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REVIEW ARTICLE

Mitochondria: Inadvertent targets in chemotherapy-induced skeletal muscle toxicity and wasting?

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Abstract Chemotherapy has been associated with increased mitochondrial reactive oxygen species production, mitochondrial dysfunction and skeletal muscle atrophy leading to severe patient clinical complications including skeletal muscle fatigue, insulin resistance and wasting. The exact mechanisms behind this skeletal muscle toxicity are largely unknown, and as such co-therapies to attenuate chemotherapy-induced side effects are lacking. Here, we review the current literature describing the clinical manifestations and molecular origins of chemotherapy-induced myopathy with a focus on the mitochondria as the target organelle via which chemotherapeutic agents establish toxicity. We explore the likely mechanisms through which myopathy is induced, using the anthracycline doxorubicin, and the platinum-based alkylating agent oxaliplatin, as examples. Finally, we recommend directions for future research and outline the potential significance of these proposed directions.

Keywords Anti-cancer chemotherapy · Skeletal muscle · Mitochondria · Toxicity

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Introduction

Cancer is a leading cause of morbidity and mortality worldwide, with approximately 14 million new cases diagnosed and 8.2 million cancer related deaths occurring in 2012 alone [1]. In most cases, the first-line anti-neoplastic treatment option is systemic chemotherapy administration, in which cells undergoing rapid, abnormal division (such as cancer cells) are successfully targeted for the chemical induction of autologous cell death pathways secondary to DNA damage [2], thereby reducing the size of, or completely abolishing, tumours [3]. However, due to their non-specific mode of action, chemotherapeutic drugs elicit significant side effects by also targeting healthy cells that maintain high proliferative potential throughout the lifespan. These include cells of the integumentary, immune, nervous, and gastrointestinal systems, which induce the notorious side effects associated with chemotherapy treatment including nausea, vomiting, hair and weight loss, and fatigue [4–6].

Much less characterised, however, is the effect of chemotherapeutic agents on the muscular system—in particular the skeletal musculature, which relies on mitotic activity to maintain "skeletal muscle turnover" and mass throughout the lifespan. Skeletal muscle also has a theoretically high propensity for DNA-mediated toxicity due to its dense nucleation compared to other cells [7]. While skeletal muscle wasting and dysfunction due to cancerous cells and the inflammatory cytokines they release (commonly termed cancer cachexia) is well documented [4], little is known about the effect chemotherapeutic agents have on the skeletal musculature. Emerging research indicates that long-term effects persist in skeletal muscle for many years after chemotherapy treatment and that they are independent of

those induced by cancer cachexia [8–10]. These adverse effects include skeletal muscle atrophy, dysfunction, insulin resistance, weakness, and fatigue, which, in addition to a multitude of side effects in other organ systems, leads to poor tolerance and treatment discontinuation and limits therapeutic efficacy [5]. Skeletal muscle-specific co-morbidities correlate with a range of negative clinical outcomes in cancer patients—these include reduced participation in activities of daily living, quality of life, and a higher risk of morbidity and mortality [11].

Mitochondria are increasingly emerging as key players in the pathogenesis of a variety of diseases. Due to the highly metabolic nature of the skeletal muscle, mitochondrial density is also high [12], and mitochondrial dysfunction and toxicity can therefore manifest as skeletal muscle-specific symptomatology which include fatigue, muscle wasting, impaired regenerative capacity, pain, exercise intolerance, and sometimes, mild-to-severe neurological symptoms. Indeed, these symptoms have been well documented in chemotherapy-treated cancer patients [5, 13–15] suggesting that anti-cancer chemotherapy may be non-specifically targeting the skeletal musculature, and perhaps even more specifically, the mitochondria to induce a variety of persistent adverse side effects.

Here, we review the current literature describing the clinical manifestations and molecular origins of chemotherapy-induced myopathy with a focus on the mitochondria as the target organelle via which chemotherapeutic agents establish toxicity. We explore the likely mechanisms through which myopathy is induced, using the anthracycline doxorubicin, and the platinum-based alkylating agent oxaliplatin as examples. Finally, we recommend directions for future research and outline the potential significance of these proposed directions with respect to the development of suitable musculoskeletal protective treatment regimes.

Potential mechanisms of chemotherapy-induced mitochondrial myopathy

Chemotherapy drugs target rapidly dividing mitotic cells to arrest specific phases of the cell cycle, with the exact mode of action varying between drugs and the chemical classes from which they derive (as summarised in Table 1)—for this reason, specific agents are used to target specific neoplasms. The anthracycline family, for example, has been used for over 50 years to treat a number of different cancers including leukaemia, prostate, ovarian, lung and breast [16, 17], with doxorubicin hydrochloride (Adriamycin®)—an anthracycline with limited therapeutic tolerability and efficacy due to its highly toxic effects on the heart—used primarily to treat solid tumours [18, 19]. A number of mechanisms of action have been proposed to explain the neoplastic cytotoxic and cytostatic nature of doxorubicin, which include: (1) DNA intercalation thus inhibiting protein biosynthesis and affecting transcription processes [20, 21]; (2) free radical formation resulting in cellular damage and apoptosis signalling and/or necrosis [22, 23]; (3) inhibition of topoisomerase II [24], an important nuclear DNA transcription enzyme; and (4) intrinsic mitochondrial apoptotic signalling [25]. As doxorubicin targets DNA as its primary cytotoxic action, it has also been hypothesised that the circular and covalently closed nature of mtDNA allows easier intercalation of chemotherapies, and thus an increased rate of transcriptional error occurs leading to mitochondrial dysfunction [25].

Mitochondrial function, and perhaps even more so, mitochondrial dysfunction, is physiologically complex and is modulated by a variety of regulators including the mitochondrial (mtDNA) and nuclear (nDNA) DNA, reactive oxygen species (ROS), nuclear and cellular signalling molecules and ATP production amongst others [26, 27]. In the first instance, chemotherapy-induced mitochondrial dysfunction has been associated with elevated levels of mitochondrial ROS (mtROS). It is well established that doxorubicin treatment causes increased ROS production as a by-product of its metabolism via a redox cycling process unique to the anthracycline class of chemotherapeutics [28–32]. Doxorubicin, which has a high affinity for the inner mitochondrial membrane (IMM) [33], accumulates on the matrix side and undergoes a single-electron reduction process at complex I (NADH oxidase) of the electron transport chain (ETC) removing electrons vital to ATP production. This process forms the free radical semiquinone species that reduces molecular oxygen to produce the highly reactive superoxide (O_2^-) molecule and subsequently the less reactive hydrogen peroxide (H_2O_2) molecule [17, 28, 32, 34, 35]. O_2^- and H_2O_2 collectively constitute the mtROS, which directly increase the state of cellular oxidative stress if not buffered effectively by endogenous antioxidants [33, 34, 36, 37]. Thus, doxorubicin acts via a two-hit mode of action on the mitochondria acting as a powerful reducer when stable, depleting ATP production and available ATP stores, and as an efficient oxidiser in its semiquinone state, producing excess mtROS.

In addition to decreasing electron flow through the ETC and thus decreasing ATP production, the single-strand DNA breaks induced by doxorubicin (and indeed other chemotherapies that directly damage DNA) induces the activation of enzymes that repair such damage albeit to the detriment of ATP stores. Poly-ADP-ribose polymerases (PARPs) are highly conserved proteins that respond to DNA damage by stimulating repair through the use of energy co-factors, in particular, the use of NAD^+ (a key mitochondrial substrate) by PARP-1 [38]. Within minutes of PARP-1 activation, the NAD^+ pool depletes by up to 20 % with the cell required

Table 1 Mode of action and reported side effects of chemotherapy agents from various drug classes

Class of agent	Common drugs	Common treatment	Mode of Action	Side effects
Alkylating agents	• Nitrogen mustards (including mechlorethamine, chlorambucil, cyclophosphoamide, ifosfamide, melphalan) • Nitroureas (including streptozocin, carmustine, lomustine) • Alkyl sulfonates (busulfan) • Triazines (including dacarbazine & temozolomide) • Ethylenimines (including thiotepa and altretamine) • Platinum-based (oxaliplatin, cisplatin, carboplatin)	• Leukemia • Lymphoma • Multiple Myeloma • Sarcoma • Cancers of the breast, ovary, lung and colorectum	Interfere with DNA base pairing, causing strand breaks and preventing replication: • DNA lesion formation • Arrest of DNA synthesis • Inhibition of RNA synthesis	• Anemia • Impaired spermatogenesis • Nausea and vomiting • General weakness
Anti-tumour antibiotics	• Anthracylcines (including daunorubicin, doxorubicin, epirubicin, idarubicin) • Actinomycin-D • Bleomyciin • Mitomycin-C • Mitoxantrone	• Wide variety of cancers	Interfere with enzymes involved in DNA replication, preventing replication: • Works at all phases of the cell cycle	• Cardiac dysfunction & toxicity • Nausea and vomiting • Muscle weakness • Hair loss
Antimetabolites	• 5-fluorouracil • 6-marcaptopurine • Capecitabine • Cytarabine • Floxuridine • Fludarabine • Gemcitibine • Hydroxyurea • Methotrexate • Pemetrexed	• Leukemias • Cancers of the breast, ovary and GI tract	Block the formation and use of nucleic acids required for DNA replication: • Substitute for nucleic acids of DNA and RNA • Interfere with DNA and RNA growth • Damage occurs during S phase	• Hair loss • General weakness • Nausea and diarrhoea
Topoisomerase Inhibitors	• Topoisomerase I inhibitors (including topotecan & irinotecan) • Topoisomerase II inhibitors (including etoposide, teniposide, mitoxantrone)	• Leukemias • Cancer of the lung, overy & GI tract	Interfere with Topoisomerase I and II: • Block DNA separation • Block DNA replication	• Nausea and vomiting • Hair loss • General weakness
Mitotic Inhibitors	• Taxanes (including paclitaxel & docetaxel) • Epothiolones (ixabepilone) • Vinca alkaloids (vinblastine, vincristine, vinorelbine) • Estramustine	• Leukemia • Lymphoma • Myeloma • Sarcoma • Cancers of the breast & lung	Interefere with mitosis in the M stage of the cell cycle	• Peripheral and central neuropathy

to replenish this loss through ATP consumption, further exacerbating inner mitochondrial membrane potential ($\Delta\Psi$) depletion and energy homeostasis perturbation [39, 40]. Additionally, the depleted NAD^+ pool impacts upon other metabolic pathways including glycolysis and the tricarboxylic acid cycle, of which various steps are dependent upon NAD^+ availability [41, 42] which culminates in decreased substrate delivery to, and ATP synthesis at, the ETC (refer to Fig. 1). Considering that skeletal muscle is a highly metabolic organ, such reductions in the capacity to generate ATP would be undesirable and ultimately lead to functional perturbations. While skeletal muscle could tolerate acute PARP activity, the chronic activation of PARP following repeated systemic exposure would be detrimental and energetically expensive to skeletal muscle [41–43].

Although PARP is classified as a nuclear protein, the discovery of a truncated mitochondrial PARP-1 suggests that PARP-1 has a direct effect on mitochondrial respiration potentially through the PARylation of mitochondrial proteins [43, 44]. In addition, PARP activation leads to reduced SIRT1 activity, mitochondrial biogenesis, and glucose clearance, and shifts skeletal muscle from the oxidative fibre type [38, 45]. Together, these metabolic changes would promote further metabolic dysfunction in chemotherapy-treated skeletal muscle. As deletion of PARP-1/2 in mice demonstrably reverses metabolic suppression by promoting mitochondrial biogenesis, improving the oxidation of fats and enhancing appetite [38, 45, 46], the pharmacological inhibition of PARPs may assist in maintaining the NAD^+ pool and preventing metabolic compromise during chemotherapy.

As previously mentioned, an increase in chemotherapy-induced mtROS production is strongly linked to mitochondrial dysfunction and damage. However, mtROS are also thought to function as signalling molecules that activate several proteolytic pathways within skeletal muscle, including caspase-3 and calpain [33, 47–49]. These pathways in-turn catalyse the release of myofilament proteins, allowing activation of the ubiquitin–proteasome system and resulting in skeletal muscle degradation [49–51]. Activation of the ATP-dependent ubiquitin–proteasome system is responsible for the muscular degradation seen in homeostatic

regulation of skeletal muscle mass and is amplified in many chronic diseases including cancer cachexia and diabetes [52–54]. Thus, doxorubicin-induced skeletal muscle atrophy is strongly associated with mitochondrial dysfunction. This dysfunction is a direct result of increased ROS production via drug metabolism as well as that due to non-specific electron leak from the mitochondrial respiratory chain which is likely induced by mtDNA and respiratory chain protein damage. These negative effects have been the basis of several investigations into chemotherapy-induced myopathies. Adachi et al. [55] have demonstrated strong evidence that the prevalence of mtDNA deletions increases with doxorubicin dosage, and exponentially more so with long-term exposure. In cardiomyocytes, mtDNA deletions could be prevented with co-therapy of the antioxidant and electron carrier coenzyme Q10 [55], suggesting that the aetiology of mtDNA mutation is via doxorubicin-induced mtROS rather than the doxorubicin semiquinone itself.

Long-term doxorubicin treatment induces significant reductions in skeletal muscle mass, strength, and endurance in cancer survivors (for detailed review, refer to [10]). Scheede-Bergdahl et al. [10] postulated that the molecular basis of these effects was due to the progressive amplification and proliferation of mtDNA mutations. Gouspillou et al. [56] have also demonstrated a reduction in muscle mass and function—thought to be due to an increase in mtROS and a reduction in mitochondrial respiration—in female C57BL/6 mice when treated with four cycles of doxorubicin (with one cycle equivalent to two 10 mg/kg doses on days one and five with 3 weeks recovery). However, no evidence of mtDNA damage post-doxorubicin therapy (as detected by long range PCR) was found [10].

Another effective class of chemotherapeutics are the platinum-derived alkylating agents, of which oxaliplatin is used predominantly for the treatment of colorectal cancer. Oxaliplatin exerts its antibiotic effects by forming platinum–DNA adducts which efficiently block DNA replication forcing cell cycle arrest and ultimately apoptosis in mitotic cells [57–59]. Both doxorubicin and oxaliplatin—although differing in their precise modes of action—have been shown to negatively affect mitochondrial function [22] and to induce deleterious effects on skeletal muscle that clinically manifest as muscle weakness [5, 17, 60] (refer to Fig. 2). Gourdier et al. [61] demonstrated that oxaliplatin treatment induces mitochondrial and energy homeostasis dysregulation in colorectal cancer cells, potentially through the direct mutation of mtDNA or via mutation of the nuclear-encoded mitochondrial proteins (refer to Fig. 1). While this effect is of obvious benefit to the induction of cell death pathways in neoplastic cells, suppression of mitochondrial function and the disruption of energy homeostasis would have detrimental consequences to somatic cells, especially in highly metabolic tissues such as the skeletal muscle. Our group has recently demonstrated that oxaliplatin treatment increases mtROS production, and reduces mitochondrial and cell viability in an in vitro C2C12 myotube culture model [22]. Oxaliplatin seems to exert immediate but reversible inhibition of key respiratory enzymes, as shown by induction of a metabolic shift towards an anaerobic glycolytic phenotype following acute administration [22]. We speculate that this phenotype shift occurs to buffer the acute suppression of respiratory function that occurs during the transport of oxaliplatin into skeletal muscle, and more specifically, the mitochondria. We speculate that oxaliplatin, specifically the platinum component, is competitively substituted for copper (Cu^{2+}) at receptor sites on the copper transporter 1 (CT1), limiting the availability of the transporter to Cu^{2+} and thereby reducing the mitochondrial Cu^{2+} pool, which is essential for normal complex IV function and oxidative phosphorylation. A study by Lutsenko et al. [62] suggests that the mitochondrial Cu^{2+} transporter, COX17, transports $Cu2^{+}$ into the mitochondria and, with the assistance of *Sco* proteins, incorporates the Cu^{2+} molecule into complex IV. Thus in addition to, or instead of, reducing the mitochondrial Cu^{2+} pool, it is possible that the entire oxaliplatin molecule is incorporated into complex IV with the potential to induce malfunction of electron flow and acceptance by molecular oxygen. An acute effect of oxaliplatin administration thus seems to be inhibition of the mitochondrial respiratory chain.

The chronic effects of oxaliplatin treatment, however, seem intrinsically related to mtDNA damage and mutation resulting in gene polymorphisms as per the single-stranded breaks induced in nuclear DNA, rather than due to compounding effects of acute respiratory chain inhibition. As mtDNA encodes for the matrix-residing components of the respiratory chain complexes which are responsible for proton pumping and initial electron transfer, a natural consequence of such damage would be reduced mitochondrial function and increased mtROS production leading to skeletal muscle atrophy, damage and wasting (refer to Fig. 1). A recent study by Wisnovsky et al. [63] highlighted the capacity for oxaliplatin to induce single-stranded breaks in the mtDNA. The group isolated the nuclear DNA damaging component of oxaliplatin and conjugated it with the N terminus of a mitochondrial-penetrating peptide (mPP). When delivered to ovarian cancer lines, the oxaliplatin-mPP molecule localised solely within the mitochondria and induced mtDNA mutation followed by mitochondrial death and the induction of cellular apoptosis. Although Wisnovsky et al.'s data [63] show that oxaliplatin is capable of causing mtDNA damage, the group failed to establish that oxaliplatin was able to independently penetrate the mitochondria in its natural form. Studies currently being undertaken by our laboratory have shown interesting results in this area.

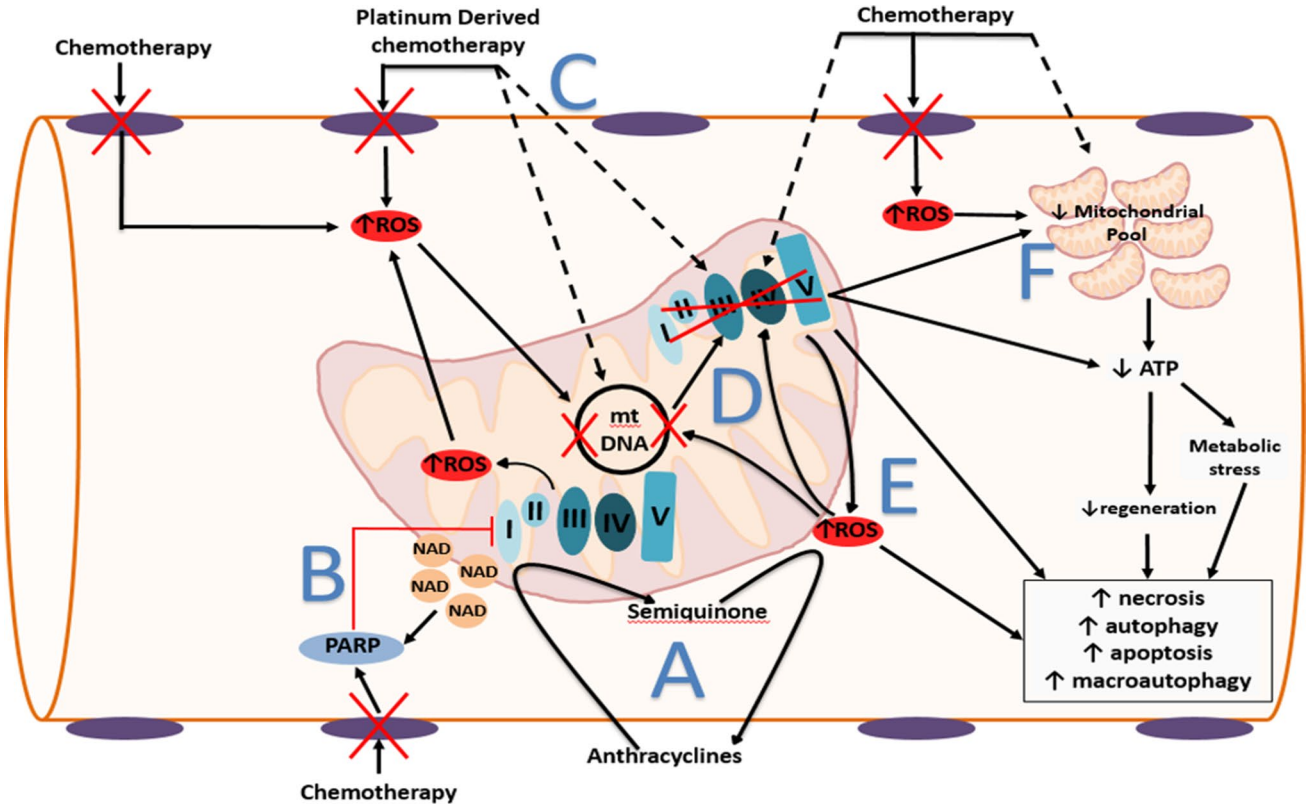

Fig. 1 Effects of chemotherapeutic agents on mitochondria and the promotion of skeletal muscle wasting. (*A*) The metabolism of anthracycline chemotherapies occurs at Complex I of the electron transport chain (ETC) within the mitochondria. The anthracycline molecule is reduced by Complex I, removing vital electrons from the ETC and transforming the anthracycline into its oxidative semiquinone, which reduces molecular oxygen to superoxide. This final reduction process returns the anthracycline to its non-semiquinone state. (*B*) Chemotherapy-induced nuclear DNA (nDNA) damage stimulates PARP-1 activity, which consumes NAD^+ (a vital mitochondrial substrate) to repair the nDNA damage. In doing so, the NAD^+ pool is rapidly depleted. This loss of NAD^+ negatively effects ATP production as well as negatively impacting various metabolic pathways including glycolysis and TCA cycle. (*C*) While the precise mechanism of oxaliplatin toxicity is unknown, likely mechanisms are intercalation of the platinum derivative into the mtDNA and the ETC complexes, and depletion of the mitochondrial Cu^{2+} pool. (*D*) mtDNA encodes for multiple components of the ETC and as such damage to the mtDNA through chemotherapy treatment and increased ROS levels perpetuates a positive-feedback loop of damage and dysfunction to the mtDNA and cellular components of the mitochondria. (*E*) mtROS can oxidise the mitochondrial membranes and damage the proteins of the ETC resulting in electron leak and an increase in mtROS production. As ROS levels increase within the cell, they upregulate atrophic pathways leading to muscle cell degradation, necrosis due to oxidative damage, autophagy and macroautophagy. (*F*) As a result of ROS-induced (and possibly chemotherapy-induced) mitochondrial dysfunction and mtDNA damage, mitophagic pathways are stimulated in order to curb the number of dysfunctional and mutated mitochondria within the total mitochondrial pool. As dysfunctional mitochondria are destroyed, the capacity of the mitochondrial pool to produce ATP is reduced resulting in depletion of the cellular ATP pool and thus induction of various autophagic, necrotic and apoptotic pathways

Our preliminary data shows that oxaliplatin-induced platinum–DNA adducts are present within neuronal mitochondrial fractions in addition to the nuclear fraction, both in a cell culture model and following systemic oxaliplatin treatment of BalbC mice [64]. We are currently investigating whether the same is true for skeletal muscle.

While we are yet to determine the precise mechanisms of oxaliplatin toxicity in skeletal muscle, our data suggests that in addition to the anthracyclines, chemotherapeutic agents from other drug classes that do not necessarily induce mtROS formation as a consequence of drug metabolism (i.e. the alkylating platinum-based chemotherapies) are also detrimental to mitochondrial function and myofiber survivability. The molecular mechanisms underlying doxorubicin toxicity in skeletal muscle and the consequential repercussions on physiological function are being increasingly documented [23, 28, 33, 65] and have established that mitochondrial dysfunction and heightened ROS production are key players. However, skeletal myopathy is a common side effect of chemotherapy exposure across all drug classes, and thus, if it has a mitochondrial origin, the initial defect seems not to be intrinsically associated with a particular mode of drug action, i.e. DNA damage versus inhibition of DNA replication. Indeed, our preliminary data in

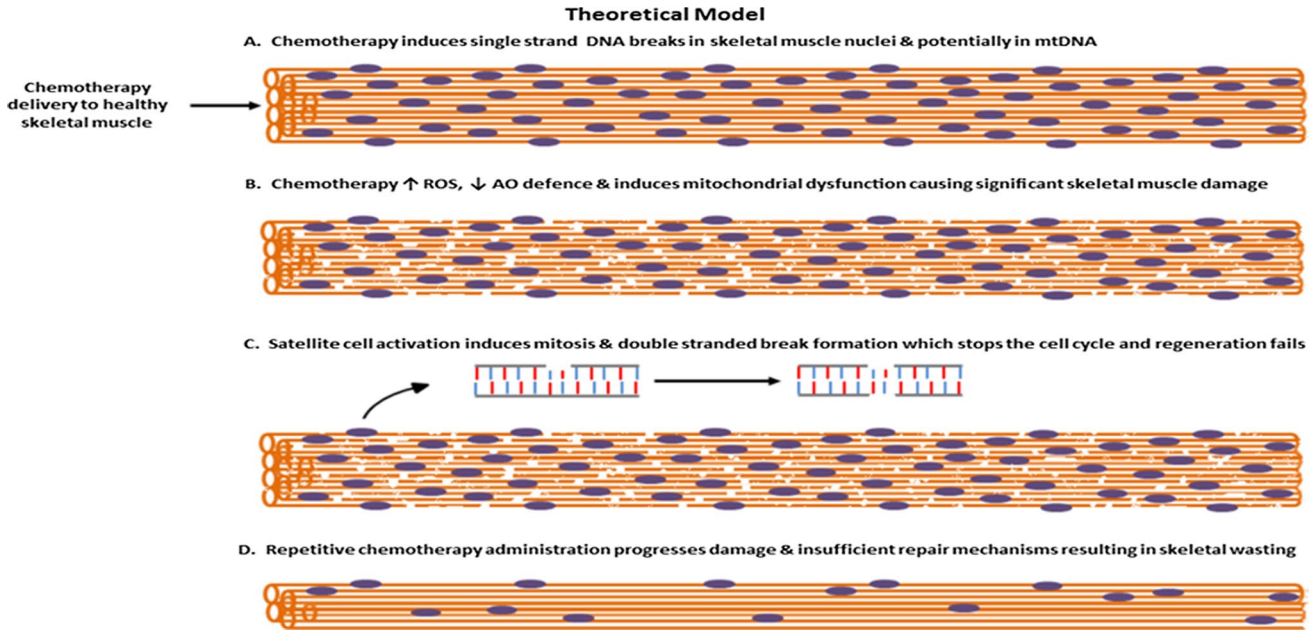

Fig. 2 Hypothetical model of chemotherapy-induced myopathy in skeletal muscle. **a** Chemotherapy is delivered to skeletal muscle which detrimentally effects nuclear DNA and potentially mtDNA. **b** Chemotherapy induces mitochondrial dysfunction resulting in increased mtROS production leading to damage of the skeletal muscle. **c** Damage sustained to the nuclear DNA is exemplified during mitosis causing a failure of satellite cell replication, and therefore, of regeneration mechanisms. **d** Long-term chemotherapy treatment results in progressive skeletal muscle damage and dysfunction due to blunted repair mechanisms

a myotube culture model indicate that both increased mitochondrial ROS production and reduced mitochondrial pool viability are consequences of treatment with chemotherapies from various drug classes including the anti-metabolite (5-fluorouracil) and topoisomerase inhibitor (irinotecan) families [22]; however, we did not observe functional deficits in myotubular mitochondrial function following exposure to these drugs as per doxorubicin and oxaliplatin. This highlights that there are both similarities and differences in the precise effects different chemotherapy agents have at the mitochondrial level and warrants further investigation. Indeed, since doxorubicin is the only chemotherapy agent that has been even moderately characterised in the literature with respect to the skeletal muscular system, there is an immediate need for the investigation of all chemotherapeutic agents in current clinical use and whether their toxic effects induce similar levels of myopathy, such that appropriate therapies can be devised to address them.

Consequences of mitochondrial dysfunction and ROS production on skeletal muscle mass

A number of recent studies investigating the molecular origin of skeletal muscle atrophy in various diseases/conditions have concluded that atrophy is almost always preceded in the first instance by increased levels of mtROS [66–70]. In a 2015 review, Sena et al. [71] outlined that mtROS production is a tightly regulated cell signalling pathway that, when excessive, induces mitochondrial and cellular protein damage thus leading to autologous mitochondrial destruction. Termed as mitophagy, this type of targeted autophagy is promoted in an attempt to attenuate elevated mtROS production by stressed mitochondria, which would otherwise inevitably induce oxidative damage, cellular energy depletion, and apoptotic/necrotic cell death. Attaix and Taillandier [72] have demonstrated that skeletal muscle mitophagy, regardless of cause, is a potent inducer of skeletal muscle wasting. Thus our hypothesis that chemotherapeutic agents (irrespective of the chemical class from which they derive) promote skeletal muscle atrophy and wasting via a mtROS/mutation-dependent mechanism seems pertinent—especially since we have demonstrated elevated mtROS levels following exposure to chemotherapy agents from a variety of drug classes [22, 73]. Indeed, Gilliam et al. [33] have shown that chemotherapy (doxorubicin) treatment causes an immediate increase (16 h post-treatment) in the established upstream muscular atrophy regulators, E3 ubiquitin ligase and Atrogin-1/MAFbx, in cardiomyocytes via a mtROS-dependent pathway. Although there is a lack of recent data on the effect mitochondrial dysfunction has on skeletal muscle atrophy, two studies have implicated ROS molecules in the induction of the FoxO family of transcription factors, which have

been shown to upregulate Atrogin-1/MAFbx atrophic signals [74, 75] (for detailed review see Bonaldo and Sandri [76]).

In addition to direct modulation of atrophic signalling pathways, mtROS have the capability to oxidatively modify protein structures [71, 77]. As chemotherapeutic agents demonstrably increase mtROS production [22], it is rational to link the subsequent increase in mtROS concentration with the modification of mitochondrial as well as other cellular proteins. A study by Kurihara et al. [78] has linked excessive ROS production with dysfunctional mitochondrial respiratory proteins which perpetuated a positive-feedback cycle of increased mtROS production, respiratory chain defects, mtDNA deletion, and ultimately mitophagy. As mitochondrial dysfunction increases, cellular energy depletion occurs which, as demonstrated by Neel et al. [79], leads to macroautophagy within the skeletal muscle in an attempt to increase substrate availability to oxidative phosphorylation and restore energy homeostasis—albeit a futile effort in the event of respiratory chain inhibition and/or defects/dysfunction. As conclusively established by Argilés et al. [13], negative alterations in energy balance act as a potent stimulus of muscle atrophy. Furthermore, Maccarrone et al. [80] have implicated increased ROS levels with the propagation of lipoxygenases which induce structural defects within the cell leading to necrosis-induced cell death, with others [81] associating ROS-induced necrosis with organelle or plasma membrane modification. With these findings reinforcing a number of previous studies [69, 82, 83], targeting mitochondrial dysfunction to reduce mtROS production is a logical intervention point through which to attenuate the initiation of muscular atrophy, macroautophagy, necrosis, and apoptosis signalling pathways, all of which have been strongly associated with chemotherapy treatment [4, 37, 84, 85].

Clinical manifestations of chemotherapy-induced myopathy

Chemotherapy-induced skeletal myopathy is thought to manifest clinically as a variety of symptoms which include varying indices of muscle pain and weakness [86], exercise intolerance [87] and intense and persistent fatigue. Incidentally, these are common symptoms associated with various metabolic diseases with mitochondrial aetiology. Emerging data also describe various metabolic syndrome-like co-morbidities in testicular cancer patients following cisplatin-based chemotherapy treatment, in which acute insulin resistance, hyperlipidemia, and abdominal visceral and subcutaneous adiposity are observed [88]. Collectively, these symptomologies highlight a probable mitochondrial aetiology, with the systemic effects resulting from an insufficiency to effectively utilise energy substrates such as glucose (leading to insulin resistance) and fats (leading to hyperlipidemia and adiposity), and the skeletal muscle-specific effects resulting from a failure of intracellular energy synthesis and homeostasis regulation.

At the myocellular level, skeletal muscle fatigue—which has been traditionally researched following intense and/or prolonged exercise [89, 90]—is associated with significant alterations in the intracellular and extracellular ionic environment, concentration and functional ratios of intracellular metabolites, calcium sensitivity of the contractile apparatus, and the production of ROS [91–93]. Indeed, these perturbations result in pain, weakness, and exercise intolerance. Fatigue is a complex phenomenon that is influenced by a plethora of factors, both physical and psychological. True skeletal muscle fatigue has been defined as any decline in performance associated with muscle activity and is strongly influenced by perturbations in neural and myocellular function [5, 94]. In the first instance, skeletal muscle mass and function is strongly regulated by both the central and peripheral nervous system, and as such, chemotherapy-induced neuropathy would strongly promote skeletal myopathy [84]. Interestingly, chemotherapy-induced peripheral neuropathy is also associated with mitochondrial dysfunction and induces escalating myopathy and weakness as dosages increase [95]. In the second instance, skeletal muscle mass and function is strongly regulated by loading, thus central and/or psychological fatigue alongside extensive hospitalisation for anti-cancer treatment would promote disuse deconditioning and atrophy [96, 97]. In the third instance, muscle mass is positively correlated with nutritional status, and thus chemotherapy-induced dysregulation of gastrointestinal function and appetite alongside promotion of nutrient malabsorption (i.e. via vomiting and/or diarrhoea) [98] would reduce the nutritional status and promote skeletal muscle wasting. This highlights the multifactorial nature of chemotherapy-induced skeletal myopathy. While there is limited research to date that has examined the mechanisms through which non-anthracycline chemotherapeutic agents might induce skeletal muscle fatigue, there is mounting literature demonstrating that symptoms persist long after chemotherapy exposure, and as such, the fatiguing effects of chemotherapeutic agents are unlike that of the reversible phenomenon observed during exercise.

A study conducted by Ness et al. [15] examined skeletal muscle function in chemotherapy-treated childhood cancer survivors, confirming that patients experience significant limitations to physical performance and are restricted from participation in daily activities several years following treatment. Post-chemotherapy-treated children also have a significantly reduced maximal exercise capacity [8, 9, 15, 60], reduced fat-free [8] and skeletal muscle mass [15], and

significant skeletal muscle weakness [8, 9, 15, 99]. Importantly Järvelä et al. [8] have established that the skeletal muscle dysfunction observed in childhood cancer survivors is not secondary to impaired cardiac muscle function, as the same results are observed in the absence of detectable cardiac dysfunction and in comparison with age-, gender-, and physical activity-matched controls [60]. Thus, chemotherapy-induced exercise intolerance, weakness, and fatigue seem intrinsically rooted in physiological maladaptations at the skeletal muscle level. A number of other groups have shown strong associations between skeletal muscle impairment and atrophy induction, which is thought to be preceded by mitochondrial dysfunction and mtROS production [10, 65–70].

Without a doubt, the chronic, long-term side effects of chemotherapy treatment on the skeletal muscular system seem most profound when chemotherapy is administered during childhood [8–10, 15, 60, 99]. Hyperplastic skeletal muscle growth and therefore, mitotic activity, is prolific during foetal and neonatal growth and ceases during early childhood in which the total fibre number is set [100, 101]. During this time, there would be a much higher propensity for chemotherapy-induced DNA damage and mutations to be quickly incorporated into the somatic skeletal muscle genome and induce repercussions on skeletal muscle structure and function that persist for life. For those chemotherapies that act to stop mitosis altogether, the result would be a systemic reduction in skeletal muscle fibre number that is unlikely to ever be entirely recovered. However, chemotherapy-induced myopathy and metabolic syndrome-like co-morbidities are also well reported in the adult population [87, 102, 103], highlighting that the damaging and atrophic side effects elicited by chemotherapy treatment are not merely segregated to cell cycle manipulation, but also directly affect mitochondrial function and energy production, skeletal muscle physiology and ultimately, the regulation of muscle mass. Thus chemotherapy-induced myopathy is likely a two-tiered phenomenon in which skeletal muscle damage and necrotic/apoptotic cell death is propagated, and the capacity for repair of that damage—especially during energy homeostasis dysregulation—is severely impaired (as summarised in Fig. 2).

Future direction and significance

Chemotherapy-induced mtROS production and DNA damage has been implicated in mitochondrial dysfunction, energy homeostasis dysregulation, mitophagy, and subsequently skeletal muscle atrophy and wasting. As a result, cancer survivors are prone to low muscle mass, poor function and heightened fatigue. Thus therapeutic interventions to ameliorate these unwanted side effects are greatly needed. We propose that the precise mechanisms through which chemotherapeutic agents induce mitochondrial and skeletal muscle toxicity and wasting be carefully characterised—particularly for those that are in current widespread clinical use—in the first instance. Further, while no single treatment has been identified to clearly ameliorate chemotherapy-induced mitochondrial dysfunction, a number of treatments have been used to treat other myopathies with similar symptomatology and which are specifically underscored by mitophagy [104, 105]. Thus targeting the mitochondria with either established or novel mitochondrial targeted therapeutics (MTT) could provide a therapeutic avenue through which to provide the skeletal musculature with protection against chemotherapy-induced toxicity. This is indeed a promising pharmacotherapeutic direction for future research.

Conclusions

The clinical repercussions of chemotherapy-induced skeletal muscle toxicity range from reduced participation in activities of daily living, chronic fatigue, exercise intolerance, depression and treatment discontinuation, to an increased risk of morbidity and mortality from myopathy-related disease [5, 94]. We have presented compelling evidence to suggest that the mitochondria are an etiological pharmacotoxic target of chemotherapy treatment which induces various co-morbidities that are overwhelmingly manifested in the skeletal muscular system. Given the persistent and severe nature of these co-morbidities, we stress the importance for a concerted research effort to develop appropriate (co-)/therapeutics to address the deleterious effects of chemotherapy-based anti-cancer therapy on the mitochondria to mitigate impacts on the skeletal muscular system.

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Compliance with ethical standards

Conflict of interest None.

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