



Exercise shapes redox signaling in cancer

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ABSTRACT

In this paper of the special issue dedicated for the Olympics 2020, we put the light on an exciting facet of exercise-oncology, which may still be unknown to some audience. Accumulating convincing evidences show that exercise reduces cancer progression and recurrence mainly in colon and breast cancer patients. Interestingly, the positive effects of exercise on cancer outcomes were mainly observed when patients practiced vigorous exercise of 6 METs or more. At the molecular level, experimental studies highlighted that regular vigorous exercise could reduce tumor growth by driving changes in immune system, metabolism, hormones, systemic inflammation, angiogenesis and redox status. In the present review, we describe the main redox-sensitive mechanisms mediated by exercise. These redox mechanisms are of particular therapeutic interest as they may explain the emerging preclinical findings proving that the association of vigorous exercise with chemotherapy or radiotherapy improves the anti-cancer responses of both interventions. Clinical and preclinical studies converge to support the practice of exercise as an adjuvant therapy that improves cancer outcomes. The understanding of the underpinning molecular mechanisms of exercise in cancer can open new avenues to improve cancer care in patients.

1. Introduction

Cancer is a complex disease that affects physical performance of patients. Advanced stages of cancer are often associated with excessive loss of skeletal muscle mass, leading to functional impairment and high risk of inactivity [1,2]. In turn, physical inactivity is a deleterious factor that aggravates cancer outcomes such as, muscle weakness and fatigue, and cancer-related mortality, through increasing chronic systemic inflammation and oxidative stress [3–5]. There is clearly a vicious deconditioning circle between “cancer, muscle frailty and physical inactivity” deteriorating the quality of life in cancer patients; it is, therefore, needful to disrupt this circle.

In this light, physical exercise has been proposed as an effective strategy that could be prescribed immediately after the diagnosis of cancer and throughout the period of anticancer treatment [6]. During the treatment, exercise may preserve muscle strength, prevent skeletal muscle loss and reduce anxiety. Exercise could also reduce the adverse side effects in patients undergoing chemotherapy [7], which helps them to accomplish their treatment, without interruption or reduction of sessions that are usually due to the critical physical state and fatigue of patients. After completion of anticancer treatment, exercise could optimize recovery, reduce cancer relapse and prevent the appearance of

late chronic complications, for which cancer survivors are at high risk (i.e. cardiovascular diseases) [8].

The impact of exercise on physical performance is an evidence so far. However, it turned out that exercise could decrease cancer incidence, with a linear dose-response relationship in breast and colon cancer [8]. Motivated by these observations, researchers aimed to investigate the impact of exercise in patients with diagnosed cancer [9]. Emerging data from breast, colon and prostate cancer indicate that physically active patients exhibited less recurrence and mortality, highlighting a possible role for exercise in the suppression of tumor growth [10,11]. This tumor-suppressive role of exercise is supported by 64% of preclinical studies [12]. These studies identified some of the anticancer mechanisms of exercise that are mainly driven by changes in systemic inflammation, immune responses, angiogenesis, hormones, insulin sensitivity and redox status [13]; the later will be the focus of our review. The ability of exercise to affect redox signaling in cancer seems to be particularly dependent on the chosen modality and intensity of training. From this perspective, here, we describe the impact of different endurance and resistance exercise modalities on tumor progression and recurrence. We discuss exercise conditions that must be brought together to induce a positive change in intra-tumor redox signaling. This review should help to design exercise protocols with

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respect to the type and intensity of exercise that are suitable to induce a significant biological changes in exercise-oncology studies.

2. Exercise recommendations in cancer patients

Frequency, intensity, time and type of exercise are determinant factors to produce an effective intervention in cancer patients. The American college of sports medicine (ACSM) recommends for healthy individuals: 20-to-60 min of aerobic exercise 3-to-5 times per week at 55% VO_{2R} and 20 repetitions of resistance exercise with an intensity corresponding to 12-to-16 rate of exertion (20 is the maximum exertion rate) 2-to-3 times per week. Cancer patients may at least practice 150 min of moderate-intensity aerobic exercise or aerobic combined to resistance exercise [14]. Flexibility or stretching is a third type of exercise that helps to maintain balance and postural stability. A stretching time of 60 s per target muscle could be practiced 2-to-3 times per week [15]. Although flexibility exercise interventions are not extensively used and well documented in cancer patients population, they appear to be safe and feasible and to improve the capacity of patients to practice exercise during home stays [16,17]. The guidelines of ACSM are similar to those of the World Health Organization (WHO), recommending a combination between aerobic and resistance exercises. In the second roundtable of ACSM held in 2018, there was sufficient evidence to conclude that specific doses of aerobic exercise, resistance exercise and combination of both types improve common cancer-related health outcomes [18].

The adherence to these guidelines is low as 10% among cancer survivors, based on the findings of two independent research groups [19,20]. Patients identified as at high risk are obese patients, men with prostate or skin cancer, women receiving multimodal therapy for breast cancer, old patients and those professionally inactive in both men and women [20,21]. The adherence to the combined guidelines correlated with a higher level of education and the absence of children living at home [22]. Patients show more engagement in either aerobic (23%) or resistance (14.5%) exercise individually, than the combination of both types [20]. They seem to prefer aerobic exercise, possibly because it is more suitable to their physical situation where fatigue and muscle weakness are current [23]. However, we must not occlude that resistance exercise is especially important to improve muscle mass and strength and, subsequently, the ability of patients to train [24]. Therefore, combination of aerobic and resistance exercises could produce the best benefits for cancer patients and survivors. Programs aiming to improve the adherence of patients to exercise combination are of particular interest. A recent study suggested that individualization of exercise intensities could improve patients' adherence to the official guidelines [24]. Also, strategies to help meet the combined guidelines may need to promote more motivational cues, favorable behavioral regulations and reflective process for both types of exercises rather than focusing on just the type of exercise in which patients are deficient [22].

3. Vigorous exercise reduces cancer progression and recurrence and improves survival

In cancer patients receiving chemotherapy, the combination of aerobic and resistance exercises resulted in a better long-term health-related fitness compared to aerobic exercise alone [25]. Despite the positive effects of aerobic and resistance exercise combination on social physical anxiety, fatigue, physical fitness, muscle strength and lean body mass [26,27], few is known about the impact of exercise type itself on cancer progression and related mortality. A solid information comes from a meta-analysis on 22 cohort studies indicating that the practice of post-diagnostic exercise meeting the physical activity guidelines was associated with reduction in breast cancer progression, new primaries and recurrence and breast-cancer specific-death [28]. Recently, a study from USA on 2863 patients found that resistance

training alone was associated with 33% lower all-cause mortality among survivors of skin cancer [29]. Another study on a larger scale included more than 370 000 patients from 11 cohort and reported that resistance training was associated with 21% and 40% lower all-cause mortality alone and when combined with endurance exercise, respectively [30]. All these data support that combination of endurance and resistance exercise could exert a synergizing effect to reduce cancer progression and mortality. However, studies performed on athletes suggest that the concurrent practice of endurance with resistance exercise could reduce the improvement in muscle strength and mass stimulated by the later [31,32]. In the absence of research comparing physical adaptations between cancer patients and athletes, we suppose that the negative interference found in athletes would be similar or even worse in patients, given their lower physical status. Therefore, for cancer patients, it could be safer to practice endurance and resistance exercises in separated sessions during the same week rather than combining both exercises in a single session; this may minimize the risk of negative interference between both types of exercise.

Literature abounds of studies addressing the impact of exercise volume or intensity, regardless exercise type, on cancer outcomes. The intensity of exercise is evaluated using metabolic equivalent task (MET), with one MET corresponds to the energy expended at rest. Moderate-intensity exercise is equivalent to 3-to-5.9 MET. High-intensity or vigorous exercise has a MET value superior to 6 and is defined as an activity that causes sweating and change in heart and respiratory rates. Early studies have shown that patients with colon cancer practicing 18-to-27 MET-hours/week or more exhibited an increase in survival-free recurrence [11]. Similarly, patients with diagnosed stage I and II colon cancer or with recurrent stage III colon cancer, exercise of 18-MET-hours/week was sufficient to prolong survival [33,34]. There was also a reduced breast cancer-specific death in patients practicing more than 9 MET-hours/week [35]. Even though there is a clear inverse correlation of higher MET values with cancer progression and mortality, the use of MET-hours/week as unit of measure could be confounding because the final MET value for each patient could be reached either by low-to-moderate intensity exercise during a long period or by the practice of high-intensity exercise for shorter periods. The unit of measure that could be privileged is MET-hours/day. However, new evidences suggest that the intensity of exercise has the greatest effect in terms of cancer progression and survival. For example, the volume of total no vigorous activity did not affect the risk of prostate cancer progression [36], while vigorous exercise, reduced 57% the risk of cancer progression [36]. The time spent in practicing vigorous exercise seems to be also important as reported in a study from Sweden demonstrating a lowered risk of prostate cancer-specific mortality for men who biked more than 20 min/day (> 5 MET-hours/day) versus less than 20 min/day [37]. Vigorous exercise at least once per week was also associated with a less likelihood to progress into metastatic-lethal prostate cancer [38]. A recent study on ~65 000 adults showed that people practicing vigorous exercise have significantly reduced cancer-related mortality [39]. Intervention with exercise in lung cancer patients followed the same trend as in breast, prostate and colon cancer. Higher levels of physical activity were associated with lower cancer-related mortality in lung cancer patients [40] (Fig. 1). It seems that vigorous exercise might be practiced regularly and during enough time to get benefits in terms of cancer progression and survival; thus, the time and frequency of vigorous exercise are important parameters to take into account for the design of vigorous exercise programs. Taking together, there is convincing evidence about a protective role of vigorous exercise in terms of physical fitness, cancer progression and recurrence and cancer-specific mortality.

4. Vigorous exercise modulates intra-tumor redox homeostasis

The high potential of vigorous exercise in improving physical performance and cancer progression in patients could reflect its ability to

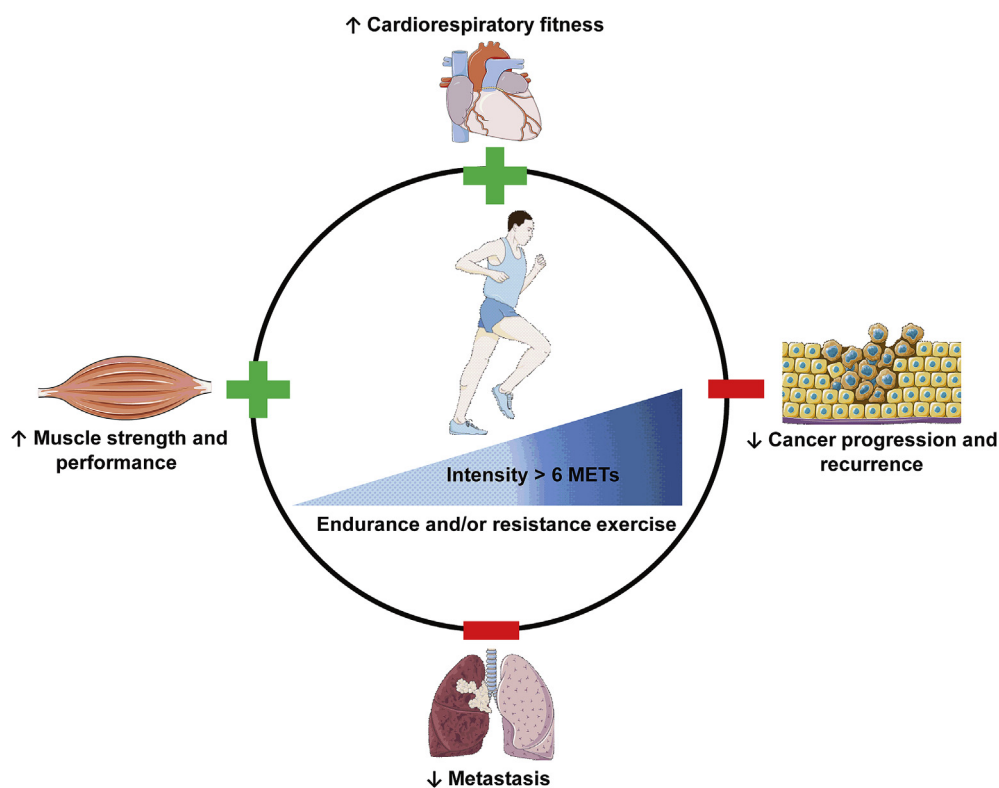


Fig. 1. The benefits of vigorous exercise. Vigorous exercise of more than 6 MET improves cardiorespiratory fitness and muscle strength. Vigorous exercise reduces the risk of cancer progression and the evolution into lethal metastasis.

modulate pro-oncogenic signaling pathways that are not affected by simply practicing recreational activities. One of the most important molecular hallmarks of cancer is oxidative stress (OS) [41]. OS is defined as a “disruption of the redox balance towards an increase in pro-oxidant over the capacity of antioxidants, leading to a perturbation of redox signaling and control and/or molecular damage” [42]. Oxidative damage in cancer patients are correlated with poorer survival or even with more advanced stages of cancer [43,44]. We and others, have previously documented numerous clinical and preclinical studies showing high levels of oxidative damage in multiple organs of both cancer patients and animal models of cancer [45–47]. Particularly, intra-muscular and intra-tumor OS contribute to cancer-related skeletal muscle atrophy and cancer growth [48,49], respectively, thereby controlling several aspects of cancer pathophysiology. Interestingly, emerging evidences indicate that combination of moderate-intensity endurance and resistance exercise reduced protein carbonyls and reactive oxygen and nitrogen species (RONS) levels in skeletal muscles of mice bearing colon 26 tumor [50]. These exercise-dependent redox changes are reproducible in patients with ovarian, pancreatic and breast cancer, showing that endurance and resistance exercise programs increased total antioxidant capacity and reduced levels of protein carbonyls in the blood [51]. The ability of exercise to correct redox imbalance at systemic and muscular levels, raised the question about its ability to induce equivalent changes in tumor tissue.

Our laboratory has previously shown that forced treadmill exercise reduced prostate cancer growth, in rats bearing subcutaneous AT-1 tumor, by reducing the intra-tumor levels of DNA oxidative damage, 8-oxoguanine (8-oxoG), and lipid peroxidation markers TBARS and 4-Hydroxynonenal (4-HNE) [52]. Contrariwise, less-vigorous training by voluntary wheel running failed to affect intra-tumor oxidative damage (i.e. 4-HNE and protein carbonyls) in different tumor types ([53] and unpublished data). Accordingly, voluntary running did not affect intra-tumor protein carbonyls levels and tumor growth in mice bearing subcutaneous PC-3 prostate tumor (unpublished data); these differences

are not due to tumor location, as mice bearing orthotopic prostate cancer did not benefit from wheel running and developed similar tumors compared with untrained mice [54]. The comparison between these different studies is difficult due to protocols heterogeneity. However, four main factors could influence the ability of an exercise intervention to modulate tumor growth and intra-tumor OS: 1) exercise intensity (forced treadmill vs voluntary wheel running), 2) protocol length, 3) tumor type and 4) tumor stage. For the last factor, studies using mice models of cancer initiation showed that voluntary wheel running was sufficient to reduce tumor development; however, the impact on intra-tumor OS was not assessed [55]. Therefore, forced treadmill might be necessary to reduce the growth of already established tumors, which is more useful from a therapeutic point of view. These data strongly suggest that the anticancer benefits due to significant changes in intra-tumor redox balance could be mainly reached by high-intensity exercise. Although exercise alone seems to induce an antioxidant effect on tumor, its combination with radio- or chemotherapy induces rather a pro-oxidant response. This is an interesting aspect when we know that radiotherapy and many chemotherapeutic agents mediate an important part of their anticancer effects by increasing the intracellular levels of RONS [56]. Combination of radiotherapy with training on treadmill in mice bearing subcutaneous prostate tumor significantly reduced tumor growth compared to radiotherapy alone (in revision). Lemke and collaborators reported that treadmill training combined with temozolomide, a chemotherapeutic agent, reduced orthotopic glioblastoma growth compared to intervention with temozolomide alone [57]. These effects were attributed to an increase in intracellular levels of RONS in glioma cells [57]. Others have shown that exercise facilitated the accessibility of chemotherapeutic drugs into tumor by improving intra-tumor vascularization [58,59]. OS markers were not measured in these studies but the proposed mechanisms involved modulation in oxygen-sensing machinery and hypoxia, which are intimately linked to redox homeostasis.

Based on the abovementioned studies we can conclude that exercise

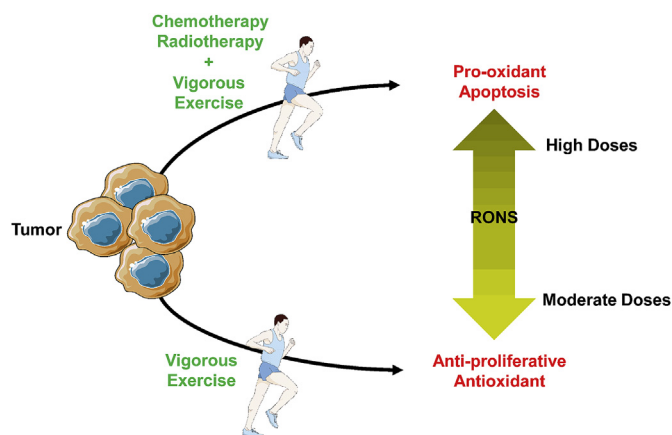


Fig. 2. A hypothetical scheme illustrating the differential impact of vigorous exercise on intra-tumor redox signature. Exercise alone is expected to produce an antioxidant response within tumor resulting in an anti-proliferative effect. While, the combination of exercise with radio/chemotherapy induces rather a pro-oxidant response promoting tumor cell death. More details about the mechanisms behind both responses are given in paragraph 4.

differentially modulate the intra-tumor redox signature. These differential responses could be explained by the paradoxical mechanisms through which moderate-to-high intensity exercise promotes the generation of moderate levels of RONS in tumor that activate the expression of numerous antioxidant genes [60] via the Keap-Nrf2 system and transcriptional factors like peroxisome proliferator-activated receptor gamma coactivator (PGC-1 α) (reviewed in Refs. [61,62]). Whereas, when exercise is combined to radio- or chemotherapy, RONS resulting from both interventions may provoke an additive effect that kills cancer cells. Additionally, if the tumor naturally exhibits high levels of RONS, intervention with exercise is expected to induce a pro-oxidant effect as well. Arguments in favor of these interpretations are well documented in the literature, for example, providing an extra source of RONS by overexpressing pro-oxidant enzymes improves the efficacy of chemotherapeutic drugs [63]; very high levels of intracellular RONS compromise DNA repair mechanisms [64], which end by promoting cell death. Altogether, vigorous exercise alone or combined with conventional anticancer therapies could reduce tumor growth by differentially modulating intra-tumor redox homeostasis (Fig. 2).

5. Exercise affects redox-sensitive pathways in tumor

After noticing that intra-tumor oxidative damage are modulated by exercise in a way slowing cancer cells growth or promoting their death, it becomes intuitive to question on *How exercise could mechanistically affect intra-tumor redox signaling and homeostasis?*

5.1. Production of skeletal muscle-specific myokines

To answer this question, many hypotheses can be proposed. For example, mechanical stimuli could highly affect tumor characteristics depending on tumor location, but this remains highly speculative. Nowadays, evidences from literature converge to support that the ability of exercise to affect intra-tumor oxidative balance is the result of a multi-step process that starts within skeletal muscles. In response to exercise, skeletal muscle is the first organ solicited and produces a cluster of cytokines and growth factors called myokines (reviewed in Ref. [65]). Skeletal muscle is considered as an endocrine organ given its ability to secrete biologically active myokines encapsulated into extracellular vesicles that influence the whole body [61,66]. Skeletal muscle cells can also secrete microRNAs into circulation, which in turn are transported into tumor cells through exosomes, microvesicles or lipid-base complexes such as HDL [67]. Indeed, multiple microRNAs,

like miR-221 and miR-133, are supposed to affect main signaling pathways including PI3K-Akt and MEK-ERK that regulate tumor cell proliferation and survival (reviewed in Ref. [67]). Other tissues could also secrete chemicals, like adipomyokines produced by adipose tissue, in response to exercise [68]. Myokines act in an autocrine manner on skeletal muscle to induce beneficial adaptations but could also travel the bloodstream to exert paracrine and endocrine effects on other organs [69]. In cancer, a crosstalk between skeletal muscle and tumor takes place. On the one hand, tumor-derived mediators induce skeletal muscle atrophy (reviewed in Refs. [45,70]). On the other hand, exercise-related myokines could reach tumor to affect its growth; this point will be discussed in the present paragraph. It is possible that the types of myokines and mechanisms controlling their production from muscles of tumor-bearing individuals could be different from those of normal skeletal muscles. However, for the moment, no evidence about such difference exists, which pushes us to suppose that mechanisms are quite similar.

In skeletal muscles, the production of myokines is by itself a process regulated in a redox-dependent manner. The AMP-activated protein kinase (AMPK) is particularly activated in response to exercise [71–73]. Three main pathways are involved: (1) increase Ca²⁺ leakage from the sarcoplasmic reticulum, which in turn promotes the auto-phosphorylation of calmodulin-dependent kinase II (CaMKII) [74], (2) increase AMP:ATP ratio [73] and (3) activation of Sestrin-2 [75]. All these events lead to the activation and stabilization of LKB1 kinase that phosphorylates AMPK on the Thr172 site of the α -subunit. Activation of AMPK increases the mRNA expression of *PGC-1 α* and can also directly phosphorylate PGC-1 α and stabilize its expression in the nucleus [76]. The epinephrine/cAMP/PKA/CREB pathway could also induce the expression of *PGC-1 α* after exercise [77,78]. The nuclear accumulation of PGC-1 α promotes the expression of antioxidants, myokines, and other genes involved in angiogenesis and mitochondrial biogenesis [79,80] (Fig. 3). Indeed, RONS produced by xanthine oxidase and NADPH oxidase (NOX) [81] as well as mitochondria [82] stimulate the abovementioned mechanisms leading to AMPK phosphorylation at Thr172 residue and the subsequent activation of PGC-1 α -derived myokines.

5.2. Impact of myokines on tumor cells

Studies linking myokines to cancer used to treat cancer cells with serum from trained and untrained humans or animals. For example, treatment of LNCaP prostate cancer cells with serum from trained humans inhibited their growth by 31% and reduced their ability to form tumors in immune-deficient mice [83]. Secretome analysis revealed many myokines produced in mice and humans in response to exercise such as, secreted protein acidic and rich in cysteine (SPARC), leukemia inhibitory factor (LIF), myostatin, apelin, musclin, irisin, interleukin-6 (IL-6), IL-8, and IL-15 [84]. Hojman and collaborators identified oncostatin M (OSM) as a myokine produced after exercise and able to reduce the proliferation of MCF7 breast cancer cells *in vitro* [85]. Munoz et al. found similar results with MCF7 cell line after treatment with the muscle-isolated protein F-Substance [86]. Others have shown that irisin enhanced the cytotoxicity of doxorubicin in MDA-MB-231 breast cancer cells compared to non-malignant cells MCF-10a, indicating the presence of an interesting selectivity of myokines toward malignancy [87]. SPARC is one of the most studied and characterized myokines. In the early 2000s, SPARC was found to induce anti-proliferative effects on carcinomas through its receptors present on the surface of cancer cells [88,89]. More recently, it has been shown that SPARC can reduce the number of aberrant crypts and colon tumorigenesis in mice [90]. SPARC mediated its anti-cancer effects by attenuating intra-tumor oxidative damage [91] and production of H₂O₂ [92]; these effects could be due to a higher transcription of antioxidant genes thanks to PGC-1 β [93]. The reduction in H₂O₂ levels resulted in a reduced expression of cyclins A1, D1 and E2 and cell cycle arrest of tumor cells [92].

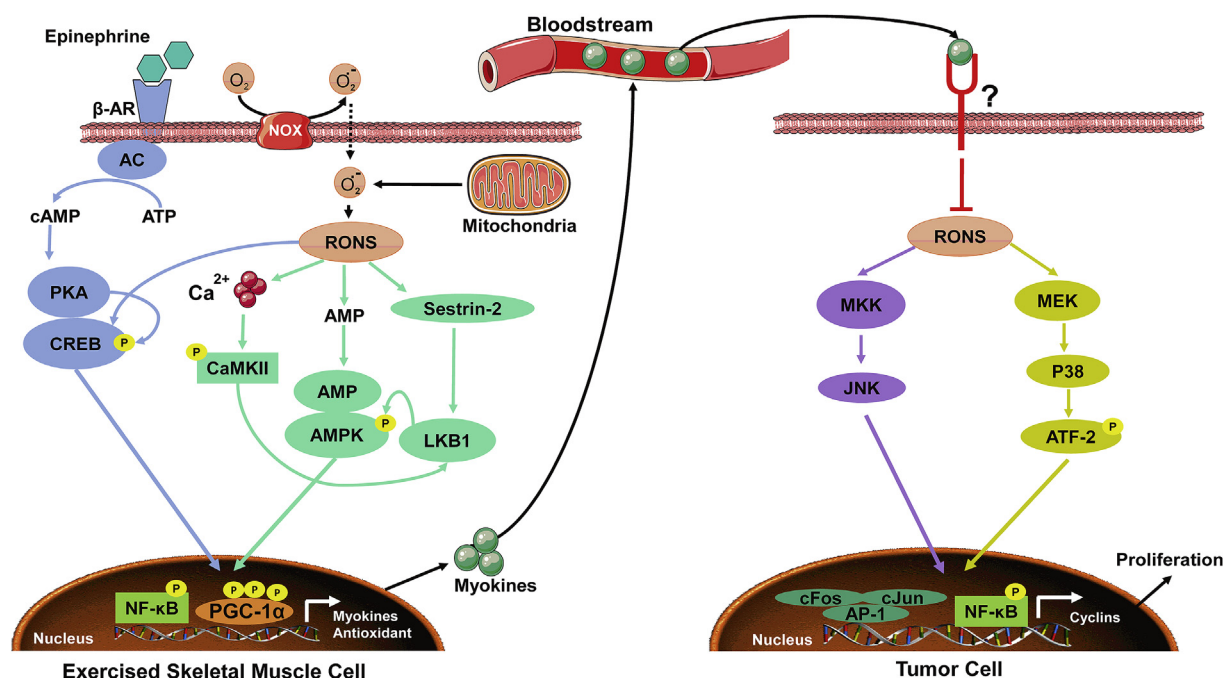


Fig. 3. Intra-muscular and intra-tumoral redox-sensitive mechanisms driven by exercise. Firstly, in exercised skeletal muscle cells, hormones like epinephrine and/or RONS activate a series of pathways such as, AMPK and cAMP/PKA/CREB, leading to the nuclear translocation of transcriptional factors like NF- κ B and PGC-1 α and transcription of genes encoding antioxidant enzymes and myokines. Secondly, skeletal muscle myokines are released into the bloodstream where they can reach tumor cells. We suppose that myokines will bind specific receptors on tumor cells and inhibit RONS-mediated activation of signaling pathways including MKK/JNK and MEK/p38 (basal levels of RONS are high in tumor cells given their accelerated metabolism), which results in less nuclear translocation of AP-1 and NF- κ B transcriptional factors and less transcription of cyclin genes involved in cell proliferation. Some data indicate that myokines could also drive apoptosis of tumor cells but the mechanisms are still poorly elucidated.

Mechanistically, SPARC-mediated reduction in H_2O_2 decreased the activation of p38-MAPK and JNK pathways that converge to promote AP-1 and NF- κ B transcriptional activities [92], which in turn could be responsible for the expression of cyclins, like cyclin D1 [94] (Fig. 3). Interestingly, SPARC also inhibited AP-1 and NF- κ B activities in cancer-associated fibroblasts and tumor-associated macrophages, thereby inhibiting inflammation produced by both populations in tumor micro-environment to nourish tumorigenicity [92,95]. Altogether, these data indicate that redox-dependent processes tightly regulate both the production of myokines from skeletal muscle and myokines-mediated anti-cancer effects observed in different cancers.

6. Clinical implications and perspectives

Physically active cancer patients are more confident concerning their health status and express less fear of cancer recurrence comparing to less active or sedentary patients [96]. This could be due to the increased awareness and accumulating evidences about the beneficial effects of physical activity in reducing cancer progression and recurrence. In this review, we report a positive role for exercise on cancer progression in humans. Regular vigorous exercise of more than 6 MET reduced cancer progression and improved survival in breast, colon and prostate cancer, with emerging evidence in lung cancer as well. One recent study reported that exercise of at least 4.5 MET improves colorectal cancer-specific survival only in tumors with low immune cells infiltrate [97]; this could explain the heterogeneous responsiveness of patients to exercise depending on the sub-molecular features of tumor. Although exercise less than 6 MET could improve fatigue, physio-social anxiety and cardiorespiratory fitness, it seems not sufficient to affect cancer progression and survival. We conclude that vigorous exercise is needed to improve cancer outcomes. The combination of endurance and resistance exercises according to ACSM and WHO guidelines should produce the best benefit for cancer patients in terms of disease

progression and disease-free survival. Strategies to augment the adherence of patients to international physical activity guidelines are under development. Preclinical findings show that the combination of vigorous exercise with radiotherapy or chemotherapy improved the anti-cancer response in rodents; future clinical studies can investigate this possibility in patients undergoing conventional therapies.

The downside of exercise practice is that patients exercising regularly are more prone to take antioxidant supplements [98–100]. The prevalence of supplements is high in educated and physically active cancer patients, because antioxidant supplementation refers to a healthy lifestyle [101]. Contrary to this imaginary, scientists found that antioxidants blunt the beneficial effect of exercise in humans [102,103]. In rodents, combination of antioxidants with exercise neutralized the beneficial effects of exercise alone on tumor growth [104]. As depicted in Fig. 3, many exercise benefits on skeletal muscle cells and tumor cells are mediated by RONS; supplementation with antioxidants is expected to block these mechanisms. Even though RONS play a key role in cancer development, it is becoming clear that we also need them to beat cancer. Antioxidants could be also deleterious for cancer patients especially those undergoing chemotherapy or radiotherapy [105]. At the molecular level, antioxidants may interfere with the RONS-generating mechanisms of radiotherapy or chemotherapy. Given the limited research supporting the use of antioxidants in cancer, physicians prohibit the use of antioxidants for patients during their anti-cancer treatment [105]. So, combination of antioxidants with exercise or with chemo/radiotherapy must be avoided as it reduces the anti-cancer potential of the mentioned interventions. Patients with specific antioxidant deficiencies could benefit from supplementation after completion of their anti-cancer treatment on a single-patient basis.

Patients with advanced stages of cancer can suffer from excessive weight loss, muscle wasting, fatigue, anemia and cardiorespiratory troubles [1,106]. Applying moderate-to-vigorous endurance and resistance exercise in these conditions could be limited [107]. The

evaluation of feasibility and safety of such exercise interventions in patients with advanced stages of cancer could be unallowable for ethical or physical reasons. In the absence of clear directive concerning physical activity, patients and their families will turn more easily to risky alternatives by fear from cancer progression or recurrence. From there, one of the remained unanswered questions in the field is *How to make exercise benefits accessible for patients with advanced cancer and functional impairment?* The answer could come from the recent technological advances achieved in the last few years. High throughput analysis of proteome, phospho-proteome and secretome will allow the identification of new myokines and the understanding of regulatory mechanisms of new or already known myokines. As a first approach, analysis could be performed on a simple culture system consisting of skeletal muscle cells subjected to electrical pulse stimulation *in vitro*, which mimics skeletal muscle contraction *in vivo*. A list of the most abundant myokines could be then established and validated in exercised animals and humans. Recombinant form of selected myokines could be tested at different doses in animals bearing the most frequent malignancies (i.e. lungs, colon, pancreas, liver, prostate and breast cancer). The combination of myokines that have the widest anti-cancer response on different cancer types could be considered as clinically relevant. In addition, myokines with selective but powerful anti-cancer effect on one cancer type are interesting candidates. Finally, a combination of myokines endowed with high anticancer activity and low side effect could be tested in cancer patient trials. We speculate that the administration of myokines directly would produce a more rapid and effective anticancer effect compared to existing exercise mimicking-strategies. Actually, ideas to emulate exercise effects have been proposed in the early 2000s, by administrating multiple agonists that could stimulate some of the signaling pathways activated by exercise itself, into individuals unable to exercise [108]. For example, AICAR that activate the AMPK-PGC-1 α signaling, involved in myokines production, has been proposed as an effective exercise mimetic that recapitulates exercise-induced genes expression in rodents' skeletal muscles, without exercising [109]. Reports show that the use of exercise mimetics, in the form of pills, improves survival and cardiovascular complications [110,111]; the majority of the research was performed in link with cardiovascular diseases or muscle endurance and confirmations are still needed for cancer. Nonetheless, we are not promoting in any way the use of exercise mimetics to replace physical activity or to treat the syndrome of inactivity. The effects of exercise touch many organs and are very complex to be simply reproduced by using a combination of pills. The best way to get complete health benefits is to practice "real" exercise [112]. However, in case where advanced cancer patients cannot exercise correctly, exercise-mimicking strategies (agonists for exercise signaling or myokines) become an essential and tolerated alternative. As low-intensity exercise could be feasible in advanced cancer patients [113], the combination of low-intensity exercise with low doses of exercise mimetics is expected to provide the best exercise-related benefits.

Author contributions

MA and AR conceived and designed the paper. MA wrote the paper. SD collected data mentioned in the text as "unpublished" or "in revision". MA and AR edited and revised the manuscript. MA, SD and AR approved the final version of manuscript.

Declaration of competing interest

The authors of the present manuscript declare no conflict of interest.

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