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The Emerging Role of Skeletal Muscle Metabolism as a Biological Target and Cellular Regulator of Cancer-Induced Muscle Wasting

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Abstract

While skeletal muscle mass is an established primary outcome related to understanding cancer cachexia mechanisms, considerable gaps exist in our understanding of muscle biochemical and functional properties that have recognized roles in systemic health. Skeletal muscle quality is a classification beyond mass, and is aligned with muscle's metabolic capacity and substrate utilization flexibility. This supplies an additional role for the mitochondria in cancer-induced muscle wasting. While the historical assessment of mitochondria content and function during cancer-induced muscle loss was closely aligned with energy flux and wasting susceptibility, this understanding has expanded to link mitochondria dysfunction to cellular processes regulating myofiber wasting. The primary objective of this article is to highlight muscle mitochondria and oxidative metabolism as a biological target of cancer cachexia and also as a cellular regulator of cancer-induced muscle wasting. Initially, we examine the role of muscle metabolic phenotype and mitochondria content in cancer-induced wasting susceptibility. We then assess the evidence for cancer-induced regulation of skeletal muscle mitochondrial biogenesis, dynamics, mitophagy, and oxidative stress. In addition, we discuss environments associated with cancer cachexia that can impact the regulation of skeletal muscle oxidative metabolism. The article also examines the role of cytokine-mediated regulation of mitochondria function regulation, followed by the potential role of cancer-induced hypogonadism. Lastly, a role for decreased muscle use in cancer-induced mitochondrial dysfunction is reviewed.

Keywords

Mitochondria; disuse; cytokine; hypogonadism

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1. Introduction

Improving survival and quality of life are inherent goals for successful treatment of cancer patients, and also the expectant translational impact of basic cancer research. Cancer cachexia, the unintentional loss of body weight, has an established adverse effect on these treatment objectives [1–3]. Cachexia development is not associated with all cancers, but the progression of cachexia is directly associated with cancer patient morbidity and mortality. While cachexia has been reported to account for a significant number of cancer deaths [4,5], successful treatment of the cachectic cancer patient remains elusive. The difficulty in treating cancer cachexia parallels the condition's underlying complex and multifactorial nature, which can vary with the underlying disease severity. Consequently, for biomedical research to either promote the discovery or enhance existing therapeutic approaches to effectively treat cachexia, the facets of body weight loss that are the critical lynch pins for survival need to be further established. There is evidence that cancer-induced weight loss is associated with global endocrine and metabolic abnormalities [6,7], and the disrupted function of many tissues and organs, including the gut, brain, heart, liver, and adipose [8–10]. Nevertheless, for some time, critical importance has been placed on cancer-induced skeletal muscle mass loss [5].

The longstanding interest in skeletal muscle with cancer cachexia appears to be a logical extension of the importance of muscle for health maintenance during aging [11,12]. Skeletal muscle also has an established role for maintaining health during obesity, and in patients with many chronic diseases [11,13,14]. Nonetheless, the mechanistic explanation of how skeletal muscle conveys these health properties is still being revealed. Until recently, research examining cancer cachexia mechanisms in preclinical models placed significant emphasis on skeletal muscle mass as the primary outcome [15]. However, there are considerable gaps in our understanding of muscle biochemical and functional properties that have established roles in either systemic health or life quality. These health consequences are less often investigated. The reality is that skeletal muscle has properties extending beyond mass that can convey health benefits to the cancer patient. To this end, the response of skeletal muscle to increased use may also convey health benefits beyond mass. Skeletal muscle quality is a current method of classifying muscle, and is aligned with muscle's metabolic capacity and substrate utilization flexibility [16]. Furthermore, skeletal muscle can serve an endocrine function through the secretion of myokines [17,18]. Disruption of the endocrine function or metabolic quality in cachectic muscle could impact health and survival, and also regulate the muscle's microenvironment [19]. Muscle quality can also be expanded to encompass the regulation of muscle anabolic and catabolic processes, which can regulate metabolic and endocrine functions. The response of skeletal muscle to external stimuli such as inflammation, hormones, and contraction requires integrated cellular signaling pathways involving several organelles and structures. However, the involvement of muscle mitochondria in the regulation of both wasting and metabolic quality has become firmly established [20]. Consequently, the role of the mitochondria in the regulation of cancer-induced muscle wasting has received significant attention during the past several years [20,21].

Mitochondria content aligns with the oxidative metabolic capacity of a myofiber, and has been classically used to define a muscle phenotype, in conjunction with myosin expression and functional properties [22]. However, muscle oxidative metabolism is not a static property; mitochondrial content and function are altered by a host of stimuli, including increased and decreased use, systemic inflammation, and systemic hormonal signaling [23,24]. In addition to cellular ATP production, mitochondria function has an established role in intracellular processes regulating muscle apoptosis, autophagy, and protein turnover [25]. Oxidative metabolism has emerged as a biological target of cancer-induced muscle wasting, and mitochondria loss has been well characterized across many cachectic conditions [26–28]. Interestingly, as little as 5 years ago the discussion surrounding the regulation of cancer cachexia-induced muscle wasting often considered a somewhat narrow role for mitochondria that often aligned with energy flux and wasting susceptibility. A growing body of evidence has successfully expanded this discussion and linked mitochondria dysfunction to cellular processes regulating myofiber wasting [27]. The primary objective of this literature review is to examine the emerging role of skeletal muscle oxidative metabolism as a biological target of cancer cachexia and also as a cellular regulator of cancer-induced muscle wasting. While the review covers concepts from the fields of muscle biology and physiology, content related to wasting is specifically delimited to cancer research using preclinical models and human patients. A description of how cancer cachexia affects muscle mitochondria and oxidative metabolism will be described, but this topic has recently been reviewed [20]. The review will then discuss potential regulators of muscle mitochondria function during the progression of cancer cachexia. Specifically, inflammation, hypogonadism, and muscle use will be scrutinized for the regulation of cancer cachexia-induced mitochondrial changes. Lastly, altered skeletal muscle oxidative metabolism and mitochondrial function, as a regulator of muscle wasting, will be discussed.

2. Skeletal Muscle Oxidative Metabolism and Cancer Cachexia

2.1 Myofiber phenotype's role in cancer-induced wasting susceptibility

Human skeletal muscle contains myofibers with a heterogeneous mix of oxidative and glycolytic metabolic capacities. The expression level of metabolic enzymes, and substrate storage involving glycogen and lipid abundance, also contribute to differential metabolic capacities. The plasticity of the muscle metabolic phenotype can be a function of innervation and use involving contraction and loading [29,30]. Furthermore, functional parameters related to fatigability and speed of contraction typically mirror the fibers' metabolic capacity [22]. Sensitivity to many types of atrophic stimuli is also a function of metabolic phenotype. Decreased use (i.e. bed-rest, spaceflight) induces a more rapid atrophy in slow-oxidative muscle fibers than primarily glycolytic muscle [31], while glycolytic fibers demonstrate greater age-induced atrophy and hypoplasia [32]. The majority of studies with rodent cancer cachexia models demonstrate more hindlimb wasting in primarily glycolytic muscle when compared to primarily oxidative muscle [15,33,34]. However, the examination of myofiber cross-section, rather than whole muscle mass, has demonstrated decreases in both glycolytic and oxidative myofibers with cancer cachexia [35–37]. The duration of the cachexia in rodent studies may also be a factor in the wasting outcomes involving oxidative skeletal muscle. The $Apc^{Min/+}$ mouse, which often undergoes cancer cachexia for several weeks, has

consistently demonstrated decreased mass of the oxidative soleus muscle [38–40]. Besides wasting susceptibility, the oxidative soleus muscle has been reported to demonstrate more regeneration and/or necrosis when compared to more glycolytic muscle [40]. Further studies are needed to determine if cancer-induced fatigue and force production impairments are related to oxidative myofiber regeneration with cancer cachexia. The effect of oxidative metabolism on cachexia susceptibility may be linked to the heterogeneous population of mitochondria in red and white muscle [41], but additional research is needed to demonstrate this as a mechanism of glycolytic fiber wasting with cancer. Although clear evidence exists that muscle metabolic phenotype influences the response to many stimuli that alter muscle mass, during late stages of cachexia atrophy of both glycolytic and oxidative muscle has been reported [42]. Further study is needed to establish if decreased use related to inactivity plays a prominent role in oxidative muscle fiber wasting with cancer cachexia. It is also interesting to speculate if decreased muscle use, which corresponds with the sedentary behavior that accompanies cachexia can affect muscle sensitivity to systemic cachectic mediators, such as cytokines.

2.2 Muscle oxidative metabolism capacity and mitochondria content during cancer cachexia

Oxidative metabolism is central to skeletal muscle metabolic homeostasis [20,43] and frequently quantified by mitochondria content, mitochondria respiratory capacity, and the activity of enzymes involved in the Krebs cycle and the electron transport chain (Figure 1). Understanding skeletal muscle's capacity for oxidative metabolism has been a cornerstone of muscle biology and physiology research for over 40 years [43]. During this time the scientific examination of muscle has extended beyond the classical descriptions of muscle phenotype, and has evolved into mechanistically understanding the regulation of metabolic plasticity related to muscle use, disease, and aging. Initial breakthroughs examining muscle oxidative metabolism established metabolic plasticity with increased and decreased muscle use, which were linked to the capacity for whole body oxygen consumption (fitness) and exercise endurance [23]. While it is established that muscle mitochondria content and function are increased by exercise [44], the mechanistic basis of this plasticity is still being investigated today. As clearly demonstrated by the extensive number of studies published during the past 15 years [43], understanding changes in muscle oxidative metabolism and mitochondria function have become a fundamental focus of aging research investigating sarcopenia, frailty, and quality of life in the elderly. Additionally, there is strong evidence that wasting diseases alter muscle oxidative metabolism [45].

The well-described disruption of skeletal muscle oxidative metabolism reported with many cachectic conditions involves muscle mitochondria loss [25–28,46]. Although red and white skeletal muscle differ dramatically in both mitochondria density and the importance of oxidative metabolism, cancer cachexia reduces mitochondrial content and oxidative protein expression in both muscle types in the mouse hindlimb [26]. The loss of muscle oxidative capacity in the later stages of cancer cachexia also corresponds with the development of severe insulin resistance in several rodent models [10,47]. Insulin sensitivity as well as lipid metabolism are impaired in cancer patients with recent weight loss [7]. However, in lung cancer patients exhibiting significant weight loss muscle oxidative capacity has been

reported to be preserved [48]. Further study is needed to determine the relationship between muscle oxidative capacity declines and the specific type of cancer; lung cancer can promote rapid weight loss, which could differentially affect oxidative capacity when compared to less aggressive body weight loss. Interestingly in humans, cancer is often accompanied by aging and decreased muscle use, which are not normally accounted for in studies employing animal cancer cachexia models.

Since glycolytic muscle has been reported to be more sensitive to cachectic stimuli, there has been an interest in determining if muscle oxidative metabolism might inherently confer resistance to cancer cachexia. There is clear evidence that hindlimb myofibers from tumor bearing rodents undergo atrophy regardless of the succinate dehydrogenase activity level [26,36,37,49]. Regardless, mitochondria dysfunction is an established regulator of myofiber protein turnover [21,25], and gaps remain in our understanding of whether the fiber metabolic phenotype can produce differential regulation of cellular muscle wasting processes. Outside of the diaphragm muscle [50], load-bearing hindlimb muscle has been studied almost exclusively in highly glycolytic muscle. While heterogeneous populations of mitochondria in red and white muscle have been reported [41], differential responses of these subpopulations to cancer cachexia has not been clearly established. Further examination of myofiber oxidative metabolism and its interaction with cachectic stimuli is certainly warranted; there is likely a high prevalence of oxidative fibers in the aging cancer patient [12]. Additionally, the wasting of oxidative myofibers could be more dramatically impacted by decreased muscle use, which is documented with cancer cachexia in human and rodent studies [38,51–53]. Related to oxidative myofiber sensitivity to cachectic stimuli, the roles and potential regulatory interactions between decreased use, suppressed oxidative metabolism, and mitochondrial dysfunction need to be more firmly established.

An additional line of inquiry has examined if skeletal muscle's metabolic plasticity can be exploited to prevent cancer-induced muscle wasting. Is there a therapeutic benefit of increasing muscle oxidative metabolism above basal levels? While successful outcomes related to the induction of oxidative capacity could involve muscle mass, blocking metabolic dysfunction could also serve to improve the patient's survival. While there is encouraging evidence that exercise [47,53–55] and nutraceuticals [56] may be beneficial in conferring resistance to cachexia, the complexity of the systemic responses to these treatments complicates the mechanistic interpretation of the findings. These interventions cannot be directly linked to oxidative metabolism, as they target many systemic parameters and diverse muscle-signaling pathways. Additionally, many of these treatments regulate tumor growth and function that are involved in creating the cachectic milieu [46,54,55,57–59]. Intervention studies often measure tumor size, but this may not account for the tumor's capacity to create a cachectic environment. A less examined paradigm with clinical significance is the restoration of mitochondrial content in cachectic muscle. Research is needed to establish the constraints, if any, that severe cachexia places on the metabolic plasticity of muscle.

2.3 Mitochondrial biogenesis during cancer cachexia

Myofiber mitochondrial content is subjected to regulation that allows responsiveness to the cellular environment. This cellular metabolic plasticity has been well studied and includes

the coordinated processes of mitochondrial biogenesis, fission/fusion, and mitophagy. The disturbance of any of these processes can disrupt muscle metabolism [60]. Mitochondrial biogenesis is required for the maintenance of muscle mitochondria content and function, and the coordinated events essential for this process have been reviewed in detail elsewhere [61,62]. The peroxisome-proliferator gamma-activated receptor (PGC-1) family of co-activators has been described as the 'master regulators' of muscle oxidative metabolism. PGC-1α regulates mitochondrial biogenesis by nuclear translocation and activation of oxidative gene transcription [63], and was first identified for its role in brown adipose tissue adaptive thermogenesis [64]. PGC-1α loss reduces mouse muscle mitochondrial content and disrupts mitochondrial function [65], while PGC-1α over-expression increases muscle mitochondrial protein expression [66]. PGC-1α transcriptional control involves mitochondrial proteins, mitochondrial transcription factor A (Tfam), and nuclear respiratory factor-1 (NRF-1) and NRF-2 [62,63]. Several PGC-1 isoforms have also been identified. PGC-1β drives the specific expression of MHC IIX fibers, and is associated with an increase in oxidative phenotype [67]. The PGC-1α4 isoform regulates IGF-1 and myostatin signaling, and is associated with muscle hypertrophy rather than oxidative capacity [68]. There has been substantial interest in understanding if PGC-1α has a regulatory role in cancer-induced muscle wasting. There is strong evidence that wasting and metabolic dysfunction decrease muscle PGC-1α expression in humans and rodents [69–75]. Muscle PGC-1α expression is also decreased with cancer cachexia [26,47,51]. Numerous studies examining PGC-1α overexpression by either *in vivo* transfection or transgenic mice have found protection from skeletal muscle atrophy due to decreased use [76–79], starvation [78], and cytokine administration [80]. Fewer studies have examined the role of PGC-1α in preventing cancer cachexia induced muscle wasting. PGC-1α overexpression is not sufficient to block Lewis lung carcinoma (LLC)-induced muscle wasting [81]. However, the ability of cachectic muscle to restore mitochondria function after cachectic loss has not been determined. While our knowledge of PGC-1 co-activators continues to advance, it is apparent that PGC-1α controls multiple pathways that regulate mitochondrial content and function in skeletal muscle, and further work is needed to determine how this can both affect and benefit cachectic muscle.

The control of PGC-1α activity occurs through upstream mediators, and provides critical metabolic responsiveness to the cellular environment [43]. Sirtuin 1 (Sirt1) deacetylation of PGC-1α increases its activity, but the function of Sirt1 in cancer-induced muscle wasting has not been clearly established. Sirt1 mRNA expression in cachectic muscle has been reported to be a function of muscle phenotype, being reduced in the cachectic gastrocnemius mouse muscle, but not in the soleus [26]. Interestingly, both the cachectic gastrocnemius and soleus muscles have reduced muscle mitochondria content. AMP-activated protein kinase (AMPK) is a potent regulator of skeletal muscle metabolism, and can be activated by cellular energy status, calcium levels, and cytokine signaling [82,83]. AMPK can regulate mitochondrial content through PGC-1α-dependent mitochondrial biogenesis and ULK1-dependent stimulation of mitophagy [82]. Exercise and pharmacological agents can stimulate AMPK activation and PGC-1α expression in skeletal muscle [84–88]. AMPK can bind to and phosphorylate PGC-1α [86], thereby increasing the activity and transcription of this transcriptional co-activator. While the AMPK-PGC-1α axis can stimulate mitochondrial

biogenesis, this signaling is disrupted in mouse models of cancer cachexia. Wasting skeletal muscle from *Apc*$^{Min/+}$ mice exhibits chronically elevated AMPK activity, which does not translate to changes in either mitochondrial content or PGC-1α expression [26,47,51]. Interestingly, elevated AMPK is observed in skeletal muscle lacking PGC-1α [89]. Since interleukin-6 (IL-6) can stimulate AMPK and reduce PGC-1α expression in myotubes [47], further research is needed to determine if chronic AMPK activation is a result of circulating inflammatory cytokines or metabolic energy stress in cachectic muscle. Systemic IL-6 inhibition in *Apc*$^{Min/+}$ mice can increase mitochondrial content, PGC-1α expression, and mitochondrial protein expression while attenuating the progression of cancer cachexia [47], but a direct regulatory effect has not been established. Understanding the disrupted relationship between AMPK, PGC-1α, and mitochondria biogenesis in cachectic muscle is needed to develop therapies to improve muscle metabolic quality and patient health.

The p38 mitogen-activated protein kinase (MAPK) family plays a critical role in skeletal muscle metabolism. The selective activation of p38 MAPK isoforms (α, β, and γ) can promote distinct cellular metabolic processes. Skeletal muscle p38β MAPK activation can regulate protein catabolism in cachectic muscle [90,91]. p38 MAPK signaling can also regulate muscle PGC-1α activity [92–94]. Activation of p38 MAPK signaling by voluntary exercise or transgenic overexpression can increase muscle PGC-1α gene expression [95]. However, the response to muscle contraction appears specific to p38γ MAPK, as the loss in p38α or p38β MAPK does not affect endurance exercise metabolic adaptation [96], while the loss of muscle p38γ suppresses contraction-induced PGC-1α gene expression [96]. The role of p38γ-PGC-1α regulation of mitochondrial biogenesis with increased contractile activity warrants further investigation to determine if it can be targeted in cachectic muscle.

2.4 Mitochondria dynamics during cancer cachexia

The maintenance of the myofiber mitochondrial network is critically important for adaptation to altered metabolic demands [97,98]. Mitochondrial dynamics involve the coordinated processes of fission and fusion, which can affect mitochondrial function (Figure 2) [99,100]. Mitochondrial fusion expands myofiber mitochondria networks, and fusion proteins 1 and 2 (Mfn1/2) and optic atrophy protein 1 (OPA1) are important regulators of the process [60]. In healthy individuals, mitochondrial fusion is associated with PGC-1α protein expression, citrate synthase activity, and mitochondrial creatine kinase [101]. A reduction in Mfn2 has been observed in muscle from type 2 diabetic [102,103] and obese patients [103]. During the progression of cachexia in mouse hindlimb muscle, Mfn1/2 protein expression is suppressed during the initial stages of cachexia [47], which suggests that altered fusion is an initial event in the cancer-induced disruption of muscle oxidative capacity. Mitochondrial fusion protein expression appears to be IL-6 sensitive. Systemic IL-6 over-expression *in vivo* decreases muscle mitofusion protein expression in *Apc*$^{Min/+}$ mice, whereas IL-6 receptor (IL-6r) antibody administration increases Mfn2 expression in cachectic mouse muscle [47]. Direct effects of IL-6 on Mfn2 expression was shown, as the treatment of primary human muscle cultures by IL-6 reduced Mfn2 gene expression [103]. Mfn2 gene expression is regulated by PGC-1α and PGC-1β [104,105]. PGC-1α overexpression rescues Mfn1/2 expression during unloading-induced atrophy [77]. Extending our understanding of the mechanisms that suppress mitochondrial fusion during cancer cachexia, and determining if

this process can serve as a therapeutic target to improve muscle metabolic function are warranted.

Mitochondrial fission, the division of the organelle, is regulated through the expression of dynamin-related protein-1 (DRP1) and Fission protein 1 (Fis1) [60]. Increasing fission results in fragmented mitochondria, while a reduction in fission increases mitochondria networks [106]. Unlike fusion proteins, muscle Fis1 expression is not induced until the more severe stages of cachexia in mice [47]. Increased Fis1 expression in cachectic muscle is not affected by inherent oxidative capacity, being increased in both oxidative and glycolytic muscles [46]. Fis1 expression also appears to be IL-6 sensitive, increasing with systemic IL-6 over-expression in $Apc^{Min/+}$ mice and decreasing with IL-6r antibody administration during the progression of cachexia [47]. These effects may be due to direct actions of IL-6 on the muscle, as IL-6-treated myotubes increase Fis1 protein expression [47]. Fis1 was also demonstrated to regulate the atrophic process of skeletal muscle [27]. Related to regulation of muscle mass, the over expression of Fis1 has been shown to be pro-apoptotic [107–109], associated with the production of reactive oxygen species [25], and is also capable of activating protein degradation [27]. Muscle apoptosis has been observed in human and rodent models of cancer cachexia [38,110–113]. In $Apc^{Min/+}$ mice apoptosis was only observed in severely cachectic muscle [38], which coincides with Fis1 expression [26]. Mitochondria fission activates AMPK, which regulates FOXO3 independently of Akt activation [27]. Both denervation- and starvation–induced muscle atrophy activate AMPK, and the knockdown of either AMPK or FOXO can prevent mitochondrial dysfunction and atrophy [27]. Exercise also can affect muscle mitochondrial dynamics, by increasing fission and suppressing fusion [99,114,115]. However, in $Apc^{Min/+}$ mice exercise attenuated the IL-6 induction of mitochondrial fission and FOXO [47]. While evidence suggest that the regulation of mitochondrial fission and fusion is able to control muscle wasting, as it relates to cancer cachexia, significantly less is understood about the role of mitochondria dynamics and its own regulation. Nonetheless, the restoration of mitochondrial dynamics in cachectic muscle may be a therapeutic target for improving overall function.

2.5 Mitophagy and cancer cachexia

Maintaining mitochondrial quality requires the removal of damaged mitochondria [60]. Autophagy is an essential cellular process for lysosomal-dependent degradation of organelles, and selective removal of damaged or dysfunctional mitochondria is known as mitophagy. This process is linked to mitochondrial dynamics [116]. The molecular components of the autophagy-lysosomal pathway involve several autophagy-related genes (Atgs) [117]. Deletion of Atg7 results in skeletal muscle atrophy, mitochondria abnormalities, and disorganization of sarcomeres [118]. The myofiber requires a coordinated balance between mitochondrial biogenesis and mitophagy, and a cancer-induced disruption in this balance could cause decreased mitochondrial content and the accumulation of dysfunctional mitochondria. Indeed, alterations in mitochondria morphology that indicate dysfunction (i.e., swelling, electron-lucent areas, vesicle-like structures) have been observed in cachectic skeletal muscle [36,119]. Activation of the autophagy-lysosomal system can be observed during the initial stages of weight loss [120–123], and muscle lysosomal enzyme activity has been correlated with weight loss in cancer patients [124]. Rodent cancer cachexia models also

demonstrate increased muscle expression of autophagy and lysosomal proteins [46,117,125,126]. Muscle autophagy can be regulated by the FOXO family and mTOR signaling, which are established controllers of muscle mass [27,127]. In $Apc^{Min/+}$ mice the expression of autophagy proteins is not increased until the muscle is severely cachectic [46]. Interestingly, in cachectic cancer patients there is evidence for the induction of muscle autophagy-lysosomal processes, while activation of the ubiquitin proteasome system in human cancer patients is more equivocal [122,123,128–130]. Also, the link between oxidative metabolism and autophagy is less clear in humans; a decrease in muscle oxidative metabolism has not been reported in some cachectic human cancer patients [48]. As it relates to physical activity, oxidative muscle fibers display higher levels of autophagy flux [131], and exercise can stimulate autophagy [131–133]. Further work is needed to determine if contraction is a stimulus that can restore cachectic muscle's disrupted balance between mitochondria biogenesis and mitophagy.

2.6 Mitochondria uncoupling and ROS formation during cancer cachexia

Reactive oxygen species (ROS) are molecules that contain an oxygen free radical and can be produced in multiple cellular locations [134]. Superoxide is the most commonly-generated ROS, with hydrogen peroxide being a more stable derivative [134]. ROS are natural byproducts of biochemical reactions and can serve as cellular signaling molecules [135]. While only a small percentage of mitochondrial oxygen is converted to ROS [136,137], this production can increase in response to increased contractile activity, decreased use, or chronic disease [135]. While ROS has a role in cellular signaling during physiological conditions, aberrant ROS production can lead to muscle dysfunction through the oxidation of proteins, lipids, and DNA [138,139]. Muscle atrophy is associated with mitochondrial dysfunction and the production of reactive oxygen species (ROS) [135]. Glycolytic muscle appears to be more susceptible to oxidative stress [41]. Additionally, subsarcollema (SS) mitochondria can produce higher levels of ROS and are preferentially lost when compared to intermyofibrillar (IMF) mitochondria [140,141]. Inflammation can also affect muscle ROS production. Tumor necrosis factor (TNF) is a cytokine that has been associated with increased mitochondrial ROS production [142]. Evidence suggests that muscle oxidative stress is increased in some, but not all rodent models of cancer cachexia [42,110,143,144]. In addition, higher levels of ROS and oxidative stress has been reported in cachectic lung cancer patients [145], and LLC conditioned medium increases ROS production in C2C12 muscle cells [146]. However, determining the contribution of mitochondrial ROS production to the regulation of mechanisms controlling increased catabolic signaling in cachectic muscle warrants further examination.

Mitochondrial uncoupling proteins (UCPs) have been implicated in the control of energy metabolism during cancer cachexia, and may also play a role in the regulation of ROS production in skeletal muscle [147]. Mitochondrial UCPs are membrane proteins that mediate proton leakage and uncouple respiration to produce thermogenesis instead of ATP synthesis [5]. UCP-1 is expressed in adipose cells and has been implicated in 'browning' of white adipose tissue during cancer cachexia [148]. In contrast, UCP-2 and -3 have been associated with skeletal muscle wasting [5]. While some researchers have reported increased UCP-2 or UCP-3 expression in cachectic human and rodent skeletal muscle [149–155], others

have reported reduced expression [26]. The differential responses observed may be related to the tumor model used, as well as the fasted state of the animal. Skeletal muscle UCP-2 and -3 gene expressions are induced in response to fasting conditions [156,157], which can vary between studies. However, when food intake has been controlled, muscle UCP-2 and -3 gene expression is increased in cachectic muscle [152,154]. Future research is needed to define the significance of muscle UCP expression and its relationship to mitochondrial dysfunction during the progression of cancer cachexia.

3. Cancer Cachexia-Induced Regulation of Skeletal Muscle Oxidative Metabolism

3.1 Cytokine mediated regulation of muscle oxidative metabolism

Systemic inflammation is recognized as a hallmark of cancer cachexia [8], and circulating cytokines are established initiators of the muscle wasting process (Figure 3) [38,158]. Changes in cytokines may be related to the tumor and/or the host response to the tumor [159]. The cellular signaling linking inflammatory mediators to disrupted protein turnover has been widely researched [8,15]. Specific to cancer cachexia, perturbations in cytokines such as IL-6, TNF, TNF-like weak inducer of apoptosis (TWEAK), and myostatin have been implicated in muscle wasting processes [8,160,161]. While often proposed, the evidence directly linking inflammation to cancer cachexia-induced mitochondrial dysfunction is only beginning to emerge [146].

IL-6 is a pleiotropic cytokine that has been implicated in the regulation of skeletal muscle metabolism and cachexia in both animal models and cancer patients [48,145,161–163]. IL-6 binding to its receptor complex can activate several intracellular signaling pathways including JAK/STAT signaling. Manipulating systemic IL-6 can affect the disruption of muscle oxidative metabolism during cancer cachexia, but these approaches have not provided direct evidence for the action of IL-6 signaling in myofibers. Systemic IL-6 overexpression disrupts muscle mitochondrial biogenesis and dynamics [47], while IL-6 receptor antibody administration attenuates mitochondrial loss and disrupted oxidative metabolism in cachectic skeletal muscle [26,47,164]. A role for mitochondrial STAT3 in basal cellular respiration has been described [165], and it has been proposed that the accumulation of mitochondrial STAT3 may alter ETC function and ROS production, and produce mitochondrial dysfunction [166]. A role for STAT3 in the disruption of skeletal muscle oxidative metabolism with cancer cachexia has yet to be established. The subcellular localization of STAT3 in non-muscle cells has been implicated in the regulation of autophagy [167], and nuclear STAT3 can promote or suppress target genes regulating autophagy. Interestingly, JAK/STAT3 also has been implicated in the nuclear/cytosolic shutting of FOXO-1 and -3 in $CD4^+$ T cells [168]. While this has not been described in cachectic skeletal muscle, a better understanding of IL-6 and STAT3 regulation of mitophagy in cachectic muscle is warranted.

TNF is an inflammatory cytokine elevated in the circulation with certain cancers and some rodent cancer cachexia models [6,145]. TNF predominantly activates the canonical NF-κB signal transduction pathway, which has been implicated in muscle oxidative metabolism

regulation [169]. The canonical NF-κB pathway involves the nuclear localization of the p65/p50 heterodimer complex. This occurs through the degradation of IκBα, which is regulated by IKKβ kinase activity [170]. Activation of the classical signaling pathway impairs mitochondrial biogenesis and oxidative capacity, and alters mitochondrial morphology [169]. In addition, NF-κB signaling has also been shown to suppress muscle mitochondrial gene expression, oxygen consumption, and ATP production [171,172]. Interestingly, non-canonical signaling can also result in mitochondrial NF-κB localization and suppression of mitochondrial gene expression [173]. While NF-κB signaling is activated in multiple rodent models of cancer cachexia [51,174,175], direct actions of this pathway regulating skeletal muscle oxidative metabolism during the progression of cancer cachexia remain to be established.

TWEAK, a member of the TNF superfamily, transduces intracellular signaling through the fibroblast growth factor-inducible 14 (Fn14) receptor [160]. Pathological conditions can increase muscle Fn14 expression to amplify TWEAK signaling [176]. TWEAK-Fn14 signaling is associated with muscle atrophy [177], and the regulation of skeletal muscle oxidative capacity [178,179]. TWEAK inhibits oxidative metabolism in skeletal muscle [178], possibly through the repression of PGC-1α and the activation of the NF-κB [80]. TWEAK loss causes enhanced skeletal muscle mitochondrial content and oxidative capacity [178], whereas TWEAK overexpression decreases mitochondrial density [80]. Interestingly, PGC-1α overexpression can prevent the induction of Fn14 expression during muscle atrophy [80]. Given the interrelationship between NF-κB, TWEAK signaling, and PGC-1α, strategies to target this interaction could have therapeutic potential for rescuing disrupted muscle oxidative metabolism due to cancer.

Myostatin, a transforming growth factor-β (TGF-β) superfamily member, is involved in the regulation of skeletal muscle growth and differentiation [180]. Myostatin binding to ActRIIB phosphorylates downstream effector Smad2/3, and results in the translocation of the Smad2/3 and Smad4 complex to the nucleus, where it regulates the transcriptional suppression of genes responsible for myogenesis [181]. Elevated circulating and muscle myostatin has been reported in tumor-bearing mice [182,183], and myostatin- associated signaling can disrupt protein turnover leading to muscle catabolism [180]. Myostatin has been identified as part of the C26 tumor secretome, and C26-induced cachexia in mice results in a significant reduction in mitochondria content [159]. Additionally, C26-conditioned media can increase ROS production and oxidative stress in C2C12 myotubes [159]. Similar to other cytokines, the direct evidence for myostatin regulation of muscle oxidative metabolism in cachectic muscle is still being established.

3.2 Hypogonadism regulation of muscle oxidative metabolism

Gonad function has a significant role in whole body homeostasis through the production of sex steroids. The capacity for this regulation changes throughout the lifespan, and can also be affected by disease, energy balance, and body composition [6,184,185]. Although hypogonadism is commonly mentioned as an environment associated with cachexia [1], significant gaps remain in our understanding of gonad dysfunction’s regulatory role in cancer-induced muscle wasting. While circulating sex steroids decline with hypogonadism

in both the female and male, far more is known about hypogonadism as it relates to cachexia in the male condition. Hypogonadism can indirectly affect muscle wasting through the regulation of other environments related to anemia, insulin resistance, and inflammation, which are also targeted by cancer [184,186,187]. However, circulating sex steroids also have direct effects on many tissues, including muscle and bone [188]. There is clear evidence that estrogen and testosterone have regulatory functions related to skeletal muscle mass, metabolism, and ability to repair from injury [189–192]. Low testosterone in the male can decrease strength and muscle mass in the absence of disease [193,194], and many diseases, including cancer, can decrease circulating testosterone [6,184]. Estrogen deficiency can affect muscle mass retention in the aged female, decrease the ability to recover from atrophy, and adversely affect muscle metabolism and the regulation of protein turnover [189,192,195]. Additionally, since the median age of diagnosis of colon, lung and pancreatic cancers is over 70 years of age, the vast majority of women are post-menopausal when these potentially cachectic cancers are diagnosed [196,197]. Sex hormone therapy in males and females has been widely examined in adults for a range of health benefits, and also to determine the inherent health risks of the specific therapies [198–200]. Beyond effects in patients with conditions related to disease and gonad dysfunction, sex hormone replacement therapy in the aged female and male has been extensively examined [200,201]. The interaction of these therapies with aging has clinical significance for cancer patients, who can exhibit age-induced changes in gonad function at the time of cancer diagnosis [6,184]. Testosterone therapy has convincing effects on muscle mass and strength in both old and young males [202,203]. Estrogen replacement in animal models has demonstrated positive effects for muscle recovery from atrophy, and a growing body of evidence currently supports a role for hormone replacement in muscle mass retention in the post-menopausal female [200]. Beyond being a therapeutic target, further understanding hypogonadism's mechanistic role in the disruption of muscle protein turnover and oxidative metabolism is certainly warranted, given the known effects of sex steroid loss on muscle, and also the evidence regarding gonadal function in cachectic cancer patients and animal models of cancer cachexia.

While decreased circulating testosterone has not been reported with all types of cancer, lowered total or bioavailable testosterone has been reported in male cancer patients, and also in cachectic cancer patients [6,186,187]. While not widely examined in rodent cancer models, decreased circulating testosterone accompanies the progression of cachexia in the $Apc^{Min/+}$ mouse, and circulating testosterone levels are correlated with hindlimb muscle loss [204]. However, further work is needed to determine if this effect is related to the specific type of cachexia model or degree of cachexia, as tumor-bearing rats have been reported not to show decreases in circulating testosterone [205]. A complex response that involves muscle phenotype and sex is found when examining skeletal muscle responses to either increased or decreased testosterone levels. Rodent skeletal muscle associated with reproductive functions demonstrates extreme sex steroid sensitivity compared to locomotor hindlimb muscle [206,207]. Additionally, muscles within the rodent hindlimb appear to have different sensitivities to testosterone and estrogen [189,207,208]. Muscle sensitivity to sex hormone levels is affected by muscle androgen and estrogen receptor expression (AR and ER, respectively) [209]. Circulating hormone levels, muscle regeneration, muscle loading, and aging can all affect muscle AR expression [190,191,210,211]. Related to cancer cachexia,

muscle AR expression is decreased in cachectic $Apc^{Min/+}$ mouse muscle [204]. The time course of decreased circulating testosterone and muscle AR expression in male $Apc^{Min/+}$ mice during the progression of cachexia corresponds to muscle mitochondria loss [47]. Interestingly, independent of disease, orchiectomy can cause a similar reduction in mouse muscle mitochondria content and oxidative metabolism [191,212].

Studies examining overexpression and loss of the AR and ER have established a role for sex hormone signaling in the regulation of muscle metabolism. Similar to overall hormone responsiveness, the studies to date reveal a complex regulation by sex steroid receptors that are affected by both muscle phenotype and sex. AR overexpression increases rat EDL muscle myoglobin expression and mitochondrial enzyme activity [213]. However, muscle fatigue resistance is increased with the global AR [214] or ERβ [215] deletion in a muscle- and sex-specific manner. Myofiber-specific AR loss can increase the percentage of type I oxidative fibers in the soleus muscle, but not the fast-glycolytic EDL muscle [207]. Estrogen signaling through the ERα and ERβ can regulate mitochondrial biogenesis and function through transcriptional regulation of NRF-1 and Tfam [216]. Additionally, ovarian function loss in mice is associated with muscle mitochondrial dysfunction, which is attenuated by estrogen replacement [217]. Emerging regulatory networks have demonstrated how muscle anabolic and catabolic signal transduction pathways are intertwined with mitochondrial function, and cellular sex hormone signaling also overlaps with these processes. Ovariectomy increases the activation of PPARα and lean body mass in rats [218,219], and muscle PPARδ expression, as well as PDK-4, UCP-2, and FOXO1 expressions, are suppressed [220]. In addition to the induction of mTOR signaling [191], testosterone administration can increase muscle PGC-1α and COXIV expression, while AR deletion suppresses their expression [221]. Related to muscle mass and use, muscle AR expression is associated with resistance training responsiveness in humans [222]. Further work is needed to establish if the hypogonadal state during cancer cachexia impedes muscle metabolic plasticity related to increased use and mechanical loading.

3.3 A role for decreased muscle use

Traditionally, cancer-induced environments related to anorexia, inflammation, insulin resistance, hypogonadism, and anemia have played an acknowledged role in the regulation of skeletal muscle wasting [1]. All of these environments have the potential to directly or indirectly regulate skeletal muscle oxidative metabolism. Weakness and fatigue are acknowledged outcomes of cachexia, and are discernable by measurements of decreased strength, oxygen consumption (VO_2 max), and physical activity level in the cachectic patient [1]. Interestingly, physical inactivity and decreased muscle use have been well documented with cancer cachexia, but often they are characterized as an outcome of wasting, and not a contributor to the process. While resting energy expenditure has been shown to increase in cachectic cancer patients, total energy expenditure has been reported to decrease, coinciding with decreased physical activity level [52,223]. Rodent models of cancer-induced cachexia have shown a dramatic decrease in voluntary physical activity compared to healthy mice [51,58]. During the progression of cachexia in $Apc^{Min/+}$ mice the decrease in physical activity precedes weight loss [38]. While physical inactivity and sedentary behavior are established causes of skeletal muscle metabolic dysfunction and atrophy [141,224–226],

until recently cancer patient physical inactivity was not clearly acknowledged as a potential contributor to the cachectic muscle phenotype. There are clear gaps in understanding physical inactivity's contribution to muscle wasting and metabolic dysfunction in the cachectic cancer patient that warrant further investigation.

While numerous and varied definitions have been used to characterize exercise and physical activity, the most physiologically relevant descriptions involve the performance of an activity that increases energy expenditure above the basal level [227]. Increasing energy expenditure might seem counterintuitive for preventing wasting disease; however, physical activity is often associated with an increase in lean body mass [228]. Additionally, a convincing body of research has demonstrated that the health benefits of regular physical activity extend far beyond energy expenditure [229]. In patients with metabolic syndromes, increased physical activity can regulate restoration of metabolic homeostasis [224,230]. Conversely, inactivity is an acknowledged risk factor for decreased health and the development of chronic metabolic disorders [231,232]. The physical activity-induced health benefits and the decrements related to inactivity can be directly related to skeletal muscle metabolic function. Increased physical activity can improve skeletal muscle oxidative metabolism through mitochondria function [233–235] and efficient substrate utilization involving fatty acid oxidation [236] and glucose transport [237]. Increased muscle use can shift muscle towards a more oxidative phenotype [43,238] without necessarily promoting muscle growth [239]. Improving mitochondrial content and function could therefore have significant ramifications on muscle metabolic homeostasis in cachectic skeletal muscle.

Endurance exercise-induced improvements in mitochondria function involve processes related to biogenesis, mitophagy, and mitochondrial dynamics [62,240], which can be disrupted in cachectic muscle [20,47,112]. Conversely, decreased physical activity results in altered signaling pathways leading to loss of skeletal muscle mass and decreased muscle oxidative metabolism [241–244]. PGC-1α is highly responsive to muscle contraction and has been extensively examined for the regulation of oxidative metabolism by physical activity [87,245]. Decreased skeletal muscle use suppresses PGC-1α expression [61,78] and coincides with decreased mitochondrial content and associated protein expression [226]. Additional signaling pathways sensitive to muscle use can regulate oxidative metabolism through PGC-1α, AMPK, FOXO and mTOR interactions [25,170,246]. All of these signaling pathways have demonstrated some degree of disruption in cachectic muscle [180]. While the role exercise on whole body oxidative metabolism is well established, less is known about the effect of muscle contraction on oxidative metabolism in the cachectic patient. However, initial investigations into exercise and muscle contraction during the progression of cachexia in the $Apc^{Min/+}$ mouse have demonstrated positive outcomes related to the rescue of suppressed muscle anabolic signaling, mitochondrial content, and mitochondrial biogenesis [51,54]. There is a clear rationale for further investigation to determine if cachectic muscle maintains contraction and physical activity-induced metabolic plasticity.

In addition to exercise involving repeated contraction, skeletal muscle phenotype is extremely responsive to increased or decreased loading [247]. Skeletal muscle has well-developed networks that transduce loading conditions to intracellular signaling. A critical pathway in this network is integrin signaling [247]. Muscle sensitivity to stretch is a classic

paradigm that demonstrates the potency of mechanical signaling for the induction of growth [248]. Altered mechanical signaling in muscle induced by increased or decreased load can affect both muscle mass and oxidative metabolism. Decreased loading in both humans and rodents induces muscle atrophy that is more rapid in oxidative myofibers [24,249,250]. Several components of load muscle sensitive signaling pathways are altered with cancer cachexia. Protein kinase B/Akt is highly responsive to muscle loading and unloading conditions. Akt can regulate both protein turnover and metabolic regulation in muscle [170,251–254]. Unloading-induced atrophy decreases Akt phosphorylation, which can affect mTOR and FOXO signaling [170]. As discussed earlier, in addition to FOXO and mTOR signaling's well-described regulation of protein turnover [252], they also regulate mitochondria function and autophagy [253]. Unloading-induced muscle atrophy also activates NF-κB, which has regulatory roles involving both muscle protein degradation and oxidative metabolism [170]. Although mTOR, FOXO and NF-κB have well-described roles in cancer-induced wasting and disuse, the regulation of these pathways and their effectors may differ between conditions [170]. To this end, exercise and stretch can also activate muscle NF-κB signaling [255–257], in addition to activating mTOR by Akt independent signaling [258]. Further research is needed to determine the consequences of simultaneously activating disuse and cachectic signaling pathways in muscle. The effects of countering inactivity with increased muscle use, while the cachectic environment is present, also warrants additional study. Doing so will allow for an improved understanding of the common and stimulus-specific regulatory mechanisms involved in muscle wasting.

4. Conclusion

Muscle oxidative metabolism has an established role in metabolic health, which centers on mitochondria function. Beyond muscle metabolism and substrate utilization, mitochondria maintain skeletal muscle homeostasis through the regulation of protein turnover, autophagy, and apoptosis. As it relates specifically to cancer cachexia, the role of skeletal muscle oxidative metabolism in wasting has recently begun to emerge. In this review, we assessed the growing body of evidence that highlights muscle mitochondria and oxidative metabolism as a biological target of cancer cachexia. While muscle metabolic phenotype can influence the response to cachectic stimuli, both glycolytic and oxidative muscles waste in late stage cancer cachexia. However, further work is needed to establish if the rate of wasting and the susceptibility to cachectic stimuli are influenced by metabolic phenotype. Additionally, further research needs to be established if the mechanisms disrupting protein turnover are differentially regulated in oxidative and glycolytic muscle. While the loss of muscle mitochondrial content and a reduction in overall oxidative metabolic capacity are consistent findings in cachectic rodent muscle, skeletal muscle oxidative capacity changes in human cancer patients requires further investigation. Furthermore, it is unclear if elevating mitochondrial content is sufficient to prevent or reverse cancer-induced muscle wasting associated with impaired mitochondrial function. Next, evidence for the dysfunction of mitochondria related to critical wasting mechanisms in cachectic muscle was examined. There is evidence across different preclinical cancer models that skeletal muscle mitochondrial biogenesis, dynamics, mitophagy, and oxidative stress can all be disrupted in cachectic muscle. Further research will be required to clearly establish these mitochondrial

alterations as potential biological targets for treating cancer cachexia. Furthermore, the cancer-induced systemic disruptions causing mitochondria dysfunction need to be better understood. Lastly, we examined how systemic alterations associated with cancer cachexia could impact the regulation of skeletal muscle oxidative metabolism. Current evidence suggests increased catabolic cytokines and decreased sex steroids accompany disrupted muscle oxidative metabolism during the progression of cachexia. Moreover, physical inactivity accompanies skeletal muscle wasting in cachectic rodents and human cancer patients. Related to decreased muscle use, it is not well understood if inactivity can interact with cytokine signaling to amplify the catabolic response in cachectic muscle. While muscle activity is a potent regulator of mitochondrial quality and function, further investigation is warranted to determine the response of cachectic skeletal muscle to increased use, and if increased activity leads to an improved anabolic state. Clearly defining the interactions between muscle use and systemic perturbations on mitochondrial oxidative metabolism will provide greater mechanistic insight to the drivers of cancer-induced muscle wasting. This understanding will have significant implications for future therapeutic treatments in the cachectic cancer patient.

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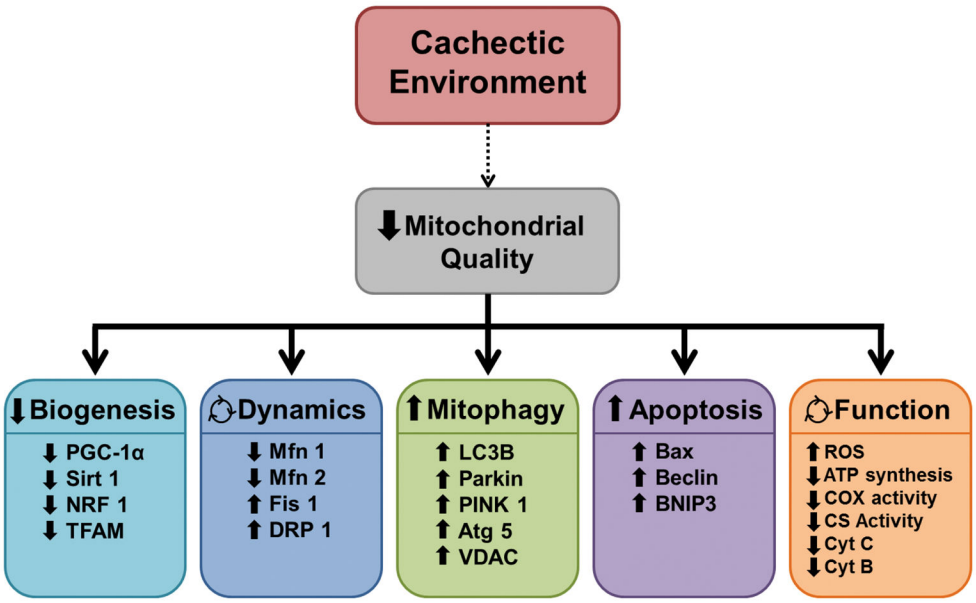

Figure 1. Cancer cachexia associated disruptions in muscle oxidative metabolism

Mitochondrial biogenesis, dynamics, autophagy (mitophagy), apoptosis, and function are all used to measure mitochondrial quality in order to quantify muscle oxidative capacity. In the cachectic environment there is a decrease in mitochondrial biogenesis quantified by decreased peroxisome proliferator-activated receptor γ coactivator 1 alpha (PGC-1α), sirtuin 1 (Sirt1), nuclear respiratory factor 1 (NRF1), and mitochondria transcription factor A (TFAM). The cachectic environment has also been shown to alter mitochondrial dynamics by increasing mitochondrial fission proteins, fission 1 (Fis1) and dynamin-1-like protein (DRP 1) while decreasing mitochondrial fusion proteins, mitofusion 1 and 2 (Mfn1/2). There is a reduction in present mitochondrial content due to increased mitochondrial autophagy (mitophagy) and apoptosis seen by increased in all isoforms of light chain 3 (LC3), parkin, PTEN-putative kinase 1 (PINK 1), autophagy 5 (Atg 5), voltage-dependent anion channel (VDAC), bcl-2-associated X protein (Bax), beclin, and BCL2/adenovirus E1B 19 kd-interacting protein 3 (BNIP3). While mitochondrial function can be an effect of the previous 4 groups there is also evidence of a direct link to altered mitochondrial function by decreased ATP synthesis, cytochrome c oxidase (COX) activity, citrate synthase, protein and mRNA expression of cytochrome B and C (Cyt B and C), and increase reactive oxygen species (ROS).

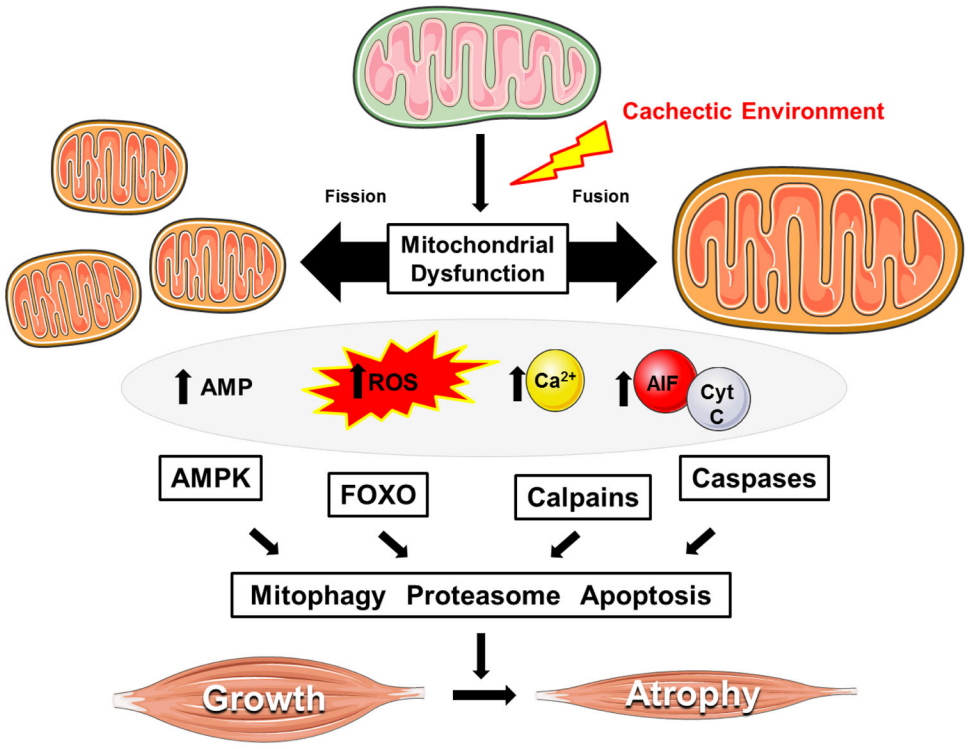

Figure 2. Mechanisms related to skeletal muscle mitochondria dysfunction that can regulate cancer-induced wasting

The progression of cancer cachexia is associated the disruption of mitochondrial quality (i.e. biogenesis, dynamics, mitophagy), which can lead to the accumulation of dysfunctional mitochondria. Impaired mitochondrial function promotes energetic stress, ROS production, and the cytoplasmic localization of calcium and pro-apoptotic factors. Several key catabolic signaling pathways are activated leading to skeletal muscle atrophy, as well as further impairments in muscle oxidative metabolism. Abbreviations: Adenosine monophospate (AMP). 5′ adenosine monophosphate-activated protein kinase (AMPK). Apoptosis-inducing Factor (AIF). Cytochrome C (Cyt C). Forkhead Box O (FOXO). Figure was made with Servier Medical Art (http://www.servier.com/Powerpoint-image-bank).

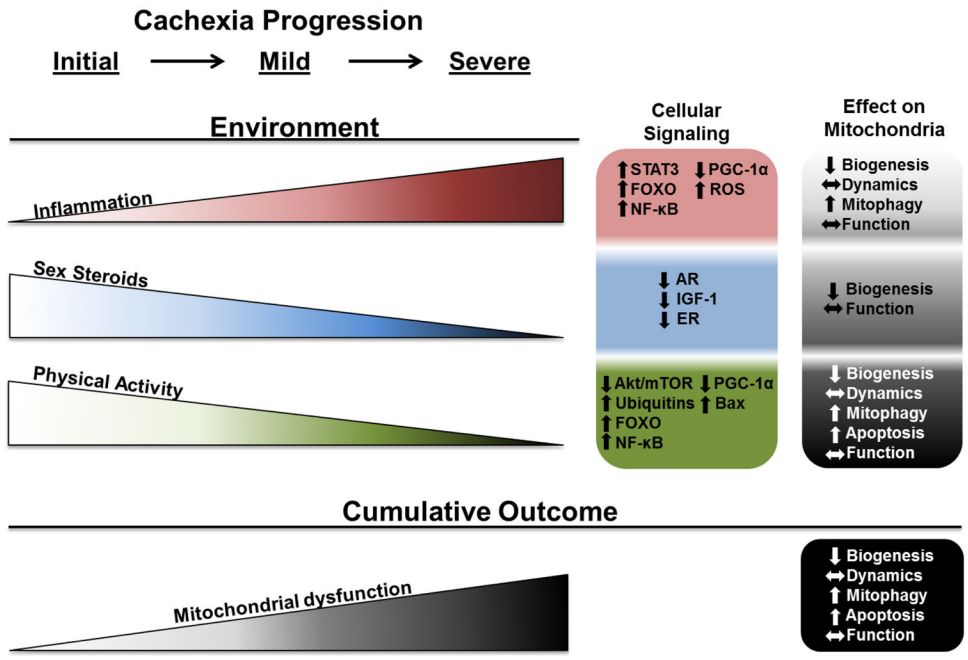

Figure 3. Cancer-induced cachectic environments and their relationship to skeletal muscle mitochondrial dysfunction during the progression of cancer cachexia

Increases in inflammation and decreases in sex steroids and physical activity disrupt mitochondrial quality throughout the progression of cachexia. Inflammation through systemic interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), TNF-like weak inducer of apoptosis (TWEAK), and myostatin increase throughout cachexia progression result in the activation of STAT3, NF-κB, FOXO, and PGC-1α signaling as well as the generation of reactive oxygen species (ROS). These signaling pathways result in decreased biogenesis, altered dynamics, increased mitophagy, and altered function in cachectic muscle mitochondria. Sex steroids (testosterone and estrogen) and their respective nuclear receptors (androgen and estrogen receptors) decrease throughout cachexia progression. These can negatively regulate anabolic signaling related to insulin-like growth factor 1 (IGF-1). These signaling pathways result in decreased mitochondrial biogenesis and altered mitochondrial function. Physical activity decreases throughout cancer cachexia progression resulting in decreased signaling through Akt/mTOR, and PGC-1α, while increasing signaling through FOXO, NF-κB, Bax, and ubiquitins. Decreased physical activity results in decreased biogenesis, increased mitophagy and apoptosis, and altered mitochondrial dynamics and function. While these factors can work independently, the culmination of systemic factors and decreased use can negatively impact muscle oxidative capacity through the regulation mitochondrial biogenesis, dynamics, mitophagy, apoptosis and function.