Review

MOLECULAR METABOLISM

Epigenetic modulation of the gut—muscle axis in pompe disease: Microbiota fingerprints to cellular and molecular pathomechanisms

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ABSTRACT

Inter-organ cross-talk is increasingly recognised as a fundamental determinant in the pathogenesis of neurodegenerative and neuromuscular disorders, modulating neuroinflammation, protein misfolding, and cellular dysfunction through systemic mediators such as cytokines, adipokines, and growth factors. In neuromuscular diseases, particularly Pompe disease, muscle degeneration is tightly linked to impaired autophagy and chronic inflammation. Recent evidence highlights the gut microbiota as a key regulator of innate and adaptive immune responses, exerting direct effects on skeletal muscle and supporting the existence of a gut—muscle axis. Dysbiosis has been proposed to influence myopathy progression, suggesting that modulation of the intestinal ecosystem may hold therapeutic relevance. Consequently, interventions employing probiotics, prebiotics, and targeted nutritional compounds have emerged as promising strategies to modulate immune activity, attenuate inflammation, and enhance autophagic efficiency, thereby contributing to the restoration of intestinal eubiosis and complementing enzyme replacement therapy. In parallel, epigenetic mechanisms are gaining prominence as additional modulators of pathogenic pathways, with the potential to influence microbiome composition and function. Collectively, these insights position the gut—muscle axis as a central regulatory node in Pompe disease and a compelling target for personalised nutritional and nutraceutical approaches. This review aims to provide a comprehensive examination of the gut—muscle axis and its implications in Pompe disease. Understanding how nutrient-induced changes in microbial gene expression may be harnessed to develop novel, synergistic therapeutic strategies could ultimately improve clinical outcomes and enhance the quality of life of affected individuals.

1. INTRODUCTION

Pompe disease is a genetic, metabolic and hereditary disease defined by a deficiency of the lysosomal enzyme acid alpha-glucosidase (GAA). This enzyme is responsible for glycogen degradation and when it is absent or deficient, glycogen accumulates within lysosomes. The literature clearly indicates that such accumulation is detrimental to cellular integrity and contributes to progressive tissue degeneration. This phenomenon has been most extensively observed in the cases of skeletal, cardiac, and smooth muscles [1]. This leads to muscle disorganisation, cytotoxicity, and the release of creatine kinase (CK) into the blood, a condition known as hyperCKemia, which indicates muscle damage and inflammation [2]. The disease is marked by impaired autophagy, an essential process for cell survival and adaptation. This leads to oxidative stress, loss of intracellular homeostasis, and muscle degeneration. Although the primary pathogenic mechanism is well defined, it is increasingly clear that disease progression and phenotypic variability cannot be explained solely by enzyme deficiency. Current studies suggest the involvement of systemic regulatory networks, including immune responses, metabolic pathways and epigenetic mechanisms, which may potentially modulate muscle degeneration and therapeutic efficacy. Epigenetic regulation, including DNA methylation, histone modifications and non-coding RNAs, may therefore influence specific disease pathways and modulate the phenotype. In the context of Pompe disease, epigenetic alterations could influence the autophagic flux, lysosomal biogenesis, muscle fibre homeostasis and the inflammatory pathways. Regarding the modulation of the inflammatory response in muscle pathophysiology, the gut microbiota emerges as a key modulator. Through its vast genetic heritage (the microbiome), the gut microbiota represents a very important epigenetic factor for the organism's well-being interacting on physical, chemical and psychological levels. Recent evidence attributes a crucial role to the microbiota in controlling oxidative stress, mitochondrial function, neuromuscular junction integrity and insulin sensitivity, as well as in modulating chronic immune-inflammatory responses [3]. These effects are achieved through the activation of specific cell signalling pathways related to autophagy, such as AMPK and mTOR. These pathways underlie complex interaction among the intestine and muscle that goes in both directions. Indeed, preclinical studies have evaluated the existence of

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an intestine—muscle axis [4]. The muscle, in consequence of the secretion of myokines and other bioactive molecules, has been defined as an endocrine organ, thereby exerting a systemic action that can also influence the composition and functionality of the microbiota itself [5]. Clinically, alterations in the microbiota have been observed in elderly people and in sarcopenic and cachectic patients, correlating with physical frailty and loss of muscle mass. Intestinal dysbiosis has been shown to compromise the integrity of the intestinal epithelial barrier (IEB), resulting in increased permeability and subsequent bacterial translocation and immune activation, triggering chronic systemic inflammation that in turn worsens muscle function [6]. In this context, the intestinal microbiota could be considered a relevant systemic modulator. In physiological conditions, microbiota-derived metabolites, notably short-chain fatty acids (SCFAs) such as butyrate, propionate, and acetate, modulate pivotal signalling pathways associated with autophagy. These microbiota-derived metabolites also exert a significant influence on energy metabolism and systemic inflammatory status. Nevertheless, when dysbiosis occurs, this condition can be altered with reduced SCFA production, increased intestinal permeability and activation of low-intensity chronic inflammatory responses [7]. Despite the absence of direct data regarding the composition and function of the microbiota in Pompe disease, sustained pro-inflammatory conditions, along with the typical mitochondrial and autophagic dysfunction of the disease, may result from microbial imbalance. Furthermore, a healthy gut microbiota, through the production of bioactive metabolites, has the potential to enhance the regulation of muscle energy metabolism, positively modulate the process of autophagy, and regulate inflammatory mechanisms. Consequently, a comprehensive investigation of the gut—muscle axis in Pompe disease may unveil groundbreaking insights, such as the targeted modulation of the microbiota (employing nutritional, prebiotic, or probiotic strategies) as a complementary intervention to enzyme therapy, aimed at enhancing functional muscle recovery. Nutrition should not be regarded as a mere supportive factor, but rather as an active modulator of muscle metabolism and autophagy, with the capacity to influence the effectiveness of drug treatment. Furthermore, analysing the response to different classes of nutrients is essential. In order to evaluate and optimise strategies aimed at improving patients' quality of life, it is crucial to understand how variations in gene expression in the microbiome influence metabolic and physiological processes. Integrating enzyme therapy and personalised nutritional interventions could establish a comprehensive therapeutic approach to managing Pompe disease [8,9]. The extant literature has demonstrated that factors such as diet, physical activity, sleep, the circadian cycle, environmental pollutants, antibiotics, and psychosocial stress experienced by the individual influence the composition of the microbiota [10—16] thereby also modifying its adaptive contribution to the entire human organism. Consequently, the identification of specific nutraceuticals and dietary profiles designed to enhance autophagic flux and cellular bioenergetics may yield novel therapeutic opportunities, particularly if substantiated by multicentre and longitudinal studies.

2. THE ALTERATION OF THE AUTOPHAGY MECHANISM IN POMPE DISEASE

The muscle tissue damage in Pompe disease has often been associated with progressive enlargement of lysosomes, with accumulation of glycogen in the intermyofibrillar space, resulting in lysosome rupture, release of glycogen into the plasma, and displacement of myofibrils [17]. Secondary alterations to autophagy are the result of this accumulation. This overload has been demonstrated to compromise the degradation of autophagosomes, resulting in an abnormal accumulation of undegraded autophagic vesicles and cytotoxic material within muscle cells. The obstruction of the autophagic flux consequently engenders significant cellular stress, interfering with intracellular homeostasis and exacerbating muscle degeneration. In view of the above, interference with autophagy processes, which are already impaired by lysosomal accumulation, is a key factor in the pathogenesis of the disease, particularly in muscle tissue, where progressive structural and functional alteration of the fibres is observed [1]. Specifically, the activity of mTORC1 is reduced due to decreased phosphorylation of its downstream targets: 4 E-BP1 (eukaryotic translation initiation factor 4 E-binding protein 1) and S6K1 (S6 kinase 1). Meanwhile, AMPK is hyperactivated, most likely due to an energy deficit (an increased ADP/ATP ratio) in the diseased muscle fibre. This directly activates autophagy through the phosphorylation of ULK1 [18]. The role of the mTORC1 and AMPK signalling pathways in the pathophysiology of muscle damage was investigated using cellular and animal models affected by GAA enzyme deficiency. The analysis focused on GAA-deficient multinucleated myotubes, which mimic lysosomal glycogen accumulation and impaired autophagy, and on the muscle tissue of mice lacking the same gene [1]. Levels of phosphorylation of the main downstream effectors of the mTORC1 complex, namely the repressive protein 4 E-BP1 and the ribosomal kinase S6K1, were significantly reduced, as evidenced by decreases in the ratios between phosphorylated and total forms of p-4E-BP1^{S65} and p-S6K1$^{T421/S424}$. This evidence suggests a reduction in mTORC1 complex activity. The suppression of mTORC1 activity was further confirmed by the decrease in phosphorylation of ribosomal protein S6 at residues S$^{235/236}$. This event was found to be dependent on S6K1 activity, suggesting an overall impairment of mTORC1-mediated anabolic signalling in the pathological context examined [1]. However, in contrast to the observations made in the mTORC1 pathway, a significant increase in AMPK phosphorylation (p-AMPK^{T172}) was detected in the myotubes and muscle tissue of the knockout models, suggesting its activation. Concurrently, an escalation in the phosphorylation levels of the principal effectors downstream of AMPK, including TSC2^{S1387} and ACC^{S79} (acetyl-CoA carboxylase), was observed, thereby substantiating the functional activation of this kinase within the pathological scenario [19]. In order to substantiate this finding, a high ADP/ATP ratio was identified in the muscle of KO (knock-out) mice. The presence of this ratio indicates intracellular energy depletion, that is well-documented for its ability to induce the activation of AMPK, a central metabolic sensor [18,20,21]. In particular, the defect in mTORC1 signalling is associated with aberrant inhibition mediated by the AMPK-TSC2 pathway, with a blockage of the pathway interfering with the function of Rheb, a key activator of mTORC1. Experimental manipulations, such as TSC2 silencing or Rheb overexpression, have demonstrated the capacity to reactivate mTORC1, thereby reversing muscle atrophy and eradicating autophagic accumulation in mouse models of Pompe disease [20]. The amino acid arginine has been identified as a modulator capable of activating mTORC1 by promoting the dissociation of TSC2 from the lysosome and releasing the inhibition of Rheb. Short treatments with arginine in cells and mouse models resulted in the restoration of mTORC1 activity, thus indicating a potential integrative therapeutic approach for Pompe disease and, moreover, potentially other lysosomal storage disorders and muscle atrophy. In summary, modulation of the TSC2-Rheb pathway and reactivation of mTORC1 represent promising strategies for counteracting muscle dysfunction in Pompe disease (Figure 1). In line with existing research, modulation

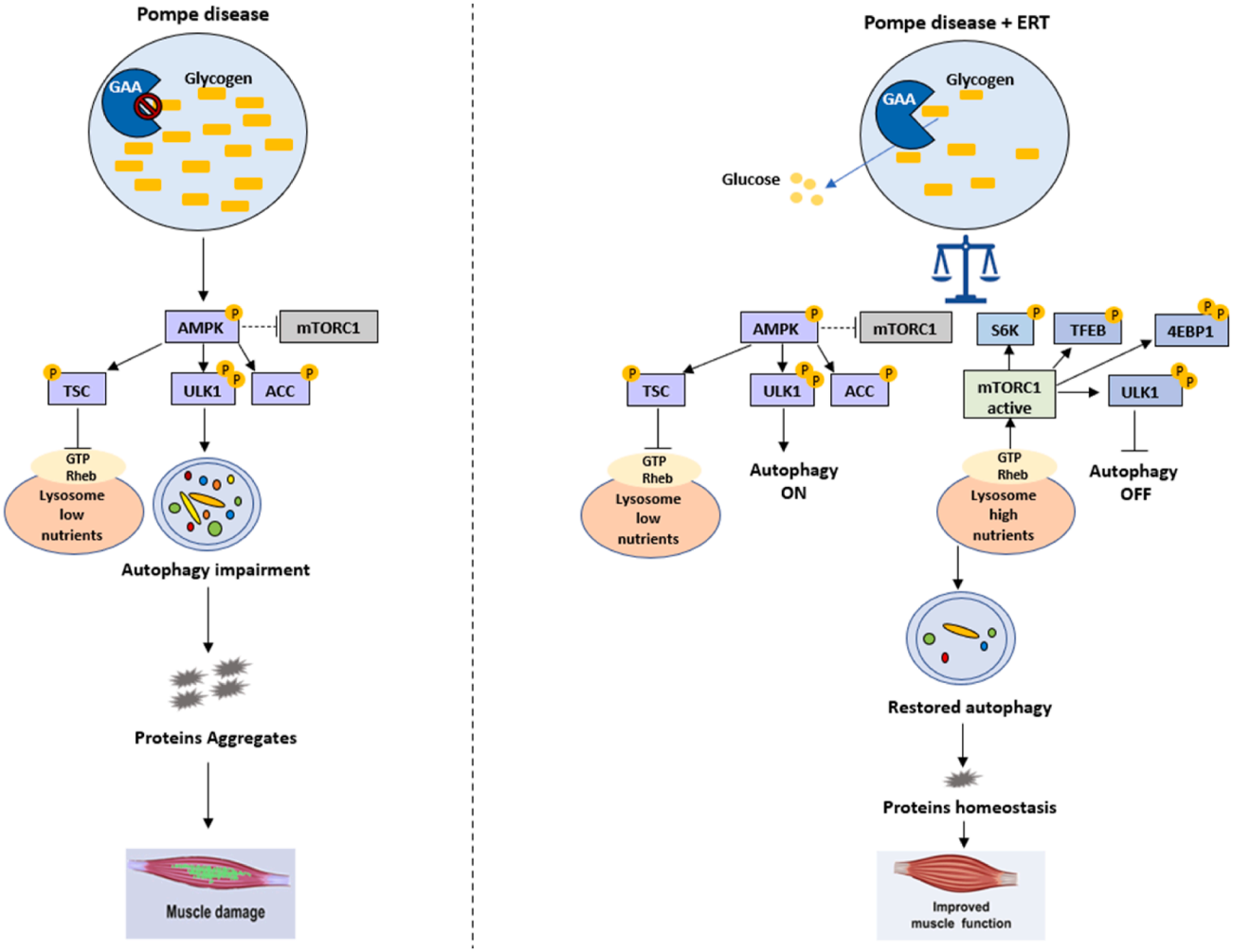

Figure 1: Schematic representation of molecular mechanism alterations in Pompe disease and the effects of enzyme replacement therapy (ERT) on autophagy. On the left, GAA deficiency leads to glycogen accumulation, AMPK hyperactivation, reduced mTORC1 activity, impaired autophagy, and protein aggregate formation, resulting in muscle damage. On the right, ERT administration reduces the lysosomal load, restores the balance between AMPK and mTORC1, reactivates autophagic flux and promotes protein homeostasis, improving muscle function.

of these pathways has been shown to significantly impact disease progression. Specifically, genetic inhibition of TSC2 has been observed to enhance protein synthesis, reduce muscle atrophy, and prevent the accumulation of autophagosomes. This, in turn, has been shown to promote a better response to enzymatic replace therapy treatment (ERT) [18]. Alongside autophagy mechanisms, the role of inflammation in the muscular pathogenesis of Pompe disease must be considered. Specifically, as a secondary inflammatory response induced by muscle damage and increased serum creatine kinase (CK) levels, it is a pivotal factor in determining the extent of tissue degeneration. Consequently, an exhaustive examination of the inflammatory profile is imperative to obtain a comprehensive understanding of the inflammatory response, comprehend the interplay between lysosomal metabolism and immune response, and formulate therapeutic strategies aimed at modulating inflammation.

3. THE INFLAMMATORY PROFILE IN THE MUSCULAR PATHOGENESIS OF POMPE DISEASE

Atypical pathological glycogen accumulation within the lysosomes of skeletal and cardiac muscle cells has been shown to cause progressive structural and functional disorganisation of muscle tissue. The resultant lysosomal overload has been shown to induce cellular dysfunction and compromise cell integrity, leading to muscle fibre lysis and subsequent release of cytosolic enzymes, including creatine kinase (CK), into the bloodstream [2]. HyperCKemia is a sensitive biochemical biomarker of muscle damage and can be an early indicator of myopathy [22,23]. Specifically, high CK levels in the context of Pompe disease have been shown to correlate with both the degree of muscle degeneration and secondary inflammatory phenomena. The immunopathogenic mechanisms underlying hyperCKemia include the release of pro-inflammatory cytokines and other bioactive mediators by damaged muscle cells, as well as the activation of innate and adaptive immune responses [24]. The events described above contribute to perpetuating tissue damage, thereby establishing a vicious cycle between glycogen accumulation, cytolysis and inflammation. The present study hypothesises that pathogenic mutations in the GAA gene may lead to a decrease in GAA enzyme activity and trigger a series of transcriptional responses in Pompe disease. Recent research conducted by Zhang's group examined the crucial role of immune cells in the onset and progression of Pompe disease. This investigation involved the analysis of immune cells from patients

diagnosed with Pompe disease and control samples. The characterisation of immune cells was conducted through the CIBERSORT method, which facilitated the analysis of their composition. The identification of differentially expressed genes (DEGs) was achieved through the utilisation of bioinformatics and machine learning algorithms, facilitating the analysis of variations in immune cell types based on their gene expression profiles in muscle tissue from Pompe disease patients in comparison with a control group [25]. Immunoprofilometric analysis revealed significant alterations in the peripheral immune composition of subjects with Pompe disease compared to healthy controls. Dysregulation was observed in several innate and adaptive immune subpopulations, including memory B cells, plasma cells, regulatory T cells (Tregs), activated natural killer (NK) cells, monocytes, M0 macrophages, resting and activated dendritic cells, eosinophils and neutrophils. Concurrently, an analysis of the gene expression of GPNMB, CALML6 and TRIM7 was conducted to investigate their correlation with the degree of immune infiltration in affected muscle tissue. Given the emerging role of immune mediators in the pathophysiology of Pompe disease, it is hypothesised that these genes act not only at the myocellular level, but also actively modulate local immune—muscle interactions. The results showed significant correlations between the expression levels of these genes and different immune populations. GPNMB was associated with γδ T lymphocytes, plasma cells, activated NK cells, and eosinophils; CALML6 showed relationships with γδ T lymphocytes, plasma cells, NK cells (both resting and activated), neutrophils, and eosinophils; and TRIM7 correlated with resting NK cells, neutrophils, and activated mast cells [25]. This evidence thus suggests that GPNMB, CALML6 and TRIM7 may represent pivotal regulatory nodes in the network of immune and inflammatory interactions that contribute to the pathogenesis of Pompe disease. Consequently, the demonstration of differential levels of expression between healthy and diseased subjects indicates the potential of these genes as prognostic biomarkers. The modulation of these factors has the potential to provide novel diagnostic and therapeutic perspectives. In particular, they could serve as potential drug targets for interventions that are combined with ERT [25]. In the field of inflammation, another focal point in the modulation of the inflammatory response, pertaining to the network of immune and inflammatory interactions and muscle pathophysiology, is the role of the gut microbiota in lysosomal storage diseases. Emerging evidence indicates the role of the microbiota as a regulator of fundamental processes such as oxidative stress, mitochondrial function, neuromuscular junction integrity, insulin sensitivity, as well as systemic and chronic immuno-inflammatory responses [3]. The aforementioned effects are mediated by the activation of specific cellular signalling pathways. In recent years, several studies have highlighted the existence of a bidirectional communication network between the gut microbiota and skeletal muscle. Endocrine properties enable skeletal muscle to secrete myokines and other bioactive molecules that exert systemic effects on multiple tissues throughout the body, including the gut microbiota [5].

4. BIDIRECTIONAL GUT—MUSCLE AXIS

Skeletal muscle is the largest metabolic organ, representing approximately 50% of total body mass [26] It is primarily known for its role in influencing bone density, insulin-stimulated glucose uptake, fatty acid oxidation, and whole-body protein metabolism [5]. In addition, skeletal muscle has metabolic and endocrine properties through the release of growth factors and cytokines, which allow communication with other systems, such as the digestive system, including the microbial population residing in the gut [27]. The gut is the main site of the human microbiota and an important regulator of metabolism and immunity. Intestinal microorganisms synthesise a wide range of metabolites, including short-chain fatty acids, secondary bile acids, and neurotransmitter precursors. These act as important energy sources and modulators of inflammatory processes, significantly influencing the physiology and metabolism of skeletal muscle via multiple signalling pathways [3,28].

This reciprocal interaction establishes a bidirectional gut—muscle axis, which is essential for maintaining metabolic and physiological homeostasis in the body [5]. Preclinical studies conducted on murine animal models have provided strong evidence supporting the presence of a bidirectional relationship between the gut and the muscles. These studies have demonstrated that muscle atrophy is related to a reduction in body mass in mice lacking gut microbiota. Furthermore, they have shown that microbiota transplantation from pathogen-free mice can reduce muscle atrophy [4].

Another preclinical study shows that reducing the gut microbiota in mice through antibiotic treatment causes muscle atrophy and decreased muscular endurance [29].

Supporting these preclinical findings, at the clinical level, it has been observed that alterations in the gut microbial status are evident in elderly individuals, sarcopenic, and cachectic patients. Specifically, inter-individual variability in the composition of the gut microbiota can influence muscle mass and function. In the elderly individuals, an increase in the number of Oscillospira and Ruminococcus and a reduction in the number of Barnesiellaceae and Christensenellaceae have been found to be associated with physical frailty and sarcopenia [30]. In fact, intestinal dysbiosis can profoundly compromises the integrity of the intestinal epithelial barrier (IEB), whose permeability is finely regulated by the microbiota through multiple molecular mechanisms, including the action of short-chain fatty acids (SCFAs) that increase levels of arachidonoylglycerol (2-AG) and oleoylglycerol (2-OG), preserving its structural cohesion [6]. More specifically, the microbiota significantly influences the functionality and health of skeletal muscle tissue by regulating complex pathophysiological processes, such as oxidative stress, mitochondrial function, neuromuscular connectivity, inflammation, and the immune response. Notably, it plays a role in activating systemic and chronic inflammatory signals and signalling pathways, which depend primarily on the expression of Toll-like receptor 4 (TLR4), the activation of nuclear factor kappa-B (NF-κB), and the phosphorylation of c-Jun N-terminal kinase (JNK). An imbalance in microbial flora can damage epithelial cells and intercellular junctions. This promotes bacterial translocation and activates lymphoid tissue associated with the intestinal mucosa. This results in the recruitment of naïve T and B cells, triggering an innate immune response. This process leads to a chronic inflammatory cascade that fuels systemic inflammation and alters muscle function. This process results in a chronic inflammatory cascade that fuels systemic inflammation and impairs muscle function. Increased intestinal permeability, for example, facilitates the passage of microbial metabolites such as indoxyl sulphate (IS) and lipopolysaccharide (LPS) into the systemic circulation. These metabolites then exert pro-inflammatory and oxidative effects [31]. IS, in particular, is a bacterial derivative of tryptophan that promotes the production of inflammatory cytokines (TNF-α, IL-6 and TGF-β1) and reactive oxygen species (ROS). This contributes to skeletal muscle fibre atrophy and reduced contractile force, as demonstrated in cellular and animal models [32,33].

5. GUT MICROBIOTA AND MUSCLE FUNCTION: NEW THERAPEUTIC FRONTIERS IN POMPE DISEASE

The role of the gut microbiota in regulating physiological functions, including muscle metabolism, has seen a surge in interest. The microbiota is defined as the collection of microorganisms such as bacteria, fungi, archaea and protozoa that colonise various parts of the body, particularly the gastrointestinal (GI) tract. The microbiota is now considered a true metabolic and endocrine organ [34,35]. The ability to interact with the host organism through the production of bioactive metabolites, immune modulation and communication with distant organs makes it vital to the regulation of systemic homeostasis [36]. It is noteworthy that positive modulation can be achieved through targeted nutritional interventions, with particular attention to the use of specific dietary supplements (e.g. probiotics, prebiotics and postbiotics). This renders them of particular interest in the restoration of eubiosis and enhancement of muscle function (Figure 2).

In the context of Pompe disease, the modulation of the microbiota through dietary interventions has emerged as a promising strategy for enhancing the sarcopenic phenotype, which is characterised by reduced muscle mass, strength, and physical endurance. Intervening on the gut—muscle axis has the potential benefit of slowing the progression of muscle atrophy, improving quality of life and complementing existing drug therapies, while offering a non-invasive and customisable approach. It is essential to emphasise that the microbiome, defined as the set of genes present in the microorganisms of the microbiota, represents an integrative functional component of the human genome. Indeed, it is estimated that over 99% of the genetic material present in the human organism derives from these microbial communities. This substantial genetic reserve confers upon the microbiota a considerable and diffuse influence on the body's vital functions, thus rendering it a pivotal component in the medical field of the future. Consequently, the strategic therapeutic intervention of restoring and maintaining a healthy microbiota is not only pivotal in the prevention of chronic diseases, but also in the integrated management of rare diseases such as Pompe disease. The integration of clinical nutrition, microbiota modulation and drug therapy has the potential to create new scenarios for optimising muscle function and improving clinical outcomes. In the light of mounting evidence on the gut—muscle axis, particularly in Pompe disease, it is crucial to explore ways in which the gut microbiota can be modulated for therapeutic purposes. The homeostasis or dysregulation of the hypothalamic—pituitary axis is governed by a range of environmental and behavioural determinants. Among these, lifestyle, with particular reference to unbalanced diets, sedentary lifestyles and chronic stress, are the main determinants of dysbiosis, i.e. the pathological alteration of the composition and functions of the gut microbiota. In this regard, the adoption of healthy eating habits, supplemented by specific nutraceutical approaches, is a strategic lever for restoring intestinal eubiosis and, consequently, supporting muscle and systemic function in individuals with neuromuscular disorders. It is evident that the functional triad of probiotics, prebiotics and postbiotics plays a pivotal role in this regard, given its capacity to exert a favourable influence on the composition and metabolic activity of the intestinal microbial community [37—39]. Unlike probiotics, postbiotics are devoid of live microbes, a property that renders them particularly advantageous for patients who are frail or immunocompromised., Among the most studied postbiotics are short-chain fatty acid (SCFA). In particular,

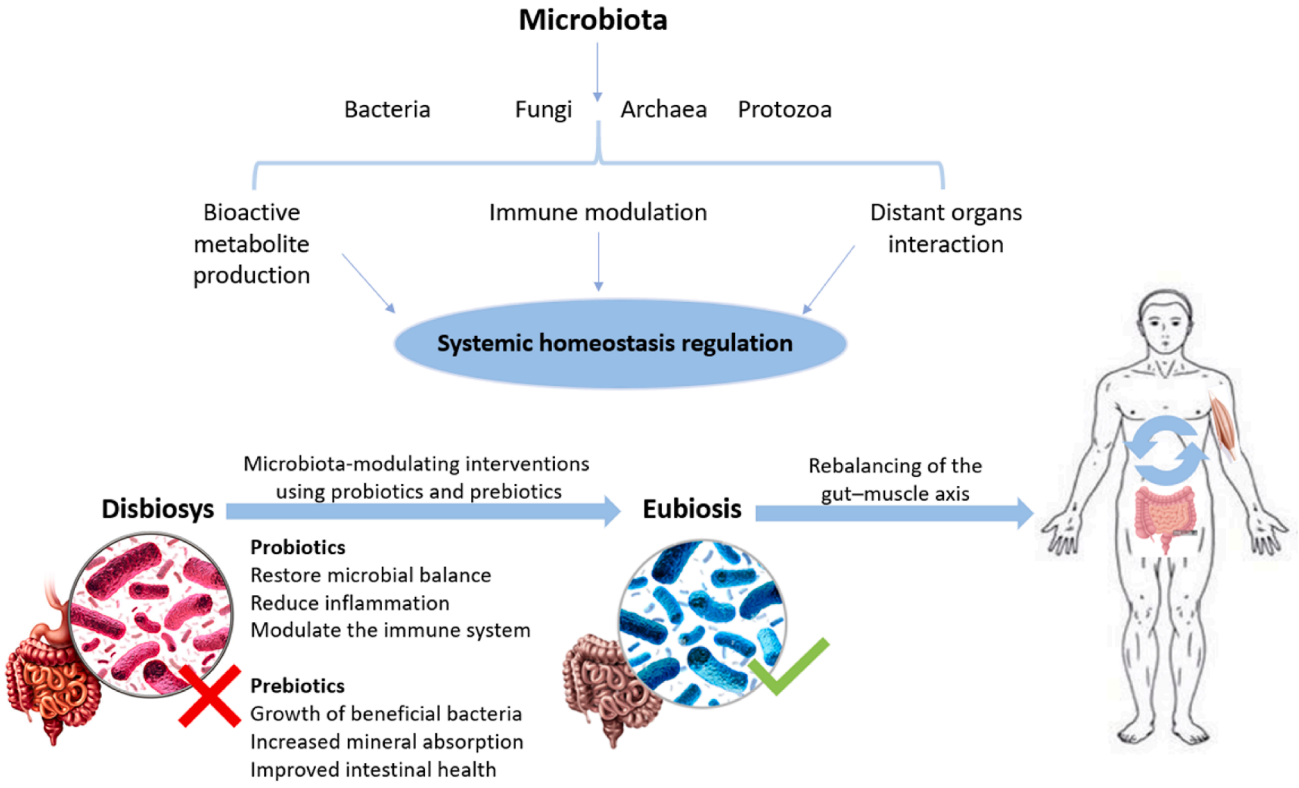

Figure 2: Diagram illustrating the role of gut microbiota in regulating systemic homeostasis. Intestinal dysbiosis (left) compromises the physiological balance of the body. Probiotics and prebiotics can be used to resolve this issue. Eubiotic microbiota (right) will help maintain metabolic, immune and muscle function at a systemic level by restoring the gut—muscle axis.

butyrate has been found to be the primary energy source for intestinal epithelial cells (IECs), thereby contributing to the maintenance of mucosal barrier integrity and the modulation of the immune response. Extensive evidence supports its immunomodulatory and anti-inflammatory activities, underscoring its potential role in the prevention of chronic inflammatory diseases. (such as ulcerative colitis and Crohn's disease) and in oncology (e.g. colorectal cancer) [40—43]. On a molecular level, short-chain fatty acids (SCFAs) exert their effects via activation of G protein-coupled receptors (GPCRs) (GPR41, GPR43, GPR109A) which mediate communication between the microbiota and the host immune system [38]. This biochemical signalling is fundamental to the balance between innate and adaptive immunity, influencing not only intestinal dynamics but also systemic responses, including muscular and metabolic ones. In relation to of Pompe disease and neuromuscular disorders more generally, the systemic effect of SCFAs, particularly their impact on reducing oxidative stress, improving insulin sensitivity and modulating muscle inflammation, further reinforces the importance of nutritional strategies aimed at modulating the microbiota. [8,9,44]. Nutritional supplementation with probiotics, prebiotics and postbiotics is therefore a complementary and potentially synergistic approach to conventional therapies in the management of Pompe disease and other conditions characterised by muscle dysfunction and systemic inflammation. In addition to its pivotal role in modulating the composition and function of the gut microbiota, diet also plays a strategic role in the clinical management of Pompe disease. In this context, the nutritional approach cannot be limited to intestinal support alone, but must also be geared towards preserving muscle mass and preventing protein catabolism. International guidelines for the nutritional management of patients with Pompe disease advocate constant monitoring of nutritional status and calorie and protein intake, with particular attention to energy balance [45—47]. A diet with a high protein density, providing 25—30% of total calorie intake, is a strategic nutritional parameter for supporting muscle protein turnover and limiting the progression of muscle catabolism, a particularly critical condition in patients with Pompe disease, especially in advanced stages or with reduced motor capacity. Implementing a diet with a high protein density, providing 25—30% of total calorie intake, is a strategic nutritional parameter for supporting muscle protein turnover and limiting the progression of muscle catabolism, a condition particularly critical in patients with Pompe disease, especially in advanced stages or with reduced motor capacity [48,49]. Proteins have been shown to play a key role in preserving lean body mass and supporting muscle anabolic processes in a clinical context already compromised by lysosomal enzyme deficiency and pathological glycogen accumulation. Additionally, it is essential to ensure an adequate total calorie intake, tailored to the individual's energy expenditure, remaining physical activity and metabolic status, in order to avoid negative energy balance situations, which could accelerate muscle atrophy and worsen functional performance. Although enzyme replacement therapy (ERT) is currently the most effective standard treatment for Pompe disease, it is not a cure and has limitations in completely counteracting the progression of the disease, particularly in the muscles. While the literature has proposed a number of additional therapeutic approaches that may be considered complementary, none of these approaches have yet been subjected to clinical validation as a co-treatment in combination with ERT. In this setting, recent evidence indicates that oral L-alanine supplementation (LAOS) effectively reduces muscle catabolism in experimental model systems. In addition to modulating the composition and functionality of the gut microbiota, diet also plays a strategic role in the clinical management of Pompe disease. In this particular scenario, which integrates specific nutritional approaches with advanced metabolic strategies, the most recent literature confirms the findings of the research group led by Tarnopolsky, which has contributed significantly to outlining the scientific rationale for the use of nutritional co-therapies in Pompe disease. Tarnopolskyand colleagues have documented how, in this context, ketogenic diets (KD) characterised by a high lipid intake (55—60%), moderate protein content (30—35%) and marked carbohydrate restriction (5—10%) have been proposed as substrate reduction therapy (SRT) [47—50]. Based on research conducted to date, it would appear that inducing nutritional ketosis (with plasma ketone body concentrations between 0.5 and 3 mM) may offer therapeutic benefits. In fact, it not only reduces glucose availability, but also influences molecular mechanisms relevant to the pathogenesis of Pompe disease, such as autophagy, oxidative stress and inflammatory processes [51—57]. Among ketone bodies, D-β-hydroxybutyrate has exhibited promising effects, including the reduction of reactive oxygen species, the inhibition of lipid peroxidation and protein oxidation, the improvement of endogenous antioxidant defences (e.g. superoxide dismutase, catalase), the promotion of mitochondrial respiration and the enhancement of ATP synthesis [56]. In preclinical models of hereditary muscle diseases, this compound has been shown to enhance muscle protein synthesis (MPS) and reduce both muscle and systemic protein breakdown (MPB), thereby preserving skeletal muscle mass (SM) [58,59]. In comparison with ketogenic diets, a more flexible dietary model is the low-carbohydrate, high-protein (LCHP) diet, typically comprising 35—40% fat, 25—30% protein, and 30—35% carbohydrates. This dietary approach has been proven to enhance quality of life and generate benefits comparable to those of the KD, while concurrently being more tolerable and sustainable in the long term. An alternative approach involves the use of exogenous ketones or ketone precursors (such as 1,3-butanediol), which enable the induction of a state of nutritional ketosis without the necessity of adherence to restrictive dietary regimens. These strategies appear to hold considerable therapeutic potential, both in regard to their direct metabolic effects and their ability to mitigate the muscle deterioration that is typical of Pompe disease [47,60]. Finally, supplementation with complete protein sources (e.g., whey, casein), essential amino acids (EAAs), branched-chain amino acids (BCAAs) and creatine has also been proposed as nutritional support that can act synergistically with existing therapies, particularly in patients at high risk of malnutrition or in advanced stages. However, the most recent evidence suggests that EAAs, BCAAs and essential amino acids have greater anabolic and therapeutic potential, providing a rational basis for future combined clinical studies [20,61]. Therefore, a diet rich in fermentable fiber, such as the Mediterranean diet, may enhance not only intestinal function but also muscle function through the targeted production of biologically active postbiotic metabolites.

6. GUT MICROBIOTA AS A BIOMARKER OF HEALTH STATUS

The gut microbiota contributes to human well-being by supporting key metabolic functions, such as energy production and storage, as well as the fermentation and absorption of undigested carbohydrates [4,62]. This symbiotic relationship has exerted strong selective pressure, making the microbiota a relevant biomarker of an individual's health status. A considerable number of studies have investigated its role in regulating the immune system, liver function, intestinal metabolism and even behaviour. However, the impact of this phenomenon on skeletal muscle has only recently been explored [4]. Emerging evidence indicates that the gut microbiota influences

muscle function by modulating oxidative stress, mitochondrial activity, neuromuscular connectivity, insulin resistance, and systemic inflammatory responses. These effects are mainly mediated by pro-inflammatory signals involving TLR-4 receptors, the NF-kB factor and JNK [5] kinase. In addition, skeletal muscle functions as an endocrine organ, producing myokines and cytokines that exhibit systemic effects, including on the gut microbiota [27]. It has been hypothesised that irisin, a hormone secreted by muscle and adipose tissue, may be implicated in the modulation of microbial composition. In fact, significant alterations in microbiota diversity are observed in mice knockout for the Fndc5/irisin gene [63,64]. These interactions provide robust support for the existence of a bidirectional gut—muscle axis. Furthermore, studies on germ-free mouse models reveal the presence of muscle atrophy and mass reduction, effects that are reversible through microbiota transplantation from healthy animals, suggesting a direct causal role of the microbial community in the regulation of muscle physiology [4]. In light of this research, Dow's group reported a case study in 2018 presenting the case of a 21-month-old Hispanic girl with Pompe disease and B-cell immunodeficiency, who developed recurrent infections with Clostridium difficile resistant to conventional antimicrobial treatments. Despite prolonged and compliant use of metronidazole and pulsed-dose vancomycin, the patient experienced nine recurrent episodes characterised by fever, foul-smelling diarrhoea and respiratory distress. Following a 12-month period of therapeutic interventions that proved ineffective, a faecal microbiota transplant (FMT) was performed, with the mother being the donor. This intervention resulted in complete resolution of symptoms and, after a 5-year period in which symptoms remained stable, the patient was considered to be in remission. The case study demonstrates the efficacy and cost-effectiveness of FMT as a therapeutic modality in treating refractory Clostridium difficile infections in paediatric patients with complex comorbidities, thereby attenuating the associated morbidity. However, the authors emphasise the need for further studies to be carried out on a scientific basis in order to confirm the safety and efficacy of this procedure in children [65]. This finding aligns with the observations reported in Pompe disease studies, which also highlight a substantial involvement of the gut—muscle axis in other hereditary neuromuscular disorders. Among these, Duchenne muscular dystrophy (DMD) is considered a paradigmatic model in which genetic alterations affecting the structural proteins of the sarcolemma are accompanied by systemic dysfunctions that also involve the gut microbiota [27]. Manifestations such as constipation, altered motility and pseudo-obstruction are frequent and attributable to atrophy of the intestinal smooth muscle, resulting in reduced fluid and calorie intake and the development of dysbiosis [27,66]. Taken together, these findings suggest that the interaction between the gut microbiota and muscle function is not a phenomenon exclusive to Pompe disease, but may represent a pathogenic mechanism common to several hereditary myopathies. The gut microbiota thus acts as a local modulator of the intestinal environment, as well as a systemic regulator capable of influencing muscle physiology, gene expression and the course of neuromuscular diseases.

7. MODULATION OF MICROBIOME GENE EXPRESSION

The gut microbiome, the result of a process of co-evolution with the human host, represents a dynamic ecosystem capable of profoundly influencing systemic physiology through the modulation of genetic, epigenetic and neuroendocrine processes. Beyond its role in digestion and metabolism, its composition and functional activities modulate both local and systemic immunity, confer protection against pathogenic challenges, and enable signaling interactions with distant tissues such as skeletal muscle. Evidence on the role of the microbiome in the gut—muscle axis and epigenetic mechanisms opens up new therapeutic approaches. However, targeted studies are still required to clarify the molecular mechanisms underlying these interactions and to validate their clinical efficacy. It is evident that there is a potential point of convergence between the microbiome and the epigenetics of the TSC2 (Tuberous Sclerosis Complex 2) gene, which encodes the tuberin protein. Functioning as a suppressor of the mTORC1 signaling cascade, this protein plays a central role in the regulation of cell growth, energy homeostasis, and mitochondrial biogenesis. Mutations in TSC2 are the basis of tuberous sclerosis, but the mTOR pathway is also implijurcacated in numerous muscular and metabolic disorders. Recent evidence suggests that the gut microbiota may modulate the mTOR pathway via metabolites such as SCFAs (e.g., butyrate), which act on epigenetic and post-transcriptional pathway, potentially influencing the expression or functionality of genes such as TSC2 [67]. Furthermore, signals derived from the microbiome may interfere with mTOR activity indirectly, through chronic inflammation or oxidative stress, both of which are known to alter TSC1/TSC2-mTOR signalling. Consequently, the crosstalk between the microbiome, epigenetic modifications, and the TSC2/mTOR axis is an emerging focus in research, offering potential avenues for the development of nutrigenomic and microbiota-directed interventions for muscle-related and hereditary conditions. The process is based on the modulation of the gut microbiome, which plays a crucial role in defining all genetic functions and environmental interactions of the totality of microorganisms living in a given environment, such as the human gut. A pivotal function of the intestinal microbiota is resistance to colonisation, which is defined as the ability of the microbial community to protect the host from invasion by enteric pathogens including enterohemorrhagic Escherichia coli (EHEC) O157:H7 [68,69]. This pathogen is responsible for the development of adherence-effacement (AE) lesions, which can lead to severe gastroenteritis, haemorrhagic diarrhoea and, in some cases, haemolytic-uraemic syndrome [70,71]. The microbiome has been found to be effective in counteracting infection by competing directly with pathogens or by modulating the intestinal barrier's defences and the local immune response [72,73]. However, the molecular mechanisms underlying this protection remain partly unexplored. A study conducted by Samantha A. Scott et al. showed that activation of the dopaminergic D2 receptor (DRD2) in the intestinal epithelium, induced by microbial metabolites derived from dietary supplementation with L-tryptophan, confers protection against Citrobacter rodentium, an AE (attack and eradicate) murine pathogen commonly used as a model for studying EHEC infections [74,75]. This work highlights a microbial-host metabolic axis involving neuroendocrine signals in the defence against intestinal infections. In addition to the genetic component, a growing body of evidence indicates that epigenetic mechanisms, such as DNA methylation, histone modifications and non-coding RNAs, are crucial in regulating disease severity and progression. In DMD, for instance, the dysregulation of muscle microRNAs (miR-1, miR-206, miR-486) has thus been demonstrated to be associated with defects in regeneration and increased fibrosis. Furthermore, bioactive nutritional compounds such as epigallocatechin gallate (EGCG, an important component of GTE) have been found to reduce muscle fibre necrosis, improve muscle resilience and delay the onset of the disease [76,77]. Similarly, (−) -epicatechin (EC), the main flavonoid found in cocoa, has been shown to improve mitochondrial function, reduce oxidative stress and minimise fibrosis in skeletal and cardiac muscle [78]. Omega-3 fatty acids, including eicosapentaenoic acid

(EPA) and docosahexaenoic acid (DHA), have been demonstrated to offer anti-inflammatory benefits in mouse models through a reduction in inflammation and oxidative stress, a modulation of epigenetic pathways, and an improvement in muscle function [79,80]. Analogously, phenotypic variability and heterogeneous response to enzyme replacement therapy (ERT) in Pompe disease, a type II glycogenosis caused by GAA enzyme deficiency, suggest epigenetic involvement. Recent studies hypothesise that the expression of GAA and the pathways associated with both autophagy (autophagy) and inflammation may be modulated by epigenetic signals and non-coding RNAs [81]. In light of the observations made in DMD, incorporating epigenetically active nutritional compounds could be a useful additional therapeutic approach for Pompe disease. The hypothesis that targeted dietary interventions, when combined with ERT, could improve clinical response by modulating the molecular environment of the muscle, is one that merits further investigation. However, further research is required to validate these approaches and elucidate the mechanisms involved. Consequently, the gut microbiome fulfils a dual role in maintaining mucosal integrity and influencing the systemic molecular environment. This active modulator exerts a significant impact on various physiological processes, including gene expression, epithelial signalling, and muscle physiology. The study presents a novel framework for investigating the gut—organ axis and for the rational design of microbiota-targeted nutritional or pharmacological approaches to preserve homeostatic balance and reduce susceptibility to inflammatory, infectious, and degenerative conditions.

8. DISCUSSIONS AND CONCLUSIONS

Alteration to the autophagic mechanism and inflammation appear to be two key concepts in the development and progression of Pompe disease. Autophagic blockage, caused by the accumulation of glycogen in the lysosomes, leads to high levels of CK, which is closely related to the secondary inflammatory response with consequent muscle dysfunction. The inflammatory response is indeed a key determinant of the extent of tissue degeneration. Although this topic has been extensively discussed in the literature, this review aims to underscore that, in recent years; the gut—muscle axis has emerged as an important modulator of the immune response. The microbiota, through its influence on immune cell activity, has also been shown to correlate with skeletal muscle tissue. These observations suggest the existence of a bidirectional communication between the intestinal microbiota and skeletal muscle in the pathophysiology of the disease, with a potential association between intestinal dysbiosis and muscle degeneration. In light of the potential contribution of the intestinal microbiota to Pompe disease, the involvement of the gut—muscle axis could open new perspectives both in the field of rare metabolic disorders and in that of microbiology. Indeed, the restoration of a eubiotic state—achievable through specific nutritional strategies and through the use of probiotics, prebiotics, and nutraceuticals—may promote the regulation of immune responses, the mitigation of inflammatory processes, and the stabilization of autophagic mechanisms, with potential positive effects on skeletal muscle function. The analysis of changes in the microbial gene expression profile induced by different classes of nutrients therefore emerges as an essential step for defining targeted and personalized interventions. Accordingly, a deeper investigation of the interactions between the intestinal microbiota and muscle tissue would thus help clarify the mechanisms underlying this bidirectional communication and their potential impact on the disease. Moreover, within the context of precision medicine, the combination of ERT and nutritional therapy may support the treatment of Pompe disease by counteracting the effects of muscle dysfunction and the autophagic and inflammatory processes characteristic of the condition, ultimately ensuring a better quality of life for affected patients.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

Marika Venezia: Writing — review & editing, Writing — original draft, Visualization, Validation, Resources, Methodology, Investigation, Formal analysis, Conceptualization. **Maria Russo:** Writing — review & editing, Writing — original draft, Visualization, Validation, Resources, Methodology, Investigation, Formal analysis, Conceptualization. **Paolo Colomba:** Investigation. **Carmela Zizzo:** Formal analysis. **Martina Vinci:** Visualization, Methodology, Investigation, Formal analysis, Conceptualization. **Emanuela M. Marsana:** Visualization, Methodology, Formal analysis. **Annalisa D'Errico:** Investigation. **Irene Giacalone:** Formal analysis. **Giovanni Duro:** Writing — review & editing, Visualization, Validation, Supervision. **Marta Moschetti:** Writing — review & editing, Writing — original draft, Visualization, Validation, Supervision, Resources, Methodology, Investigation, Formal analysis, Conceptualization.

DECLARATION OF COMPETING INTEREST

The authors declare that they have no competing financial or non-financial interests that could have influenced the work reported in this paper.

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