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Exercise against tumor- and chemotherapy-induced muscle wasting

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Abstract

Cancer cachexia is a severe muscle wasting syndrome associated to cancer and distinct from anorexia, which is often present in this condition. Muscle wasting is exacerbated in cancer patients by chemotherapy treatments. Indeed, chemotherapy itself can induce muscle wasting in animal models in the absence of cancer. Exercise is currently proposed in multimodal therapies for cancer patients. Both endurance and resistance exercise are safe and do not seem to provoke further damage to a frail muscle tissue due to tumor dependent dystrophin downregulation. Through its pleiotropic effects, the benefits of exercise spam from a shift from pro- to anti-inflammatory cytokines, to direct effects on muscle fibers, such as an amelioration of the autophagic flux and pathways involved in protein metabolism. In addition, exercise positively affects the muscle stem cell niche, favoring a pro-myoogenic environment. Since tumor- and chemotherapy-induced muscle wasting share molecular mechanisms, exercise may have the potential to counteract both disease- and therapy-related side effects and to rescue muscle homeostasis.

Introduction

Cancer-cachexia is a syndrome characterized by a severe decrease of body weight, accounted for by specific loss of skeletal muscle and adipose tissues. Cachexia, which is distinct from anorexia, is due to a combination of reduced food intake and metabolic changes, including high energy expenditure, excess catabolism and inflammation [1]. Cachexia is linked to the production of cytokines by the tumor itself or the immune system of the host, which play a major role in the regulation of muscle wasting [2]. Pro-inflammatory cytokines, such as IL-6, act as double-edged swords since they recruit NK cells to attack tumor cells [3], but also induce a systemic metabolic stress response that blocks the effects of anti-cancer immunotherapy [4]. The pivotal role of fat tissue in driving the chronic inflammation that triggers cachexia was recently recognized [5, 6]. Skeletal muscle tissue is enriched in various stem cells but not in inflammatory cells in cachexia [7]; nonetheless, it is a primary target of pro-inflammatory cytokines, which induce muscle fiber atrophy and stem cell dysregulation and apoptosis [8-10].

Cachexia is associated to a large extent with cancers of the pancreas, esophagus, stomach, lung, liver and bowel; this group of malignancies is responsible for 50% of all cancer deaths worldwide [1] and cachexia is directly accountable for the death of about 20% of all cancer patients [11]. Being associated with poor prognosis and a lower quality of life for patients, cachexia remains a major challenge in the management of cancer patients to date.

Muscle wasting in cachexia affects striated muscles [12, 13], with important gender differences , likely linked to sex hormones [14]. Great progress is being made in the understanding of the molecular mechanisms underlying muscle wasting, with a central role played by proteasome-mediated protein degradation [15]. As a consequence, several treatments are now being proposed to specifically counteract muscle wasting [16-18].

Chemotherapy remains the elective treatment for different cancers since it directly induces the death of tumor cells and helps endogenous host responses against cancer [19]. However, chemoterapy may induce muscle wasting, too, and loss of skeletal muscle during chemotherapy is prognostic of poor survival [20]. Consequently controlling muscle wasting especially in chemotherapy-treated patients is of the greatest importance. In spite of this, few studies have investigated this phenomenon up to date.

In this concise review the effects of exercise on cancer- and chemotherapy-induced muscle wasting are discussed.

Cachexia as a multisystemic syndrome: the relevance of tissue-tissue interactions

Although cachexia is characterized above all by fat and lean body mass wastage, fat and skeletal muscle tissues are unlikely to be the only tissues directly involved in this multifactorial, complex syndrome.

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Special Issue: Assisted Exercise

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The neuroendocrinology of the cachectic response to chronic illness is well known and has recently been reviewed by Weekers [21]. As far as skeletal muscle wasting is concerned, there appears to be a marked interaction with at least two other tissues, i.e. fat and the intestinal epithelium. Fat tissue is the primary energy store and an important endocrine organ, which in turn affects muscle homeostasis. High fat content (not simply BMI) correlates with a lower risk of mortality and decreased weight loss from lean tissue (22, 23). While decreased food intake due to anorexia is widely recognized as a contributing factor to the negative balance of muscle homeostasis in cachexia, the role of poor absorption of nutrients by the intestine was highlighted more recently. The proposed model is a vicious circle in which organ failure induces chronic inflammation, which in turn damages the intestinal barrier. The intestinal mucosa becomes infected by a wide range of bacteria. LPS may further exacerbate the damage to the mucosa, which in turn leads to reduced efficiency in nutrient absorption [24]. It is becoming consistently clear that systemic inflammation could be considered the common denominator of the many clinical and metabolic consequences of the cachexia syndrome. Chronic physical exercise has been associated with down regulation of inflammation [25, 26] and suggested as a non-pharmacological strategy for both the prevention and treatment of several chronic diseases [27]. Aerobic training in particular, has been implicated with reduction of systemic inflammation [28]. Bearing in mind that cachexia is systemic, and that muscle wasting is but one of the many symptoms of the syndrome, it appears that any efforts aiming at attenuating its effects should be envisaged as to affect the organism as a whole. It seems quite clear that strategies which are simply designed to prevent muscle loss fail to reverse other aspects of the condition, despite the specific improvements reported. It has thus been proposed to adopt exercise training as a strategy to overcome systemic inflammation in cachexia, therefore counteracting muscle wasting.

Why exercise is effective against cancer-induced muscle wasting

Resistance exercise training is defined as multiple repetitions of static or dynamic muscular contractions performed against a high load or resistance. Resistance training increases muscle mass in healthy subjects and attenuates muscle wasting associated with ageing [29]. Endurance exercise training consists of performing low- to medium-intensity exercise for long periods of time. Endurance training (such as running, cycling, or swimming) involves the use of several large groups of muscles and tends to be aerobic. Adaptations to endurance exercise include improved oxygen delivery to muscles and their increased oxidative capacity [30]. There are many clinically relevant reasons to recommend exercise for patient populations. Exercise training 1) will attenuate the physical deconditioning that patients typically experience upon diagnosis; 2) may optimize functioning when used as adjunctive therapy to standard pharmacological or surgical treatments; 3) may reduce secondary cardiovascular risk factors and attenuate other clinical consequences of the disease and/or treatment; 4) will optimize quality of life and possibly improve overall outcomes by improving physical functioning.

Although there are good reasons to recommend regular exercise in patient populations, this is not a straightforward endeavor in patients with chronic disease. In fact, physical exercise is also known to induce an acute inflammatory response and oxidative stress in healthy subjects as well as in patients [31]. A major concern regarding the use of exercise is exercise-induced damage. For instance, in Rheumatoid Arthritis (RA) the concern that inflamed joints might be exposed to mechanical damage during exercise is widely diffuse. In cancer cachexia a deregulation of the dystrophindistroglycan complex has been reported suggesting that the skeletal muscle is particularly exposed to mechanical damage in these patients [32]. From the above the question arises whether to exercise or not to exercise in cachexia. With the aim of addressing this therapeutic dilemma, we performed a meta-analysis on scientific studies from the last decade dealing with exercise performed by cachectic patients [33]. We observed differential effects exerted by exercise, depending on the pathology considered and the kind of exercise performed: a global positive effect of exercise was observed when all the pathologies considered were pooled together; also, a significantly positive effect of exercise was observed in patients affected by RA. On the contrary, when RA was excluded from the analysis the effects of exercise on cachexia were not significant. Considering separately the kind of exercises performed, it is interesting to observe how resistance exercise had positive, statistically significant effects on cachexia as opposed to endurance exercise [33]. However, several publications followed this metanalysis paper highlighting the beneficial effects of endurance exercise.

For instance, to further investigate the beneficial effects of exercise on cancer cachexia, our group exploited an animal model of cancer cachexia (tumor-bearing mice doing wheel running) and we showed that endurance exercise totally rescues muscle wasting [34]. In particular, we found that cancer triggers the induction of the autophagic markers LC3b and p62 in skeletal muscle in both mice and carcinoma patients. This scenario looks deleterious to muscle as well as to other tissues; however, in a counterintuitive manner, autophagy is not deleterious per se as a mechanism of muscle tissue catabolism: it is the block of autophagy progression which occurs in the presence of a cancer which dysregulates muscle metabolism contributing to muscle wasting. With this reasoning, we gave to tumor-bearing mice pharmacological treatments that promote autophagy and we noticed that they restored muscle homeostasis by modulating autophagy in cancer cachexia [34]. In the same context, we showed that aerobic exercise or exercise mimetics (AICAR) promoted autophagy and had comparable, beneficial effects on muscle homeostasis.These observations shed light on a possible mechanism underlying the beneficial effects observed in cancer patients who perform a moderate amount of physical activity, and highlight the role of autophagy-triggering drugs as a potential therapeutic approach to treating cancer patients.

In addition, in skeletal muscle endurance exercise regulates ubiquitin ligase activity [34], increases Heat shock protein 60 and induces peroxisome proliferator- activated receptor gamma coactivator α1 expression [35]. Endurance exercise also affects the muscle fiber niche and promotes satellite cell myogenic differentiation [36]. At organismal level, exercise has beneficial, immunological and hormonal effects [37, 38]. For the all above, endurance exercise is now proposed as a treatment for cancer cachexia [39].

Exercise and the side effects of chemotherapy

In the paper entitled «Chemotherapy-induced muscle wasting: association with NF-κB and cancer cachexia» the group headed by Denis Guttridge, at the Ohio State University, studied the effects of cisplatin, a common anti-cancer therapeutic agent, in a cancer cachexia animal model. The latter consisted in mice bearing a subcutaneously grafted colon carcinoma, the C26 tumor (40). Guttridge and co-workers found that «although cisplatin is able to reduce tumor burden as expected, muscle wasting in mice nevertheless persists. Strikingly, cisplatin alone was seen to regulate muscle atrophy, which was independent of the

commonly implicated ubiquitin proteasome system» (Damrauer et al., in press) This study appeared for the first time in Basic and Applied Myolgy in 2008 and for its relevance is now republished in European Journal of Translational Myology in 2018. It is worth noting that then another group had reported opposite findings, i.e. that chemotherapy inhibits protein breakdown and promotes protein synthesis [41, 42], however, both studies showed that cisplatin induced body weight loss and muscle wasting in healthy mice, suggesting that chemotherapy does indeed induce muscle loss. Very likely, cisplatin triggers multiple responses in muscle tissue, which ultimately lead to muscle fiber atrophy while the role of protein ubiquitination and proteasome-mediated degradation remains controversial. Clearly these studies were relevant in addressing cancer cachexia in the presence of chemotherapy, which contributes to mimicking clinical settings better.

As mentioned above, Guttridge's laboratory did not suggest a role for proteasome-mediated protein degradation during chemotherapy, while Attaix's group found that chemotherapy reduced proteasome-dependent protein degradation, both in the absence or presence of a tumor [41] (see also Damrauer et al., in press). A possible explanation is that the first group did not directly measure proteasome activity, but rather Murf1 expression. Murf1 is a muscle specific ubiquitin ligase which leads proteins to the proteasome, but it is not unique in its role and could be redundant with other ubiquitin-ligases, such as Atrogin1. In addition Murf1 provides an indirect estimate of protein degradation.

Interestingly, although, cisplatin induces Nf-KB expression, the latter is increased in muscle in the presence of a tumor and is sufficient to trigger muscle wasting [43]: thus a mechanism is produced whereby chemotherapy induces Nf-kB dependent muscle wasting. The fact that NF-kB targets not only muscle fibers but also muscle stem cells [44] suggests that chemotherapy may reach multiple targets, in addition to muscle fiber protein metabolism. Indeed, the findings that NF-kB is involved in both tumor- and chemotherapy-induced muscle wasting suggested that common pathways are activated. This has been recently confirmed by the group of Andrea Bonetto, at Indiana University [45]. By using a comprehensive approach based on liquid chromatography followed by mass spectrometry they compared the skeletal muscle proteome in C26-tumor bearing and chemotherapy treated mice (chemotherapy consisting of 5-fluorouracil (5-FU), Leucovorin (LV) and CPT-11, a combination also known as Folfiri). Authors found that cancer and chemotherapy promote the down-regulation of 235 and 345 muscle proteins, respectively, the vast majority of which were modulated in common [45]. Mitochondrial dysfunction, TCA cycle, fatty acid metabolism, and Ca2+ signaling were among the altered pathways detected [45]. Further insights about muscle mitochondria dysregulation following chemotherapy came from the same group which proved that mitochondrial depletion is MAPK-dependent [46]. This is consistent with previous findings that muscle wasting is associated with up-regulation of ERK1/2 and p38 MAPKs [47]. In an elegant, recent study Bonetto and co-workers proposed the inhibition of the activin receptor 2B (ACVR2B) signaling to counteract both cancer- and chemotherapy-induced muscle wasting, by using ACVR2B/Fc, a soluble ACVR2B fusion protein and inhibitor of receptor downstream signaling [48]. ACVR2B/Fc was effective not only in counteracting Folfiri-induced skeletal muscle loss, but also the Folfiri negative effects on bone mass [48].

Given that cancer and chemotherapy activate common pathways in muscle and exercise has proven effective against cancer-induced muscle wasting, several research groups have been prompted to study whether physical activity can have beneficial effects during chemotherapy as well. Indeed, several epidemiological studies and clinical trials suggest that both resistance and endurance exercise should well be an integral part of supportive care for cancer patients undergoing chemotherapy [49-51]. Taken together these studies provide a rationale for using treatments to both counteract tumor growth and to reduce the side effects of chemotherapy.

The most relevant research on chemotherapy-induced muscle wasting are summarized in a recent review published in European Journal of Translation Myology [52]. The European Journal of Translation Myology has published many papers related to muscle wasting linked to mobility disorders [53-59], to muscle atrophy in sarcopenia and disease states [60-62], and to physical exercise [63, 64]. Originally devoted to biology, physiology, diagnostic, and to the rehabilitation of skeletal muscle tissue, the journal is now moving forward to cover additional fields in myology, thus taking on a broader medical and clinical interest. Exercise biological effects are usually reported in specialized journals, such as Sports Medicine [65] or The Physician and Sportsmedicine [66]. We suggest, instead, that a greater number of transdisciplinary journals, such as Biology, engineering and Medicine [67, 68] and European Journal of Translation Myology [69-71] dedicate original data articles and special issues to the effects of exercise with medical implications. This policy would give greater visibility to exercise training protocols for medical applications and would favor the incorporation of exercise into multimodal therapies against complex, multiorgan syndromes such as cachexia [72,73].

Conclusions

The following conclusions can be drawn from the above: 1) cachexia is a severe complication of many pathologies, particularly cancer, but also a side effect of chemotherapy; 2) cachexia should be counteracted since it accounts for a significant percentage of deaths, it affects the patients' quality of life and interferes with therapy for the primary disease; 3) even though incomplete, current knowledge on the mechanisms of cachexia allows to set the goal of a therapy against cachexia, possibly acting at different levels of intervention; this is not in contrast with the fact that (4) the therapy of cachexia also consists in the primary disease therapy; 5) ideally, cachexia should be prevented rather than cured; 6) exercise may play a major role in both prevention of cachexia and rescue of lean mass, thanks to its systemic effects.

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