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Regulation of myokine expression: Role of exercise and cellular stress

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ABSTRACT

Exercise training is well known to improve physical fitness and to combat chronic diseases and aging related disorders. Part of this is thought to be mediated by myokines, muscle derived secretory proteins (mainly cytokines) that elicit auto/paracrine but also endocrine effects on organs such as liver, adipose tissue, and bone. Today, several hundred potential myokines have been identified most of them not exclusive to muscle cells. Strenuous exercise is associated with increased production of free radicals and reactive oxidant species (ROS) as well as endoplasmic reticulum (ER)-stress which at an excessive level can lead to muscle damage and cell death. On the other hand, transient elevations in oxidative and ER-stress are thought to be necessary for adaptive improvements by regular exercise through a hormesis action termed mitohormesis since mitochondria are essential for the generation of energy and tightly connected to ER- and oxidative stress. Exercise induced myokines have been identified by various *in vivo* and *in vitro* approaches and accumulating evidence suggests that ROS and ER-stress linked pathways are involved in myokine induction. For example, interleukin (IL)-6, the prototypic exercise myokine is also induced by oxidative and ER-stress. Exercise induced expression of some myokines such as irisin and meteorin-like is linked to the transcription factor PGC-1α and apparently not related to ER-stress whereas typical ER-stress induced cytokines such as FGF-21 and GDF-15 are not exercise myokines under normal physiological conditions. Recent technological advances have led to the identification of numerous potential new myokines but for most of them regulation by oxidative and ER-stress still needs to be unraveled.

1. Introduction

Exercise training is well known to improve physical fitness and to combat chronic diseases such as diabetes as well as other aging associated disorders [1,2]. Exercise has been labeled the “real polypill” in the prevention of cardiovascular disease [3]. An important aspect of exercise is the improvement of musculoskeletal fitness associated with an enhanced health status and quality of life [4]. The major effector and target of exercise, skeletal muscle has the unique capability to increase its energy expenditure over 1000-fold during intense exercise which necessitates an integrated response from several organ systems such as the sympathoadrenal and cardiovascular system in order to meet these energy demands [5]. The last decade revealed the importance of an organ crosstalk between skeletal muscle and other organs such as liver and adipose tissue led by the search for “exercise factors” communicating the energy demand of an active muscle to other organs [6]. These muscle derived secretory factors are called “myokines”, a term first suggested over 10 years ago by the group of Pedersen for interleukin 6 (IL-6) and other cytokines produced by skeletal muscle [7]. The increased oxygen consumption during physical exercise results in an elevated generation of free radicals and reactive oxidants species (ROS) which have been recognized as important signaling molecules [8]. It is important to emphasize that general terms such as “free radicals” or “ROS” include several different reactive molecules with different origin, reactivity and fate [9]. Thus, we here aim to follow the recent recommendation to avoid the use of abbrevations such as ROS when the actual species are known or described [10].

It is now well accepted that oxidative stress elicits a hormesis response with low levels having health promoting, adaptive effects whereas prolonged exposure to high ROS levels induces cellular damage [11,12]. In addition, it has been suggested that exercise-induced oxidative stress plays a role in the induction of cellular defense mechanisms, leading to decreased incidences of stress-related diseases and retardation of the aging process [13].

Exercise does not only increase ROS production but also acutely activates the unfolded protein response (UPR) an important component of the cellular adaptation to endoplasmic reticulum (ER) stress [14,15]. Induction of the UPR was proposed to mediate

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metabolic adaptations to exercise [14]. The Sarcoplasmic reticulum (SR) of skeletal muscle is a specialized form of ER. By acting as a storage depot for calcium and regulating its release during myofibrillar contraction, the SR has a critical role in muscle contraction and the maintenance of muscle homeostasis. ER-stress is linked to mitochondria dysfunction and ROS generation in muscle [16] and there is accumulating evidence that ER-stress is an adaptive mechanism in skeletal muscle during exercise but also in response to diet alterations [17].

Already several years ago in an opinion piece Scheele et al. emphasized the link between ROS and physical exercise responses and suggested that the generation of superoxide and hydrogen peroxide from muscle mitochondria is crucial for the induction of pro-inflammatory cytokines as myokines [18]. Since then, numerous new potential exercise induced myokines have been identified as described in a number of recent reviews [19–21]. However, the link between oxidative and ER-stress and their respective role in the exercise-induced production of myokines has so far received very little attention. Therefore, here we put a special focus on our current knowledge of the role of reactive oxidants and ER-stress in the induction of myokines and their relation to exercise or cellular stress adaptation. Furthermore, as there is still some controversy in the literature about true exercise-induced myokines, we aim to distinguish between myokines induced by cellular stress such as metabolic and mitochondrial disease or by exercise and muscle training (Fig. 1).

2. The role of muscle in exercise induced health benefits

Exercise is a rather broad term which comprises different exercise types such as anaerobic or resistance (strength) training versus aerobic, cardiovascular endurance training. Also, metabolic

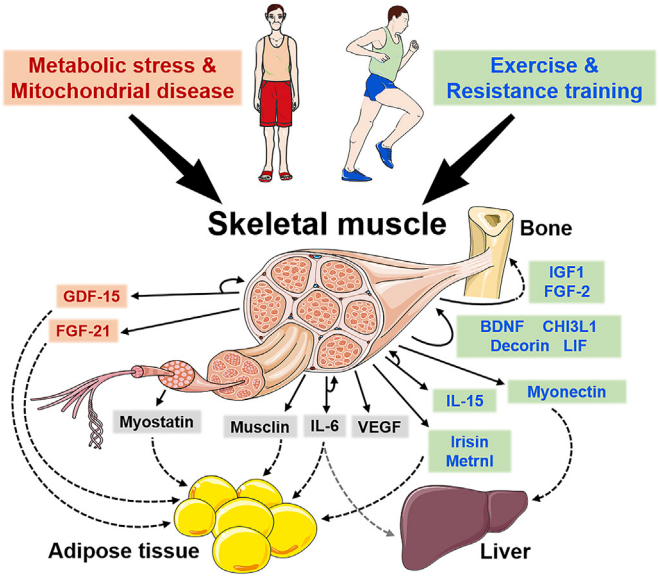

Fig. 1. Overview on cellular stress- and exercise-induced myokines. Skeletal muscle training and exercise-induced myokines (blue) in contrast to myokines induced by cellular stress (red) such as metabolic and mitochondrial disease. Skeletal muscle induction of musclin, IL-6 and VEGF (black) are reported for both conditions (cellular stress as well as exercise). Myostatin expression was found to be increased in muscle atrophy but decreased by both endurance and resistance exercise. Muscle injury with exercise releases FGF-2 from muscle cells into the circulation, as well as IGF-1, suggesting a muscle-bone interaction [166]. BDNF (brain-derived neurotrophic factor); CHI3L1 (Chitinase-3-like protein 1); FGF (fibroblast growth factor); GDF-15 (growth differentiation factor-15); IGF1 (insulin-like growth factor 1); IL (interleukin); LIF (leukemia inhibitory factor); Metrnl (meteorin-like); VEGF (vascular endothelial growth factor). See text for further details. This figure was created using Servier Medical Art (http://www.servier.com).

effects of acute exercise are very different from metabolic adaptations to exercise training. In this light, it is not surprising that the relation between exercise and metabolic health benefits is highly complex. A single bout of strenuous exercise induces responses similar to those induced by infection or sepsis, that is increased markers of inflammation [22]. On the other hand, exercise is considered as a mean to control and counteract systemic low-grade inflammation associated with a number of non-communicable diseases such as atherosclerosis and type 2 diabetes [23,24]. Skeletal muscle is composed of different, highly specialized fibers and shows an enormous plasticity regarding its structural and functional properties especially in adaptation to exercise associated stimuli such as neuronal activation, mechanical loading, and contractile activity [25]. This adaptation is the result of coordinated alterations in gene expression of muscle cells that are induced during each bout of contractile activity [26]. Repeated, transient bursts of gene expression and thus mRNA levels are apparently essential for cellular adaptations to exercise. Skeletal muscle gene expression is affected very differently by an acute exercise bout or training which is also reflected by myokine gene expression. In a human study Catoire et al. found only a minor overlap between myokines released by acute exercise and in response to exercise training [27]. Exercise induced adaptive changes in skeletal muscle are highly complex and largely dependent on the type of exercise training. Whereas endurance (aerobic) training increases respiratory capacity and mitochondrial content of skeletal muscle, strength or resistance (anaerobic) training leads to a muscle hypertrophy resulting in increased maximal contractile force output [28]. Adaptations to exercise include an array of physiological responses in the whole organism largely in response to the increased energy and oxygen demand of the exercising muscle. Furthermore, muscle contraction per se, the elevated energy expenditure, and the increased substrate turnover during exercise are key features of exercise-mediated effects on metabolic health. Because of the different adaptive effects of endurance and resistance training respectively, a combination of both is considered to be most effective for health improvements [29].

3. Oxidative and ER-stress in skeletal muscle

Historically, oxidative stress - defined as an excessive load of free radicals and ROS - has been linked to aging and pathogenesis of disease due to induction of cellular damages. This is known as the “free radical theory of aging” [30]. The mitochondrial respiratory chain complexes I and III are sites of superoxid production in response to an increased mitochondrial activity during muscle contraction. In addition, there are other sources of superoxide such as 5-lipoxygenase, cyclooxygenase, sarcolemmal NADPH oxidases (NOXs), and xanthine oxidase [11,31]. Interestingly, in a recent review Mason & Wadley suggested that these non-mitochondrial sites are primarily responsible for an increased oxidative stress signaling during exercise [32]. Oxidative stress during a single bout of strenuous exercise results in cellular damage as evident by elevated levels of lipid peroxidation, amino acid carbonylation, and DNA damage. This partially decreases physiological functions and results in limited adaptive responses. However, regular exercise, due to the constant shift between exercise and rest periods, leads to the induction of antioxidant and damage repair systems resulting in protection against oxidative stress and attenuation of the aging process, leading to health promotion [11,33]. This is analogous to the hormesis phenomenon classically known from toxicology. Indeed, a hormesis action termed mitohormesis commonly explains the apparent paradox of both increased free radical and ROS production and increased