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Gut microbiota and regulation of myokine-adipokine function

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Both skeletal muscle and adipose tissue are considered as endocrine organs due to their ability to produce and secrete several bioactive peptides (e.g. myokines and adipokines). Those bioactive molecules are well known for their capacity to influence whole-body homeostasis and alterations in their production/secretion are contributing to the development of various metabolic disorders. While it is well accepted that changes in the composition and functionality of the gut microbiota are associated with the onset of several pathological disorders (e.g. obesity, diabetes, and cancer), its contribution to the regulation of the myokine-adipokine profile and function remains largely unknown. This review will focus on myokines and adipokines with a special interest on their interaction with the gut microbiota.

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Introduction

It is now well established that the gut microbiota can influence an individual's health status. Various underlying mechanisms have been proposed and both direct and indirect mechanisms of action have been described for specific bacterial metabolites, such as short-chain fatty acids (SCFAs), bile acids, branched chain amino acids, indole propionic acid, and endocannabinoids [1]. In addition to bacterial components, many endogenous factors can be influenced by the gut microbiota. Myokines and adipokines, produced and secreted by the skeletal muscles and adipose tissues respectively, may be considered as potential mediators. In this review, we start by introducing myokines and adipokines and then focus on the crosstalk between these molecules and the gut microbiota, taking a particular interest on how they affect metabolic homeostasis of the whole body.

Myokines

In the body, there are different type of muscles (skeletal, cardiac, smooth), which perform different functions based on their location. They are mainly responsible for maintaining and changing body posture, producing force and motion, generating heat (both through shivering and non-shivering), as well as facilitating movement of internal organs, such as the heart, digestive organs, and blood vessels [2,3]. Skeletal muscle is the largest organ in the human body, accounting for about 30% of body mass in women and 40% in men, though muscle mass is affected by several conditions such as fasting, physical inactivity, cancer, obesity, untreated diabetes, hormonal changes, heart failure, AIDS, chronic obstructive pulmonary disease (COPD), or aging [4]. Skeletal muscle acts as an endocrine organ, as muscle cells, called myocytes, are able to synthesize and release several cytokines and bioactive molecules in response to muscular contraction (major physiological stimulus) and other stimuli (e.g. nutrients, stress, environmental factors, metabolic dysfunction) [2,5]. Interleukin (IL)-6 was the first muscle-secreted protein to be identified in the bloodstream [6]. In contrast to the deleterious effects (e.g. insulin resistance, impaired glucose metabolism) associated with elevated plasma concentration of IL-6 during obesity and diabetes [7], the release of IL-6 after muscle contraction was associated locally (within the muscle) with an increase in glucose uptake and fat oxidation via an activation of AMP-activated protein kinase (AMPK) and/or phosphatidylinositol 3-kinase (PI3-K) [6].These effects are mediated by the binding of IL-6 to its specific transmembrane alpha receptor (ILRα) which form a complex that induces the homodimerization of the glycoprotein (gp)-130 (also known as IL6Rβ) leading to downstream signaling pathways [6]. IL-6 may also act distally. In the liver, it stimulates hepatic glucose production during exercise. In the adipose tissue, it acts as a lipolytic hormone, accelerating free-fatty acids release [6,8]. These beneficial effects of IL-6 highlight the cross talk between skeletal muscle and liver/adipose tissue. IL-6 secreted in response to exercise was also associated to enhance insulin secretion by increasing glucagon-like peptide (GLP)-1 secretion from the intestinal L-cells and the pancreatic alpha-cells [9]. However, the different discrepancies observed for the role of IL-6 on metabolism are still debated. It was also proposed that IL-6 may arbitrate the anti-inflammatory effects of exercise via the inhibition of pro-inflammatory cytokines, like the endotoxin-induced tumor-necrosis factor alpha (TNF-α), and the stimulation of anti-inflammatory

cytokines production such as the IL-1 receptor antagonist, IL-10, and the soluble TNF receptor [6,8,10]. More than ten years ago Pedersen *et al.* suggested that cytokines like IL-6, but also other proteins, that are produced, expressed and secreted by muscle fibers and act as autocrine/paracrine as well as endocrine mediators to perform biological functions should be classified as myokines [6]. Most exert their effects via specific receptors (both transmembrane and nuclear), that are expressed in various tissues and organs (e.g. liver, adipose tissue, brain), thus influencing different metabolic pathways [11–13]. Several secretome studies performed *in vivo* (mouse and human), *in vitro* (mouse and human muscle cell lines) and *ex vivo* (culturing exercised rats muscle) have let to the characterization and the identification of several myokines secreted by the skeletal muscle [14–21]. Although the definition is clear, caution is warranted when searching the current literature, as the term 'myokine' is often erroneously used to designate all proteins that originate from the skeletal muscle. A recent review has described in detail the proposed myokines and the different methods used for their identification and validation [22]. These include myostatin, IL-8, IL-15, irisin, fibroblast growth factor (FGF) 21, myonectin (also known as CTRP15), brain-derived neurotrophic factor (BDNF), decorin, meteorin-like (Metrnl)-1, musculin, secreted protein acidic and rich in cysteine (SPARC) [23,24]. IL-8 and BDNF primarily exert their effects in autocrine and/or paracrine manner, and are involved in angiogenesis and AMPK-mediated fatty acid oxidation respectively. Others act either locally (autocrine and paracrine) or distally (endocrine), thereby being involved in the regulation of several metabolic pathways (e.g. regulation of the skeletal muscle growth, body weight regulation, energy homeostasis, glucose homeostasis, brown-fat-like development, systemic lipid homeostasis, hypertrophy and myogenesis) [23,24]. As the field is still relatively new, the myokine family is expected to grow as research continues.

Although, a link between immune changes and skeletal muscle contractile activity (exercise) has been proposed almost 20 years ago [25], possible mechanisms are not yet fully deciphered. Recent data suggest that exercise and its variables (volume, intensity, density) influence the myokine profile production [26], and that certain myokines (e.g. IL-6) lie at the basis of the reduction in the production of pro-inflammatory cytokines (e.g. TNF-α and IL-1β), thereby contributing to reduced systemic inflammation, eventually leading to a decreased risk of developing insulin resistance and type 2 diabetes [27]. Additionally, myokines, such as BDNF, IL-6, IL-13, IL-15, Irisin, and FGF21, are known to exert an important role in mediating the health-promoting effects of regular physical activity through their ability to affect lipid and glucose metabolism [27]. Of note, many myokines (e.g. IL-6, TNF-α and myostatin) are also produced by the adipose tissue and are therefore referred to as adipo-myokines. They are thought to be involved in the interplay between adipose tissue and skeletal muscle [28]. In 2013, Raschke and Eckel [29], described the interplay between adipo-myokines as two sides of the same coin. This description refers to their ability to exert beneficial or adverse effect on the target tissue depending on their circulating concentrations. A more recent study in mice revealed that Metrnl, another adipo-myokine, is a critical regulator of muscle regeneration that acts directly on immune cells (e.g. macrophages) to promote an anti-inflammatory/pro-regenerative environment and myogenesis. These effects were explained by the ability of Metrnl to signals directly to macrophages via a signal transducer and activator of transcription (Stat)-3-dependent mechanism, while activating muscle cells (e.g. satellite cells) proliferation indirectly through macrophages-induced insulin-like growth factor (IGF)-1 secretion [30••,31]. Although, both myokines and adipokines have autocrine, paracrine, and endocrine effects within their corresponding tissues and their target tissues, two different classification standards are needed. Given that skeletal muscle tissue is the largest tissue present in our body in a physiological healthy status, an alteration in the lean muscle mass/fat mass ratio can be considered an important element in the alteration of the adipokine-myokine profile in addition to being a predictor of insulin resistance and metabolic syndrome. We assume that this is the main reason for which myokines and adipokines cannot be classified under the same standard.

Adipokines

The adipose tissue has long been regarded as an inert tissue that stores and releases energy under the form of lipids. This view has changed dramatically following new insights into the dynamics of this metabolically active organ. It is now well accepted that the adipose tissue also serves as an important endocrine organ capable of synthesizing a wide variety of biologically active compounds that regulate whole body homeostasis [32]. These bioactive peptides, referred to as adipokines, can act either locally as autocrine and paracrine factors or systemically as endocrine factors, and they have been implicated in the regulation of several metabolic pathways [32]. Already in 1987, Siiteri suggested that adipose tissue had an endocrine function, based on its capacity to interconvert steroid hormones [33]. Later in 1994, the discovery that the adipokine leptin was able to signal the energy status of the periphery to the central nervous system was the major breakthrough confirming the adipose tissue as a crucial endocrine organ [34]. In the years that followed, the adipose tissue secretome was characterized in depth by several proteomic profiling approaches [35,36]. To date, more than 600 secretory proteins have been identified within the adipose tissue, but it is expected that this number could still increase as the adipose tissue secretome is further characterized [35]. Not all these proteins are adipokines secreted by

adipocytes, as many factors originate from the non-adipocyte matrix of adipose tissue composed of connective tissue matrix, nerve tissue, stromovascular cells, and immune cells [37,38]. Leptin, adiponectin, resistin, chemerin, visfatin, vaspin, apelin, omentin, and hundreds more adipokines have been studied and characterized for their main actions [32]. Local (autocrine and paracrine) actions of adipokines (e.g. adiponectin, chemerin, IL-6, TNF-α) include regulation of adipogenesis, adipocyte metabolism, immune cells migration, and insulin sensitivity. Systemic (endocrine) effects of adipokines such as leptin, adiponectin, resistin, chemerin, and apelin involve the modulation and regulation of different biological processes such as glucose metabolism, insulin secretion, inflammation, blood pressure, cardiomyocyte contraction, lipid metabolism, appetite, and satiety [32]. Like myokines, adipokines exert their effects through the activation of specific receptors that can be both transmembrane or nuclear proteins [32].

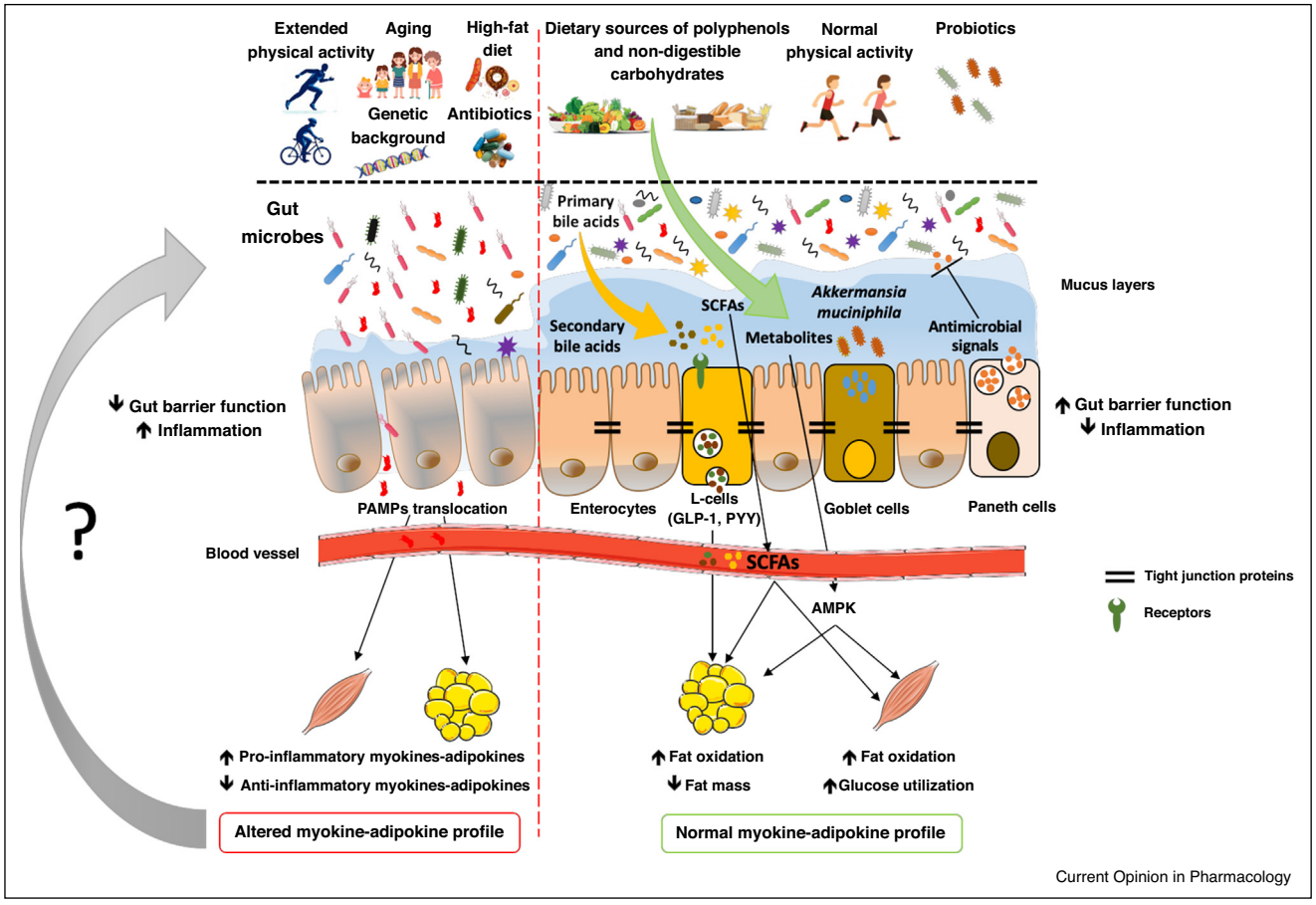
In accordance with anatomical location, the adipose tissues can generally be divided into two main depots: visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT). Taking into account phenotype, functional role, and gene expression profile, they can be further classified as either white, brown or beige [39]. The adipose tissue secretome is not ubiquitous, but is depot-specific and it is strongly influenced by systemic and local components associated with inflammation, insulin resistance, obesity and more [40]. Further adding to the complexity, the different adipose tissues expresse a plethora of receptors (both transmembrane and nuclear) to integrate and respond to the afferent signals from the periphery and the central nervous system [37,41]. It is this complex intrinsic network of receptors and ligands that enable the different adipose tissues to be implicated in the regulation of many biological processes such as energy metabolism, neuroendocrine function, and immune function [37,41]. It is therefore not surprising that a dysregulation of this signaling balance between periphery and adipose tissue is associated with the onset of several pathologies. For example, the adverse metabolic consequences of adipose tissue excess which occur during obesity can disrupt the normal production/function of several adipokines, and the altered adipokines profile maybe partially explain the link between obesity and inflammation, metabolic and cardiovascular comorbidities [42]. However, the underlying mechanisms that connect adipokines and obesity-related inflammation and metabolism are still not clearly understood [43]. Interestingly, several studies (*in vivo* and *in vitro*) have highlighted the role of certain adipokines (leptin, resistin, adiponectin, visfatin) in mediating the cross talk between skeletal muscle and adipose tissue in the context of insulin sensitivity through their ability to affect insulin signaling pathways, glucose transporter 4 (GLUT-4) translocation and modulate insulin-mediated skeletal muscle glucose uptake [44]. An important limitation of those type of studies is the use of cells derived from rodent skeletal muscle, which are characterized by a different fiber type composition and metabolic characteristics as compared to human skeletal muscle [44]. Of note, the negative effects of certain pro-inflammatory adipokines [e.g. TNF-α, monocyte chemoattractant protein-1 (MCP-1) also known as CCl2] secreted abundantly during metabolic disorders can to some extent be counterbalanced by the protective properties of skeletal muscle-secreted peptides [8]. As described for the myokines, growing evidence highlight that physical activity may partly exerts its beneficial effects via alterations in the adipokine profile through an increase in the secretion of anti-inflammatory adipokines and reduction in pro-inflammatory adipokines [45].

Gut microbiota: link to the myokine-adipokine function?

Besides the well described effects of exercise and nutrients on the development of the adipose tissue and muscles, the role of gut bacteria is becoming more and more described in the literature. Indeed, the tremendous number of bacteria that are living in our gastrointestinal tract are dialoguing not only directly with our intestinal epithelial cells but also indirectly with different organs at distance from the gut [1]. Therefore, we propose that the gut microbiota could be one of the neglected environmental factors implicated in the regulation of the myokine-adipokine profile. How the gut microbiota affects myokine-adipokine production and/or function is still poorly understood. However, a connection between microbes and myokines-adipokines may be found in the well-known ability of the gut microbiota and their resulting metabolites to affect different host metabolic pathways [46,47].

A growing body of evidence suggests that alterations in the composition and/or function of the gut microbiota during pathological conditions, sometimes referred to as 'dysbiosis', play a key role in the onset of several metabolic disorders that include obesity, type 2 diabetes, liver disease, but also cancer and even neurological disorders [48]. Changes in the gut microbiota composition have been linked to gut barrier dysfunction (e.g. reduced mucus layer thickness, disruption of the tight junction proteins, decreased secretion of antimicrobial peptides) (Figure 1), leading to the translocation of pathogen associated molecular patterns (PAMPs) able to induce an abnormal host immune response and low-grade inflammation [48] (Figure 1). Modifications in bile acids profiles, decreased secretion of gut peptides, and lower production of short chain fatty acids (SCFAs) and higher levels of branched-chain amino acids have also been observed during dysbiosis [49]. Given the important contribution of the gut microbiota in maintaining a good state of health and well-being, its modulation is

Figure 1



Link between gut microbiota and myokine-adipokine function. Schematic illustration of the several factors influencing the gut microbiota composition and how the gut microbiota and its derived metabolites have an important role in the control of the gut barrier function, bacterial compounds translocation, metabolic functions, and myokine-adipokine production. Although the link between gut microbiota and myokine-adipokine function is still unclear. AMPK, AMP-activated protein kinase; GLP-1, glucagon-like peptide-1; PYY, peptide YY; PAMPs, pathogen associated molecular patterns; SCFAs, short-chain fatty acids.

considered an important tool to prevent or treat dysbiosis associated-metabolic disorders [1].

Several endogenous and exogenous factors affect the gut microbiota composition (e.g. diet, physical activity, antibiotics, genetic background) [1] (Figure 1). Among the different strategies that have been proposed to beneficially modulate the gut microbiota, dietary interventions, including supplementation with prebiotics (a substrate that is selectively utilized by host microorganisms conferring a health benefit, i.e. certain fibers and polyphenols) [50] and/or probiotics (live microorganism that, when administered in adequate amounts, improve host health) are considered the most feasible and efficient [49].

There are several mechanisms by which the microbiota can regulate host metabolism and health, many of which can be traced back to microbial metabolites [1]. Among these bacterial metabolites are the SCFAs that are produced by bacterial fermentation of indigestible foods (i.e. dietary source of polyphenols and complex carbohydrates) in the gastrointestinal tract (Figure 1) [51,52]. SCFAs bind to specific G protein coupled receptors (GPCRs) (i.e. GPR41 and GPR43), and the resulting activation of those receptors triggers the release of glucagon-like peptides (GLP-1 and GLP-2) and peptide YY (PYY) (Figure 1) which are involved in the control of energy homeostasis, fat storage, improvement of the gut barrier function, metabolic inflammation, glucose metabolism, and gut transit time [51]. Metabolites coming from polyphenols are able to activate AMPK via phosphorylation and modulating some proteins involved in adipogenesis, lipogenesis, and lipolysis in different tissues [52] (Figure 1).

Bile acids are also strongly influenced by the microbiota. Indeed, primary bile acids are converted in secondary bile

acids via microbial modification in the gut [53]. While, primary bile acids are synthesized in the liver and are secreted in the duodenum where they emulsify ingested fats to be solubilized for digestion and absorption, they are also able to bind to specific receptors (i.e. TGR5 and FXR) expressed in the intestinal cells (Figure 1). TGR5 is a GPCR expressed on the enteroendocrine L-cells and its activation induces the secretion of GLP-1 and improves liver function and glucose tolerance in obese mice [54], whereas farnesoid X receptor (FXR) is a nuclear receptor that plays a key role in maintaining glucose tolerance and insulin sensitivity in a different manner than that observed for the enteroendocrine regulation [55]. A few studies on rodents have also described the role of primary bile acids supplementation in the modulation of the gut microbiota and their ability to influence serum level of adiponectin [56,57].

In 2007, we were the first to demonstrate that mice fed a high-fat diet develop a pro-inflammatory phenotype closely associated with an increase in the circulating levels of lipopolysaccharides (LPS), an endotoxin found on the cell membranes of Gram-negative bacteria. This condition was defined as metabolic endotoxemia [58]. Once in circulation, LPS reaches several organs including liver, adipose tissue and muscle where it perturbates their normal metabolism and participates in the onset and progression of inflammatory and metabolic diseases (Figure 1) [59]. Increases in circulating LPS have also been described in humans after a high-fat meal, with even worse effects in obese individuals [60]. Besides LPS, other PAMPs have been associated with a causal role on the regulation of similar metabolic pathways (Figure 1) [49].

Many other studies provide evidence for a causal role of the gut microbiota in metabolic regulation. For example, the pioneering work by Backhed *et al.* [61] was the first to show that germ-free mice (mice lacking a gut microbiota) were characterized by a lower fat mass and that colonizing these germ-free mice by transplanting a gut microbiota, induced increased fat mass together with higher production of leptin [62]. In 2008, Membrez *et al.* [63] described that mice treated with a cocktail of antibiotics were characterized by a lower fat mass and higher circulating levels of adiponectin. These data were in accordance with the findings that eradicating the vast majority of the gut microbiota in mice by using antibiotics and, at the same time, feeding them with a high-fat diet reduced low-grade inflammation, slowed fat mass development and improved insulin sensitivity [64]. Inversely to the leptin levels, the adiponectin levels are drastically decreased during obesity and low levels of adiponectin anticipate the development of diabetes and cardiovascular diseases [65,66]. During obesity, the altered adipokine secretion profile is also characterized by a high secretion of pro-inflammatory adipokines such as MCP-1, TNF-α and IL-6, which participates to the diabetic pathogenesis [65]. Mice having a genetic deficiency in the *ob* gene that codes for leptin (mutant *ob/ob* mice) are characterized by an altered gut microbiota and are severally obese with higher fat mass and lower muscles mass [67]. We discovered that changing the microbiota by using prebiotics (i.e. oligofructose) was associated with a lower fat mass, but a higher muscle mass [67]. In addition to the modulation of the gut microbiota composition, we and others have also shown that prebiotic feeding in rodents increased the number of L-cells in the distal part of the small intestine (jejunum) as well as in the lower part of the large intestine (proximal colon), and boosted the production and the release of the active form GLP-1, GLP-2, and PYY in the portal vein (for review Ref. [47]). As described above, SCFAs and bile acids are among the metabolites able to induce the release of those gut peptides (Figure 1). We also found that prebiotics are able to restore leptin sensitivity in high-fat diet-induced obese and diabetic rodents, thereby suggesting that the microbiota could be targeted to restore appropriate production of different adipokines [68]. Along these lines, it has been shown that mice lacking Myd88 specifically in the intestinal epithelial cells displayed significantly lower leptin levels when exposed to a high-fat diet as well as a lower resistin level, an adipokine involved in the development of insulin resistance [69]. Altogether, this set of data strongly suggest that the gut microbiota plays a major role in the regulation of different adipokines and that this is tightly associated with the activity of the innate immune system in the gut.

Of note, not all obese people develop metabolic comorbidities and some remain 'metabolically healthy'. Klöting *et al.* [70] demonstrated that 'healthy' obese individuals had higher insulin-sensitive adiponectin levels than obese insulin-resistant subjects associated with a lower inflammatory tone and a reduced adipose-tissue macrophages infiltration. Beside the direct link between obesity and changes in the adipokine profile, so far, there is not yet evidence showing that this profile is modulated independently of fat mass changes. However, we hypothesize that targeting the adipose tissue via a modulation of the gut microbiota may represent a novel strategy to modulate the adipokine profile (e.g. increase of 'beneficial' adipokines such as the adiponectin).

In addition to prebiotics, probiotics have also been shown to be beneficial on aspects of obesity, steatosis, and insulin resistance. In this context, the next-generation beneficial bacterium, *Akkermansia muciniphila*, a mucin degrading bacterium that resides in the mucus layer (Figure 1) is gaining much attention. This bacterium is naturally present in the human digestive tract in large quantities (up to 3–5%) but decreases significantly with obesity and several other diseases [71]. Because of its health-promoting potential, it has been the focus of many recent studies. In mice, our group

was the first to describe its ability to delay the development of diet-induced obesity and insulin resistance, namely via the modulation of the energy homeostasis and restoration of the gut barrier function (e.g. increase in the mucus layer thickness) (Figure 1) [72,73•,74•]. The abundance of *A. muciniphila* was also associated with higher L-cell activity (e.g. GLP-1 and GLP-2 secretion) which has been hypothesized as a key mechanisms by which this bacterium improves the gut barrier function and reduce metabolic endotoxemia [67,68]. In humans, a placebo-controlled study in overweight/obese insulin-resistant volunteers confirmed that supplementation with *A. muciniphila* could prevent the worsening of several metabolic parameters [75•].

The important role of the gut microbiota in tuning the host muscle metabolism in response to dietary and environmental changes, was further demonstrated by recent experimental animal studies. Lahiri *et al.* [76••] observed that germ-free mice displayed reduced muscle mass and signs of muscle atrophy with reduced muscle strength. They hypothesized that microbes and their metabolites, such as SCFAs, regulate skeletal muscle mass and function. Treating germ-free mice with a cocktail of SCFAs (a mix of acetate, butyrate and propionate) resulted in a reduced expression of *Atrogin-1* and an increased expression of myoblast determinant protein 1 (*MyoD*), two key muscle genes associated with muscle atrophy and muscle differentiation respectively, and could partly restore muscles trength. Virtue *et al.* [77••] showed how tryptophan-derived metabolites produced by the gut microbiota controlled the expression of specific *microRNAs* in white adipocytes in mice to regulate energy expenditure and insulin sensitivity.

Whether alteration in the composition and functionality of the gut microbiota can also be associated with modulation in the myokine-adipokine profile and function is a plausible, but little explored possibility (Figure 1). As briefly mentioned above, physical activity plays a key role in the modulation of the myokine-adipokine profile. Additionally, a recent, and elegant human and animal study demonstrated that physical activity can significantly impact on the composition of the gut microbiota and induce changes in the production of SCFAs, γ-aminobutyric acid, and branched-chain amino acids, thereby conferring metabolic benefits on glucose homeostasis and insulin sensitization in peripheral tissues [78•]. A study in elite rugby players showed that athletes have a greater gut microbial diversity compared to sedentary individuals [79•]. Interestingly, rugby players also had a high abundance of the species *A. muciniphila* [79•].

When it comes to the effects of exercise, duration and intensity of the physical activity are two important factors affecting the metabolism of several organs and tissues [80]. Although normal physical activity is considered to be beneficial for general health, extensive and prolonged exercise (endurance training) has been associated with an increase in intestinal permeability, compromising gut barrier function and resulting in the translocation of bacterial cell wall components such as LPS (Figure 1) [81,82]. This may ultimately lead to a transient state of inflammation which could potentially affect the myokine-adipokine profile. However, further studies are required to validate this hypothesis. Another way that the gut microbiota could affect host metabolism, is by chemically interacting with host cells and regulating gene expression via epigenetic events such as DNA methyltransferases, DNA hydroxylases, histone acetyltransferases, histone deacetylases and histone methyltransferases. These effectors are mediated by gut derived metabolites such as SCFAs, particularly acetate and butyrate [83]. Since SCFAs are produced by fermentation of indigestible carbohydrates, this would be in agreement with studies reporting how dietary factors act on epigenetic pathways [84]. Interestingly, physical activity itself has also been associated with epigenetic adaptations, that are translated into gene-specific regulation of inflammatory and metabolic processes in human skeletal muscle under condition of high-fat diet [85•].

Although it is evident from the literature that the gut microbiota has the capacity to change the profile of myokines and adipokines, it is less clear whether this interaction is bidirectional: can myokines/adipokines modulate gut microbiota composition? In a recent review, Andrews *et al.* [86] described that different cytokines and chemokines can exert either positive or negative effects on the intestinal epithelial barrier integrity. For example, TNFα, interferon-γ, and other interleukins can alter tight junction morphology and may indirectly impact on gut microbial communities, as studies have shown that disruption of the gut barrier permeability impacts on the intestinal microbiome [87,88••]. It is therefore possible that myokines and adipokines can exert similar effects.

Conclusion

Taken together these findings suggest a close connection between diet, physical activity, gut microbiota, bacterial metabolites, gut barrier function, inflammation, and the regulation of the myokine-adipokine function. The identification of novel mediators and a better understanding of how these processes are linked mechanistically may eventually result in the discovery of new potential therapeutic strategies in the prevention of metabolic disorders. In particular, nutritional and non-nutritional strategies that target the gut microbiota, thereby modifying the profile of myokines and adipokines, may be of great importance.

Conflict of interest statement

P.D.C. is inventor of patent applications dealing with the use of *Akkermansia muciniphila* and its components in the context of obesity and related disorders. P.D.C. is co-founder of A-Mansia Biotech SA.

CRediT authorship contribution statement

Francesco Suriano: Conceptualization, Methodology, Writing - original draft, Writing - review & editing. **Matthias Van Hul:** Conceptualization, Methodology, Writing - original draft, Writing - review & editing. **Patrice D Cani:** Conceptualization, Methodology, Supervision, Funding acquisition, Writing - original draft, Writing - review & editing.

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References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1. Cani PD *et al.*: **Microbial regulation of organismal energy homeostasis**. *Nat Metab* 2019, **1**:34-46.
2. Lee JH, Jun HS: **Role of myokines in regulating skeletal muscle mass and function**. *Front Physiol* 2019, **10**:42.
3. Periasamy M, Herrera JL, Reis FCG: **Skeletal muscle thermogenesis and its role in whole body energy metabolism**. *Diabetes Metab J* 2017, **41**:327-336.
4. Kalyani RR, Corriere M, Ferrucci L: **Age-related and disease-related muscle loss: the effect of diabetes, obesity, and other diseases**. *Lancet Diabetes Endocrinol* 2014, **2**:819-829.
5. Leal LG, Lopes MA, Batista ML Jr: **Physical exercise-induced myokines and muscle-adipose tissue crosstalk: a review of current knowledge and the implications for health and metabolic diseases**. *Front Physiol* 2018, **9**:1307.
6. Pedersen BK, Febbraio MA: **Muscle as an endocrine organ: focus on muscle-derived interleukin-6**. *Physiol Rev* 2008, **88**:1379-1406.
7. Lazar MA: **How obesity causes diabetes: not a tall tale**. *Science* 2005, **307**:373-375.
8. Pedersen BK, Febbraio MA: **Muscles, exercise and obesity: skeletal muscle as a secretory organ**. *Nat Rev Endocrinol* 2012, **8**:457-465.
9. Ellingsgaard H *et al.*: **Interleukin-6 enhances insulin secretion by increasing glucagon-like peptide-1 secretion from L cells and alpha cells**. *Nat Med* 2011, **17**:1481-1489.
10. Pedersen BK: **Exercise-induced myokines and their role in chronic diseases**. *Brain Behav Immun* 2011, **25**:811-816.
11. Carson BP: **The potential role of contraction-induced myokines in the regulation of metabolic function for the prevention and treatment of Type 2 diabetes**. *Front Endocrinol (Lausanne)* 2017, **8**:97.
12. Giudice J, Taylor JM: **Muscle as a paracrine and endocrine organ**. *Curr Opin Pharmacol* 2017, **34**:49-55.
13. Kupr B, Schnyder S, Handschin C: **Role of nuclear receptors in exercise-induced muscle adaptations**. *Cold Spring Harb Perspect Med* 2017, **7**.
14. Bostrom P *et al.*: **A PGC1-alpha-dependent myokine that drives brown-fat-like development of white fat and thermogenesis**. *Nature* 2012, **481**:463-468.
15. Chan CY *et al.*: **Identification of differentially regulated secretome components during skeletal myogenesis**. *Mol Cell Proteomics* 2011, **10** M110 004804.
16. Henningsen J *et al.*: **Dynamics of the skeletal muscle secretome during myoblast differentiation**. *Mol Cell Proteomics* 2010, **9**:2482-2496.
17. Evers-van Gogh IJ *et al.*: **Electric pulse stimulation of myotubes as an in vitro exercise model: cell-mediated and non-cell-mediated effects**. *Sci Rep* 2015, **5**:10944.
18. Roca-Rivada A *et al.*: **Muscle tissue as an endocrine organ: comparative secretome profiling of slow-oxidative and fast-glycolytic rat muscle explants and its variation with exercise**. *J Proteomics* 2012, **75**:5414-5425.
19. Scheler M *et al.*: **Cytokine response of primary human myotubes in an in vitro exercise model**. *Am J Physiol Cell Physiol* 2013, **305**:C877-86.
20. Hartwig S *et al.*: **Secretome profiling of primary human skeletal muscle cells**. *Biochim Biophys Acta* 2014, **1844**:1011-1017.
21. Raschke S *et al.*: **Identification and validation of novel contraction-regulated myokines released from primary human skeletal muscle cells**. *PLoS One* 2013, **8**:e62008.
22. Whitham M, Febbraio MA: **The ever-expanding myokinome: discovery challenges and therapeutic implications**. *Nat Rev Drug Discov* 2016, **15**:719-729.
23. Hoffmann C, Weigert C: **Skeletal muscle as an endocrine organ: the role of myokines in exercise adaptations**. *Cold Spring Harb Perspect Med* 2017, **7**.
24. Schnyder S, Handschin C: **Skeletal muscle as an endocrine organ: PGC-1alpha, myokines and exercise**. *Bone* 2015, **80**:115-125.
25. Pedersen BK, Hoffman-Goetz L: **Exercise and the immune system: regulation, integration, and adaptation**. *Physiol Rev* 2000, **80**:1055-1081.
26. Piccirillo R: **Exercise-induced myokines with therapeutic potential for muscle wasting**. *Front Physiol* 2019, **10**:287.
27. Eckardt K *et al.*: **Myokines in insulin resistance and type 2 diabetes**. *Diabetologia* 2014, **57**:1087-1099.
28. Gorgens SW *et al.*: **Exercise and regulation of adipokine and myokine production**. *Prog Mol Biol Transl Sci* 2015, **135**:313-336.
29. Raschke S, Eckel J: **Adipo-myokines: two sides of the same coin–mediators of inflammation and mediators of exercise**. *Mediators Inflamm* 2013, **2013**:320724.
30. •• Baht GS *et al.*: **Meteorin-like facilitates skeletal muscle repair through a Stat3/IGF-1 mechanism**. *Nat Metab* 2020, **2**:278-289
This study identifies Metrnl as an important regulator of muscle regeneration and as an important therapeutic target to promote tissue repair via Stat3/IGF-1 mechanism.
31. Chazaud B: **A macrophage-derived adipokine supports skeletal muscle regeneration**. *Nat Metab* 2020, **2**:213-214.
32. Fasshauer M, Bluher M: **Adipokines in health and disease**. *Trends Pharmacol Sci* 2015, **36**:461-470.
33. Siiteri PK: **Adipose tissue as a source of hormones**. *Am J Clin Nutr* 1987, **45**:277-282.
34. Zhang Y *et al.*: **Positional cloning of the mouse obese gene and its human homologue**. *Nature* 1994, **372**:425-432.
35. Lehr S, Hartwig S, Sell H: **Adipokines: a treasure trove for the discovery of biomarkers for metabolic disorders**. *Proteomics Clin Appl* 2012, **6**:91-101.
36. Lehr S *et al.*: **Identification and validation of novel adipokines released from primary human adipocytes**. *Mol Cell Proteomics* 2012, **11** M111 010504.
37. Kershaw EE, Flier JS: **Adipose tissue as an endocrine organ**. *J Clin Endocrinol Metab* 2004, **89**:2548-2556.
38. Fain JN *et al.*: **Comparison of the release of adipokines by adipose tissue, adipose tissue matrix, and adipocytes from visceral and subcutaneous abdominal adipose tissues of obese humans**. *Endocrinology* 2004, **145**:2273-2282.

39. Oikonomou EK, Antoniades C: **The role of adipose tissue in cardiovascular health and disease**. *Nat Rev Cardiol* 2019, **16**:83-99.

40. Landecho MF *et al.*: **Relevance of leptin and other adipokines in obesity-associated cardiovascular risk**. *Nutrients* 2019, **11**.

41. Tozzi M, Novak I: **Purinergic receptors in adipose tissue as potential targets in metabolic disorders**. *Front Pharmacol* 2017, **8**:878.

42. Ouchi N *et al.*: **Adipokines in inflammation and metabolic disease**. *Nat Rev Immunol* 2011, **11**:85-97.

43. Balistreri CR, Caruso C, Candore G: **The role of adipose tissue and adipokines in obesity-related inflammatory diseases**. *Mediators Inflamm* 2010, **2010**:802078.

44. Nicholson T *et al.*: **The role of adipokines in skeletal muscle inflammation and insulin sensitivity**. *J Inflamm (Lond)* 2018, **15**:9.

45. Golbidi S, Laher I: **Exercise induced adipokine changes and the metabolic syndrome**. *J Diabetes Res* 2014, **2014**:726861.

46. Postler TS, Ghosh S: **Understanding the Holobiont: how microbial metabolites affect human health and shape the immune system**. *Cell Metab* 2017, **26**:110-130.

47. Rastelli M, Knauf C, Cani PD: **Gut microbes and health: a focus on the mechanisms linking microbes, obesity, and related disorders**. *Obesity (Silver Spring)* 2018, **26**:792-800.

48. Cani PD, Jordan BF: **Gut microbiota-mediated inflammation in obesity: a link with gastrointestinal cancer**. *Nat Rev Gastroenterol Hepatol* 2018, **15**:671-682.

49. Cani PD: **Human gut microbiome: hopes, threats and promises**. *Gut* 2018, **67**:1716-1725.

50. Gibson GR *et al.*: **Expert consensus document: the International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of prebiotics**. *Nat Rev Gastroenterol Hepatol* 2017.

51. Canfora EE, Jocken JW, Blaak EE: **Short-chain fatty acids in control of body weight and insulin sensitivity**. *Nat Rev Endocrinol* 2015, **11**:577-591.

52. Van Hul M, Cani PD: **Targeting carbohydrates and polyphenols for a healthy microbiome and healthy weight**. *Curr Nutr Rep* 2019, **8**:307-316.

53. Wahlstrom A *et al.*: **Intestinal crosstalk between bile acids and microbiota and its impact on host metabolism**. *Cell Metab* 2016, **24**:41-50.

54. Thomas C *et al.*: **TGR5-mediated bile acid sensing controls glucose homeostasis**. *Cell Metab* 2009, **10**:167-177.

55. Ma K *et al.*: **Farnesoid X receptor is essential for normal glucose homeostasis**. *J Clin Invest* 2006, **116**:1102-1109.

56. Zhang L *et al.*: **Farnesoid X receptor signaling shapes the gut microbiota and controls hepatic lipid metabolism**. *mSystems* 2016, **1**.

57. Islam KBMS *et al.*: **Bile acid is a host factor that regulates the composition of the cecal microbiota in rats**. *Gastroenterology* 2011, **141**:1773-1781.

58. Cani PD *et al.*: **Metabolic endotoxemia initiates obesity and insulin resistance**. *Diabetes* 2007, **56**:1761-1772.

59. Cani PD *et al.*: **Involvement of gut microbiota in the development of low-grade inflammation and type 2 diabetes associated with obesity**. *Gut Microbes* 2012, **3**:279-288.

60. Vors C *et al.*: **Postprandial Endotoxemia linked with chylomicrons and lipopolysaccharides handling in obese versus lean men: a lipid dose-effect trial**. *J Clin Endocrinol Metab* 2015, **100**:3427-3435.

61. Backhed F *et al.*: **The gut microbiota as an environmental factor that regulates fat storage**. *Proc Natl Acad Sci U S A* 2004, **101**:15718-15723.

62. Balland E, Cowley MA: **New insights in leptin resistance mechanisms in mice**. *Front Neuroendocrinol* 2015, **39**:59-65.

63. Membrez M *et al.*: **Gut microbiota modulation with norfloxacin and ampicillin enhances glucose tolerance in mice**. *FASEB J* 2008, **22**:2416-2426.

64. Cani PD *et al.*: **Changes in gut microbiota control metabolic endotoxemia-induced inflammation in high-fat diet-induced obesity and diabetes in mice**. *Diabetes* 2008, **57**:1470-1481.

65. Freitas Lima LC *et al.*: **Adipokines, diabetes and atherosclerosis: an inflammatory association**. *Front Physiol* 2015:304.

66. Achari AE, Jain SK: **Adiponectin, a therapeutic target for obesity, diabetes, and endothelial dysfunction**. *Int J Mol Sci* 2017, **18**.

67. Cani PD *et al.*: **Changes in gut microbiota control inflammation in obese mice through a mechanism involving GLP-2-driven improvement of gut permeability**. *Gut* 2009, **58**:1091-1103.

68. Everard A *et al.*: **Responses of gut microbiota and glucose and lipid metabolism to prebiotics in genetic obese and diet-induced leptin-resistant mice**. *Diabetes* 2011, **60**:2775-2786.

69. Everard A *et al.*: **Intestinal epithelial MyD88 is a sensor switching host metabolism towards obesity according to nutritional status**. *Nat Commun* 2014, **5**:5648.

70. Kloting N *et al.*: **Insulin-sensitive obesity**. *Am J Physiol Endocrinol Metab* 2010, **299**:E506-15.

71. Cani PD, de Vos WM: **Next-generation beneficial microbes: the case of *Akkermansia muciniphila***. *Front Microbiol* 2017, **8**:1765.

72. Everard A *et al.*: **Cross-talk between *Akkermansia muciniphila* and intestinal epithelium controls diet-induced obesity**. *Proc Natl Acad Sci U S A* 2013, **110**:9066-9071.

73. • Plovier H *et al.*: **A purified membrane protein from *Akkermansia muciniphila* or the pasteurized bacterium improves metabolism in obese and diabetic mice**. *Nat Med* 2017, **23**:107-113

This study shows for the first time that oral supplementation of *Akkermansia muciniphila* purified membrane protein (Amuc_1100) or the pasteurized bacterium induces metabolic benefits in obese and diabetic mice.

74. • Depommier C *et al.*: **Pasteurized *Akkermansia muciniphila* increases whole-body energy expenditure and fecal energy excretion in diet-induced obese mice**. *Gut Microbes* 2020:1-15

This study demonstrates novel insights into the role of *Akkermansia muciniphila* in reducing body weight and fat mass in diet-induced obese mice.

75. • Depommier C *et al.*: **Supplementation with *Akkermansia muciniphila* in overweight and obese human volunteers: a proof-of-concept exploratory study**. *Nat Med* 2019, **25**:1096-1103

This study reveals for the first time the beneficial effects associated with the supplementation of the species *Akkermansia muciniphila* in overweight and obese human volunteers.

76. •• Lahiri S *et al.*: **The gut microbiota influences skeletal muscle mass and function in mice**. *Sci Transl Med* 2019, **11**

This study provides evidence that the gut microbiota and their metabolites influence the muscle mass and function in germ-free mice.

77. •• Virtue AT *et al.*: **The gut microbiota regulates white adipose tissue inflammation and obesity via a family of microRNAs**. *Sci Transl Med* 2019, **11**

This study shows that specific microbiota-derived metabolites such as tryptophan regulate the expression of miR181 in the white adipose tissue of mice and tightly regulate energy expenditure, adiposity, white adipose tissue inflammation and insulin sensitivity.

78. • Liu Y *et al.*: **Gut microbiome fermentation determines the efficacy of exercise for diabetes prevention**. *Cell Metab* 2019

This study demonstrates that gut microbiota and their metabolites are important mediators of the benefits of exercise in overweight men with prediabetes.

79. • Clarke SF *et al.*: **Exercise and associated dietary extremes impact on gut microbial diversity**. *Gut* 2014, **63**:1913-1920

This study demonstrates that gut microbiota is influenced by the exercise and dietary habits.

80. Mach N, Fuster-Botella D: **Endurance exercise and gut microbiota: a review**. *J Sport Health Sci* 2017, **6**:179-197.

81. Gisolfi CV: **Is the GI system built for exercise?** *Physiology* 2000, **15**:114-119.

82. Jeukendrup AE *et al.*: **Relationship between gastro-intestinal complaints and endotoxaemia, cytokine release and the acute-phase reaction during and after a long-distance triathlon in highly trained men**. *Clin Sci (Lond)* 2000, **98**:47-55.

83. Miro-Blanch J, Yanes O: **Epigenetic regulation at the interplay between gut microbiota and host metabolism**. *Front Genet* 2019, **10**:638.

84. Zhang Y, Kutateladze TG: **Diet and the epigenome**. *Nat Commun* 2018, **9**:3375.

85. • Laker RC *et al.*: **Transcriptomic and epigenetic responses to short-term nutrient-exercise stress in humans**. *Sci Rep* 2017, **7**:15134
This study shows that physical activity induces epigenetic adaptations in human skeletal muscle.

86. Andrews C, McLean MH, Durum SK: **Cytokine tuning of intestinal epithelial function**. *Front Immunol* 2018, **9**:1270.

87. Rahman K *et al.*: **Loss of junctional adhesion molecule a promotes severe steatohepatitis in mice on a diet high in saturated fat, fructose, and cholesterol**. *Gastroenterology* 2016, **151**:733-746 e12.

88. •• Wu M *et al.*: **The dynamic changes of gut microbiota in Muc2 deficient mice**. *Int J Mol Sci* 2018, **19**
This study evidences that genetic deletion of *Muc2* gene is associated with alterations of the gut microbiota, development of colitis, and colorectal cancer.