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Review

The beneficial role of exercise in mitigating doxorubicin-induced Mitochondrionopathy

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ABSTRACT

Doxorubicin (DOX) is a widely used antineoplastic agent for a wide range of cancers, including hematological malignancies, soft tissue sarcomas and solid tumors. However, DOX exhibits a dose-related toxicity that results in life-threatening cardiomyopathy. In addition to the heart, there is evidence that DOX toxicity extends to other organs. This general toxicity seems to be related to mitochondrial network structural, molecular and functional impairments. Several countermeasures for these negative effects have been proposed, being physical exercise, not only one of the most effective non-pharmacologic strategy but also widely recommended as booster against cancer-related fatigue.

It is widely accepted that mitochondria are critical sensors of tissue functionality, both modulated by DOX and exercise. Therefore, this review focuses on the current understanding of the mitochondrial-mediated mechanisms underlying the protective effect of exercise against DOX-induced toxicity, not only limited to the cardiac tissue, but also in other tissues such as skeletal muscle, liver and brain. We here analyze recent developments regarding the beneficial effects of exercise targeting mitochondrial responsive phenotypes against redox changes, mitochondrial bioenergetics, apoptotic, dynamics and quality control signalling affected by DOX treatment.

1. Introduction

Doxorubicin (DOX, or Adriamycin) is an anthracycline used in the treatment of a wide range of cancers, including hematological malignancies, many types of carcinoma, soft tissue sarcomas and has demonstrated significant activity against solid tumors. However, despite the well-known efficacy of this antineoplastic agent, DOX clinical use is limited due to a dose-dependent development of cardiovascular toxicity, which can lead to congestive heart failure and can be fatal [1]. Furthermore, DOX toxicity also affects other organs besides the heart, including skeletal muscle, liver and brain. It has been proposed that multiple sequential exposures to DOX treatment, together with lifestyle changes, including physical inactivity, increase the possibility of cardiovascular disease among breast cancer survivors [2]. Indeed, due to the recent advances in early diagnosis and efficacy cancer therapy, cardiovascular disease is considered the predominant cause of mortality in breast cancer survivors among older women [3].

DOX-induced cellular dysfunction is associated with increased oxidative damage and apoptosis, involving mitochondrial changes in the process [4–7]. Published data also suggest that DOX disturbs the proper balance between mitochondrial fusion and fission mechanisms that are essential for healthy cell and mitochondrial regulation [8]. Moreover, DOX may unbalance cellular and mitochondrial quality control regulation [9,10]. Together, the shifts of these processes from regulatory and adaptive to disruptive are thought to contribute to the cellular dysfunctional phenotype observed during and after DOX treatments and may represent therapeutic targets against the related side-effects.

The limitation of DOX clinical use compromises its effectiveness in

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the reduction or elimination of tumor cell growth. Therefore, an ongoing challenge in cancer treatment is to exploit the DOX anti-tumor effects, while minimizing tissue toxicity in general, and particularly, cardiac toxicity and the associated mitochondrial damage. One of the most studied non-pharmacological and promising strategies used to counteract DOX side effects is chronic physical exercise [11,12]. Considering the important role of mitochondrial disturbances in DOX-related toxicity and, accounting for the beneficial role of physical exercise on mitochondrial function in control and DOX-treated animals is enough evidence to justify the critical role of those organelles in the cross-tolerance phenomenon.

The present review briefly highlights some recent published data supporting the role of exercise, particularly chronic interventions, as a strategy to mitigate DOX-induced cardiac toxicity, targeting the mitochondrial-driven mechanisms including antioxidants and apoptotic signalling, mitochondrial dynamics and quality control. The cross-tolerance effect of exercise against the deleterious effects of DOX in other tissues, including skeletal muscle, liver and brain are also briefly addressed.

2. Mechanisms of DOX-induced mitochondrial toxicity

Several mechanisms have been proposed to explain DOX-induced cardiomyopathy, suggesting that this is a multifactorial process. Generally, mitochondria involvement in DOX-induced cardiotoxicity could be explained by the activation of DOX molecule into a more reactive semi-quinone at mitochondrial complex I, leading to the formation of superoxide anion and resulting in increased oxidative stress [13–16]. Moreover, the possible existence of a heart specific isoform of the NADH dehydrogenase (mitochondrial complex I) able to initiate DOX redox cycling and, consequently, promoting additional reactive oxygen species (ROS) formation, may be a critical step of DOX-induced deterioration of cardiac function and onset of chronic clinical cardiotoxicity [13,17,18]. The elevated affinity of DOX by cardiolipin, the higher mitochondrial content and the lower antioxidant capacity of cardiac tissue compared to other tissues, justify the decreased heart capability of dealing with the increased oxidative stress induced by DOX [7,19]. Consequently, several authors have already discussed that DOX-induced increased oxidative damage is associated with mitochondrial bioenergetics disruption, interference with calcium homeostasis and enhanced apoptotic signalling through the increased susceptibility to mitochondrial permeability transition pore (mPTP) opening [1,6,7,11,12]. Additionally, it has been proposed that DOX-induced toxicity to cardiomyocytes associated with increased ROS production is accompanied by decreased levels of oxoguanine-DNA glycosylase-1 (OGG1), a major DNA glycosylase that hydrolyzes oxidized-guanine (8-oxo-dG) to guanine, and with increased mtDNA damage [20–22].

Differences in location, biochemical properties, morphology and organization between subsarcolemmal and intermyofibrillar mitochondrial sub-populations [23,24], can lead to subtle differences in their sensitivity and responsiveness to metabolic challenges including exercise [25,26]. Differences in the impact of DOX toxicity between cardiac mitochondrial sub-populations have also been reported. Kavazis [27] and co-workers suggested that subsarcolemmal mitochondria accumulate greater amounts of DOX, while intermyofibrillar mitochondria are more susceptible to apoptotic and autophagic responses following acute DOX treatment.

During stressful conditions, cardiac myocytes respond by triggering a defense mechanism, involving selective sequestration and subsequent degradation of the dysfunctional mitochondria before they cause metabolic rupture of even the activation of cell death [28]. Besides energy production, a critical role of mitochondria to ensure proper cardiac muscle contraction involves the regulation and adaptations in mitochondrial network structure [29]. The mitochondrial plastic features are driven from the dynamic interaction of mitochondrial fusion, fission, auto(mito)phagy and biogenesis, which ensures proper organization of the mitochondrial network [30]. DOX-induced cardiotoxicity has been suggested to be associated with fragmentation of the mitochondrial network [20,31,32], and to the inhibition of mitochondrial fission protects the heart against DOX-induced cardiac injury [33]. Moreover, the loss of mitochondrial connectivity can predispose cardiomyocytes to apoptosis [34,35], and/or mitochondrial division can designate dysfunctional organelles with low membrane potential for mitophagy [36].

The precise mechanisms linking DOX cardiomyopathy to mitochondrial dynamics, apoptosis and auto(mito)phagy are still largely unknown. Opposing results regarding the effects of DOX treatment on auto(mito)phagic flux suggest both the adaptive and maladaptive consequences described next, probably dependent on the severity of the stimulus: DOX treatment (i) attenuates Parkin-mediated mitophagy [37], (ii) causes a shift from autophagy to apoptosis [38], and (iii) induces autophagy, probably acting as an adjuvant mitigating strategy against DOX-induced myocardial damage [38–40]; others associate DOX treatment with elevated autophagic signalling, suggesting that increased autophagy mediates DOX-induced cardiotoxicity [9,10,41–44]. The most common pathways underlying DOX-induced cardiac mitochondrial toxicity are briefly summarized in Fig. 1.

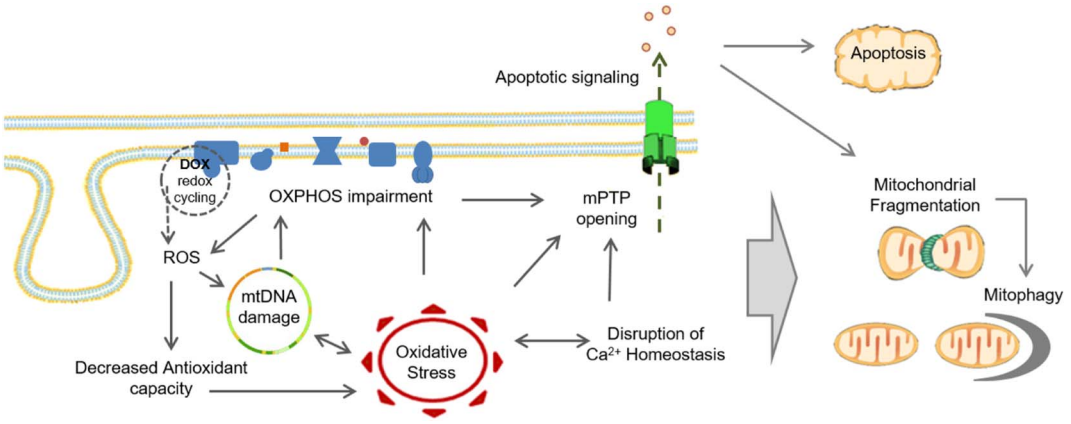

Fig. 1. Mechanisms of DOX-induced cardiac mitochondrial toxicity. DOX is reduced by complex I, forming a highly reactive semiquinone, initiating a redox cycle after reacting with oxygen and releasing ROS in the process. DOX-increased ROS generation compromises antioxidant machinery and damages lipids, proteins and nucleic acids, consequently resulting in an inhibition of oxidative phosphorylation, mitochondrial depolarization, ATP depletion, loss of calcium (Ca^{2+}) loading capacity, increase susceptibility to mPTP opening and release of pro-apoptotic proteins. In addition, mtDNA damage is also evident after DOX exposure. Together, these events may also result in mitochondrial fragmentation and contribute to an increased auto(mito)phagy signalling.