



DOES PHYSICAL EXERCISE ADAPTIVE-RESPONSE AND CANCER-RELATED CACHEXIA SHARE COMPONENTS OF THE UBIQUITIN PROTEASOME SYSTEM?

A resposta adaptativa ao exercício físico e a caquexia relacionada ao câncer compartilham componentes do sistema ubiquitina-proteassoma?

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ABSTRACT

Cachexia is a multifactorial syndrome characterized by a progressive loss of body mass, primarily in the skeletal muscle tissue and secondarily in the unilocular adipose tissue, resulting in patients' physical deterioration. The incidence of cachexia might be associated with a pathological pro-inflammatory state, common amongst cancer patients. The loss of mass and skeletal muscle function is promoted by the activation of the proteolytic ubiquitin-proteasome system (UPS) in the muscle fibers. Usually, pharmacological and nutritional treatments are mostly ineffective, despite the possible attenuation protein catabolism in skeletal muscle fiber in individuals with cancer-associated cachexia. However, it has been shown that the experience of regular physical exercises can reverse the skeletal muscle catabolic state in the cancer-associated cachexia. Intriguingly, the mechanisms related to exercise-induced adaptation might be shared with those triggered by cancer-related cachexia. Therefore, there are gaps in research regarding these shared mechanisms, especially when considering the effect of physical exercise in cachectic cancer individual. The present study addresses the known biological mechanisms of physical exercise regulating protein synthesis and hypothesizes a possible modulation of UPS in the cachexia associated with the various diseases.

Keywords: Cancer, cancer-related cachexia, skeletal muscle fiber, physical exercises, aerobic exercise, resistance exercise, resistance training; strength training; intracellular proteolytic system via ubiquitin proteasome.

RESUMO

A caquexia é uma síndrome multifatorial caracterizada pela perda progressiva de massa corporal, principalmente no tecido muscular esquelético e, secundariamente, no tecido adiposo unilocular, resultando na deterioração física dos pacientes. A incidência de caquexia pode estar associada a um estado pró-inflamatório patológico, comum em pacientes com câncer. A perda de massa e função do músculo esquelético é promovida pela ativação do sistema proteolítico ubiquitina-proteassoma (SUP) nas fibras musculares. Geralmente, os tratamentos farmacológicos e nutricionais são, em sua maioria, ineficazes, apesar da possível atenuação do catabolismo proteico na fibra muscular esquelética em indivíduos com caquexia associada ao câncer. No entanto, foi demonstrado que a prática regular de exercícios físicos pode reverter o estado catabólico do músculo esquelético na caquexia associada ao câncer. Curiosamente, os mecanismos relacionados à adaptação induzida pelo exercício podem ser compartilhados com aqueles desencadeados pela caquexia relacionada ao câncer. Portanto, existem lacunas na pesquisa sobre esses mecanismos compartilhados, especialmente quando se considera o efeito do exercício físico em indivíduos com câncer caquético. O presente estudo aborda os mecanismos biológicos conhecidos do exercício físico que regulam a síntese proteica e levanta a hipótese de uma possível modulação do UPS na caquexia associada a diversas doenças.

Palavras-chave: Câncer, caquexia relacionada ao câncer, fibra muscular esquelética, exercícios físicos, exercício aeróbico, exercício de resistência, treinamento de resistência; treinamento de força; sistema proteolítico intracelular via proteassoma ubiquitina.

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INTRODUCTION

Cachexia is a multifactorial syndrome characterized by the progressive loss of skeletal muscle tissue, in the presence or absence of adipose tissue loss, which cannot be reversed by conventional nutritional support⁽¹⁻⁵⁾.

This situation may occur in patients with cancer, chronic renal disease (CRD), heart failure (HF), chronic obstructive pulmonary disease (COPD), and other diseases^(1,2,6-10).

The prognosis of cachexia is cachexia is negatively associated with survival^(1,11-13). In cancer, the mortality of 40% of the patients is directly associated with cachexia^(3,13,14).

Previous studies have shown that individuals with cancer-associated cachexia present proteolytic degradation mainly due to the hyperactivation of the caspase-3 enzyme and the ubiquitin proteasome system (UPS), which may be associated with metabolic acidosis, insulin resistance, growth hormone resistance, chronic systemic expression of proinflammatory cytokines (leptin, α -1 melanocortin, acid glycoprotein, ceruloplasmin, C-reactive protein and others) and high production of glucocorticoids and angiotensin-2^(11,15). Therefore, it is reasonable to infer that the marked decrease in skeletal striated muscle content can be stimulated by the lack of control of the UPS^(6,12,16-18).

UPS is a proteolytic pathway of selective degradation of intracellular proteins and differs from other pathways due to its consumption

of adenosine triphosphate (ATP)⁽¹⁷⁾. Due to their importance in the process of protein degradation, some experimental therapeutic strategies aim to inhibit the UPS pathway⁽¹⁸⁾. However, alternative and effective forms of treatment, and especially of low cost, still need to be further investigated. In contrast, the regular practice of physical exercise has been suggested as a non-pharmacological therapeutic step to prevent and / or reverse the excessive muscular catabolism underlying the cachexia associated with cancer^(19,20). This recommendation is based on the fact that physical exercise (mainly resistance exercise) induces overexpression of the phosphoinositide 3 kinase / protein kinase B / mechanistic target of rapamycin pathway (PI3K / Akt / mTOR), which increases protein synthesis and inhibits proteolysis induced by the UPS pathway⁽²¹⁾. In addition, physical exercise decreases inflammation, oxidative stress and insulin resistance, providing a balance between protein degradation and synthesis^(20,21). Therefore, the deteriorating events of cachexia in cancer patients could be counter-balanced by increased energy expenditure (above basal levels) induced by body movements produced by the skeletal musculature. Consequently, the systematic organization of these physical activities (physical exercise) can be an important and low-cost strategy used to minimize the damages caused by cachexia excessive proteolysis^(19,20). Therefore, the purpose of this article is to formulate a hypothesis about the mechanisms of physical exercise in the

regulation of UPS and its possible effects in the treatment of cachexia. The further elucidation of this hypothesis (figure 1) should improve the understanding and definitely establish physical

exercise as an efficient and cost-effective treatment directly aimed for cachectic patients affected by various diseases.

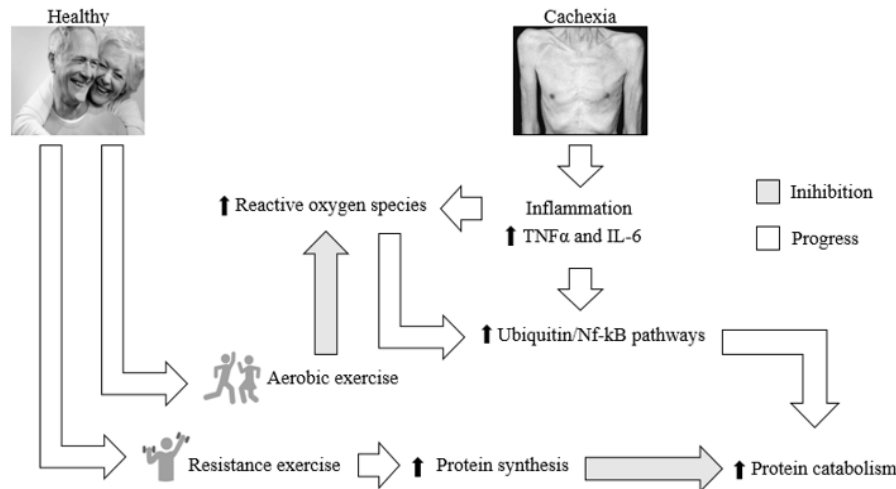


Figure 1 - Hypothesis of possible pathways modulated in healthy individuals and cachexia associated with cancer which might be influenced by physical exercise. Aerobic exercise contributes by attenuating the reactive oxygen species system activity, consequently contributing to the decrease in the ubiquitin-proteasome system activity. In addition, resistance exercise promotes increased protein synthesis, thus directly inhibiting the catabolic process.

General overview of cancer-related cachexia

Cancer-related cachexia (CRC) is currently defined as a multifactorial, often irreversible, paraneoplastic syndrome that is characterized by an involuntary weight loss (WL) caused mainly by progressive morphofunctional changes in the skeletal striated muscle tissues, in the presence or absence of morphofunctional modifications in the adipose tissues. In general, CRC is not reversed by conventional nutritional support and, clinically, promotes a progressive functional weakness of individuals with cancer. About 30% of deaths occurring in patients with cancer are promoted by CRC, especially due to the occurrence of respiratory failure caused by marked skeletal muscle weakness⁽¹⁻³⁾.

The etiology and pathogenesis of the CRC still has many aspects to be clarified. The occurrence of variation in the tumor phenotype or the host genotype might contribute to the development of CRC. The participation of pro-cachectic chemical mediators released from cancer cells or immune cells have a pivotal role in the assembly of many metabolic changes in target organs (skeletal muscle tissue, adipose tissue, brain, liver and others) during cachexia. Numerous pro-cachectic mediators influence the reduction of lipid stores in adipose tissues, but primarily, their greater influences occur in skeletal muscle fibers, which suffer a drastic dystrophy. Consequently, a generalized muscular weakness that seems to be

determined in a higher extent by the increased protein catabolism than by decreased protein synthesis in muscle tissue. Moreover, important metabolic changes in muscle tissue promote an increase in resting energy consumption⁽⁴⁻⁸⁾. In individuals with CRC, the loss of body weight is one of the most prevalent findings (rates between 50% and 80%, depending on the type of cancer) related to cancer progression. Although this condition is more frequently diagnosed in individuals with advanced malignancy, it has been evidenced that the weight loss begins during in the early stages of cancer (pre-cancer), when the primary malignancy may not even be clinically noted. Although the presence of anorexia (loss of appetite and/or early satiety during feeding) is frequently reported by patients with cancer, the decrease in food intake alone might not be the sole responsible for the increased physical consummation demonstrated by the patients. In patients with cancer, it has been observed that the progressive loss of skeletal muscle, accompanied or not by loss of adipose tissue, precedes the decrease in the consumption of food by patients. Additionally, nutritional supplementation or pharmacological stimulation of appetite in these individuals are unable to reverse the CRC⁽⁹⁻¹³⁾.

Clinically, CRC can be understood as a continuous process composed of three stages: pre-cachexia, cachexia, and refractory cachexia. However, not all patients with cancer go through this spectrum. In pre-cachexia, early clinical and metabolic signs such as, anorexia and glucose

intolerance, may precede substantial involuntary weight loss ($\leq 5\%$ of the individual's regular WL). The risk of progression of CRC varies and depends on factors such as the type of cancer and its staging, the presence of systemic inflammation, low food intake, and the lack of response to antineoplastic therapy. Patients with WL $> 5\%$ in the last 6 months, and a body mass index (BMI) of less than 20 kg/m² are considered cachectic. Refractory cachexia occurs in individuals with an advanced or rapidly progressive staging of cancer, who do not respond to antineoplastic therapy frequently. At this final stage, there is active catabolism promoted by malignancy and there is minimal possibility of WL recovery^(14, 15). Notably, both the amount and rate of WL occurring in individuals with CRC are directly related to high rates of morbidity and mortality in patients^(16,17).

General overview of the ubiquitin-proteasome proteolytic pathway

The ubiquitin-proteasome system represents the major, highly selective, intracellular protein degradation pathway found in eukaryotic cells. The UPS make its proteolytic action in two main steps: the first step consists in the substrate labeling, and the second step consists in the substrate degradation. In this complex proteolytic machinery occurs the participation of a 76-amino acid ubiquitin (Ub) polypeptide, or even polymers of Ub (polyUb), that are responsible for labeling substrates that need to be degraded via an isopeptide link between the C-terminus of Ub and a specific

lysine on the target substrate. In the second step, the 26S proteasome, a multicatalytic ATP-dependent chambered protease, is responsible for recognizing, translocation, and degradation of target substrates that are covalently linked to Ub or polyUb^(18,19).

The enzymatic process of Ub insertion into target molecules is known as ubiquitination. This process represents a reversible post-translational modification of a target substrate that will affect its fate, function, localization, protein-protein interaction, or stability. In this way, this epigenetic modification plays critical roles in regulating a broad range of pathophysiological processes in eukaryotes^(20,21). This diversity of roles is dependent of the length and topology of the Ub chains attached to the target substrate and the specificity and catalytic activity of certain enzymes (E1, Ub enzyme activating; E2, Ub enzyme conjugating; and E3, Ub enzyme ligating) that are required for labelling a target substrate. In human genome, occurs the encoding of several E1 enzymes, 35 E2 enzymes, and more than 500 E3 enzymes that are responsible for reaction of ubiquitination⁽²²⁾. Ub itself can be ubiquitinated at any of its seven lysines residues (K6, K11, K27, K29, K33, K48, or K63) and creating PolyUb chains. The type of modification of target substrate can occur as monoubiquitination, multiple monoubiquitination, and linkage of polyUb chains. Moreover, Ub can also be joined by a peptide bond to the N-terminus of another Ub with formation of a linear Ub chain, or to the N-terminus of the Ub-like protein (small ubiquitin-like modifier, SUMO). However,

knowledge about what makes a particular lysine residue and/or a particular substrate a good target for ubiquitination it is still a matter for debate⁽²³⁻²⁶⁾.

In concern to intracellular proteolytic pathway, Ub acts as a tag for degradation of specific substrates. In order to be recognized, captured, and posteriorly degraded by 26S proteasome, all protein substrate might exhibit the target signal (tag) (the presence of the Ub or polyUb conjugate to one or more ϵ -amine of lysine (Lys) residues in the target substrate). A LysK48-linked polyUb chain is thought to be the minimum signal for binding to the 26S proteasome. Moreover, a target substrate requires at least the presence of one or more tetraUb chain to be efficiently degraded by 26S proteasome^(25,27,28). Initially, E1 enzyme is responsible for energy-dependent covalent attachment Ub within the target substrate, which promotes activation of Ub by reacting its C-terminal (Gly75-Gly76) carboxylate with ATP to form a Ub-AMP adenylate. Posteriorly, Ub-AMP adenylate is captured by a catalytic cysteine residue of E1 leading to the formation of a thioester intermediate bond between Ub and E1 (Ub~E1). Subsequently, the Ub~E1 transfer Ub to form a Ub~E2 conjugation, via a transthioesterification reaction, with a Ub thioester intermediate. E3 ligases confer specificity of ubiquitination and play crucial roles in almost every cellular process, including substrate degradation^(29,30). E3 ligases have been categorized in three classes according to their enzymatic mechanisms:

- i. Homologous to the E6-AP C-terminus

(HECTs, E3 transfer the Ub from the E2 to an active site cysteine in the E3 before conjugating the Ub to the substrate), ii. Really Interesting New Genes (RINGs, E3 simply target E2 to the substrate), and iii. Ring-BetweenRing-Ring (RBRs, E3 ligase from RBR family may bind to both the E2 and the target substrate, promoting isopeptide bond formation with a substrate lysine)(31). Notably, the covalent Ub bonds can be reversed by specific deubiquitinating enzymes (DUBs). Many DUBs whose role is related to dynamic regulation of UPS through regulation of the quantity and activity of both E3 ligase and substrate. The DUBs are part of Ub ligase complexes that regulate proteolysis by directly interacting with and co-regulating ligases; altering the level of substrate ubiquitination; hydrolyzing or remodeling Ub and polyUb-substrates; acting in specific intracellular locations and changing the localization of the target protein; and acting on target substrate linked to 26S proteasome to facilitate or inhibit proteolysis⁽³²⁻³⁴⁾.

The 26S proteasome is a family member from AAA+ superfamily of ring-shaped P-loop NTPases (ATPases Associated with diverse cellular Activities). This superfamily of enzymes exerts many energy-dependent cellular activities. In turn, the 26S proteasome exerts a pivotal role for intracellular proteolytical activities^(35,36). The 26S proteasome is formed by a holoenzyme in chamber format 20S core particle (CP), comprising 28 related polypeptides, which represents a powerful and selective proteolytic

machinery, that is capped on one or both ends by a 19S regulatory particle (RP) (also known as the 19S particle and PA700), which is responsible for recognizing the molecular signaling, removal of Ub or polyUb tag from substrate, and substrate unfolding and translocation into the CP for degradation. The 26S proteasome orchestrates its diverse catalytic activities using dynamic conformational mechanisms to regulate the timing of its activity; its selection of substrates; and for protein degradation⁽³⁷⁾.

Soon after substrate has been target, this substrate is recognized as a signal by RP, which contains a heterohexameric ATPase ring and many additional specialized subunits. RP exhibits subunits and proteasome-associated factors positioned sequentially in a way that facilitates the manipulation of target substrate (i.e., recognition, deubiquitylation, the opening of the CP α -ring gate, and unfolding and translocation of target substrate into the CP) from the outer edges of the RP toward the CP pore for degradation. Due to these roles, RP functions as a highly regulated gatekeeper for the majority of proteasome substrates. Although many aspects of the RP atomic structure have not been completely determined yet, it has been evidenced that the RP gets organized into two subcomplexes, known as lid and base. The RP lid is a structure composed by the canonical six proteasome/COP9 signalosome/initiation complex domains (Rpn3, 5, 6, 7, 9, and 12), two Mpr1/Pad1/N-terminal subunits (Rpn8 and Rpn11), which contributes

isopeptidase activity to recycle ubiquitin moieties from the protein substrates, and a Sem1 protein, which also exhibit functions of recognizing and deubiquitylation of target substrate. The lid appears to act as a clamp that straddles the long edge of the RP, contacting both the base and the CP α -ring and keeping the RP and CP adhered. The RP base is a protein complex consisting of nine subunits: six RP triphosphatases (Rpt1-6), which form a heterohexameric AAA+ ATPase ring that contacts the surface of the CP α -ring and promotes the ATP-dependent unfolding force on substrate in order to facilitate its translocation into proteolytic chamber of CP for degradation, and three RP non-ATPases subunits (Rpn1, 2, and 13), which seem to act as scaffolds for positioning of the target substrate and other factors dock (Rpn 1 and 2) or acting as polyUb-substrate receptors (Rpn 13). The RP subunits are responsible for removing the polyUb tag and unfolding of the target substrate^(38,39). After removal of polyUb chains from target substrate due to action of DUBs, the Ub is released in the cytoplasm. The entrance into CP is usually occluded by N-terminal tails of specific α -subunits, which form an ordered gate that must be opened only for target substrates^(40,41). As the substrate must pass through a narrow central pore, it must be unfolded by AAA+ ATPases (Rpt ring) of RP. This ATPase ring also promotes ATP hydrolysis through a nucleophilic attack on the ATP gamma-phosphate by an activated water molecule, lead to movement of the N-terminal

and C-terminal AAA subdomains relative to each other. With this, it generates mechanical forces that are amplified by other ATPase domains within the same oligomeric structure, which push the unfolded substrate through central pore until it reaches the CP proteolytic chamber. This chamber is topologically defined by the inner surfaces of the four stacked heteroheptameric rings, two consisting of seven different alpha-subunit proteins (α -subunits 1-7) and the other two of seven different beta-subunits (β -subunits 1-7) that are assembled in to an $\alpha 7/\beta 7/\beta 7/\alpha 7$ architecture. The proteolytical chamber contains multiple catalytically active sites, which exhibit threonine residue (Thr1) residues at the amino terminal of the $\beta 1$ -, $\beta 2$ -, and $\beta 5$ -subunits. These multiple active sites ensure a rapid degradation of substrates that entered into CP hydrolytic chamber. Following proteolysis, short peptides derived from the substrate are released^(42,43).

It has been showed that exists a global regulation of the UPS that is mediated by direct modulation of the proteasome by regulators that directly associate with it, or promoting post-translation modifications in it, or promoting the transcription of genes for proteasome subunits⁽⁴⁴⁾.

Role of physical exercises in regulating UPS

The biological adaptations promoted by physical exercise have a recognized potential in the prevention of various diseases and the promotion of health in general^(19,20). One of the

important adaptations of physical exercise is the maintenance and / or hypertrophy of skeletal striated muscle tissue. This tissue corresponds to about 40% -50% of the total body mass and is fundamental in the synthesis of myokines regulating metabolism and general homeostasis. In contrast, exacerbated catabolism of muscle tissue negatively contributes to survival and is associated with mortality^(45,46).

Physical training promotes a favorable internal environment for the balance of protein synthesis and degradation rates within the skeletal striated muscle which has the capacity to adapt to the various stimuli of physical training^(15,47). Aerobic training exerts a high demand over oxidative metabolism, increasing the synthesis of peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1- α) and its interaction with the cAMP response element-binding protein (CREB), stimulating an upregulation for biogenesis mitochondrial^(48,49). In addition, it helps decrease insulin resistance, facilitating protein synthesis^(20,48).

In strength training, exercise can promote a substantial increase in the cross-sectional area of the muscle and improve the functional responses of muscle strength and power, as well as synthesize various hormones, anti-inflammatory cytokines and trophic factors, which positively influences function^(48,50). Such an anabolic response occurs predominantly via the insulin-like growth factor-1 / PI3K / Akt / mTOR (IGF1 / PI3K / Akt / mTOR) protein integration pathway, which

is highly expressed after the end of a resistance exercise bout (2051). Resistance exercise provides antagonistic effects to the activation of UPS because, while it increases protein catabolism, resistance exercise stimulates the increase of muscle hypertrophy after its completion⁽⁵²⁾. Interestingly, patients with rheumatoid arthritis submitted to resistance training show an increase in muscle IGF-1 synthesis^(52,53), which stimulates the IGF-1 / PI3K / Akt / mTOR pathway, potentializing protein synthesis⁽⁵³⁻⁵⁵⁾.

During the end of the resistance exercise, the activation of the signaling cascade proteins regulates the transcription and translation processes, consequently increasing the synthesis of proteins^(56,57). Thus, it is able to promote greater activation of Akt in the acute and chronically time⁽⁵⁷⁾. It is important to note that in addition to the increased activation of mTOR, promoted initially by the production of IGF-1 and leading to a cascade of activation by PI3K, pyruvate dehydrogenase kinase 1 and 2 (PDK1 and PDK2) and Akt, inhibition of the glycogen enzyme synthase kinase beta (GSK-3 β), reducing the inhibition of protein synthesis and contributing to skeletal muscle hypertrophy⁽⁵⁷⁾. In addition, remodeling of the skeletal muscle is also promoted by the calcineurin / NFAT pathway and by the satellite cells⁽⁵⁸⁾. The calcineurin / NFAT pathway is involved in the transition / modulation mechanism of skeletal striated muscle fibers which is regulated according to extrinsic (mechanical loading,

electrical stimulation) and / or intrinsic stimuli (intracellular levels of glycogen, ATP, K⁺, Ca²⁺, O₂)⁽⁵⁹⁾. When Ca²⁺ ions are elevated during the process of muscle contraction, the calcineurin pathway is activated, which later induces gene transcription and muscle remodeling. Therefore, this pathway is related to the alteration of the phenotypic profile of the skeletal striated muscle fibers according to the intensity and volume targeting of the physical training⁽⁶⁰⁾. On the other hand, satellite cells are found between the basal lamina and the sarcolemma of the skeletal myocyte and have the capacity to specialize and fuse, structuring new muscle fibers^(61,62). The differentiation leads to muscle hypertrophy after damage as a function of microleakage factors, such as resisted exercise⁽⁶³⁾, which initiates the acute inflammatory response, which provides an increase in the migration of macrophages and neutrophils to the muscular structure. Such response is important to activate the action of satellite cells through IL-6, promoting an anabolic environment after the resistance training session ^(55,63).

In addition to the aforementioned mechanisms of muscle integrity control, it should be emphasized that all these phenomena present an indirect relation with UPS, since physical exercise generally contributes to the maintenance and / or increase of the skeletal muscle structure in antagonism to the various mechanisms of action of the UPS⁽²⁰⁾. However, it is possible to speculate a direct relationship between physical

exercise and UPS. The Akt stimulation promoted by the mechanical deformation of the muscle fibers in the resistance exercise session promotes the phosphorylation of the fork-head Box o family transcription factor (FOXO), inhibiting the incitation of the transcription of UPS ubiquitins ligases^(50,58,64) (Figure 2). Resistance exercise overload would result in a decrease in UPS action, since FOXO inhibition reduces the gene expression of the ubiquitin ligase proteins atrogin-1, muscle RING finger 1 (MuRF1) and muscle atrophy F-box (MAFbx), reducing ubiquitination and, consequently, muscle catabolism^(50,58,64,65). Therefore, resistance-induced skeletal muscle hypertrophy may occur due to the activation of IGF-1 / PI3K / AKt / mTOR and inhibition of FOXO and GSK3-β^(64,65).

Some studies illustrate a direct relation of the physical exercise in the UPS related to the suppression of FOXO isoforms, while other findings support the anti-inflammatory and antioxidant mechanisms of the exercise, highlighting the biological phenomena indirect to the UPS. Konopka et al showed that elderly women who underwent aerobic exercise reduced the amount of FOXO3A and myostatin after 12 weeks of training⁽⁶⁶⁾, suggesting that even aerobic exercise may contribute to the regulation of protein synthesis. In vitro, it was demonstrated that the IGF1 / PI3K / Akt pathway may block the ubiquitin ligase-positive regulation induced by the action of dexamethasone on the activation of MuRF1 and MAFbx, promoting a blockade

of FOXO. This study showed that signaling for muscle hypertrophy inhibited the action of FOXO^(64,65,67), allowing to speculate about a possible inhibition of UPS. In addition, cultured myotubes submitted to atrophy showed decreased activity of the PI3K / AKT pathway when the activation of FOXO transcription factors and induction of atrogin-1 occurs. However, treatment with IGF-1 or overexpression of Akt inhibited the expression of FOXO and atrogin-1^(64,65,67) which reinforces the antagonistic relationship of these pathways.

In human quadriceps muscle biopsies, a 10% increase in muscle hypertrophy was observed immediately after 8 weeks of resistance training, with an increase in the synthesis of phospho-Akt, phospho-GSK-3B and phospho-mTOR. This increased activity was accompanied by decreased FOXO1 isoform. On the other hand, ceasing of the training is followed by a 5% decrease in skeletal muscle structure, a decrease in phospho-Akt and GSK-3 and an increase in FOXO1^(64,65,67,68).

In a study with short-term resistance training with elderly and young adults, training was associated with an increase in the synthesis rate of the main contractile proteins in mixed muscles in both the elderly and young adults⁽⁶⁹⁾. Another experimental model study with females Wistar rats performing electrostimulation twice a week for six weeks resulted in 13.9 and 14.4% hypertrophy in the extensor digitorum longus and anterior tibial muscles, respectively^(69,70). In a distinct setup, female Sprague-Dawley rats trained in different

intensities (~55%, ~65% and ~75% of the maximum oxygen consumption) for 10 weeks on a motorized treadmill. In all muscles, citrate synthase (CS) activity increased with exercise duration. The changes induced by training in superoxide dismutase (SD) and glutathione peroxidase (GPX) activities increased significantly in the analyzed muscles, reinforcing the contribution of aerobic training to the antioxidant activity⁽⁷¹⁾.

Although the acute response of physical exercise results in catabolism, the post-exercise compensatory process rebalances the organic system, stimulating protein synthesis and inhibiting UPS activating agents. Such phenomena produce a positive response in the preservation of the skeletal muscle structure, showing encouraging prospects for the treatment of cachexia⁽⁴⁵⁾.

Regular physical exercise could potentiate the inhibition of UPS components in favor of skeletal muscle hypertrophy in individuals with cancer-related cachexia

The previously described mechanisms of physical exercise promote cellular alterations, which can lead to improvements in CRC development and outcomes^(45,46). An important example is increased insulin sensitivity and improved endothelial function, associated with increased physical capacity and reduced fatigue, promoted by aerobic exercise in cancer patients⁽⁴⁶⁾. In addition, the increase in the synthesis of anti-inflammatory cytokines (eg IL-10) and, consequently, the elevation of the expression of proinflammatory

cytokine antagonists (eg IL-1ra), contribute to the reduction of chronic inflammation, an ideal environment for the maintenance and/or increase of muscle tissue volume^(45,46).

It is important to emphasize that for the regulation of muscular integrity, both aerobic exercise and resistance exercise are fundamental. However, effects with a direct relation on the muscle cell are seen in response to resistance training, since in addition to decreasing chronic inflammation, it promotes the protein synthesis responsible for the increase in the cross-sectional area of muscle fibers^(48,72). Such direct and indirect mechanisms of inhibition of UPS in addition to the antioxidant, anti-inflammatory and anabolic effects of physical exercise create a favorable environment for the potentiation of treatment for patients with CRC.

In line with this hypothesis, there might be a role for exercise in the maintenance or hypertrophy of skeletal muscle^(47,73). Literature in general is scarce in relation to the central theme of this article, however, there are strong evidences associating these mechanisms with CRC condition. In fact, a the increased activity of FOXO induced by glucocorticoid secretion and by the action of myostatin, is a typical situation in several chronic diseases due to the chronic inflammatory condition characteristic of CRC^(15,65,66).

A study of mast cell mice treated with RNA oligonucleotide showed that when there is a reduction in FOXO-1 expression, there is a decrease in myostatin concentrations and inversely, there is an increase in skeletal muscle volume⁽⁶⁵⁾.

A study where the physiological importance of FOXO activation in the progression of muscle atrophy associated with cachexia in mice inoculated with lung carcinoma cells was verified, showed that the inhibition of the transcriptional activity of FOXO prevents muscle fiber atrophy during cachexia and induces hypertrophy⁽⁶⁴⁾. Complementarily, Walker 256 tumor-bearing rats submitted to a resistance training and fish oil supplementation paradigm presented attenuated cachexia and reduction of tumor growth⁽⁷⁴⁾. In addition, despite the indirect relationship of aerobic training, Swiss mice inoculation with C26 submitted to 4 days of voluntary aerobic activity showed lower tumor growth and increased skeletal muscle mass⁽⁷⁵⁾.

Taken together our hypothesis could be better depicted in the model presented in Figure 2. In that schematic representation, we sought to bring together the current scientific research enlightening the potential role for physical exercise as a non-pharmacological treatment for cachexia associated with cancer in the molecular perspective.

CONCLUSION

Although there is still no complete understanding of the role of physical exercise in UPS in the cachectic individual, it is of note that the various biomolecular manifestations involved in the physical exercise-related processes of protein synthesis and catabolic inhibition might be useful in the treatment of cachectic cancer patients. The mechanisms connecting these effects should encompass the FOXO's pathway, with a possible role in the process of consolidating UPS's understanding in this sensitive population. Therefore, clinical and experimental studies on the subject should be encouraged in order to improve the understanding of the molecular mechanisms involving the UPS during physical exercises performed by individuals with cancer-associated cachexia. The achievement of consistent evidence regarding the role of physical exercise in direct and indirect molecular regulation of UPS in skeletal muscle fibers will be fundamental significance for the establishment of newer e lesser burdening therapeutic strategies for cachexia treatment.

Competing interests:

The authors have declared that no competing interests exist.

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Observação: os/(as) autores/(as) declaram não existir conflitos de interesses de qualquer natureza.