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Aerobic and resistance training dependent skeletal muscle plasticity in the colon-26 murine model of cancer cachexia

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ABSTRACT

Purpose. The appropriate mode of exercise training for cancer cachexia is not well-established. Using the colon-26 (C26) mouse model of cancer cachexia, we defined and compared the skeletal muscle responses to aerobic and resistance training.

Methods. Twelve-month old Balb/c mice were initially assigned to control, aerobic training (AT; wheel running), or resistance training (RT; ladder climbing) (n = 16–17/group). After 8 weeks of training, half of each group was injected with C26 tumor cells, followed by 3 additional weeks of training. Body composition and neuromuscular function was evaluated pre- and post-training. Muscles were collected post-training and analyzed for fiber cross-sectional area (CSA), Akt-mTOR signaling, and expression of insulin-like growth factor-I (IGF-I) and myogenic regulatory factors.

Results. Total body mass decreased (p < 0.05) in C26 (–8%), AT + C26 (–18%), and RT + C26 (–15%) but not control. Sensorimotor function declined (p < 0.05) in control (–16%), C26 (–13%), and RT + C26 (–23%) but not AT + C26. Similarly, strength/body weight decreased (p < 0.05) in control (–7%), C26 (–21%), and RT + C26 (–10%) but not AT + C26. Gastrocnemius mass/body weight tended to be greater in AT + C26 vs. C26 (+6%, p = 0.09). Enlargement of the spleen was partially corrected in AT + C26 (–27% vs. C26, p < 0.05). Fiber CSA was lower in all C26 groups vs. control (–32% to 46%, p < 0.05); however, the effect size calculated from C26 and AT + C26 was large (+24%, d = 1.04). Phosphorylated levels of mTOR in AT + C26 exceeded C26 (+32%, p < 0.05). RT + C26 showed greater mRNA

Abbreviations: AT, aerobic training; RT, resistance training; C26, colon-26; DXA, dual energy x-ray absorptiometry; CSA, cross-sectional area; IGF-IEa, insulin-like growth-factor I-Ea isoform; IGF-IEb, insulin-like growth-factor I-Eb isoform; MuRF1, muscle ring finger 1; mTOR, mammalian target of rapamycin.

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expression ($p < 0.05$) of IGF-IEa (+79%) and myogenin (+126%) with a strong tendency for greater IGF-IEb (+127%, $p = 0.069$) vs. control.

Conclusions. Aerobic or resistance training was unable to prevent tumor-induced body weight loss. However, aerobic training may have preserved function, reduced the inflammatory response of the spleen, and marginally rescued muscle mass possibly through activation of mTOR. Aerobic training may therefore have therapeutic value for patients with cancer cachexia. In contrast, resistance training induced the expression of genes associated with muscle damage and repair. This gene response may be supportive of excessive stress generated by high resistance loading in a tumor-bearing state.

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1. Introduction

Cachexia is a life-threatening condition that develops in approximately half of all cancer patients and accounts for roughly 20–30% of cancer-related deaths [1–3]. Key features of cancer cachexia include unintended weight loss, skeletal muscle atrophy, and impaired physical function [1]. As a direct consequence of these changes, the ability to perform activities of daily living is compromised and quality of life is reduced [4]. To address this unmet medical need, research has focused on defining the cellular and molecular signals regulating disease onset and progression, as well as the various pharmacologic and nutritional agents with preventive or inhibitory properties [5]. Because cachexia is a multifactorial syndrome that arises or progresses from a number of events (e.g. tumor-specific products, inflammation, physical inactivity), it has been suggested that effective therapeutic strategies would require multiple arms [5].

Of the therapies currently being investigated, exercise has received the least attention [6]. Based on the well-defined skeletal muscle adaptations to contractile activity in health and disease [7–11], exercise may be an effective therapy for cancer cachexia [12,13]. In broad terms, exercise can be classified as low muscular tension sustained for a prolonged period (i.e. aerobic exercise), or high muscular tension generated intermittently (i.e. resistance exercise). Typical training adaptations to the former include increased mitochondrial content, capillary density, and exercise capacity [14–16] whereas the latter has been shown to promote myofibrillar protein synthesis, whole muscle and myofiber hypertrophy, and/or enhanced contractility [17–20]. Each exercise mode, therefore, provides benefits that may alleviate cancer cachexia.

At present, exercise therapies in cachectic cancer patients have not been rigorously evaluated [5,21]. Consequently, limited data exist to inform the application of exercise in clinical practice. Possible explanations for the lack of information include physical frailty in patients that compromises exercise adherence, limited availability of personnel qualified to supervise training in this population, and/or the need for specialized facilities and equipment [13]. To date, experimental approaches have been confined to pre-clinical models, of which studies provide evidence that aerobic training preserves muscle mass in the presence of tumor load [22–24]. Interestingly, resistance training has been implemented to a lesser degree despite being a potent anabolic stimulus that promotes muscle hypertrophy,

enhanced contractile function, and signaling events favoring muscle growth/preservation [6,25]. For instance, inhibited insulin-like growth factor-I (IGF-I) activity along with enhanced myostatin signaling has been reported in skeletal muscles of several cancer cachexia models [26–28]. Resistance overload on the other hand, promoted IGF-I pathway activation and suppressed myostatin signaling while preserving muscle mass in other cachexia-related syndromes [29]. Such load-mediated events may collectively alter protein turnover in a manner that also protects against cachectic muscle wasting.

Among the few pre-clinical investigations, resistance exercise was modeled using electrical stimulation or the surgical ablation of synergistic muscles [30,31]. While these highly invasive methods induce rapid hypertrophy (+30–50% in 1–2 weeks) [32,33], they do not accurately reflect the mechanical stress of resistance exercise in humans on the basis of the timeframe required for training-induced muscle growth (>6 weeks). As an alternative, we and others have previously achieved skeletal muscle overload in rodents through weighted ladder climbing [34,35]. In our hands, this form of chronic overload produced a hypertrophic response similar to resistance training in humans [18,36]. To our knowledge, this method of resistance loading has not been previously investigated in pre-clinical cancer cachexia models, nor has it been evaluated in comparison to the more often-studied aerobic exercise mode. The purpose of this study, therefore, was to define and compare the skeletal muscle responses to aerobic and resistance training in a well-established murine model of cancer cachexia [37–39]. This pre-clinical approach intended to better understand the role of classical exercise training modes for this debilitating condition. We hypothesized that resistance training would: 1) ameliorate the adverse effects of cachexia on body composition, functional performance, and muscle size to a greater extent than aerobic training; and 2) induce changes in muscle gene expression profiles and signaling events to favor protein synthesis and suppress protein degradation.

2. Materials and Methods

2.1. Animals and Design

Female Balb/c mice (12-months old, Harlan Laboratories) were randomly assigned to control ($n = 17$), resistance training (RT, $n = 16$), or aerobic training (AT, $n = 16$). Mice in the training

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