; CDCA, chenodeoxycholic acid; DCA, deoxycholic acid; LCA, lithocholic acid; TGR5, Takeda G protein–coupled receptor 5; FXR, Farnesoid X receptor; FGF19, fibroblast growth factor; bAAms, bacterial amino acid metabolites; KAT, kynurenine aminotransferases; 5-AVAB, 5 aminovaleric acid betaine; IVA, isovanillic acid; IVAS, isovanillic acid 3-O-sulfate; DHFA, dihydroferulic acid; DHFA-4S, dihydroferulic acid 4-O-sulfate; IL6, interleukin-6; TNFα, tumor necrosis factor-α; FGF21, fibroblast growth factor 21; LPS, lipopolysaccharides; TLR4, Toll-like receptor 4; QSMs, quorum sensing molecules; IGF1, insulin-like growth factor 1; AAs, amino acids

and protein metabolism in skeletal muscle tissues both in vitro and in vivo in mice. Furthermore, SCFAs have the potential to increase skeletal muscle mass retention, blood flow, and insulin sensitivity, and to preserve an oxidative phenotype. These effects appear to be mediated by the activation of the AMPK, the peroxisome proliferator–activated receptor δ (PPAR-δ), and the peroxisome proliferator–activated receptor γ coactivator-1α (PGC-1α), and the inhibition of histone deacetylases (HDACs) [43••]. Among other studies, Walsh and colleagues reported that butyrate prevents many muscle alterations related to aging [44]. Chronic administration of butyrate to conventional old mice protected against muscle atrophy in hindlimb muscles, prevented intramuscular fat accumulation, increased markers of mitochondrial biogenesis, and reduced markers of oxidative stress and apoptosis. Administration of a mix of SCFAs to germ-free mice increased the muscle weight of one muscle out of four, increased the hindlimb grip strength, and reduced the muscle expression of *Atrogin-1* while inducing *Murf-1* [22••]. Furthermore, SCFA administration to germ-free mice did not modify the muscle expression of *Tfam*, *Rapsyn*, *Lrp4*, and genes involved in mitochondrial function. This observation that treating germ-free mice with short-chain fatty acids only partly reversed the skeletal muscle impairments seen in these mice led to the postulate that other mechanisms are at play.

One of the best demonstrations to date of the in vivo contribution of gut microbiota–derived SCFAs to muscle function has been brought by the Kostic team [45•]. They observed an increase in the *Veillonella* relative abundance in marathon runners post-marathon and isolated a strain of *Veillonella atypica* from stool samples. Inoculation of this strain into mice significantly increased exhaustive treadmill run time. Using ^{13}C3-labeled lactate in mice, they demonstrated that serum lactate crosses the epithelial barrier into the lumen of the gut. As *Veillonella* utilizes lactate as its sole carbon source and produces propionate, the authors showed that intrarectal instillation of propionate reproduces the increased treadmill run time performance observed with *V. atypica* gavage. Taken together, the authors concluded that *V. atypica* improves run time via its metabolic conversion of exercise-induced lactate into propionate, which is thought to serve as an energy source to other metabolic organs.

These set of studies clearly put forward the interest to promote SCFA production in human subjects to improve muscle physiology. However, at this stage, only associations have been put forward in observational cohorts [46, 47] and interventional trials demonstrating an impact of gut microbiota–derived SCFAs on muscle physiology in humans are lacking.

Bile Acids Primary bile acids are bile acids that are produced in hepatocytes. The main primary bile acids are cholic acid (CA) and chenodeoxycholic acid (CDCA). Secondary bile acids include all bile acids that are produced through the microbial metabolism of primary bile acids. The main secondary bile acids are deoxycholic acid (DCA) and lithocholic acid (LCA) [48•, 49•]. These bile acids can either be in their free form or conjugated to aAA through a hepatic reaction.

Bile acids are potent signaling molecules exerting diverse actions through bile acid–activated receptors [48•, 49•]. Among them, the Takeda G protein–coupled receptor 5 (TGR5; also known as GPBAR1) is of particular interest for muscle physiology, with some contradicting results. Indeed, the activation of TGR5 in muscle cells leads to oxygen consumption and increased energy expenditure through the activation of the cAMP-dependent iodothyronine deiodinase 2 (DIO2) [50]. Sasaki and colleagues showed using gain- and loss-of-function models that TGR5 fosters muscle differentiation and hypertrophy while reducing the ubiquitin-proteasome pathway [51]. In contrast, Abrigo and colleagues showed that TGR5 is mandatory for the in vitro pro-atrophy effect of CA and DCA [52]. Finally, muscle-specific overexpression of TGR5 improved glucose clearance in glucose-intolerant mice [53]

A second molecular player that links bile acids to muscle physiology is the Fibroblast Growth Factor 19 (FGF19). FGF19, the human ortholog to mouse FGF15, is a protein produced in the intestine under the transcriptional control of the Farnesoid X receptor (FXR), another bile acid receptor. Interestingly, FGF19 caused skeletal muscle hypertrophy in vitro and in vivo in healthy mice [54, 55] while ileal FXR activation with the intestine-specific FXR agonist fexaramine increased skeletal muscle protein synthesis in aged mice [55]. Among others, FGF19 promoted the expression of proteins involved in mitochondrial biogenesis (e.g., PGC-1α and TFAM) and reduced ROS production upon palmitic acid–induced stress [56].

Bacterial Amino Acid Metabolites (bAAms) Although most dietary AAs and peptides are absorbed in the small intestine, substantial amounts can enter the large intestine. There, these AAs can be metabolized in to bAAms by bacteria. Only a few bAAms have been linked to a change in muscle cell physiology and/or molecular pathways. These include p-cresol sulfate, imidazole propionate, and indoxyl sulfate. Additional bAAms may also be of interest in this context, such as kynurenine, 5 aminovaleric acid betaine, and phenylacetylglutamine.

P-cresol arises from the bacterial transformation of tyrosine and phenylalanine and is extensively conjugated in p-cresol sulfate and p-cresol glucuronide, two uremic toxins. In vivo, p-cresol sulfate triggered, among others, ectopic redistribution of lipid and altered insulin signaling in the skeletal muscle [57]. In vitro experiments using C2C12 mouse myotubes support a direct effect of p-cresol sulfate on insulin signaling pathways [57]. Furthermore, p-cresol sulfate augmented

hypertrophy and fibroblast collagen synthesis in neonatal rat cardiac myocytes [58]. P-cresol sulfate also exhibited anti-proliferative and/or pro-apoptotic effects in cardiomyocytes in vivo and in H9C2 cardiomyoblasts [59, 60].

Imidazole propionate derives from the microbial fermentation of histidine and can induce insulin resistance by impairing insulin signaling at the level of the insulin receptor activation and subsequent activation of mammalian target of rapamycin complex 1 (mTORC1) [61]. Among others, the authors showed that administration of imidazole propionate to germ-free mice for 3 days increased S6 kinase 1 (S6K1) phosphorylation, a marker of mTORC1 activation, and reduced the protein level of insulin receptor substrate 2 (IRS2) in the soleus muscle.

Indoxyl sulfate results from the sulfation of indole, a bacterial metabolite of tryptophan [18, 62]. Indoxyl sulfate likely plays a significant role in uremic sarcopenia. Indeed, indoxyl sulfate accumulated in the muscle of mouse models of chronic kidney diseases (CKD) [63]. In C2C12 myotubes, indoxyl sulfate reduced cell proliferation and impaired mitochondrial function [63–65]. In mice, chronic exogenous administration of indoxyl sulfate reduced body weight and skeletal muscle weight [64]. Furthermore, indoxyl sulfate was found to be negatively correlated to skeletal muscle index in patients undergoing chronic hemodialysis [66]. In an attempt to delineate to which extent indoxyl sulfate contributes to CKD-associated muscle wasting, Enoki and colleagues administered AST-120, a charcoal absorbent that binds indole in the gut, to mice suffering from CKD [67]. Such treatment reduced muscle indoxyl sulfate levels and muscle expression of *Atrogin-1* and *myostatin* (a negative regulator of muscle mass and function), and improved exercise capacity. Counterintuitively, indole-3-propionic acid, also arising from bacterial degradation of tryptophan, showed rather anti-inflammatory and pro-proliferative effects on muscle cells [68].

Kynurenine is another metabolite that can arise from microbial catabolism of tryptophan. Contrarily to indole derivatives, kynurenine is also largely produced by the host, thanks to the host enzyme indoleamine 2,3-dioxygenase 1 (IDO1) which catalyzes the transformation of tryptophan into kynurenine [69]. Kynurenine levels are also indirectly affected by the gut microbiota through the modulation of tryptophan availability to the host and the stimulation of the activity of IDO1 [69]. Upon exercise, PGC-1α1 is activated and enhances the expression of kynurenine aminotransferases (KATs), which convert kynurenine and α-ketoglutarate into kynurenic acid and glutamate [70•]. The glutamate generated through this transformation then fosters mitochondrial respiration and bioenergetic efficiency of glucose oxidation [70•]. Whether the gut microbiota imprints muscle metabolism by modulating kynurenine bioavailability has not been investigated yet.

The 5 aminovaleric acid betaine (5-AVAB), also known as trimethyl-5-aminovaleric acid (TMAVA) among other terminologies [71], arises from the bacterial metabolism of trimethyllysine (and likely other AAs). It can also be provided through the diet and produced endogenously [71, 72•]. 5-AVAB reduced fatty acid oxidation in mouse cardiomyocytes by reducing the cellular level in carnitine [71, 72•]. Such reduction in carnitine levels is, at least partially, mediated by an inhibition of a cell membrane carnitine transporter (OCTN2) [73]. In vivo, 5-AVAB altered the cardiac energy metabolism, leading to an inhibition of fatty acid oxidation, myocardial lipid accumulation, and an aggravation of cardiac hypertrophy in high-fat diet-fed mice [72•]. 5-AVAB was also found in the skeletal muscle in similar amounts in germ-free and conventional mice [71]. Whether 5-AVAB also impacts skeletal muscle cell physiology is currently undetermined.

Bacterial Metabolites Arising from the Transformation of Polyphenols The bioavailability of dietary (poly)phenols is very low. Most of them reach the colon where they are catabolized by the gut microbes, producing metabolites that are much better absorbed than the original (poly)phenols, and that show biological effects in the colon and systemically [74].

Isovanillic acid 3-O-sulfate (IVAS) arises from isovanillic acid (IVA) and its subsequent sulfation [75•]. IVA is a gut microbial metabolite derived from cyanidin 3-O-glucoside, a phenolic compound present in berries. IVAS displayed insulin-like properties and increased the effects of insulin on glucose uptake in differentiated human skeletal muscle myoblasts (LHCN-M2) by increasing glucose transport via phosphoinositide 3-kinase (PI3K) signaling and glucose transporter type 4 (GLUT4) translocation. IVAS also upregulated glucose transporter type 1 (GLUT1), GLUT4, and PI3K p85α proteins, and increased phosphorylation of Akt/PKB (protein kinase B). Interestingly, IVAS action was not dependent of its sulfation, as IVA exerted similar effects on glucose uptake [75•].

Dihydroferulic acid 4-O-sulfate (DHFA-4S) is the sulfate form of dihydroferulic acid (DHFA) which is produced through the gut microbial transformation of a range of phenolic compounds [75•]. DHFA is absorbed in the colon and is then sulfated by intestinal and hepatic sulfotransferases. DHFA-4S promoted glucose uptake, mostly evident after chronic high glucose concentration exposure of LHCN-M2 muscle cells [75•]. Contrary to IVAS, its mechanism of action on muscle glucose uptake has not been described.

Urolithin A (UA) and urolithin B (UB) are generated from ellagitannin and ellagic acid, which are both phenolic compounds, via the gut microbiota after the ingestion of some fruits [76, 77••, 78]. UA and UB display some beneficial effects on muscle metabolism. Indeed, UA prevented the tumor necrosis factor-α (TNFα)–induced activation of nuclear

factor-kappa B (NF-κB) signaling and protein degradation via the ubiquitin-proteasome pathway [78]. UA demonstrated promising results in a phase 1 study with 36 healthy elderly male and female volunteers where UA was administrated for 28 days [77••]. Indeed, Andreux and colleagues described that UA provides a benefit for age-related decline in muscle mitochondrial health with an increase in mitochondrial biogenesis and function, including fatty acid oxidation capacity. Microarray analyses performed on the mRNA from the vastus lateralis skeletal muscle demonstrated that UA administration exerts effects on the muscle comparable to a regular exercise regimen [77••]. UB enhanced differentiation, promoted protein synthesis by activating mTORC1 signaling mediated by the androgen receptor, and inhibited protein degradation by down-regulating the ubiquitin-proteasome pathway in C2C12 myotubes [76]. In vivo experiments with mini-osmotic pump delivering UB confirmed the hypertrophy effect of UB, with the induction of muscle hypertrophy in healthy mice and a reduction of muscle atrophy after sciatic nerve section [76].

Hippurate is a glycine conjugate of benzoic acid formed in hepatic and kidney mitochondria, and through gut bacterial metabolism of dietary components, primarily polyphenols [79]. It is commonly seen as a general marker of metabolic health reflecting gut microbiota diversity and composition [79], but is also considered a uremic toxin that accumulates in CKD [80]. Hippurate increased glucose oxidation in primary human skeletal muscle cells [81] while its impact on mitochondrial function appears to be context-dependent [80, 81].

Other Molecular Players Beyond Bacterial Metabolites Many other molecular players in this crosstalk can also be envisioned, such as inflammatory cytokines, lipopolysaccharides, quorum sensing molecules, growth factors, and amino acids (Fig. 1). Inflammatory cytokines (such as TNFα and interleukin 6, IL6) are involved in the regulation of muscle atrophy [2•] and a dampening of their production upon gut microbiota modulation is associated to a reduction of muscle atrophy [82, 83]. Lipopolysaccharides (LPS) are bacterial wall components that induce inflammation through their binding to the Toll-like receptor 4 (TLR4). LPS altered muscle progenitor cells in mouse and chicken embryos [84] and induced muscle atrophy through TLR4 in C2C12 myotubes and in mice [85]. LPS levels in the blood are controlled among others by the gut barrier function. As an increased gut barrier permeability is present in many pathological contexts, including in cachectic mice [86, 87], one possibility is that this increased gut barrier permeability leads to a higher LPS translocation from the intestine to the blood, and thereby contributes to muscle atrophy [9]. Quorum sensing molecules (QSMs) mediate the intra-bacterial communication and are released by bacteria upon stress conditions [88•]. Some of these molecules have been found in the plasma and urine, demonstrating their absorption, and suggesting that QSMs may be involved in the microbiota-host crosstalk. In this context, De Spiegeleer and colleagues showed that many QSMs reduce muscle cell viability and induce inflammation in C2C12 myotubes. IGF1 is an anabolic hormone that sustains muscle growth [2•] while FGF21 is sufficient to induce muscle loss and mediates muscle atrophy and weakness under fasting [91, 88•]. Levels of growth factors such as insulin-like growth factor 1 (IGF1) and the fibroblast growth factor 21 (FGF21) have been shown to be modulated by the gut microbiota [89, 90]. In germ-free mice, IGF1 genic expression is reduced in the muscle [22••, 89] while its circulating levels are reduced [89] or not altered [22••] depending of the studies. To which extent the microbiota can control muscle physiology through the modulation of the levels of these hormones remains unclear at this stage. Finally, considering that the gut microbiota affects the host AA metabolism, many teams proposed that modulation of the AA bioavailability through the bacterial utilization of these AA or the de novo production of AAs (especially branched-chain amino acids) could also affect the muscle [10, 92–95].

Role and Therapeutic Interest of the Gut Microbiome in Cancer-Associated Muscle Atrophy

One of the pathological contexts in which this gut microbiota–muscle axis has been investigated is cancer cachexia. Cachexia affects up to 85% of the cancer patients and is one of the primary causes of morbidity and mortality associated with cancer [96]. Cachexia has been defined as "a multifactorial syndrome characterized by an ongoing loss of skeletal muscle mass (with or without fat mass loss) that can be partially but not entirely reversed by conventional nutritional support" [97]. This disorder is thought to result from the combination of reduced food intake and metabolic changes, including elevated energy expenditure, excess catabolism, and inflammation [96, 98]. There is currently no defined standard of care that effectively prevents or counteracts cancer-associated tissue wasting even though such interventions are anticipated to have an important positive impact on overall tumor disease outcome [99].

In this context, our team highlighted a common, reproducible, anorexia-independent microbial signature (characterized mainly by an increase in *Enterobacteriaceae*) in preclinical models of cancer cachexia, in strong association with several cachectic features [86, 87, 100, 101]. Other teams confirmed this alteration of gut bacteria in mouse models of cancer cachexia and showed changes in gut fungi [102–104]. More recently, we showed reduced cecal SCFA levels and bile acid

dysmetabolism in cachectic mice [105, 106•, 107]. In humans, two publications reported alterations in the gut microbiota of cancer patients with cachexia compared to cancer patients without cachexia [108•, 109•]. One of these teams also reported a reduction in fecal acetate, and a trend toward a reduction in other fecal SCFAs [109•]. Alterations in blood bile acid levels were also reported in colorectal and lung cancer patients with cachexia versus patients without cachexia [106•, 108•]. Among others, plasma bile acids (mainly total bile acids and tauro-CDCA) were found to be increased upon cachexia, positively correlated to systemic inflammation, and negatively associated to survival in a cohort of 94 patients with colorectal cancer [106•].

In this context, our team reported that nutritional interventions which target the microbiota, such as prebiotics or probiotics, have the potential to decrease cancer progression; reduce morbidity, muscle atrophy, and fat mass loss; and increase survival of cachectic mice [82, 86, 100, 110]. Among others, we showed that restoring the population of lactobacilli, through the administration of rationally selected bacterial strains, counteracts muscle atrophy and decreases systemic inflammation in a mouse model of leukemia and cachexia [82]. This reduction in muscle atrophy upon lactobacilli administration was also reported in another mouse model of cancer cachexia [83]. However, whether SCFAs play a role in the beneficial effects of prebiotics and probiotics on the muscle in cancer cachexia has not been determined yet. Administration of cholestyramine, a bile acid sequestrant, to cachectic mice reduced the hepatic bile acid load and dampens hepatic inflammation, with a trend toward a reduction in muscle atrogenes [106•]. To which extent cholestyramine affected the systemic blood bile acid profile was not determined. Furthermore, treatment with ursodeoxycholic acid (UDCA), a bile acid commonly used in the treatment of chronic cholestatic diseases, reduces the TGR5 activation capacity of the blood of these mice and reinforced the induction of the genes involved in the ubiquitin-proteasome pathway [107]. Altogether, these studies raise the possibility of a modulatory effect of bile acids, whose profile is modulated by the gut microbiota, on muscle wasting in cancer cachexia, with TGR5 as a potential therapeutic target.

Conclusions

The reports published over the last decade clearly establish the ability for the gut microbiota to modulate directly or indirectly muscle function and mass. The understanding of the mechanisms underlying this gut-muscle axis is at its infancy and such exploration has the potential to deliver novel, much-needed therapeutic tools to tackle muscle wasting, in cancer cachexia but also in other diseases associated with muscle wasting, such as chronic kidney disease, liver fibrosis, and age-related sarcopenia.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that the review manuscript was written in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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