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Resistance Exercise's Ability to Reverse Cancer-Induced Anabolic Resistance

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Abstract

Skeletal muscle has the dynamic capability to modulate protein turnover in response to anabolic stimuli, such as feeding and contraction. We propose that anabolic resistance, the suppressed ability to induce protein synthesis, is central to cancer-induced muscle wasting. Furthermore, we propose that resistance exercise training has the potential to attenuate or treat cancer-induced anabolic resistance through improvements in oxidative metabolism.

Summary for TOC

Resistance exercise training can reverse cancer-induced anabolic resistance through improved oxidative metabolism.

Keywords

Protein Synthesis; Skeletal Muscle; Cancer Cachexia; Mitochondrial Function; Quality Control; Muscle Contraction; mTORC1; Oxidative Metabolism

INTRODUCTION

Cancer cachexia is a complex skeletal muscle wasting disease that accounts for 20–40% of cancer-related deaths and contributes to patient morbidities (e.g. toxicity, poor chemotherapy adherence, impaired activities of daily living) and mortality (1). Currently, cancer patient survival is negatively affected by a lack of treatment options. The absence of successful therapies for the cachectic condition likely results from the disease's multimodal etiology and the heterogeneity of cancer pathology amongst patients (1, 2).

Skeletal muscle mass is maintained by balancing protein synthesis and breakdown, which fluctuates throughout a 24-hour period (3). The regulation of protein turnover is influenced by circulating hormonal and inflammatory signals as well as varied responses to caloric

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input and activity level (3, 4). The inability to stimulate protein synthesis in response to anabolic stimuli, termed anabolic resistance, has been observed in aging and wasting conditions (5–7). Furthermore, disrupted proteostasis and oxidative metabolism are well-described in cachectic muscle (8–10). However, the mechanisms of cancer-induced anabolic resistance are not thoroughly understood. A promising therapeutic option for overcoming anabolic resistance in cancer patients is resistance exercise training (7, 11), which can increase skeletal muscle mass and metabolic flexibility in healthy adults (4, 12–14).

Regular physical activity and exercise provide clear benefits for individuals with chronic diseases (11, 15). Indeed, resistance exercise induces systemic and muscular adaptations, such as antioxidant production (16), hypertrophy (13), protein turnover (12), increased oxidative capacity (17), upregulation of hormetic factors (4), and turnover of mitochondria (17). Hypertrophic adaptations to resistance exercise can be correlated with intermuscular signaling rather than systemic changes (13). Additionally, resistance exercise can suppress intrinsic skeletal muscle signaling that has been associated with cachexia development and progression (11). Resistance exercise-induced muscle gene expression and intracellular signaling have the potential to induce anabolic responses while in a catabolic systemic environment (18). Given that a substantial number of cancer patients are cachectic at the time of diagnosis (1), investigating the effects of resistance exercise on the cachectic muscle pathology is clinically significant.

In this review we explore the hypothesis that cancer-induced anabolic resistance is a critical driver of muscle wasting and can be associated with dysfunctional oxidative metabolism. Furthermore, resistance exercise training has the potential to improve cachexia-induced anabolic resistance and mitochondrial dysfunction. First, we discuss how resistance exercise regulates muscle protein synthesis through mTORC1 and the role of oxidative metabolism in this process. We then define the cancer-induced mechanisms that could be responsible for anabolic resistance in cachectic muscle, highlighting the importance of muscle oxidative metabolism and mitochondrial function. Lastly, we consider resistance exercise's ability to attenuate cancer-induced anabolic resistance and mitochondrial dysfunction in cachectic muscle.

RESISTANCE EXERCISE'S REGULATION OF MUSCLE PROTEIN SYNTHESIS

Resistance exercise is a potent stimulator of skeletal muscle protein synthesis, which is critical for muscle hypertrophy (3, 4). Translational control of muscle protein synthesis is tightly coupled to cellular growth and metabolism, as has recently been reviewed (8). The synthetic potential of muscle proteins is articulated by ribosomal capacity and the efficiency of mRNA translation, which contributes to the physiological anabolic response following resistance exercise (4, 8). Regulation of muscle protein synthesis by nutrients, hormones, and contraction can be mediated by the mammalian/mechanistic target of rapamycin (mTOR) (19). mTOR is a serine/threonine kinase that functions in two distinct complexes, mTOR complex 1 (mTORC1) and 2 (mTORC2), to regulate specific processes, dependent on cellular demands (19). mTORC1 regulation of both translational capacity and efficiency

is responsive to endogenous (e.g. ATP concentrations) and exogenous (e.g. mechanical stretch) stimuli that converge on mTORC1 through several distinct upstream signaling cascades (Figure 1) (4, 19, 20). mTORC1 initiates protein synthesis by phosphorylating the eukaryotic initiation factor 4E binding protein 1 (4E-BP1) and the p70 ribosomal S6 kinase (p70S6K) (19). The hyperphosphorylation of 4E-BP1 prevents its binding to eukaryotic initiation factor 4E (eIF4E) and subsequent formation of 4E-BP1-eIF4E complex, thus relieving the inhibition on translation initiation (19). In addition, S6K1 activation by mTORC1 has been implicated in cap-dependent translation, elongation, and ribosomal biogenesis (19). Indeed, mTORC1 is critical for the integration of protein synthesis and anabolic signaling in skeletal muscle and is a potential target for treatment of cancer-induced anabolic resistance.

A single bout of resistance exercise can stimulate myofibrillar and mitochondrial protein synthesis for several hours in healthy adults (12, 14). Exercise intensity, workload, nutritional state, and training status can all affect the duration and magnitude of this response (21, 22). mTORC1 activation holds an established role in resistance exercise-induced muscle protein synthesis. Indeed, increased muscle protein synthesis and hypertrophy through stimulated contractions or mechanical loading in mice is associated with mTORC1 activation (20, 23). Furthermore, rapamycin administration inhibits mTORC1 in humans, blocking the resistance exercise-mediated induction of protein synthesis (24). A single bout of resistance exercise can induce mTORC1-lysosomal translocation at the cell periphery, which serves to facilitate pro-synthetic signaling in human skeletal muscle (25). Evidence also suggests that the induction of mTORC1 activation through mechanical signaling can occur independent of Akt signaling (23). Collectively, these studies suggest that mTORC1 cellular localization and activation are critical for resistance exercise-induced effects on muscle protein synthesis. However, further investigation is required to determine if these mechanisms are viable in cachectic skeletal muscle.

Protein synthesis is an energetically demanding process, which is needed for cellular respiration and mitochondrial function (26). Oxidative metabolism consists of several compartmentalized processes that ultimately serve to produce ATP, and it is closely linked to overall mitochondrial quality and function. Mitochondrial biogenesis, dynamics (fusion and fission), and mitophagy are processes that articulate mitochondrial quality (9, 27, 28). Given that mTORC1 function is associated with cellular energy homeostasis, the fact that it has been implicated in the regulation of these physiological processes is not surprising (19, 29). Mitochondrial biogenesis is regulated in part by nuclear receptors (e.g. estrogen-related receptor (ERR α)) and transcriptional coactivators (e.g., peroxisome-proliferator gamma-activated receptor (PGC-1 α)) (29). mTORC1 inhibition can disrupt YY1 and PGC-1 α association to negatively regulate transcription of the nuclear-encoded mitochondrial genes (29). mTORC1 can also regulate nuclear-encoded mitochondrial mRNAs and mitochondrial ribosomal protein translation through a 4E-BP1-dependent mechanism (19). Additionally, mitochondrial hyperfusion and cytotoxicity can be regulated through mTORC1-dependent translation of mitochondrial fission process 1 (MTFP1) (30). Autophagy inhibition can also occur by mTORC1 phosphorylation of pro-autophagic UNC-51-like kinase (ULK1) (19). While mTORC1 and mitochondrial function are strongly integrated, further study is required to determine the effect of resistance exercise on the regulation of these mechanisms.

Nevertheless, there is evidence for mTORC1 regulation of mitochondrial homeostasis, which could have significant implications in muscle wasting.

Resistance exercise training has a substantial potential to improve mitochondrial function in healthy individuals (17, 21). Variations in metabolic capacity and mitochondrial content within myofibers are observed in the myosin heavy chain (MHC) delineated skeletal muscle fiber types (4, 10). Myofibers classified as “fast” glycolytic (type II(B,X)), “fast” oxidative-glycolytic (type IIA), and “slow” oxidative (type I) differentially regulate oxidative phosphorylation (OXPHOS), the process of producing ATP (4, 10). Interestingly, an increase in contractile activity has been shown to improve oxidative capacity in both oxidative and glycolytic muscle fibers (31, 32). Proteins and mRNA levels responsible for OXPHOS are increased by resistance exercise, including those regulating the electron transport chain (ETC), nicotinamide phosphoribosyltransferase (NAMPT), COXIV, mitochondrial respiration, and oxidative capacity (17). In addition to direct effects on mitochondrial oxidative capacity, resistance exercise can improve metabolism through the induction of glucose transporter type 4 (GLUT-4) concentrations at the cellular membrane (33). Similarly, insulin-like growth factor 1 (IGF-1) is upregulated during resistance exercise. Enhanced activity in the GLUT-4 and IGF-1 pathways can increase the productivity of glycolytic metabolism, upstream of OXPHOS to ultimately bolster ATP production (4, 33). Therefore, by improving the oxidative capacity of mitochondria, resistance exercise could precipitously serve to increase the pro-synthetic capacity of skeletal muscle proteins in response to anabolic stimuli.

MECHANISMS OF ANABOLIC RESISTANCE IN CACHECTIC MUSCLE

Given that cachexia is a progressively intensifying condition, small diminutions in muscle mass over the diseases evolution could have long-term ramifications related to prognosis, outcome, and survival (1, 2). Recently, it has been suggested that decrements in post-prandial muscle protein synthesis (8%–10%) could promote significant muscle loss over time (34). Typically, the anabolic response to nutritional input (*e.g.*, insulin, IGF-1, branched chain amino acids (BCAAs)) or muscle contraction is observed within several hours after acute stimulus (12, 14, 35). Anabolic stimuli can cause an increase in skeletal protein synthesis that is accompanied by a suppression of protein breakdown (3, 34). Indeed, increasing circulatory BCAAs through diet or supplementation can act as a highly potent stimulator of synthesis in a dose-dependent manner (34–36). Unfortunately, the onset of anabolic resistance results in a blunted or absent response to anabolic stimuli, which can disrupt proteostasis, diminish the muscle’s ability to stimulate protein synthesis, and ultimately result in net protein breakdown (6, 34, 37, 38). The lack of anabolic sensitivity within cancer patients to nutrition and exercise may greatly contribute to muscle wasting.

In cachectic pathology, the net balance of skeletal muscle turnover is skewed negatively, which is exacerbated as cachexia progresses (Figure 2) (38, 39). Disrupted proteostasis is observed in early stages of weight loss (<5%) in clinical cancer models (37, 40, 41), but the temporal progression of anabolic resistance and the contribution to overall muscle wasting have not been clearly defined. Cancer patients can still induce protein synthesis in response to protein-rich nutrients (40), but this induction is severely impaired and is further

diminished with the progression of cachexia (39, 41). While a high carbohydrate diet or insulin-sensitizing medication can increase muscle protein synthesis in cachectic lung cancer patients (37), the anabolic response to increased protein and/or carbohydrates has not been thoroughly investigated during the initiation and progression of cachexia. Additionally, while BCAAs can stimulate muscle protein synthesis through mTORC1 signaling, the effect of BCAAs on tumor metabolism may have implications for systemic metabolism and anabolic resistance (1). While this has not been thoroughly investigated in cancer cachexia, BCAA administration has increased skeletal muscle protein synthesis in tumor-bearing mice without any measurable effect on tumor mass (36).

Disrupted mTORC1 signaling (36, 42) and impaired mitochondrial function (27, 28) are widely investigated as critical drivers of the cachectic phenotype. Evidence suggests that aberrant muscle oxidative metabolism coincides with suppressed protein synthesis and mTORC1 signaling (8). Indeed, the expression, signaling, and positive effectors of mTORC1 are diminished in preclinical and clinical studies of wasting muscle, including its downstream targets S6K1 and 4E-BP1 (36, 42). Furthermore, it is possible that in cachectic muscle the dissociation of TSC2 from Rheb is not initiated by anabolic stimuli, leading to decreased mTORC1 signaling (25). Therefore, the muscle's sensitivity to nutrients and contraction mediated by mTORC1 may also be suppressed. mTORC1's role in integrating hormonal, nutritional, and exercise stimuli suggests that it could serve as a critical regulator for cancer-induced anabolic resistance.

Basal AMPK acts as an important sensor of nutrient availability and actively regulates the balance between anabolic and catabolic pathways (42). Indeed, the dysregulation of 5'-AMP-activated protein kinase (AMPK) may also induce anabolic resistance during cancer cachexia (26, 42). While mTORC1 and AMPK contribute cooperatively to the synthesis of mitochondria through PGC-1 α , antagonistically, AMPK counteracts mTORC1 in the stimulation of Ulk1 and mitophagy (19). Cancer-induced inflammation involving AMPK holds an established role in the disruption of mTORC1 signaling and mitochondrial quality control, as observed in cultured myotubes where the inhibition of AMPK returns mTORC1 signaling (42). Several additional lines of evidence demonstrate the ability of cancer to impair mitochondrial biogenesis, dynamics, and autophagic pathways (27, 28). The cachexia-induced metabolic disruptions involving AMPK and mTORC1 signaling have the potential to exacerbate anabolic resistance, while further stressing the muscle through increased oxidative stress and inflammation (19, 21, 26, 42).

In addition to disturbances of energy production, mitochondrial dysfunction can promote the excessive production of reactive oxygen species (ROS) in muscle (16, 27). The damaging role of ROS in skeletal muscle and wasting conditions has been reported extensively (16, 22, 27, 43). Perturbations in protein synthesis, calcium imbalances, and cellular stress from exogenous and endogenous sources can all cause and be disseminated by ROS (16). Additionally, surplus ROS production can impart oxidative stress to cellular proteins and organelles (e.g. endoplasmic reticulum) and can activate the unfolded protein response (UPR) (43). Under normal physiological conditions the UPR functions to minimize accumulation of damaged proteins and restore homeostasis within the muscle (43). Dysregulation of the UPR's mechanisms occur due to direct ROS contact as well as

perturbations in calcium regulation (e.g. CaMKII) and specific pathways involving mitophagy and apoptosis (e.g., Bcl-2) (43). Long-term activation of the UPR may contribute to atrophy and play a role in the suppression of an anabolic response within muscle. While the roles of ROS and UPR in cancer-induced muscle wasting are still being established, they have the potential to perpetuate anabolic resistance during cancer cachexia (16, 22, 27, 43).

THE EFFECT OF RESISTANCE EXERCISE ON CANCER-INDUCED ANABOLIC RESISTANCE

While the benefits of regular physical activity and exercise are well-established in preclinical models (20, 44, 45), gaps remain in our understanding of the anabolic response of cachectic muscle to resistance exercise. Nevertheless, current research suggests that resistance exercise may abrogate the wasting phenotype, increase lean muscle mass and overall bodyweight, upregulate anabolic hormones, increase chemotherapy adherence and success, and improve quality of life in patients with wasting pathology (7, 11). Preclinical studies of skeletal muscle hypertrophy have demonstrated that increased loading can prevent muscle mass loss (31), especially when performed prior to the development of cancer cachexia (45). We have reported that the anabolic response of skeletal muscle to eccentric contraction (ECC) in tumor-bearing mice includes the ability to stimulate mTORC1 signaling in response to an acute bout, while the overall capacity for protein synthesis remained suppressed (32). These results suggest a disconnect between mTORC1 activation and protein synthesis in cachectic skeletal muscle, and the nature of that disconnect warrants further investigation.

Resistance exercise has the potential to ameliorate muscle anabolic resistance through intrinsic mechanical and metabolic pathways. However, many patients with cancer cachexia exhibit reductions in their physical activity (1). Indeed, we have found that cage activity and volitional strength in tumor-bearing mice is inversely proportional to cachexia severity (44). Uncontracted muscle cannot stimulate general mechanical pathways through integrins, MAPK, and phosphatidic acid (PA) that would serve to induce protein synthesis (4). Furthermore, disrupted mTORC1 activity can hinder mechanical sensitivity to contraction and may lead to a decrease in muscle mass (23, 24). All of these changes could negatively affect muscle oxidative metabolism and exacerbate atrophy (4). Therefore, the contribution of sedentary behavior to cancer-induced anabolic resistance should be considered when examining muscle protein synthesis, especially in patients with sarcopenia (5–7). Indeed, the positive effects of muscle mechanical signaling on oxidative metabolism hold promise as an intervention to ameliorate cancer cachexia.

As discussed previously, cachectic muscles demonstrate increased levels of oxidative stress and inflammation, in addition to impaired mitochondrial function (27, 28). Studies have clearly established the benefits of resistance exercise in muscle in regard to reduction of oxidative stress (11, 22). In response to resistance exercise, muscle fibers can activate non-enzymatic and enzymatic antioxidants (e.g., superoxide dismutase, glutathione) in order to convert ROS into less reactive species, scavenge ROS, and/or limit the availability of pro-oxidants (22). Furthermore, the reduction of ROS as an effect of resistance exercise can benefit myofibrillar structure and signaling through increasing calcium sensitivity and

MAPK pathways (22). Many of these ROS-control systems are active within the mitochondria, where ROS are primarily produced (22, 43). Mitochondria also serve as a contemporaneous integration point of inflammation, often mediated through AMPK signaling (28). We have shown that AMPK signaling is elevated during IL-6-induced cachexia in tumor-bearing mice (42, 44). AMPK also inhibits mTORC1 through the upstream regulator TSC2 (tuberous sclerosis complex 2) and the subunit Raptor (42). While resistance exercise temporarily increases IL-6, chronic AMPK activation by IL-6 in cachectic muscle promotes protein breakdown, disrupts autophagic processes, and contributes to insulin resistance (28, 42, 44, 46). We have demonstrated that treadmill exercise can mitigate IL-6-induced muscle wasting in tumor-bearing mice, which coincided with AMPK activity (44). Furthermore, administration of a systemic inflammatory inhibitor (pyrrolidine dithiocarbamate (PDTC)) improved both basal (47) and ECC-induced protein synthesis (48). Indeed, a number of reports show that resistance exercise can regulate inflammatory mediators of muscle wasting (4, 11, 32, 48). Overall, homeostatic decreases of ROS and inflammation in the gross cellular environment imputed by resistance exercise may translate to a greater anabolic response and decrease wasting.

Evidence suggests that mitochondrial depletion within muscle can precede cancer-induced wasting (27). Indeed, cachectic muscle demonstrates a reduction in metabolic capacity in both oxidative and glycolytic fiber types (10, 32). Resistance exercise may prevent cancer-induced mitochondrial loss in muscle by increasing mitochondrial turnover, stimulation of biogenesis (17), and improvements to homeostatic regulation of autophagy (49), thereby minimizing muscle wasting. Exercise activates CaMKII and p38-MAPK pathways, which can stimulate mitochondrial biogenesis through AMPK (33) and PGC-1 α (4) respectively. Furthermore, we have shown that ECC can increase the relative percentage of succinate dehydrogenase activity within fibers, which was associated with increased myofiber cross-sectional area (32). Similarly, compensatory overload in tumor-bearing rats can increase muscle type I myofiber size and frequency, while decreasing relative percentage of type IIb myofibers (31), promoting the oxidative phenotype. Both mechanical overload and muscle contraction induce hypertrophy and increase muscle oxidative capacity in tumor-bearing mice, which may serve to suppress the loss of additional muscle mass. Resistance exercise is capable of attenuating cancer-induced anabolic resistance by regulating specific mechanisms related to mitochondria's role in oxidative metabolism (Figure 3). Furthermore, this information can be used to guide clinical decisions in the management of cancer cachexia.

Resistance exercise and nutrition hold established complementarity roles in the induction of muscle protein synthesis (50). While timed eating after exercise has been extensively examined in healthy and aged individuals (5, 21, 35, 50), these beneficial outcomes are not fully understood in cancer patients and tumor-bearing rodents. Coupling the ingestion of protein-rich nutrients with resistance exercise can shift the dynamic equilibrium of protein turnover in favor of hypertrophy and holds great promise for improving proteostasis in cachectic skeletal muscle (7, 12, 35). A number of pro-anabolic pathways can be exploited under this paradigm. For example, insulin and IGF-1, activated by both nutrition and exercise, hold well-defined regulatory roles in muscle growth through the increases in transcription of anabolic genes, protein synthesis, and the suppression of protein degradation (4, 11, 13). Furthermore, co-ingestion of leucine-enriched essential amino acids and

carbohydrates enhances mTOR signaling in healthy human muscle following resistance exercise (50). Indeed, resistance exercise training has proved effective at preventing wasting (11), and protein-rich nutrients are recommended in patients with advanced cancer in the early stages of weight loss (7). However, few standard of care practices are recommended regarding concurrent pro-anabolic therapies in cancer patients. While there is support for pro-anabolic cachexia treatments, dietary supplementation of BCAAs with a concomitant resistance exercise training regimen have been recommended only for individuals with sarcopenia (5, 6). Nevertheless, there is support for combining nutrition- and resistance exercise-based interventions for cancer-induced muscle wasting (6, 7, 11, 35, 36). Furthermore, nutraceutical and pharmaceutical interventions, such as insulin-sensitizing medication, may have an additive effect on the anabolic signaling induced by protein ingestion and regular resistance exercise (11, 37, 40, 48). Additional pre-clinical study is needed to determine if concomitant pro-anabolic therapies will increase sensitivity to anabolic stimuli and benefit regulation of muscle proteostasis. Investigation into this paradigm should provide a basis for future therapies that are tailored to the specific comorbidities, physical abilities, and disease state of the cancer patient.

CONCLUSION

The multifactorial nature of cancer-induced muscle wasting has hindered the development of effective treatments that would serve to improve muscle mass and function (1–3). While disrupted basal protein turnover in skeletal muscle is an acknowledged driver of cachexia-mediated muscle wasting, elucidating the mechanisms regarding suppression of anabolic sensitivity may hold more physiological relevance. Therefore, we explored the hypothesis that anabolic resistance is central to cancer-induced muscle wasting, and that resistance exercise has the potential to attenuate or treat cancer-induced anabolic resistance through improved muscle oxidative metabolism. In this review we examine the relationship between skeletal muscle mitochondrial function and quality control and the development of cancer-induced anabolic resistance. Cancer-induced muscle wasting is associated with mitochondrial dysfunction, decreased mitochondrial quality control and a reduced capacity for oxidative metabolism (8, 27, 28). Indeed, mitochondrial biogenesis, dynamics, and mitophagy processes have the capability to contribute to skeletal muscle anabolic resistance (9). Furthermore, we have attempted to highlight mTORC1's central role in the integration of mitochondrial function and anabolic signaling within skeletal muscle (19). Resistance exercise's activation of mTORC1 has the potential to improve cachectic muscle oxidative metabolism and ameliorate anabolic resistance (25, 29), which should positively impact cancer-induced loss of muscle mass and function (8).

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Key points

- Disrupted basal skeletal muscle protein turnover is an acknowledged driver of cancer-induced muscle wasting. However, elucidating mechanistic explanations of wasting related to continuous and dynamic maintenance of anabolic sensitivity within skeletal muscle may hold more physiological relevance.
- Cancer-induced muscle wasting is associated with mitochondrial dysfunction and altered mitochondrial quality control, and results in attenuated oxidative metabolism. In cachectic pathology, aberrations in mitochondrial biogenesis, dynamics, and mitophagy processes have the capability to contribute to skeletal muscle anabolic resistance.
- Resistance exercise is an anabolic stimulus that increases muscle protein synthesis through mTORC1 and can increase cachectic muscle mass and metabolic health. Improved mitochondrial function and quality control have the potential to rescue anabolic resistance. Emerging evidence suggests that resistance exercise-induced mTORC1 activation may play a role in improving mitochondrial function and quality control in cachectic muscle.

Figure 1. Induction of Muscle Protein Synthesis by Resistance Exercise Training

Resistance exercise training is capable of inducing cellular, metabolic, and mechanical adaptations within muscle. Responses to resistance exercise can be mediated by mTORC1 dependent (solid line) and independent (dashed line) mechanisms that function to stimulate protein synthesis within the muscle. The central role of mTORC1 is to mediate muscle protein synthesis (hexagons C-T-G and blue circle L indicating the codon and amino acid leucine). Ultimately, muscle protein synthesis is articulated by translational capacity (ribosomal assembly: small and large subunits of the ribosome in orange) and translational efficiency (blue and green circles indicating various amino acids). Synergistic increases in translational capacity and efficiency will increase muscle protein synthesis to promote the hypertrophic response of resistance exercise within skeletal muscle. *GLUT-4*: glucose transporter type 4; *IGF-1*: insulin-like growth factor 1. *AMPK*: 5'-AMP-activated protein kinase; *MAPK*: mitogen-activated protein kinase; *PA*: phosphatidic acid; *mTORC1*: mammalian/mechanistic target of rapamycin complex 1; *p70S6K*: ribosomal protein S6 kinase beta-1; *4E-BP1*: eIF4E-binding protein; *eIF4E*: eukaryotic initiation factor 4E.

Figure 2. Cachexia-Induced Anabolic Resistance Within Skeletal Muscle

The systemic cachectic phenotype has direct negative implications in skeletal muscle that result in the inability to stimulate muscle protein synthesis.

Figure 3. Hypothesis

We hypothesize that resistance exercise training can rescue cachexia-induced anabolic resistance in skeletal muscle through improved oxidative metabolism. This regulation is mediated through translational efficiency, translational capacity, and quality control of mitochondria.