



Mitochondrial plasticity in cancer-related muscle wasting: potential approaches for its management

Rui Vitorino^{a,b}, Daniel Moreira-Gonçalves^{c,d}, and Rita Ferreira^a

Purpose of review

Cancer cachexia represents a critical problem in clinical oncology due to its negative impact on patients' quality of life, therapeutic tolerance and survival. This paraneoplastic condition is characterized by significant weight loss mainly from skeletal muscle wasting. Understanding the molecular mechanisms underlying cancer cachexia is urgent in order to develop and apply efficient therapeutic strategies.

Recent findings

Mitochondrial dysfunction is an early event in cancer-induced muscle wasting. Decreased ability for ATP synthesis, impaired mitochondrial biogenesis, increased oxidative stress, impairment of protein quality control systems, increased susceptibility to mitophagy and to apoptosis were all shown to mediate contractile dysfunction and wasting in cancer cachexia. Anti-inflammatory therapies as well as exercise training seem to counteract muscle mass loss in part by improving mitochondrial functionality.

Summary

Given its central role in muscle wasting, mitochondrial plasticity should be viewed as a key therapeutic target for the preservation of muscle mass in cancer cachexia. Few studies have addressed the mitochondrial events modulated by cancer cachexia and contradictory data were reported. Scarcer studies have focused on the mitochondrial adaptation to anticancer cachexia strategies.

Keywords

cancer cachexia, mitochondrial biogenesis, mitochondrial plasticity, oxidative stress, skeletal muscle

INTRODUCTION

Cachexia has been recognized as an adverse outcome of cancer, present in more than 50% of patients in advanced stages of disease [1,2[■]]. Cancer cachexia is linked with compromised functional capacity, reduced tolerance to anticancer therapy and poor survival [3,4]. The prominent feature of cancer cachexia is the loss of skeletal muscle mass (with or without loss of fat mass) and force production, which contributes to the weakness and fatigue that adversely affects patients' quality of life and tolerability to therapies [4,5]. Proinflammatory and wasting cytokines, produced by both the host and tumour, are thought to be upstream mediators of muscle wasting, inducing an imbalance between protein synthesis and degradation in muscle fibres [5,6,7[■]]. A special focus has been given to the members of TGF β family, specifically myostatin and growth differentiating factor-15 (GDF-15), interleukin (IL)-6 and to members of tumour necrosis factor (TNF) super family such as TWEAK [7[■]]. Myostatin binds to the cell surface activin receptor II or IIB and activates Smad2/3 for its nuclear translocation and

transcriptional regulation of target genes. Alternatively, the noncanonical pathway might be activated and involves the induction of MAPK pathway, or the inhibition of the PI3K/Akt/GSK pathway, resulting in muscle wasting [8]. The activation of nuclear factor κ B (NF- κ B) pathway in muscle fibres by proinflammatory cytokines as TNF- α and TWEAK was also shown to induce muscle loss by mediating the overexpression of E3 ligases as MuRF-1 [6,9]. As these processes are ATP requiring [2[■],6,10[■]], alterations in mitochondrial functionality are expected to impact their regulation. However, little attention

^aQOPNA, Department of Chemistry, ^bInstitute for Research in Biomedicine – iBiMED, Health Sciences Program, University of Aveiro, Aveiro, ^cCIAFEL, Faculty of Sports and ^dDepartment of Physiology and Cardiothoracic Surgery, Faculty of Medicine, University of Porto, Porto, Portugal

Correspondence to Rita Ferreira, Chemistry Department, University of Aveiro, Campus de Santiago, 3810-193 Aveiro, Portugal. Tel: +351 234370700; fax: +351 234370084; e-mail: ritaferreira@ua.pt

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KEY POINTS

- Mitochondrial dysfunction is an early event in cancer-induced muscle wasting.
- PGC-1 proteins and UCP-3 play a key role in the modulation of mitochondrial adaptation to cancer-induced muscle wasting.
- Therapeutic strategies targeting mitochondrial biogenesis and metabolism should be envisioned for the management of cancer cachexia.
- Exercise training and anti-inflammatory drugs display an anticancer cachexia effect through the modulation of mitochondrial functionality.

has been given to mitochondrial plasticity in cancer-related muscle wasting.

MITOCHONDRIAL PLASTICITY IN CANCER CACHEXIA

Mitochondrial dysfunction is a common event reported in cancer-related skeletal muscle wasting, regardless the heterogeneity of the models used to study cancer cachexia (e.g. tumour type, site and mass). Several studies using different approaches have consistently reported the loss of oxidative capacity in cancer cachexia related muscle wasting (Table 1) [11[■],12[■],13,14[■],15,16,17[■]].

Gastrocnemius was the muscle of choice in the majority of these studies, possibly reflecting the awareness that fast glycolytic muscles are more susceptible to catabolism [7[■],18]. Oxidative muscle fibres seem to have an increased tolerance for inflammation and metabolic disturbances that occur in wasting conditions [18].

Skeletal muscles present two populations of mitochondria that are phenotypically different (e.g. variation in cellular location, biochemical properties and morphology) but coexist as a dynamic network. Subsarcolemmal mitochondria are less abundant and are responsible to fuel energy-requiring events (e.g. transport and signalling) at the level of the cellular membrane. Intermyo-fibrillar mitochondria (IMF), on their turn, seem to be responsible for covering the energetic costs of muscle contraction [16]. Moreover, these mitochondrial populations have a remarkable plasticity, allowing them to adapt differently to conditions such as exercise, unloading and ageing [16]. To the best of our knowledge, there are no studies that evaluated the different susceptibility of mitochondrial populations from skeletal muscle in cancer cachexia. Considering the higher proportion of IMF mitochondria

than subsarcolemmal mitochondria (around 80 vs. 20%, respectively), we might speculate that the majority of mitochondrial adaptations occurring in cancer cachexia affect mainly the IMF subpopulation. Nevertheless, future studies are necessary to disclose how mitochondrial populations adapt to tumour burden and its impact on muscle wasting.

THE INVOLVEMENT OF PEROXISOME PROLIFERATOR ACTIVATED RECEPTOR- γ COACTIVATOR-1 PROTEINS IN CANCER-RELATED MITOCHONDRIAL DYSFUNCTION

The skeletal muscle phenotype in cancer cachexia is characterized by a reduced number of mitochondria [7[■],11[■]] and decreased expression of regulatory factors involved in mitochondrial biogenesis [7[■],18]. Mitochondrial biogenesis is controlled by a family of coactivators as peroxisome proliferator activated receptor- γ coactivator-1 α and β (PGC-1 α and PGC-1 β). PGC-1 proteins coordinate mitochondrial fission and fusion, which is critical for mitochondrial function, morphology and distribution [16,19[■]]. Reduced expression of PGC-1 proteins and alterations in the balance between fission and fusion proteins have been implicated in several different diseases [20]. PGC-1 α coactivates mitochondrial biogenesis, the uptake and utilization of substrates for energy production. This factor regulates the expression of mitochondrial transcription factor A (Tfam), mitofusins and other genes encoding mitochondrial proteins [16]. Tfam mRNA and protein content are diminished in the gastrocnemius of cachectic animals, whether whole muscle or isolated mitochondria were analysed [11[■],19[■]]. Due to its involvement in DNA maintenance [21], decreased Tfam levels suggests impaired mitochondrial transcription, an important step in mitochondrial biogenesis. In skeletal muscle, PGC-1 β seems to be the first upstream regulator described to control mitochondrial fusion, which is regulated by mitofusins 1 (Mfn1) and 2 (Mfn2), and optical atrophy 1 (Opa1) [20,22,23]. Mitochondrial fusion proteins are also regulators of mitochondrial metabolism, being related to high mitochondrial membrane potential [16,24]. In cancer-induced muscle wasting, Mfn1 mRNA levels were shown to be decreased [21]. Regarding Mfn2, contradictory data were reported (Table 1): increase of Mfn2 mRNA levels in EDL muscle of rats inoculated with AH-130 Yoshida ascites hepatoma cells and significant decrease of Mfn2 protein in the gastrocnemius of Apc^{Min/+} mice. Despite the high degree of homology between Mfn1 and Mfn2, these proteins have distinct functions. Mfn1 is required for GTP hydrolysis-dependent mitochondrial

Table 1. Overview of the mitochondrial alterations observed in cancer-induced muscle wasting

Model of cancer cachexia	Skeletal muscle	Sample	Functional alterations	Molecular alterations	Reference
<i>Apc</i> ^{Min/+} mice	Gastrocnemius	Whole muscle	–	↓ cytochrome c, COX IV, PGC1 α , MFN1, MFN2 proteins ↑ FIS1, ATG5, LC3b, Beclin-1 proteins, Bax mRNA	[7 [•]]
Chemically induced bladder cancer	Gastrocnemius	Isolated mitochondria	↓ OXPHOS activity	↓ ATP synthase β , paraplegin, Lon, Tfam proteins ↑ protein nitration, protein carbonylation	[11 [•]]
Chemically induced bladder cancer	Gastrocnemius	Isolated mitochondria	↓ OXPHOS activity	↓ cytochrome c, ETF β , ETF-QO proteins ↑ UCP3 protein ↓ PG, CL, PA ↑ PC	[12 [•]]
PROb-BDIX	Quadriceps	Isolated mitochondria	↓ State III, uncoupled state ↓ COX	↓ UCP2 protein ↔ UCP3 protein, CL	[10 [•]]
BALB/c mice inoculated with LP07 viable cells	Gastrocnemius	Whole muscle	↔ CS activity ↓ C-I, C-II, C-IV activity; state 3	–	[13]
Wistar rats inoculated with AH-130 Yoshida ascites hepatoma cells	EDL, gastrocnemius	Isolated mitochondria	↓ SDH activity; ATP content	↑ ANT1 protein ↑ MFN2 mRNA in EDL	[14 [•]]
<i>Apc</i> ^{Min/+} mice	Gastrocnemius, soleus	Whole muscle	↓ SDH staining	↓ COX IV, cytochrome c, PGC1 α protein and mRNA, UCP3 protein in both muscles, SIRT1 protein in Gast ↓ MFN1 mRNA, MFN2 mRNA ↑ Fis1 mRNA ↔ MnSOD mRNA, Catalase mRNA, SIRT1 mRNA ↔ nitrotyrosine, 4HNE	[15]
C57Bl/6 mice inoculated with Lewis lung carcinoma	Gastrocnemius	Whole tissue	↓ ATP synthesis rate	↓ PGC1 β mRNA, SOD2 mRNA ↑ UCP3 mRNA	[16]
C57Bl/6 mice inoculated with Lewis lung carcinoma	Gastrocnemius	Whole tissue	↓ ATP synthesis, TCA cycle flux and mitochondrial coupling index	↓ PGC1 β mRNA	[17 [•]]

↑, upregulated; ↓, downregulated; ↔, no significant alterations; CL, cardiolipin; COX, cytochrome c oxidase; CS, citrate synthase; Gast, gastrocnemius; PA, phosphatidic acid; PC, phosphatidylcholine; PG, phosphatidylglycerol.

tethering, while Mfn2 acts as a signalling GTPase and might regulate the assembly of fusion complexes. Only Mfn2 is expressed on the endoplasmic reticulum (ER), being important for processes linked to ER-mitochondria interactions such as calcium homeostasis [16]. In skeletal muscle, there is a bidirectional communication between sarcoplasmic reticulum and mitochondria. By one hand, the Ca^{2+} released from sarcoplasmic reticulum stimulates mitochondria to produce ATP to meet the energetic demands of muscle contraction. On the other hand, mitochondrion exerts control over the local redox environment and thus modulates the sarcoplasmic reticulum Ca^{2+} release [14[■]]. So, the increased expression of Mfn2 in cachectic rats might reflect Ca^{2+} dysregulation and formation of permeability transition pore (PTP), leading to apoptosis and, ultimately, to muscle atrophy [14[■]]. However, it should be considered that Mfn2 could contribute differently to muscle wasting depending on the disease type and its severity [7[■]], which might explain differences reported among experimental studies (Table 1). The increased levels of Fis1 mRNA and protein in wasted muscle suggest that mitochondrial fission or fragmentation also contributes to cancer-related muscle wasting [7[■],19[■]]. Excessive fission generates isolated mitochondria that are less efficient in ATP production and consume cytosolic ATP in an attempt to maintain their membrane potential [16]. Fission is a mechanism that segregates dysfunctional or damaged mitochondria, allowing their removal through mitophagy. Indeed, a significant reduction of mtDNA copy number per nuDNA (marker of mitophagy) was observed in cultures of muscle cells treated with C-26 mouse adenocarcinoma cell line (C26 CM) and in skeletal muscles isolated from C26 tumour-bearing mice, together with an increased content of Bnip3, Atg5, Map1lc3a mRNA [21]. Bnip3 is implicated in either apoptosis or mitophagy. This protein translocates to mitochondria and disrupts mitochondrial membrane potential [16]. The participation of Map1lc3a and Atg5 in the regulation of autophagy was recently reported in the set of muscle wasting [25,26]. Atrophic muscles display higher levels of Atg5, concurrent to the induction of mitochondrial fission given by Fis1 overexpression [26]. Overall, the available data highlight that greater levels of mitochondrial fission and autophagy likely contribute to the development of a specific cancer-related muscle wasting phenotype. Nevertheless, mitochondrial fission seems to occur in later stages of cachexia [7[■]].

PGC-1 α and β reduce proteolysis by inhibiting the transcriptional activity of FoxO3 and NF- κ B, without affecting protein synthesis [21]. Even so,

NF- κ B was shown to decrease the transcriptional activity of regulators of mitochondrial biogenesis [PGC-1 α , peroxisome proliferator-activated receptor (PPAR)- α and Tfam] [27]. NF- κ B and mitogen-activated protein kinases (MAPK) play a relevant role in oxidative stress-mediated muscle wasting oxidative stress mediated muscle wasting in cancer cachexia and are associated with the reduction of activity in respiratory complexes [13]. The diminishing of ATP synthesis rate in wasted muscle was also related to the decrease of PGC-1 α and β transcripts [15,19[■],21].

THE INVOLVEMENT OF UNCOUPLING PROTEINS IN CANCER-RELATED MITOCHONDRIAL DYSFUNCTION

Overexpression of uncoupling proteins, most specifically uncoupling protein (UCP)2 and UCP3, also accounts for diminishing oxidative phosphorylation efficiency in cancer-induced skeletal muscle, in a process mediated by cytokines as TNF α [28]. However, reduced levels of UCP3 were reported in severely cachectic muscle of *Apc*^{Min/+} mice [18]. Whereas UCP2 is ubiquitously expressed, UCP3 is a characteristic of skeletal muscle, heart and brown adipose tissue [2[■],12[■]]. Apart from reducing ATP synthesis by dissipating energy as heat [17[■]], UCP3 protects mitochondria from oxidative damage [29]. In skeletal muscle, reactive oxygen species (ROS) might activate a UCP3-mediated proton leak, which in turn acts through a negative feedback mechanism to mitigate ROS production [29,30]. Indeed, no alterations of thiobarbituric acid reactive substances (TBARS), a marker of lipid peroxidation, were observed in mitochondria isolated from skeletal muscle of rats with bladder cancer [12[■]]. Still, concomitantly to the higher levels of UCP3, increased levels of carbonyl groups (marker of oxidative stress) [12[■]], and antioxidant enzymes as glutathione peroxidase [15] have been reported. The accumulation of oxidized proteins in mitochondria from wasted muscle seems to be due, at least in part, to the impaired activity of protein quality control systems [11[■]] that include mitochondrial proteases as paraplegin and Lon, and mitochondrial-shaping machinery [16]. UCP3 was also suggested to display a switch from glucose oxidation towards fat oxidation [30], but this metabolic adaptation was not verified in wasted muscle [12[■]]. Nevertheless, changes in mitochondrial fatty acids composition towards an increase of C18:2 fatty acyl chains were described and occurred in tandem with the remodelling of mitochondrial phospholipid profile. This mitochondrial adaptation to cancer cachexia was characterized by the decrease of

cardiolipin, its precursor phosphatidylglycerol and phosphatidic acid, and by the increase of phosphatidylcholine [12[■]]. Membranes rich in phosphatidylcholine are expected to be more fluid than membranes rich in phosphatidylethanolamine [31]. Considering the critical role of cardiolipin in the organization of mammalian ATP synthase and in the maintenance of inner mitochondrial membrane potential, the finding of decreased content of cardiolipin in mitochondria with impaired ability to synthesize ATP was not surprising, as the ones from skeletal muscle of tumour-bearing animals [12[■]]. Figure 1 integrates the molecular events underlying mitochondrial adaptation to cancer cachexia.

STRATEGIES FOR THE MANAGEMENT OF CANCER CACHEXIA FOCUSED ON MITOCHONDRIA

Several therapeutic approaches have been tested for the management of muscle mass loss in cancer cachexia; however, none was yet approved. The development of novel therapeutic strategies,

coupled with the standardization of design and end points in clinical trials, are expected to boost supportive oncology for the improvement of quality of life, tolerance of antineoplastic therapy and survival [4]. Among pharmacological interventions that have been tested are drugs that stimulate appetite (e.g. megestrol acetate and dronabinol), cytokine inhibitors [e.g. eicosapentaenoic acid (EPA) and mAbs], anabolic agents (e.g. corticosteroids) and myostatin antagonists [32–34]. Their early application in patients with cancer cachexia seems to be essential for maximal benefits [32,33]. Glucocorticoids are one of the most common anticachexia treatments, but they prompt adverse side-effects such as insulin resistance and adrenal suppression, being mostly used in advanced incurable cancer [35,36]. Several of these therapeutic strategies target, directly or indirectly, the molecular pathways underlying cancer-induced mitochondrial dysfunction in skeletal muscle (Fig. 2).

EPA seems to suppress mediators as proinflammatory cytokines such as interleukin (IL)-6 [32]. Megestrol acetate is a synthetic progestogen agent that

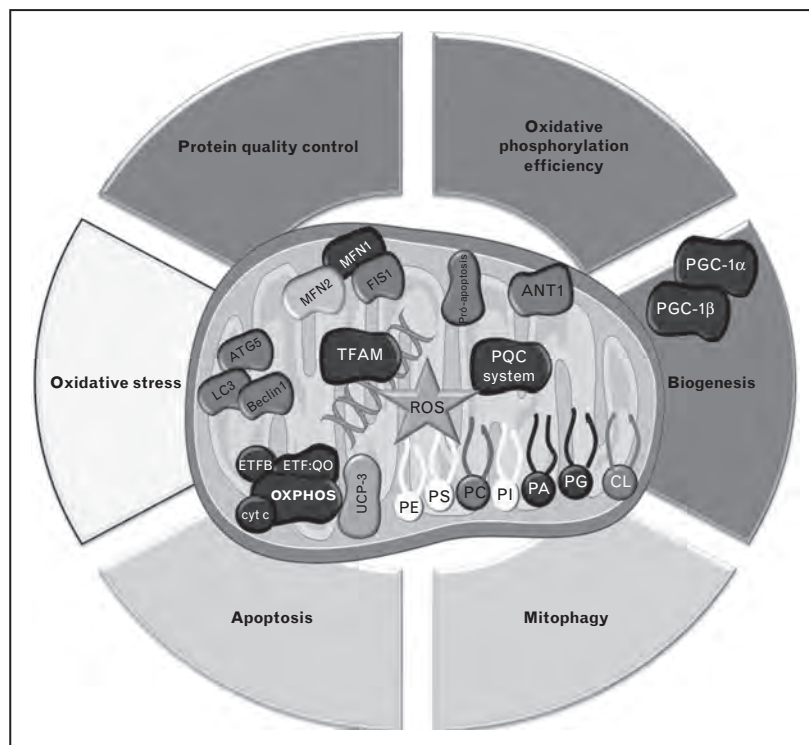


FIGURE 1. Schematic overview of the molecular pathways modulated by cancer cachexia in mitochondria from skeletal muscle. Molecules (protein, mRNA or phospholipid) present in high levels are highlighted at dark grey, in lower levels at black, with no content variations at white and, finally, molecules for which there are no consensus in literature are shown at light grey. Figure was made with Servier Medical Art. ANT1, adenine nucleotide translocator 1; ATG5, autophagy-related 5; BNIP3, BCL2/adenovirus E1B 19-kDa interacting protein 3; Cyt C, cytochrome c; ETF, electron transferflavoprotein; ETF:QO, ETF:ubiquinone oxidoreductase; FIS1, fission 1; LC3, microtubule-associated protein 1 light chain 3; MFN, mitofusin; OXPHOS, oxidative phosphorylation; PGC-1, peroxisome proliferator activated receptor gamma, coactivator 1; PQC, protein quality control; ROS, reactive oxygen species; TFAM, transcription factor A, mitochondrial; UCP-3, uncoupling protein 3.

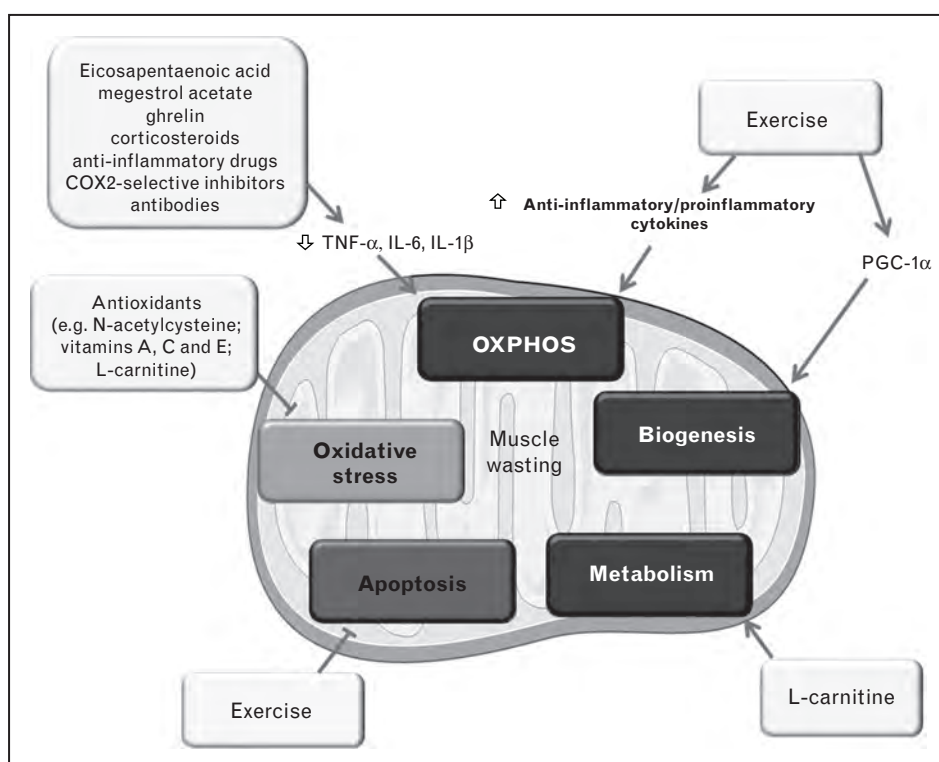


FIGURE 2. Therapeutic strategies that target, directly or indirectly, mitochondrial dysfunction in cancer-induced muscle wasting. The molecular processes upregulated in wasted muscle are highlighted at dark grey, downregulated at black, with no consensual variations at grey. Figure was made with Servier Medical Art. COX, cyclooxygenase.

apart from stimulating appetite also has an anti-inflammatory effect, reducing the levels of IL-6, IL-1 β and TNF α [37]. Ghrelin administration (or of its agonists anamorelin HCl and RC-1291) was also shown to preserve not only the skeletal muscle mass but also the muscle contraction force in both slow-twitch and fast-twitch muscle fibres [38,39,40[¶]]. Among the pleiotropic effects of this peptide hormone against cancer cachexia are the reduction of plasmatic IL-1 β , IL-6 and TNF α [38,41]. Once the action of these cytokines in skeletal muscle is modulated by NF- κ B and MAPK signalling, we might suspect that the silencing of these molecular pathways will improve functionality in respiratory chain complexes. The administration of the NF- κ B inhibitor sulfasalazine was able to restore muscle mass and performance in tumour-bearing rodents [13,42[¶]], with improved activity of respiratory chain complex I in skeletal muscle [13]. By inhibiting MAPK pathway, U0126 also restored muscle mass and force, and corrected mitochondrial chain dysfunction [13]. Some authors argue that the decrease of tumour burden promoted by the blockade of NF- κ B and MAPK pathways might have contributed to the attenuation of cancer cachexia [13,42[¶]].

By inhibiting the ubiquitin-proteasome pathway, bortezomib was able to restore muscle mass in

several models [13,42[¶]]. Nevertheless, in lung cancer-bearing mice, no improvements on body and muscle mass were observed [42[¶]]. Moreover, in cardiac muscle of rats, this therapeutic agent was shown to induce ultrastructural abnormalities within mitochondria and the decrease of ATP synthesis [43]. The antioxidant N-acetyl cysteine (NAC) was tested in tumour-bearing mice with improved outcomes in mitochondrial oxygen uptake; however, no effect on muscle mass loss was observed [13]. The dietary supplementation of L-carnitine was shown to improve muscle weight by decreasing proteasome activity and the expression of genes involved in apoptosis [40[¶]].

Beyond pharmacological approaches, exercise training appears as an attractive strategy for the management of cancer cachexia and counteract the dramatic reduction of muscle strength and endurance that characterizes this paraneoplastic condition [44[¶],45]. Exercise was shown to enhance muscle protein synthesis and attenuate catabolism, and to modulate the levels of inflammatory cytokines [19[¶],46]. The anti-inflammatory effect of endurance exercise training may be observed even at low intensity [47]. In resistance-trained tumour-bearing rats, IL-10/TNF α ratio was higher and was related to body weight gain [48]. Treadmill training

was reported to induce the expression of PGC-1 α , Mfn1 and Mfn2, and to reduce Fis1 and Bax expression in wasted muscle [19^{*}]. A single bout of endurance exercise was shown to induce a rapid and sustained increase of PGC-1 α in skeletal muscle. Indeed, PGC-1 α seems to be a central player in orchestrating many of the oxidative adaptations to exercise, with a particular focus at mitochondria plasticity [49] (Fig. 2). However, there are challenges in implementing exercise programmes to patients with established cachexia, as not all are able to undertake those programmes [46]. Exercise dose is a crucial point to be carefully evaluated on a single patient basis [44^{*},45].

CONCLUSION

Skeletal muscle is highly reliant on mitochondria for metabolic and survival purposes. So, mitochondrial dysfunction in cancer cachexia is a determinant for skeletal muscle wasting, for which contributes the diminished expression of PGC-1 proteins. The findings attained so far on this issue come from studies with animal models of cancer cachexia, possibly reflecting the ethical and methodological constraints in attaining human skeletal muscle samples for molecular studies. Nevertheless, there are some discrepancies among studies regarding skeletal muscle mitochondrial plasticity in cancer cachexia possibly due to the use of distinct animal models, type of tumour, cachexia severity and muscle sample, making the translation of findings to the clinical set difficult. Several therapies targeting cancer cachexia were shown to improve mitochondrial functionality and to attenuate muscle mass loss; however, the underlying molecular mechanisms are poorly characterized. There is a general awareness that multimodal treatments are more likely to be successful in the management of cancer cachexia, but its impact on muscle wasting needs to be clarified.

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Conflicts of interest

There are no conflicts of interest.

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