ANTIOXIDANTS & REDOX SIGNALING
Volume 38, Numbers 4–6, 2023

DOI: 10.1089/ars.2022.0149

FORUM REVIEW ARTICLE

Targeting Mitochondria and Oxidative Stress in Cancer- and Chemotherapy-Induced Muscle Wasting

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Abstract

Significance: Cancer is frequently associated with the early appearance of cachexia, a multifactorial wasting syndrome. If not present at diagnosis, cachexia develops either as a result of tumor progression or as a side effect of anticancer treatments, especially of standard chemotherapy, eventually representing the direct cause of death in up to one-third of all cancer patients. Cachexia, within its multiorgan affection, is characterized by severe loss of muscle mass and function, representing the most relevant subject of preclinical and clinical investigation.
Recent Advances: The pathogenesis of muscle wasting in cancer- and chemotherapy-induced cachexia is complex, and encompasses heightened protein catabolism and reduced anabolism, disrupted mitochondria and energy metabolism, and even neuromuscular junction dismantling. The mechanisms underlying these alterations are still controversial, especially concerning the molecular drivers that could be targeted for anticachexia therapies. Inflammation and mitochondrial oxidative stress are among the principal candidates; the latter being extensively discussed in the present review.
Critical Issues: Several approaches have been tested to modulate the redox homeostasis in tumor hosts, and to counteract cancer- and chemotherapy-induced muscle wasting, from exercise training to distinct classes of direct or indirect antioxidants. We herein report the most relevant results obtained from both preclinical and clinical trials.
Future Directions: Including the assessment and the treatment of altered redox balance in the clinical management of cancer patients is still a big challenge. The available evidence suggests that fortifying the antioxidant defenses by either pharmacological or nonpharmacological strategies will likely improve cachexia and eventually the outcome of a broad cancer patient population. *Antioxid. Redox Signal.* 38, 352–370.

Keywords: cancer, chemotherapy, wasting, antioxidants, nutraceuticals

CANCER CACHEXIA IS defined as the progressive loss of skeletal muscle mass, with or without fat loss, unresolved by conventional nutritional support (Fearon et al, 2011; Siegel et al, 2012; Thoresen et al, 2013). In recent years, the cachexia scientific community agreed on defining cancer cachexia as a multifactorial and multiorgan wasting syndrome (Argilés et al, 2018; Baracos et al, 2018), negatively impacting most cancer patients, reducing the tolerance and effectiveness of anticancer treatments, impairing the quality of life and eventually representing the direct cause of death.

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The present review is focused on highlighting the relevance of the redox homeostasis in the complex pathogenesis of cancer- and chemotherapy-induced cachexia, in the attempt to disentangle the contribution of oxidative stress to skeletal muscle wasting and dysfunction. A previously published review in this journal (Penna et al, 2020) introduces to the basic concepts on muscle wasting in cachexia and the relevance of the redox signaling in the onset of muscle depletion. Here, the main focus is the identification of critical biological processes regulated by the altered redox homeostasis in preclinical models of cancer- and chemotherapy-induced cachexia and in cancer patients, in the light of targeting such alterations with well-characterized or novel antioxidants/redox modulators.

Muscle Oxidative Stress in Cancer Hosts

The redox (oxidative/reductive) homeostasis in mature cells and tissues is determined by the tightly controlled balance between the accumulation of the physiologically produced reactive oxygen species (ROS) or reactive nitrogen species (RNS) and their clearance thanks to the endogenous antioxidant systems and exogenous antioxidants obtained through the diet or by the use of specific compounds/drugs (Neha et al, 2019). In cancer hosts, several phenomena result in local or systemic disruption of the redox homeostasis, very well characterized in cancer cells and in the tumor microenvironment (Hayes et al, 2020), less clearly in the skeletal muscle.

On the one side, impaired muscle antioxidant capacity was reported in a preclinical model (Sullivan-Gunn et al, 2011) and in muscle biopsies of cancer patients (Brzeszczynska et al, 2016), although a direct correlation with muscle wasting was not established. On the other side, opposing evidence suggests that the skeletal muscle of cancer hosts is able to activate the endogenous antioxidant defense. In rodents, C26 tumor growth stimulates in the muscle of mouse hosts an increase of the ratio Nrf2/Keap1 [Kelch-like ECH-associated protein 1-nuclear factor (erythroid-derived 2)-like 2], of CuZn superoxide dismutase (SOD1) along with the transcription of *Sod1* and *Cat* (Catalase) genes, as similarly observed in rats bearing the AH-130 tumor showing increased muscle SOD1 and catalase protein levels (Ballarò et al, 2019b; Salazar-Degracia et al, 2017).

Consistently, in humans, cachectic lung cancer patients show muscle accumulation of both SOD1 and SOD2 (Mn superoxide dismutase) in parallel to increased protein carbonylation and malondialdehyde–protein adducts (Puig-Vilanova et al, 2015). Due to both muscle extrinsic (inflammation and altered systemic metabolism) and muscle intrinsic factors (described in the following chapters), an oxidative insult is likely to occur, and the muscle antioxidant defenses could be unable to effectively counteract the detrimental action of ROS/RNS, thus contributing to muscle wasting, dysfunction, and metabolic disturbances.

Oxidative Stress in the Clinical Management of Cancer Patients

Oxidative stress plays an important role in carcinogenesis and progression of cancer, and may contribute to anorexia and cancer cachexia onset, exacerbated by the effects of antineoplastic therapies. To date, an unequivocal way to identify, classify, and treat the effects of oxidative stress in patients is lacking, making clinical management a real challenge. One of the possible clinical applications of the oxidative stress status in cancer is the use of oxidative stress markers as cancer diagnostic or progression indicators.

As an example, the biological and clinical relevance of protein oxidation as a biomarker is still limited by the availability of standardized methodologies to identify and quantify specific protein oxidative modifications, define a diagnostic cutoff and its prognostic value, and to correlate such information with the disease stage at the same time. The measurement must also be reasonably stable, collected from an accessible specimen, and its cost-effectiveness ratio has to be eventually evaluated (Marrocco et al, 2017).

Despite the increasing awareness of clinical relevance, no specific treatment or medical standard intervention exists to treat the effects of oxidative stress in cancer patients. According to the Management of Cancer Cachexia Guideline 2020 from the American Society of Clinical Oncology (ASCO) (Roeland et al, 2020), after 20 systematic reviews and 13 randomized controlled trials analysis, no pharmacological intervention has been recommended, due to limited evidence. Nonetheless, focusing on cachexia, progesterone analogs, short-term (weeks) corticosteroids administration, and physical activity have been applied only as experimental therapies in clinical trials targeting the appetite and/or as body weight enhancers.

Besides, by the close relation of oxidative stress and cancer, it has been assumed that antioxidant administration or applying pharmacological and nonpharmacological (such as exercise training) approaches could counteract the oxidative stress, and early results from clinical trials assessing the role of antioxidant therapy in cancer are promising, and the analysis of its impact on cachexia is warranted. A non-exhaustive list of recent (published in the last 5 years) clinical intervention studies targeting oxidative stress in cancer is described below.

Results from a systematic review and meta-analysis of randomized controlled trials studying coenzyme Q10 (a physiological antioxidant) supplementation effect in breast cancer patients upon conventional chemotherapy schema showed that 100 mg/daily CoQ10 supplementation for 45–90 days statistically decreased the levels of vascular endothelial growth factor, interleukin (IL)-8, and metalloproteinases 2 and 9, but no significant difference was obtained between CoQ10 supplementation and control group on tumor necrosis factor (TNF)-α, IL-6, IL-1β, CAT, SOD, glutathione peroxidase, glutathione, and thiobarbituric acid reactive substances (Alimohammadi et al, 2021), suggesting that CoQ10 supplementation might reduce some of the important markers of cancer-related inflammation.

Recently, a two-arm randomized controlled trial was conducted in patients with head and neck cancer receiving high-dose cisplatin chemotherapy concomitant with radiotherapy to investigate the potential protective effect of N-acetylcysteine (NAC) against therapy-induced toxicity (Visacri et al, 2019). Fifty-seven patients who were randomly 1:1 in parallel assigned to two groups either received 600 mg of NAC syrup, orally once daily for a week or placebo. Renal, hepatic, gastrointestinal, and myelo toxicities, clinical responses, plasma, and cellular markers of oxidative stress were analyzed.

Unfortunately, there was no statistically significant difference between the groups for all outcomes. On the contrary, NAC produced positive results in a prospective randomized controlled open-label trial, studying paclitaxel-induced peripheral neuropathy (PIPN) on 75 breast cancer patients receiving adjuvant paclitaxel 80 mg/m^2 once a week for 12 weeks (Khalefa et al, 2020). Eligible patients were randomized to either the low-dose group of 1200 mg daily NAC or the high-dose group of 1200 mg NAC twice daily. The results showed that oral high doses may decrease the incidence and severity of PIPN, and improve the quality of life.

Finally, an ongoing 3-arm parallel-group phase II randomized controlled trial in early breast cancer, The Caloric Restriction and Exercise protection from Anthracycline Toxic Effects (CREATE) study (ClinicalTrials.gov NCT03131024), is trying to determine whether the application of exercise and caloric restriction interventions shortly before receipt of each treatment can reduce anthracycline-related toxicity to the heart, aorta, and skeletal muscle, targeting short- and long-term cardiovascular health benefits, such as enhanced resilience to the effects of subsequent cancer treatment (*e.g.*, radiation, trastuzumab), aging, and infection. The study includes in the outcome measures the assessment of circulating markers of oxidative stress/antioxidants. Unfortunately, no results have been made publicly available, so far.

Regarding the relevance and impact of oxidative stress on patient prognosis, there is a lot of information obtained in the past years. A novel and useful contribution to daily clinical practice is the systematic oxidative stress score (SOS), introduced by Zhang et al (2021). Biomarkers of oxidative stress such as serum creatinine, serum albumin, total bilirubin, lactate dehydrogenase, and blood urea nitrogen were analyzed and correlated with the prognosis of 1583 operable female breast cancer patients. The authors concluded that the SOS is an independent prognostic indicator for operable breast cancer patients.

Overall, the multifactorial etiology and pathophysiology of cancer and chemotherapy response and the large number of substances involved in the control of the redox status make the studies presented here highly heterogeneous. The preliminary conclusions, summarized in Figure 1, represent the very first step on the path to conducting specific studies to design conclusive strategies and approaches in the clinical setting targeting oxidative stress in cancer. Consistently, the definition of the relevance of oxidative stress in cancer hosts, specifically in determining cachexia, is far from being well established and allowing the design and implementation of therapies targeting the redox homeostasis.

Oxidative Stress Induced by Chemotherapy in Tumor and Host Tissues

Chemotherapeutics are designed to kill cancer cells largely by disrupting cellular division. Unfortunately, chemotherapy drugs lack cellular specificity, resulting in vast cytotoxicity and the manifestation of unintended systemic complications to the chemotherapy recipient. There are a multitude of cytotoxic molecules approved for treatment of early and advanced cancer, which can be categorized based on their mechanism of action (Fig. 2A):

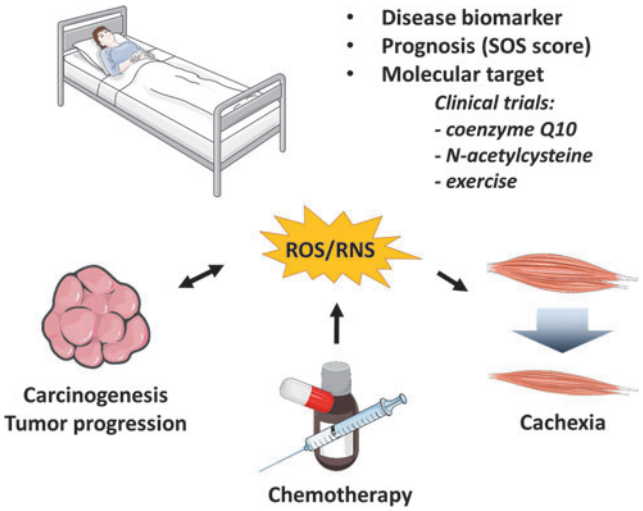

FIG. 1. Relevance of oxidative stress in cancer clinical practice. The cartoon summarizes the current main directions of clinical cancer research related to the dysregulation of redox homeostasis, potentially useful for improving diagnosis (biomarkers), prognosis (SOS score), and treatments. Systemic oxidative stress induced by both tumor growth and chemotherapy produces an insult to peripheral tissues, resulting in cachexia and muscle wasting. SOS, systematic oxidative stress.

- · Platinum-based compounds (*e.g.*, carboplatin, cisplatin, and oxaliplatin) block the transcription of DNA into RNA through crosslink formation within the DNA chain (Khalife et al, 2012).
- · Antimetabolites (*e.g.*, 5-fluorouracil, gemcitabine) masquerade as key DNA-building blocks, thereby interfering with DNA synthesis (Lansiaux, 2011).
- · Antibiotic-derived anthracyclines (*e.g.*, doxorubicin, DOX) and nonanthracyclines (*e.g.*, bleomycin and mitomycin-C) bind to the DNA preventing cell division.
- · Topoisomerase I (*e.g.*, irinotecan) or II (*e.g.*, etoposide) inhibitors disrupt relaxation of DNA supercoiling, impeding an essential cell division step (Pommier, 2006).
- · Mitotic inhibitors/taxanes (*e.g.*, docetaxel and paclitaxel) and vinca alkaloids (*e.g.*, vincristine and vinblastine) bind tubulin and interfere with chromosomal separation during metaphase (Moudi et al, 2013; Oshiro et al, 2009).

In addition to the listed mechanisms of action, some of the major unintended outcomes of anticancer treatments are an increase in oxidative stress through accumulation of ROS (Fig. 2B). Anticancer treatments can directly promote ROS production or can lead to impaired mitochondrial function, or cellular apoptosis, which can in turn further promote elevations in oxidative stress (Conklin, 2004). Indeed, mitochondria are the primary cellular site of ROS production, yet also possess inherent antioxidant defense mechanisms to constrain oxidative stress levels (Bhatti et al, 2017).

In fact, chemotherapy regimens containing drugs from the classes listed above have all been associated with mitochondrial disruption of off-target tissues, thus increasing susceptibility to increased oxidative stress (Bae et al, 2021; Campelj et al, 2021; Canta et al, 2015). As mentioned, some chemotherapeutics also directly promote high ROS.

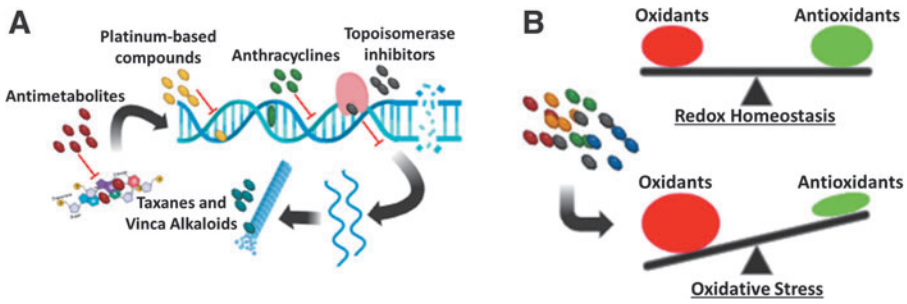

FIG. 2. Chemotherapy mechanism of action. **(A)** Schematic diagram depicting the known mechanism of action of various commonly adopted drugs in standard chemotherapeutic regimens. **(B)** Beyond the reported mechanisms of action, most of the secondary unintended effects of chemotherapy involve the increase of oxidative stress, due to the unbalance between ROS production and clearance by antioxidants. ROS, reactive oxygen species.

Anthracyclines, such as the widely studied DOX, are known to promote the highest levels of ROS among anticancer treatments. DOX can directly generate ROS through several mechanisms, including electron reduction of its quinone to semiquinone structure, metabolic breakdown through cleavage of its sugar residue, and direct interaction with metal ions such as iron (Conklin, 2004; Smuder, 2019).

Aside from anthracyclines, platinum-based compounds are known to promote high levels of oxidative stress in noncancerous tissues. The routinely used platinum-based compound cisplatin has been shown to accumulate within mitochondria, forming adducts with and impairing mitochondrial DNA function (Marullo et al, 2013).

Chemotherapy-induced muscle wasting

Anticancer treatments unfortunately have off-target consequences and are associated with the occurrence of cachexia (Crawford, 2013; Pin et al, 2018). Anticancer therapies can amplify this multiorgan syndrome, promoting lower quality of life, inability to perform routine activities, and poorer survival outcomes. Chemotherapy has a negative impact on several body organs, including brain, liver, fat, heart, kidney, and bone. It was suggested that the alterations occurring in other organs may be relevant to the onset of muscle wasting (Argilés et al, 2018; Schmidt et al, 2018); however, in the present review our focus will be mainly on skeletal muscle.

Skeletal muscle wasting is a hallmark of cachexia, and remains a focal point in both preclinical and clinical cancer cachexia research. This is particularly true with respect to skeletal muscle wasting and its potential amplification by anticancer treatments. Indeed, clinical studies have shown that administration of chemotherapy may accelerate muscle wasting in colorectal, gastric, breast, and lung cancer patients (Awad et al, 2012; Freedman et al, 2004; Klassen et al, 2017; Kurk et al, 2018; Naito et al, 2017; Poterucha et al, 2012). In a similar manner, Folfiri treatment heightens muscle wasting in C26 tumor-bearing mice (Pin et al, 2019a). The addition of chemotherapy may compound skeletal muscle wasting by the simple fact that cancer and chemotherapy promote similar dysfunctional signaling within skeletal muscle, which are discussed further below (Barreto et al, 2016a).

Aside from heightening cachexia in a setting of cancer, several experimental studies have demonstrated that chemotherapy directly causes skeletal muscle wasting (Ballaro et al, 2016; Barreto et al, 2017; Barreto et al, 2016a; Barreto et al, 2016b; Hain et al, 2019; Huot et al, 2021; Huot et al, 2019; Pin et al, 2019a; Pin et al, 2018). For example, Folfiri, a combination of 5-fluorouracil, leucovorin, and irinotecan, routinely used for treatment of solid tumors, including colon cancer, promotes muscle wasting in experimental settings.

In the widely used *in vitro* C2C12 model of mouse myotubes, Folfiri treatment promoted severe myotube atrophy, while intraperitoneal administration of Folfiri has shown weight loss, skeletal muscle wasting, and myofiber atrophy (Barreto et al, 2017; Barreto et al, 2016a; Barreto et al, 2016b; Huot et al, 2021; Pin et al, 2019a). In a similar manner, platinum-based therapies including cisplatin, carboplatin, and oxaliplatin directly promote a cachexia-like phenotype on skeletal muscle. We and others have reported myotube atrophy in C2C12 cells treated with cisplatin, as well as loss of skeletal muscle mass and fiber cross-sectional area in rodents treated with cisplatin (Damrauer et al, 2018; Essex et al, 2019; Huot et al, 2021; Sakai et al, 2014; Stacchiotti et al, 2014).

Similarly, oxaliplatin and carboplatin treatment reduce muscle mass and fiber cross-sectional area in experimental mice (Feather et al, 2018; Hain et al, 2020; Hain et al, 2019; Sorensen et al, 2017). Moreover, the commonly used anthracycline chemotherapeutic, DOX, consistently demonstrates muscle wasting in *in vitro* and *in vivo* rodent models (Ballaro et al, 2016; de Lima et al, 2018; Doerr et al, 2020; Huertas et al, 2020; Hulmi et al, 2018; Nishiyama et al, 2019; Nissinen et al, 2016; Powers et al, 2019). Recent production of second-line chemotherapeutics has spiked intending to hinder cancer advancement and metastasis, including the multikinase inhibitors sorafenib and regorafenib.

Unfortunately, much like the previously discussed chemotherapeutics, multikinase inhibitors, which are commonly used for treating colorectal, hepatocellular carcinoma, and gastric cancers, cause loss of skeletal muscle mass and myofiber atrophy (Dewys et al, 1980; Grothey et al, 2013; Huot et al, 2019; Shingina et al, 2013).

Cachexia mechanism: muscle weakness

A vast majority of cachexia research has emphasized the effects of cancer and its treatments on skeletal muscle mass. Importantly, investigation of skeletal muscle function during disease progression continues to gain traction. Indeed, like the clinical reports on muscle mass, studies from patients spanning a variety of cancers including head and neck, breast,

and lung cancer demonstrate that chemotherapy is at minimum associated with lower physical activity levels, reduced muscle force, and heightened muscle fatigue (Huy et al, 2012; Kasymjanova et al, 2009; Klassen et al, 2017; Lavigne et al, 2020; Lee et al, 2012; Naito et al, 2017; Schlesinger et al, 2014; Shi et al, 2020).

Moreover, cancer survivors have heightened levels of fatigue up to 5 years after diagnosis (Meeske et al, 2007). Meanwhile, recent work from animal studies has demonstrated that muscle fatigue and reduced activity occur before noticeable muscle wasting (Terwoord et al, 2018; VanderVeen et al, 2019), solidifying the importance of functional assessment during cachexia progression and with respect to chemotherapy administration.

Experimental chemotherapy interventions in rodents consistently demonstrate muscle weakness. Mice treated with Folfiri have lower grip strength, *in vivo* plantarflexion torque, and *ex vivo* contractile force of the extensor digitorum longus (EDL) muscle (Barreto et al, 2016b; Huot et al, 2021). In line, mice treated with cisplatin and carboplatin have reduced grip strength, *in vivo* plantarflexion torque, and EDL-specific force (Essex et al, 2019; Hain et al, 2020; Hain et al, 2019; Huot et al, 2021), while oxaliplatin treatment reduces rearing time and walking speed (Feather et al, 2018).

Studies investigating DOX administration have also consistently demonstrated reduced physical function, including reduced treadmill running performance and impaired *ex vivo* muscle force and heightened fatigability (de Lima et al, 2018; Doerr et al, 2020; Hydock et al, 2011; Powers et al, 2019). Recent work has also demonstrated muscle weakness in mice administered the multikinase inhibitors, regorafenib and sorafenib (Huot et al, 2019). Taken altogether, it is clear that a plethora of chemotherapeutic regimens directly promote a cachexia-like phenotype in skeletal muscle, inclusive of both skeletal muscle wasting and loss of muscle function.

Cachexia mechanism: heightened catabolism

With the direct and compounding negative effects that chemotherapy has on skeletal muscle mass and function, mechanistic investigations to prevent chemotherapy-induced cachexia are on the rise. Given the phenotypic similarities between cancer and chemotherapy, and the pivotal role that erratic catabolism plays in cancer-induced cachexia, investigations have assessed muscle catabolism in the context of chemotherapy.

Consistent with lower muscle mass, Folfiri treatment promotes the activation of the mitogen-activated protein kinase (MAPKs), MEK1/2, ERK1/2, and p38, all of which have demonstrated roles in experimental cancer-induced muscle wasting (Barreto et al, 2016b; Liu et al, 2018; Penna et al, 2010; Yang et al, 2017). In line with increased catabolism, the use of cisplatin in *in vivo* contexts leads to increased Atrogin-1, Muscle RING-finger protein-1(MuRF1), p38, myostatin, and nuclear factor kappa b (NF-κB), all known mediators of muscle atrophy (Chen et al, 2015; Damrauer et al, 2018; Essex et al, 2019; Sakai et al, 2019; Wu et al, 2019).

In addition, investigations have revealed increased Atrogin-1 upon DOX and oxaliplatin administration in mice (Feather et al, 2018; Hulmi et al, 2018), while treatment with the multikinase inhibitors, regorafenib and sorafenib, leads to increased markers of autophagy within skeletal muscle (Huot et al, 2019). Altogether, these experimental investigations suggest that heightened catabolism is a common denominator in cancer- and chemotherapy-induced muscle wasting.

Cachexia mechanism: suppressed anabolism

Although rampant catabolism certainly plays a role in muscle wasting, evidence also suggests impaired anabolism upon cancer and chemotherapy administration. For example, tumor growth, Folfiri and cisplatin administration individually impair the activation of the serine/threonine protein kinase AKT and the insulin-like growth factor (IGF)-1/AKT axis in rodent skeletal muscle (Barreto et al, 2016b; Chen et al, 2015; Geremia et al, 2022; Sakai et al, 2019).

Treatment of mice with oxaliplatin reduces p70S6K and pS6 protein content, which sit downstream of the IGF-1/AKT axis, suggesting protein synthesis reductions (Sorensen et al, 2017). Meanwhile, the surface sensing of translation (SUnSET) method (Goodman and Hornberger, 2013) has shown that DOX administration causes reduced skeletal muscle protein synthesis rates in mice [40]. More recent *in vitro* work has further demonstrated that treatment with DOX, paclitaxel, marizomib, or carboplatin directly causes reduced puromycin-labeled proteins (SUnSET) in C2C12 myotubes (Guo et al, 2021; Hain et al, 2021). Further investigation demonstrated that DOX, paclitaxel, and marizomib reduce ribosomal capacity of C2C12 myotubes, paralleling what is seen in cachectic skeletal muscle of tumor-bearing mice (Guo et al, 2021; Kim et al, 2021).

Cachexia mechanism: disrupted mitochondria

Arguably one of the most consistent alterations linking chemotherapy (and cancer) to oxidative stress and skeletal muscle wasting is the disruption of muscle mitochondria (Fig. 3). In this regard, Folfiri treatment promotes reduced skeletal muscle levels of peroxisome proliferator-activated receptor γ coactivator (PGC)-1α, PGC-1β, optic atrophy gene (OPA)1, Mitofusin-2, dynamin-related protein-1, and cytochrome-C, all of which contribute to regulation of mitochondrial homeostasis (Barreto et al, 2016a; Barreto et al, 2016b).

Moreover, Folfiri depleted the number and size of skeletal muscle mitochondria, and reduced succinate dehydrogenase (SDH) staining, a crucial oxidative phosphorylation enzyme (Barreto et al, 2016b). The chemotherapeutics Folfox, sorafenib, DOX, and cisplatin have also impaired muscle mitochondrial proteins, including the master regulator PGC-1α (Bae et al, 2021; Barreto et al, 2016b; Hulmi et al, 2018; Huot et al, 2019; Sirago et al, 2017). Interestingly, our recent unpublished work has demonstrated that older animals are more susceptible to cisplatin-induced depletion of mitochondrial proteins, including PGC-1α, OPA1, voltage-dependent anion channel, cytochrome-C, and cytochrome c oxidase (COX)4.

Cachexia mechanism: elevated oxidative stress

Oxidative stress can result from both mitochondrial and cytosolic ROS production, in the absence of an efficient clearance by the antioxidant systems, thus resulting in ROS

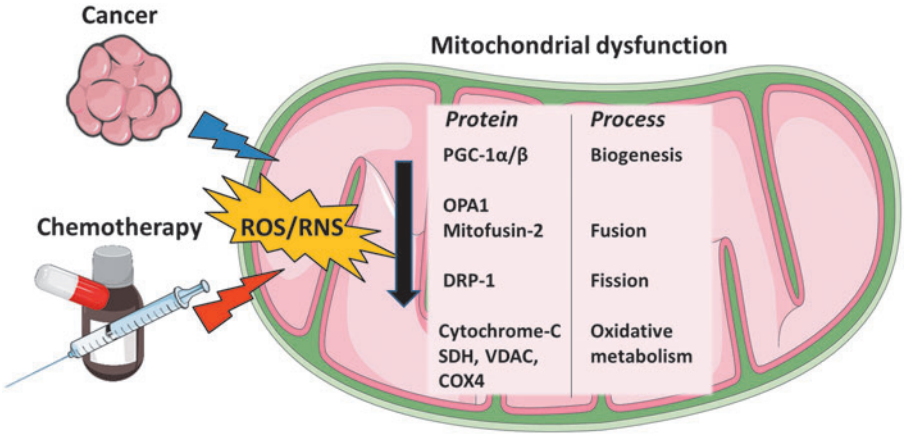

FIG. 3. Cancer- and chemotherapy-induced oxidative stress alters mitochondrial function. The protein levels of factors involved in mitochondrial homeostasis are impaired upon oxidative stress, resulting in the suppression of the associated biological process.

accumulation. Cytosolic ROS derive from the activation of the NADPH oxidases (NOX2 and NOX4) or the purine catabolic enzyme xanthine oxidase (XO). The role of cytosolic ROS production in cancer cachexia-associated muscle wasting is unclear. Indeed, the accumulation of superoxide in the muscle of tumor-bearing animals associates with reduced NOX2 protein expression, suggesting that alternative sources (likely mitochondrial) are more relevant (Sullivan-Gunn et al, 2011).

On the contrary, targeting NOX4 or XO seems effective in counteracting cancer-induced muscle wasting (Dasgupta et al, 2020; Springer et al, 2012). As chemotherapeutics promote mitochondrial dysfunction, it is understandable that oxidative stress would also be considered an important player in chemotherapy-induced muscle wasting. Also of interest, elevated serum ROS have been linked to tumor progression and prognosis in cancer patients (Kruk and Aboul-Enein, 2017; Sugimoto et al, 2019). Further, and as mentioned above, certain chemotherapeutic agents are known to promote ROS accumulation in off-target tissues. As an example, DOX accumulates within skeletal muscle mitochondria and has consistently demonstrated skeletal muscle wasting and weakness, accompanied by increased oxidative stress in experimental rodents (Doerr et al, 2020; Min et al, 2015; Morton et al, 2019; Smuder et al, 2011).

In a similar manner, rats treated with cisplatin have increased skeletal muscle oxidized peroxiredoxin and reduced SOD2, while mice treated with oxaliplatin show increased mitochondrial superoxide production (Sirago et al, 2017; Sorensen et al, 2017). Moreover, tumor- and nontumor-bearing mice treated with Folfiri have increased skeletal muscle ROS, reinforcing that anticancer treatments promote increased oxidative stress within skeletal muscle (Pin et al, 2019a).

ROS accumulation has been shown to directly promote skeletal muscle wasting, in part by promoting elevations in several catabolic signaling pathways already discussed. For example, the MAPKs (MEK1/2, ERK1/2, p38), which are increased in cachectic muscle are similarly increased by ROS accumulation (Barreto et al, 2016b; Liu et al, 2018; Penna et al, 2010; Torres and Forman, 2003; Yang et al, 2017).

In line, increased ROS promote the activation of NF-κB and the ubiquitin proteosome system, which, as mentioned, is implicated in cancer- and chemotherapy-induced muscle wasting (Birben et al, 2012; Damrauer et al, 2018; Huot et al, 2020b; Li et al, 2003; Powers et al, 2010). Moreover, while ROS can promote heighted catabolism, it is also linked to suppressing anabolic signaling, similar to what is seen in cachectic muscle. Indeed, similar to cancer and chemotherapy, elevated ROS has also shown to impair the AKT/mTOR signaling cascade, and its downstream translation effectors such as 4EBP1 (Tan et al, 2015; Zhang et al, 2009).

Interestingly, although ROS can reduce protein synthesis rates in skeletal muscle cells, recent work demonstrated that low doses of chemotherapeutic were sufficient to promote reductions in protein synthesis without imposing increases in skeletal muscle ROS (Guo et al, 2021).

Cachexia mechanism: altered neuromuscular junction

Proper muscle–nerve interaction, in particular at the neuromuscular junction (NMJ), is essential for skeletal muscle function. As mentioned, chemotherapy promotes mitochondrial abnormalities, and interestingly, skeletal muscle mitochondria are implicated in the formation, fragmentation, and maintenance of NMJs (Ahn et al, 2019; De vos et al, 2007; Magrané et al, 2012; Malkki, 2016). Meanwhile, the E3-ubiquitin ligase MuRF-1, and the myogenic regulatory factor myogenin, both dysregulated by chemotherapy, are involved in the remodeling of NMJs (Rudolf et al, 2013; Wu et al, 2019).

Furthermore, as highlighted throughout this review, cancer and chemotherapy promote ROS accumulation within skeletal muscle, and impaired redox homeostasis is strongly implicated in NMJ dismantling and dysfunction (Dobrowolny et al, 2021; Jang et al, 2010). Considering this, neuromuscular function and NMJs have begun receiving substantial attention. In fact, mice bearing cancer or receiving chemotherapy recently demonstrated reduced presynaptic NMJ staining as well as depleted NMJ proteins (Huot et al, 2021; Sartori et al, 2021). In particular, mice treated with cisplatin had reduced levels of skeletal muscle MuSK, a pivotal NMJ-scaffolding protein, and LRP4 and Dok7, membrane and cytoplasmic proteins regulating NMJ function through complex formation with MuSK (Huot et al, 2021).

Interestingly, rats treated with DOX did not show alterations in LRP4 or Dok7, and demonstrated increased MuSK, suggesting divergence of chemotherapy-induced alterations at the NMJ (Huertas et al, 2020). Yet, from a functional standpoint, cisplatin and Folfiri promoted reductions in the

estimated number of functionally connected motor units, associating loss of motor unit connectivity with skeletal muscle wasting and weakness (Huot et al, 2021). Similarly, oxaliplatin promotes enteric neuropathy and diaphragm motor alterations; though, it is unknown if these effects of oxaliplatin extend to limb musculature (McQuade et al, 2016; Webster et al, 2005).

Meanwhile, vincristine, well known to induce peripheral neuropathy, was shown to reduce axonal diameter and conduction velocity of the sciatic nerve in rodents (Boehmerle et al, 2014; Starobova et al, 2021). Yet, to our knowledge, whether vincristine disrupts the NMJ is unknown. Despite promising data emerging from preclinical models, evidence from clinical studies is unclear. A recent study showed no evidence of NMJ alterations in the rectus abdominis muscle of esophageal cancer patients with cachexia, although, in this case, morphological assessment of the NMJs was performed 4–6 weeks after cessation of chemotherapy and neuromuscular function assessment was not performed (Boehm et al, 2020).

On the contrary, in pancreatic and colorectal cancer patients, serum neural cell adhesion molecule (NCAM) and Agrin fragment increase, along with muscle NCAM positivity, suggesting NMJ degeneration and remodeling (Sartori et al, 2021). Moving forward, clinical studies should attempt to assess NMJ integrity and functional changes in patients, and assess the impact of chemotherapy administration on neuromuscular function.

Altered Energy Metabolism in Cancer- and Chemotherapy-Induced Cachexia

Energy crisis

As discussed above, cachexia caused by cancer and chemotherapy can be defined as an energy wasting syndrome, and generally associates with depletion of mitochondrial size, number, and function (Argilés et al, 2014a; Barreto et al, 2016b; Fearon et al, 2011). Oxidative stress in the skeletal muscle can either derive from cancer- and chemotherapy-induced mitochondrial dysfunction, or the metabolic alterations can poise the muscle endogenous oxidant sources driving and exacerbating the oxidative distress, which in physiological conditions would produce a eustress adaptation.

With mitochondrial disruption and oxidative stress seeming at the center of cachexia and given the necessity of mitochondria in sustaining metabolic homeostasis, it is not surprising that vast amounts of literature have demonstrated perturbed skeletal muscle and systemic metabolism in cancer cachexia. This may be since cancerous cells not only rely on glycolytic metabolism (*i.e.*, Warburg effect), but are rampant users of aerobic glycolysis as well, resulting in high-cost/low-yield ATP production and energetic disruption to its host organism (Heiden et al, 2009; Rohm et al, 2019; Warburg, 1956).

Indeed, lewis lung carcinoma (LLC) tumor-bearing mice have demonstrated reduced mitochondrial ATP production (Constantinou et al, 2011), and Folfiri reduced muscle ATP in healthy and C26 tumor hosts (Pin et al, 2019a). The latter study clarifies that cancer- and chemotherapy-induced cachexia display both common and distinct alterations in flux through the Krebs cycle and β-oxidation pathways, eventually contributing to the cachexia energy crisis. Moreover, futile high-cost energy processes including mitochondrial proton recycling, lipid turnover, and the Cori cycle can all promote excessive energy expenditure during cancer cachexia (Argilés et al, 2014a, 2014b; Kazak et al, 2015; Rohm et al, 2019).

Glucose metabolism

Cachexia caused by cancer and chemotherapy is associated with abnormal glucose metabolism, although the underlying mechanisms are unclear, likely contributed to by conflicting clinical and experimental data. The main metabolic alterations are summarized in Figure 4 and described below. Cancer cachexia is often associated with insulin resistance and thus impaired glucose handling, yet despite abnormal insulin secretion, cancer patients often present with normal fasting glucose levels (Dev et al, 2018; Tomás et al, 2002). Interestingly, clinical evidence has revealed transient hyperglycemia in as many as 30% of cancer patients receiving chemotherapy (Hwangbo and Lee, 2017).

Also suggesting impaired glucose metabolism, yet in opposite manner, cachectic mice bearing colorectal cancer or receiving Folfiri treatment display reduced plasma

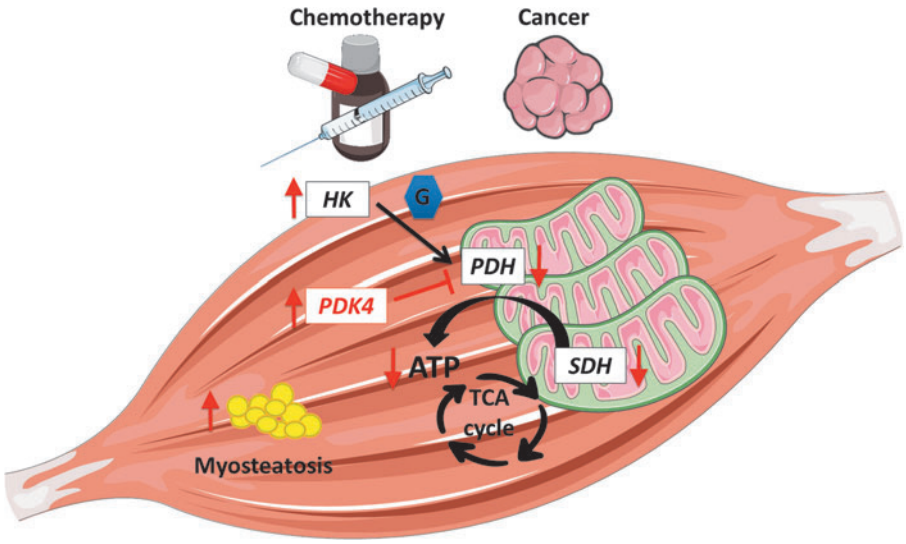

FIG. 4. Altered energy metabolism in the skeletal muscle during cachexia. Cancer and chemotherapy negatively affect glucose metabolism, reducing the uptake from the circulation, and impair the mitochondrial oxidative capacity, through the TCA cycle and the oxidative phosphorylation. As a consequence, energy failure (ATP shortage) and lipid accumulation (myosteatosis) occur. HK, hexokinase; G, glucose; PDH, pyruvate dehydrogenase; PDK4, pyruvate dehydrogenase kinase 4; SDH, succinate dehydrogenase; TCA, tricarboxylic acid.

glucose (Huot et al, 2020a; O'Connell et al, 2019; Pin et al, 2019a), in line with clinical evidence showing hypoglycemia in approximately one-quarter of pediatric patients with acute lymphoblastic leukemia undergoing maintenance chemotherapy treatment (Rosenfeld et al, 2022).

Experimental data suggest that the observed hypoglycemia in preclinical models of cancer cachexia may occur in response to heightened glucose uptake and utilization by the growing tumor, although only few evidence supports the expected elevations in systemic lactate that would ensue (Huot et al, 2020a; O'Connell et al, 2019; Pin et al, 2019a). In such regard, the lack of consistency in blood lactate levels may result from liver uptake and utilization of lactate as a gluconeogenic substrate through the Cori cycle, which is also evidenced by increased liver phosphoenolpyruvate carboxykinase in cachectic $APC^{Min/+}$ mice and mice treated with chemotherapy (Narsale et al, 2015; Pin et al, 2019a).

Tricarboxylic acid cycle and oxidative metabolism

Cancer- and chemotherapy-induced skeletal muscle wasting is also associated with alterations of the tricarboxylic acid (TCA) cycle. Skeletal muscle of mice treated with Folfiri and/or bearing C26 tumors has shown lower TCA cycle components and substrates citrate, glutamate succinate, and fumarate (Huot et al, 2020a; O'Connell et al, 2019; Pin et al, 2019a). This is further supported by reduced enzyme activity of skeletal muscle SDH, which is essential for TCA cycle and electron transport chain function, as well as pyruvate dehydrogenase (PDH), the enzyme that regulates pyruvate entry into the TCA cycle (Harris et al, 2002; Huot et al, 2020a; Pin et al, 2019a).

Of interest, PDH function is negatively regulated by pyruvate dehydrogenase kinase 4 (PDK4), which is increased in the skeletal muscle of mice bearing colorectal and ovarian cancers, as well as animals treated with Folfiri, cisplatin, and carboplatin (Pin et al, 2019b). These impairments, along with the reported reduction in several mitochondrial proteins (as discussed above), are suggestive of a net shift away from oxidative metabolism and toward a more glycolytic phenotype in the cachectic skeletal muscle (Barreto et al, 2016b; Huot et al, 2020a; Pin et al, 2015).

Interestingly, this glycolytic shift may explain the heightened susceptibility of myofiber atrophy, as type II fibers (*i.e.*, glycolytic) typically experience heighted wasting during cancer progression (Wang and Pessin, 2013). Impaired oxidative capacity, likely resulting from reduced mitochondrial content (size and number) and function in response to cancer burden and anticancer treatments, also alters lipid handling (Barreto et al, 2016b; Guigni et al, 2018; Pin et al, 2015; Shum et al, 2012). Intriguingly, during the cachexia energy crisis, skeletal muscle from rodents also demonstrates extreme increases in lipid accumulation, termed myosteatosis (Huot et al, 2020a; Rupert et al, 2021).

Targeting Muscle Mitochondrial Oxidative Stress in Cachexia

Exercise

One nonpill/supplement strategy to bolster mitochondrial function, and thus target antioxidant capacity, is by partaking in physical exercise. In particular, aerobic exercise interventions have been utilized as a potential strategy to combat muscle wasting during cancer- and chemotherapy-induced cachexia. For example, a combination of erythropoietin and low-intensity aerobic exercise provided partial protection against muscle wasting in C26 tumor-bearing mice (Pin et al, 2015). Separate work demonstrated that moderate aerobic exercise alone was sufficient to preserve muscle mass in mice with C26 tumors (Ballarò et al, 2019b).

Similarly, C26 tumor hosts undergoing a combination of aerobic and resistance exercise showed preserved muscle mass and muscle strength (Ranjbar et al, 2019), while resistance exercise preserved muscle mass in rats bearing breast cancer (Padilha et al, 2017), though not in C26-bearing mice (Khamoui et al, 2016). Interestingly, trimetazidine, a stimulator of PGC-1α and known exercise mimetic, was also shown to improve muscle mass in mice bearing C26 tumors (Molinari et al, 2017). Noteworthily, the use of exercise strategies has also shown efficacy in the presence of chemotherapy.

Aerobic exercise provided partial protection of muscle mass and muscle strength in C26 tumor hosts receiving a combination of oxaliplatin and 5-fluorouracil (Ballarò et al, 2019a). In addition, aerobic exercise training protected against skeletal muscle alterations and fatigue induced by DOX (de Lima et al, 2018; Huertas et al, 2020; Powers et al, 2019), as well as cisplatin (Sakai et al, 2017). Resistance exercise has been shown to be safe and practical in clinical settings, as demonstrated by increased muscle strength in breast cancer patients receiving chemotherapy (Mijwel et al, 2018), and by increased lean mass and muscle strength in pancreatic cancer patients (Kamel et al, 2020).

Moreover, a meta-analysis assessing exercise efficacy in patients undergoing chemotherapy treatment concluded that exercise can sustain or improve fitness levels, improve physical function and ability to perform activities of daily living, increase chemotherapy completion rates, and lower chemotherapy-induced toxicities (Cave et al, 2018). Given the already suggested benefits of exercise, future studies should work to optimize and individualize exercise prescriptions for patients undergoing anticancer treatments.

Genetic approaches targeting mitochondria

As discussed throughout this review, cancer and chemotherapy severely impair skeletal muscle mitochondrial content and function. As mitochondria are the predominant producers of cellular ROS, yet also hold inherent antioxidant defense to mitigate oxidative stress, it is no surprise that genetically targeting mitochondria is a common strategy to sustain skeletal muscle in settings of cachexia. Moreover, genetic targeting of mitochondria has shown to preserve skeletal muscle mass in other models that cause skeletal muscle atrophy and oxidative stress, including hindlimb suspension and denervation (Cannavino et al, 2014; Lawler et al, 2003; Pigna et al, 2017; Sandri et al, 2006).

Interestingly, overexpression of the mitochondrial proteins PGC-1α and Mitofusin-2 has demonstrated mixed results on preserving muscle mass in cancer cachexia (Pin et al, 2015; Wang et al, 2012; Xi et al, 2016). However, recent work illustrated that overexpression of PGC-1α was able to protect against cisplatin-induced muscle wasting and weakness, particularly in older animals, where oxidative stress tends to be elevated (Baumann et al, 2016).

Interestingly, implanting LLC tumors into SOD1 knockout mice, an established model of heighted oxidative stress, did not cause exacerbated muscle wasting compared with wild-type mice, although indices of NMJ disruption were elevated (Brown et al, 2020). In contrast, skeletal muscle overexpression of mitochondrial catalase was shown to preserve muscle mass and function in SOD1 knockout mice (Xu et al, 2021). Similarly, muscle peroxiredoxin3 overexpression scavenges mitochondrial hydrogen peroxide produced by the genetic ablation of SOD1, partially mitigating the loss of muscle mass and strength (Ahn et al, 2022). Whether targeting mitochondrial catalase or peroxiredoxin3 would prove beneficial in chemotherapy- or cancer-induced cachexia has not been investigated.

Mitochondria-targeted antioxidants

In recent years, mitochondrial drug targeting has received much attention with respect to cachexia. Drugs can be targeted to the mitochondria through conjugation to a lipophilic cation, including triphenylphosphonium (TTP^+). In particular, mitochondria-targeted antioxidants are thought to improve function and energy metabolism of the mitochondria, thereby improving skeletal muscle mass and function. An example of this is Mitoquinone Q (MitoQ), which accumulates in the mitochondria through its conjugation to TTP^+, where its ubiquinone moiety serves to elevate antioxidant capacity through reduction to ubiquinol (Broome et al, 2018).

In a recent study, C26 tumor-bearing mice treated with MitoQ were shown to have improved muscle mass, grip strength, and improved indices of energy metabolism compared with untreated tumor hosts (Pin et al, 2022). In line with the reported *in vivo* findings, MitoQ treatment prevented against DOX and paclitaxel-induced C2C12 myotube atrophy (Guigni et al, 2018).

Another class of mitochondria-targeted antioxidants are in peptide form, which contain an amino acid sequence, thereby allowing the drug to pass through and localize to the inner membrane of the mitochondria (Broome et al, 2018). An example of this is Szeto-Schiller-31 (SS-31), which targets cardiolipin, improving oxidative stress through reduction of mitochondrial ROS production (Broome et al, 2018). Recent work demonstrated that SS-31 treatment improved oxidative metabolism of skeletal muscle and provided partial protection against muscle wasting during the early stages of cachexia progression (Ballarò et al, 2021).

Separate work demonstrated that SS-31 reduced mitochondrial hydrogen peroxide production and maintained force production of the diaphragm in C26 tumor hosts (Smuder et al, 2020). In line with its effectiveness in tumor hosts, earlier work revealed that SS-31 improved skeletal muscle myofiber size and force production in rats administered DOX (Min et al, 2015). Indeed, DOX has a strong affinity for cardiolipin, an essential component of mitochondrial membranes. When complexes cardiolipin–DOX are formed, structural breakdown or mitochondrial scaffolding occurs due to lack of anchoring for cytochrome-C or lipid–protein interfaces. Further, the oxidation of cardiolipin has been implicated as a contributor to mitochondria-mediated cell death (Awad et al, 2012; Freedman et al, 2004).

SKQ1, a novel mitochondria-targeted antioxidant, was recently shown to improve *in vitro* cardiomyocyte viability in the presence of DOX (Sacks et al, 2021), yet whether SKQ1 has similar efficacy on skeletal muscle in settings of cancer- and chemotherapy-induced cachexia is unknown. It is also worth noting that the mitochondria-targeted antioxidants Mito-TEMPO and XJB-5-131 have demonstrated efficacy in preventing muscle atrophy in experimental models of chronic kidney disease and aging (Javadov et al, 2015; Liu et al, 2020), yet to our knowledge these compounds have not been investigated in cancer- and chemotherapy-induced muscle wasting.

Nutraceuticals Able to Modulate the Redox Homeostasis to Prevent Cachexia

Nutraceuticals, also known as functional foods, are defined as foods or parts of foods that provide medical or health benefits. In the last decade, several nutraceuticals such as polyunsaturated fatty acids (PUFAs), ursolic acid, curcumin, vitamins, and creatine have been implicated in numerous studies to improve circulating beneficial myokines, to improve physical performance, and to reduce oxidative stress (Aquila et al, 2020; Schiessel and Baracos, 2018; van de Worp et al, 2020). The molecules that either proved effective against cachexia and muscle wasting or that have a potential rationale for being tested are presented below and depicted in Figure 5.

Vitamins

Several vitamins are known for their antioxidant properties and have been advocated for the treatment of cachexia (Aquila et al, 2020). Among them, vitamin E is known not just for its antioxidant properties but has also been associated with the ability to reduce the oxidative damage and help stabilize cancer disease progression (Kyriakopoulos et al, 2016). However, when used to prevent mitochondrial damage in DOX-treated rats through dietary supplementation, vitamin E showed preventions of cardiac oxidative damage, but failed to prevent mitochondrial dysfunction (Berthiaume et al, 2005). Vitamin E was also found to be beneficial in a clinical trial as patients supplemented with vitamin E significantly reduced the occurrence of cisplatin-induced neuropathy (Argyriou et al, 2006). Although vitamin E shows some promise in its use to alleviate some chemotherapy-induced maladies, its benefits for counteracting cachexia are still inconclusive.

Vitamin B3, although not having direct antioxidant activity, can potentially improve the redox homeostasis by rescuing nicotinamide adenine dinucleotide (NAD)+ depletion, an alteration causing impaired muscle oxidative phosphorylation that was recently reported in tumor-bearing animals (Hulmi et al, 2020). Similarly, chemotherapy induces severe NAD+ loss due to the activation of NAD-consuming DNA repairing machinery (Houtkooper et al, 2010). Vitamin B3 supplementation proved safe and effective in treating muscle NAD+ loss in human myopathies (Pirinen et al, 2020), represents a novel option that has recently provided positive results in C26-bearing mice (Park et al, 2021). Moreover, our observations suggest that vitamin B3 is also able to counteract cancer plus chemotherapy muscle mitochondrial dysfunction (Beltrà et al, 2022), providing the rationale for human trials to confirm the therapeutic potential.

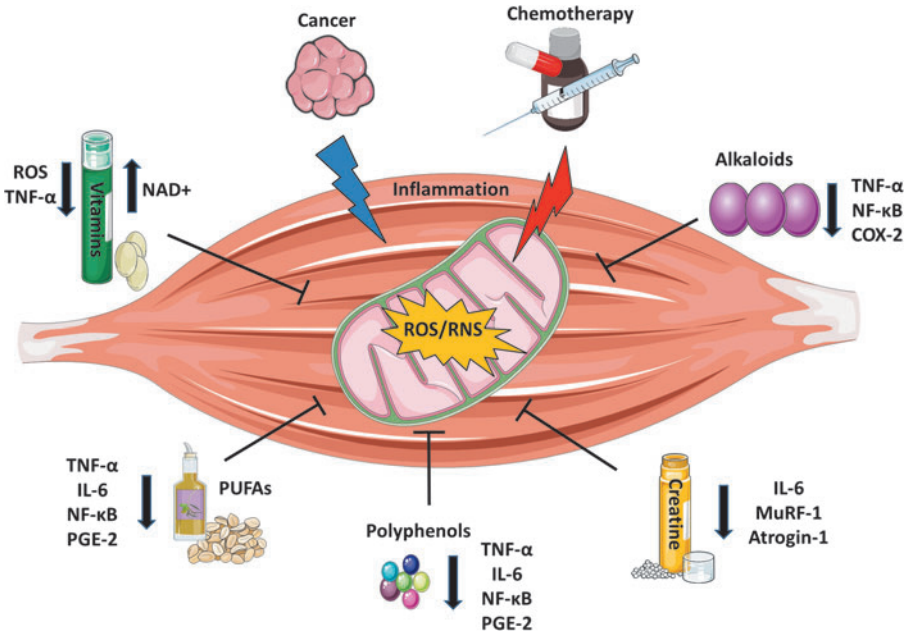

FIG. 5. Nutraceutical interventions targeting muscle redox homeostasis. Several classes of compounds, abundant in specific foods or diet formulation, have the potential to counteract cancer- and chemotherapy-induced oxidative stress, either directly or by modulating the inflammatory status. The regulation of specific cytokines or pathways is described close to every class of molecules.

Creatine

Creatine is a commonly used supplement to help improve skeletal muscle endurance and lean body mass by improving the availability of phosphocreatine in the body (Gualano et al, 2012). Further, it has been shown to be an effective antioxidant mitigating proinflammatory cytokines (Bassit et al, 2008). This has generated some interest in its ability to mitigate atrophy and skeletal muscle dysfunction associated with cancer and anticancer therapy.

A series of preclinical investigations have shown its ability to specifically prevent anthracycline, such as DOX, mediated skeletal muscle dysfunction and fatigue in both *in vitro* and *in vivo* experiments. Specifically, EDL and SOL muscles of rats incubated with creatine and exposed to DOX showed an attenuated dysfunction leading to a greater time-to-fatigue *versus* DOX alone (Bredahl et al, 2020; Bredahl and Hydock, 2017).

Further promising results have been found in preclinical cachexia models in preventing increases in IL-6, and accumulation of ubiquitin/proteasome E3 ligases in rats (Cella et al, 2020). However, there have been relatively few clinical studies examining its efficacy in prevention of cancer- or chemotherapy-related cachexia. The utilization of creatine in the clinic is complicated by its propensity to increase creatinine levels, which could be contradicting for patients at risk of renal complications (van de Worp et al, 2020).

Alkaloids

Berberine, the main alkaloid in the herbal medicine coptis, has been found to have antidiabetic, anti-inflammatory, and antimicrobial (both antibacterial and antifungal) properties. Berberine can inhibit IL-6, TNF-α, monocyte chemoattractant protein 1 (MCP1), and cyclooxygenase (COX)-2 production and expression, and has also been implicated in prevention of cancer cachexia (McCubrey et al, 2017; Tillhon et al, 2012). Some of these effects may be mediated by the Raf/MEK/ERK and the NF-κB pathways (Tillhon et al, 2012).

Further, berberine has shown some promise in alleviating the toxic effects of chemotherapy, primarily by preventing mitochondrial ROS generation through its antioxidant properties, which could prevent mitochondrial dysfunction and cell death. Berberine has been shown to reduce the intracellular AMP/ATP ratio and to improve the levels of Bcl-2 in cardiac mitochondria (Lv et al, 2012), suggesting that it could be effective in skeletal muscle as well, yet has lacked specific trails looking at preventing cancer cachexia.

Tomatidine, a natural alkaloid from the stems and leaves of tomato plants, has been recently investigated for its ability to prevent oxidative damage in diabetic and limb immobilization conditions (Dyle et al, 2014). The mechanisms of action lie in the mTOR complex 1 (mTORC1) pathway, which are thought to be upregulated, and able to reduce skeletal muscle atrophy (Adams et al, 2015; Dyle et al, 2014). This scantly studied nutraceutical ability to possibly prevent cancer- or chemotherapy-related cachexia has not been evaluated, and should be taken into consideration for future experiments.

Polyphenols

In addition to the discussed mitochondria-targeted drugs, plant-derived polyphenols can scavenge and reduce ROS, thereby improving oxidative stress. Due to their potent ROS lower capabilities, several of these plant-based compounds have been investigated in the context of counteracting cancer-induced muscle wasting.

Resveratrol (3,5,4′-trihydroxystilbene) is a phytoalexin, a class of compounds produced by many plants that has been reported to have antitumor effects in rats. The available research on this potential antioxidant has garnered mainstream attention, but with contradictory results. Thought to act through interference in the previously discussed NF-κB pathway determining atrophy, a few studies demonstrated resveratrol ability to prevent skeletal and cardiac muscle loss (Shadfar et al, 2011), and reduce tumor growth in preclinical cachexia mouse models (Wyke et al, 2004). However, when

examined with exogenous administration in rats, there was an exacerbation of cachexia, possibly due to its low bioavailability (Busquets et al, 2007). This lower bioavailability might prevent resveratrol from reducing muscle wasting, as the likelihood to reach effective levels in plasma or muscle is very low, and future use for prevention of cachexia is unlikely.

Curcumin, a polyphenol with known antioxidant properties, was recently shown to improve muscle mass and strength in mice with triple-negative breast cancer (Zhang et al, 2022). The study demonstrated that curcumin lowers skeletal muscle NF-κB activity and protein ubiquitination (Zhang et al, 2022). However, it is important to note that tumor burden was lower in curcumin-treated tumor hosts, which parallels the lower tumor burden reported in Yoshida AH-130 rats treated with curcumin, although cachexia was not attenuated in the tumor-bearing rats (Busquets et al, 2001; Zhang et al, 2022).

In contrast, recent studies in which curcumin was used alone or as part of a combination therapy demonstrated no difference in tumor burden in mice bearing colon and lung cancers (Das et al, 2022; Penedo-Vázquez et al, 2021). Further, when used in mice bearing lung cancer, curcumin improved skeletal muscle mass and mitigated strength reductions (Penedo-Vázquez et al, 2021). The same study also demonstrated improved muscle mass and muscle strength in tumor hosts treated with resveratrol, a polyphenol found in grapes, peanuts, and pine bark. However, like curcumin, studies on resveratrol efficacy in mitigating cancer cachexia are not univocal. For example, C26 tumor hosts treated with resveratrol had improved skeletal muscle mass, while resveratrol had no beneficial effects on muscle mass in LLC-tumor–bearing mice or Yoshida AH-130 rats (Busquets et al, 2007; Shadfar et al, 2011).

The list of polyphenols is still long, and several have been tested as potential treatments for cachexia. In brief, carnosol, a polyphenol derived from rosemary, has shown to protect against C26-induced atrophy of C2C12 myotubes, and body weight loss in mice bearing C26 tumors (Lu et al, 2021). Meanwhile, quercetin provides protection against muscle wasting when administered through oral gavage to $APC^{Min/+}$ mice (Vel et al, 2014), or when added to the daily feed of C26 tumor hosts (Vel et al, 2014).

In a similar manner, mice bearing HPV16 tumors have increased muscle mass upon daily dietary supplementation of the quercetin glycoside, rutin (Gil da Costa et al, 2017). In addition, the apigenin has demonstrated efficacy in preserving muscle mass in experimental models of obesity, aging, and denervation-induced atrophy (Choi et al, 2018; Choi et al, 2017; Wang et al, 2020), yet whether it can counteract cancer- and chemotherapy-induced muscle wasting is unknown.

Polyunsaturated fatty acids

PUFAs, in particular the two main omega-3 molecules eicosapentenoic acid and docosahexenoic acid, are well known and long studied in chronic inflammatory disorders for their anti-inflammatory properties, reducing the levels of the proinflammatory cytokines TNF-α and IL-6, of the chemical mediator of inflammation prostaglandin E2 (PGE2) and, consistently, inhibiting NF-κB activity. The modalities of PUFA's prevention of oxidative stress in the skeletal muscle are only partially deciphered.

Several attempts, frequently successful, to counteract muscle wasting in preclinical models of cancer cachexia using PUFAs alone or in combined therapies have been made in the last three decades (Gorjao et al, 2019). Similarly, >30 clinical studies adopting PUFA supplementations have been concluded (Gorjao et al, 2019) and, although not providing strong evidence for using PUFAs as single anticachexia agents, there is reasonable evidence to include PUFAs in nutritional interventions as part of patient-tailored multimodal anticachexia therapeutic approaches.

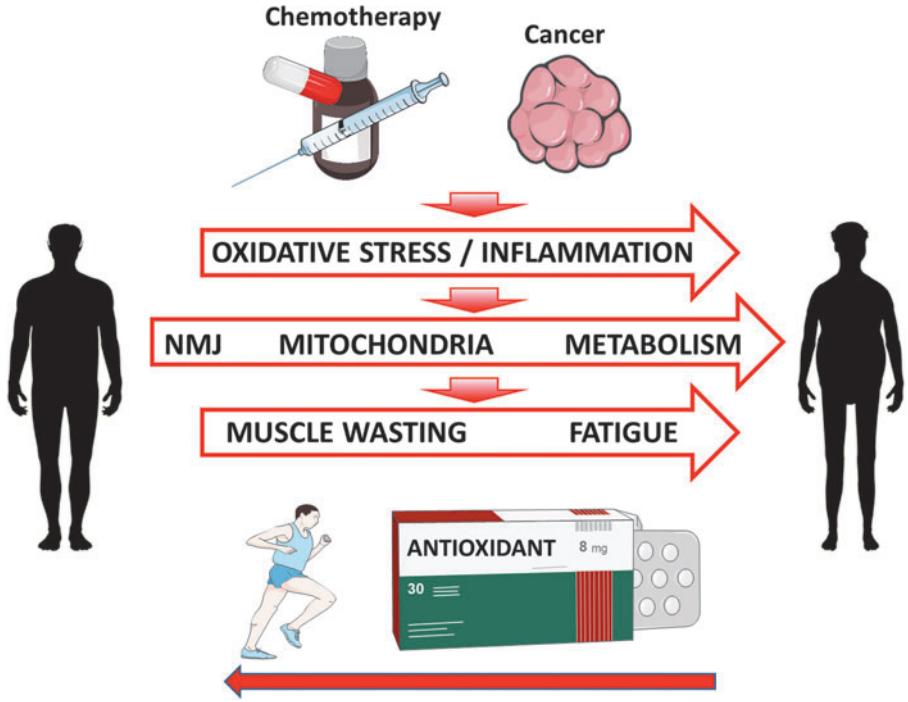

FIG. 6. Graphical summary of the pathogenesis of cachexia induced by cancer and chemotherapy. The altered redox and inflammatory homeostasis impinge on several targets in the skeletal muscle, eventually leading to the loss of muscle mass and function, associated with the onset of fatigue. Exercise training, promoting the endogenous antioxidant defense, or the use of exogenous antioxidants may counteract such cascade of events, contracting cachexia.

Conclusions

The growing evidence of oxidative stress as a pivotal, although not exclusive, determinant of both cancer- and chemotherapy-induced muscle wasting in cachexia paves the way for targeting the redox homeostasis in the attempt to counteract muscle atrophy and dysfunction. The main goals of such interventions will be the prevention of mitochondrial aberrations and the eventual impaired protein and energy metabolism occurring in muscle. Several approaches have been described in this review, ranging from exercise training or mitochondria-targeted exercise mimetics to commonly used or novel antioxidants that may work as nutraceuticals (Fig. 6).

The extended array of available therapeutic options will allow the design of patient-tailored interventions that should be based on priorities and shortcomings. As an example, physical activity should be considered the first line for those patients having no contraindications to exercise, taking advantage of the multiorgan beneficial action including the anticancer activity. The other way around, the use of antioxidants should be aimed at reducing inflammation and improving the host redox status, without favoring the growth of specific tumor types. A broad and specific assessment, taking into consideration the impact on the host and on the cancer as a whole, in an integrated approach against a multifactorial and multiorgan cancer disease is desirable.

Authors' Contribution

A.B., A.J.S., and F.P. contributed to conceptualization; J.R.H., D.B., A.R., A.B., A.J.S., and F.P. conducted investigation; J.R.H., D.B., A.R., A.B., A.J.S., and F.P. assisted with writing–original draft; F.P. contributed to writing—review and editing.

Author Disclosure Statement

All the authors declare that no competing interests that may inappropriately influence or affect the integrity of the submission exist.

Funding Information

This work was supported by Fondazione AIRC (IG 2018—ID. 21963 project, PI: F.P.) and University of Torino (Ex 60% funds). A.J.S. and D.B. were supported by grants from the National Heart, Lung, and Blood Institute (R01HL144858 and R01HL146443). A.B. was supported by grants from the American Cancer Society (132013-RSG-18-010-01-CCG) and the National Institute of Arthritis and Musculoskeletal and Skin Diseases (R01AR079379). J.R.H. was supported by a Postdoctoral Individual National Research Service Award from the National Institute of Arthritis and Musculoskeletal and Skin Diseases (F32AR079256-01A1). The icons used in the figures were obtained from Smart Servier Medical Art.

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Date of first submission to ARS Central, September 12, 2022; date of final revised submission, October 4, 2022; date of acceptance, October 22, 2022.

Abbreviations Used

ASCO = American Society of Clinical Oncology
CAT = catalase
COX2 = cyclooxygenase2
COX4 = cytochrome c oxidase
DOX = doxorubicin
EDL = extensor digitorum longus
HK = hexokinase
IGF = insulin-like growth factor
IL = interleukin
KEAP1 = kelch-like ECH-associated protein 1-nuclear factor
MAPK = mitogen-activated protein kinase
MCP1 = monocyte chemoattractant protein 1

Abbreviations Used (Cont.)

MitoQ = mitoquinone
MuRF1 = muscle RING-finger protein-1
NAC = N-acetylcysteine
NAD = nicotinamide adenine dinucleotide
NCAM = neural cell adhesion molecule
NF-κB = nuclear factor kappa b
NMJ = neuromuscular junction
NOX = NADPH oxidase
NRF2 = nuclear factor (erythroid-derived 2)-like 2
OPA = optic atrophy gene
PDH = pyruvate dehydrogenase
PDK = pyruvate dehydrogenase kinase
PGC = peroxisome proliferator-activated receptor γ coactivator
PGE2 = prostaglandin E2
PIPN = paclitaxel-induced peripheral neuropathy
PUFA = polyunsaturated fatty acid
RNS = reactive nitrogen species
ROS = reactive oxygen species
SDH = succinate dehydrogenase
SOD1 = CuZn superoxide dismutase
SOD2 = Mn superoxide dismutase
SOS = systematic oxidative stress
SS-31 = Szeto-Schiller-31
SUnSET = surface sensing of translation
TCA = tricarboxylic acid
TNF = tumor necrosis factor
TTP^+ = triphenylphosphonium
XO = xanthine oxidase