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Review

Muscle wasting: The gut microbiota as a new therapeutic target?☆

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ABSTRACT

Muscle wasting is characterized by a loss of muscle mass and strength, and occurs in several pathological conditions such as cancer, chronic heart failure, chronic infection and malnutrition. Muscle wasting can be caused by inflammation and inappropriate nutritional status. Interestingly, gut microbiota has recently been proposed as an environmental factor involved, among others, in energy sparing from the diet, and in the regulation of host immunity and metabolism. This review presents evidence supporting the existence of a gut microbiota-muscle axis and discusses the potential role and therapeutic interest of gut microbiota in muscle wasting, specifically in the context of cancer and malnutrition. This review also proposes possible molecular mechanisms underlying the gut microbiota-muscle axis.

This article is part of a Directed Issue entitled: Molecular basis of muscle wasting.

Contents

1. Introduction

Muscle wasting is characterized by a progressive loss of muscle mass and strength, and is generally due to reduced protein synthesis and/or increased degradation (Fearon et al., 2012). Muscle wasting occurs in several chronic and inflammatory diseases, such as cancer, chronic heart failure, chronic infection and malnutrition (Evans et al., 2008).

In association with fat mass loss, muscle wasting constitutes a prominent feature of the cachexia syndrome. One in four of the general population will die from cancer, and cachexia affects the majority of the patients with advanced disease (Fearon et al., 2012). Cancer cachexia reduces lifespan and life quality (Fearon et al., 2012).

Malnutrition is a general term that encompasses various forms of inadequate nutrition, including delayed growth of children and symptoms of deficiencies in vitamins, minerals, essential fatty acids and proteins (Gordon et al., 2012). Only undernutrition will be considered in this review. Globally, an estimated 52 million children under five years of age were wasted in 2011 (UNICEF-WHO-The World Bank, 2011).

The gut microbiota has been proposed to influence muscle metabolism, but molecular players supporting this gut-muscle axis remain to be identified. This review summarizes the available data concerning this gut microbiota-muscle crosstalk, with a focus on cancer cachexia and malnutrition, and presents hypotheses to explain how gut microbiota may influence muscle cells. Finally, therapeutic opportunities that could derive from the targeting of the gut microbiota will be exposed.

☆ This article is part of a Directed Issue entitled: Molecular basis of muscle wasting.

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2. Pathogenesis

2.1. Gut microbiota

The microbiota consists of 100 trillion microorganisms, which outnumber human cells in the body by at least ten-fold. The majority of the microbes reside in the gut, where they exert diverse and crucial functions. Gut microbiota induces a wide variety of host responses within the intestinal mucosa and thereby controls the gut's barrier, immune and endocrine functions. Gut microbes also influence the metabolism of host cells in tissues outside the intestine and modulate energy homeostasis and systemic inflammation (Delzenne and Cani, 2011). Dysbiosis – defined as "alterations in the composition and/or activity of the gut microbiota in association with pathological features" – has been reported in inflammatory bowel diseases, obesity and type 2 diabetes (Delzenne and Cani, 2011). A causative role for dysbiosis in obesity has been demonstrated in mice (gut microbiota transfer in germ-free mice) (Turnbaugh et al., 2006). Importantly, this causality relationship between dysbiosis and specific pathologies has not been established in humans.

2.2. Gut microbiota-muscle axis

A limited number of studies focussed on the impact of gut microbiota modulation on muscle physiology.

As a first evidence for a gut microbiota-muscle axis, Bäckhed and colleagues proposed that germ-free (GF) mice (mice devoid of microbes and kept under sterile conditions) are protected from diet-induced obesity by two mechanisms that result in increased muscle fatty acid catabolism (Backhed et al., 2007) (Fig. 1).

Firstly, AMP-activated protein kinase (AMPK) activity is increased in the muscle of GF mice. AMPK functions as a "fuel gauge" that monitors cellular energy status. AMPK activation was accompanied by an increased muscular activity of CPT-1 (carnitine:palmitoyl transferase-1), which catalyses the rate-limiting step for the entry of long chain fatty acylCoA in the mitochondria where they will be oxidized (Backhed et al., 2007).

Secondly, GF mice exhibit elevated intestinal levels of Fiaf (fasting-induced adipocyte factor), which was linked to an increased expression of PGC-1α in the gastrocnemius muscle (Backhed et al., 2007). PGC-1α (peroxisomal proliferator-activated receptor coactivator) is a prime regulator of mitochondrial content and oxidative metabolism (Backhed et al., 2007; Sandri et al., 2006). Interestingly, PGC-1α protects skeletal muscle from atrophy. Indeed, overexpression of PGC-1α in mice reduces the impact of denervation and fasting on muscle fiber diameter and on the expression of MuRF1 and Atrogin-1, two ubiquitin-ligases involved in the ubiquitin-proteasome pathway which is crucial for muscle atrophy (Sandri et al., 2006).

In 2013, Swartz et al. showed that adiposity is preserved in the Fisher 344 GF rats despite an increased intestinal FIAF expression, questioning the prominent role of intestinal Fiaf in adiposity (Swartz et al., 2013). It would have been interesting to analyze muscle AMPK and PGC-1α in these rats to further test the relevance of these two pathways potentially involved in the gut microbiota-muscle crosstalk.

Gut microbiota influences amino acid bioavailability (Fig. 1). For instance, microbial lysine production substantially contributes to the amino acid requirements of rats and pigs (Torrallardona et al., 2003). In addition, supplementation with *Lactobacillus paracasei* NCC2461 was associated with a specific fecal amino acid pattern in mice (Martin et al., 2010). Furthermore, the catabolism of dietary amino acids by the gut microbiota represents a net amino acid loss to the host (Puiman et al., 2013). Indeed, a 10-day intravenous antibiotics administration to neonatal piglets increased plasma levels of some amino acids but these changes were not accompanied by a net anabolic effect on whole body protein metabolism (Puiman et al., 2013). We cannot exclude that, in severe conditions such as undernutrition, gut microbial influence on amino acid bioavailability might become crucial, but this hypothesis requires further investigation.

Gut microbiota produces various metabolites which can reach the muscle, such as conjugated linoleic acids, acetate and bile acids (Delzenne and Cani, 2011). For instance, gut microbiota confers diversity on bile acid profile, including in peripheral tissues such as heart and kidney (Swann et al., 2011). Interestingly, bile acids increase energy expenditure in human skeletal muscle cells by promoting intracellular thyroid hormone activation via TGR5, a G-protein-coupled receptor (Watanabe et al., 2006). Moreover, bile acids also activate the nuclear farnesoid X receptor and thereby protect against muscle fat deposition (Cipriani et al., 2010).

Another pathway could be hypothetically involved in the gut microbiota-muscle axis: the Toll-like receptors (TLRs)/NF-κB pathway. Muscle-specific activation of the transcription factor NF-κB causes muscle wasting (Cai et al., 2004). NF-κB is a major downstream target of the TLRs which recognizes various pathogen-associated molecular patterns (PAMPs). For instance, TLR2 can be stimulated by peptidoglycan from Gram-positive bacteria, TLR4 by lipopolysaccharides (LPS), TLR5 by flagellin and TLR9 by nucleic acids derived from virus and bacteria (Boyd et al., 2006; Frost et al., 2006). Importantly, muscular cells were responsive to TLR2, -4 and -5 ligands (Boyd et al., 2006; Frost et al., 2006). Interestingly, TLR4 mediates muscle atrophy induced by LPS injection (Doyle et al., 2011). To our knowledge, TLR2 and TLR5 involvement in muscle atrophy has not been investigated so far.

Finally, it is conceivable that microbiota-related inflammation occurs in several cachectic diseases and malnutrition (Evans et al., 2008; Fearon et al., 2012; Hashimoto et al., 2012). Those pathologies might be associated with altered gut barrier function (Suzuki et al., 2011), which could in turn lead to an increased translocation of PAMPs prone to induce inflammation and muscle atrophy. A similar process, namely increased LPS translocation, has been proposed as driver of inflammation associated with obesity and type 2 diabetes (Cani et al., 2007, 2009).

2.3. Muscle wasting and gut microbiota in cachexia

A recent study from our laboratory revealed that gut microbiota composition is altered in a mouse model of acute leukemia harboring cachexia. Levels of caecal *Lactobacillus* spp., a bacterial genus known for its immunomodulatory properties, were decreased. Lactobacilli species were differentially affected: *L. reuteri* and *L. gasseri/johnsonii* were decreased whereas *L. murinus/animalis* remained unaffected (Bindels et al., 2012). Interestingly, restoring gut lactobacilli by oral supplementation with *L. reuteri* 100-23 and *L. gasseri* 311476 reduced the levels of systemic inflammatory cytokines, such as interleukin (IL)-6, IL-4 and monocyte chemoattractant protein (MCP)-1. In addition, restoration of lactobacilli levels led to a reduction, in gastrocnemius and tibialis muscles, of MuRF1 and Atrogin-1, but also of LC3 and Cathepsin L, two markers of the autophagy-lysosomal pathway, a major system of protein breakdown in skeletal muscle (Mammucari et al., 2007). Lactobacilli beneficial effect seems to be bacterial strain- or species-dependent. Indeed, administration of *L. acidophilus* NCFM to leukemic mice with cachexia did not reduce systemic inflammation and muscle atrophy markers (Bindels et al., 2012). Whether the anti-atrophy effect of specific lactobacilli are directly dependent on their immunomodulatory properties remains to be determined.

Interestingly, Puppa and colleagues reported in $Apc^{Min/+}$ mice, an animal model of colorectal cancer with cachexia, that gut barrier dysfunction and endotoxemia, namely increased serum LPS