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Response of Interleukins to Resistance Exercise

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Abstract

The interleukins are a major class of biologically active protein mediators, known as cytokines. These proteins are released by several body tissues, including skeletal muscle. Contracting skeletal muscle may synthesize and release several interleukins with potential hormonal effects in response to exercise. These interleukins play an important role in training adaptation, as well as have potential anabolic effects in human skeletal muscle and can be associated with hypertrophic processes.

Keywords: IL-15; Interleukins; Resistance

Introduction

The interleukins (ILs) are a class of cytokines released by numerous body tissues to control and coordinate immune responses. More than 60 cytokines have been designated as interleukins since the initial discoveries of monocyte and lymphocyte interleukins (called IL-1 and IL-2, respectively) [1]. The immune inflammatory response is recognized by playing an important role in skeletal muscle hypertrophy. Micro tears in skeletal muscle with acute resistance exercise results in the recruitment of neutrophils, macrophages, and lymphocytes to the muscle and a subsequent inflammatory response. Cytokines and growth factors released as a result of this response and contribute to skeletal muscle hypertrophy and to repairing of damaged tissues [2]. The Cytokines classified as myokinesare produced, expressed and released by muscle fibers; and exert autocrine, paracrine or endocrine effects [3].

Interleukin-6

IL-6 is the most studied interleukin and represent an important role in exercise-induced muscular growth. IL-6 is an essential regulator of satellite cell (muscle stem cell) mediated by hypertrophic muscle growth [4]. Satellite cells are muscle precursor cells that lie between the basal lamina and the sarcolemma of skeletal muscle fibers. In normal adult muscle, satellite cells are mitotically and metabolically quiescent, which are known as stem cells. With appropriate environmental signals, these satellite cells enter into the cell cycle, (i.e. are activated) to provide the precursors needed for new muscle formation in growth and repair [5].

Resistance training may cause damage to skeletal muscle, ranging from a few macromolecules of tissue to large tears in the sarcolemma, basal lamina, and supportive connective tissue, as well as damages within the contractile and cytoskeletal proteins of the myofibers. This myotrauma initiates the release of growth factors that influence satellite cells in a cascade of regenerative events, which ultimately leads to myofiber hypertrophy [6]. have found that increases in the area of the muscle fibers can occur without the addition of new myonuclei, however, myonuclear addition is required when hypertrophy reaches 26% [7]. Thus, these new myonuclei are able to increase their protein synthesis and support an enhancement of the cytoplasmic area.

IL-6 typically signals through the common gp130 receptor, with the Janus kinase/signal transducer, and the activator of transcription (JAK/STAT) pathway being the major intracellular mediators of their effects. Additionally, IL-6 may mediate protein synthesis via JAK/STAT cascade. JAK/STAT activation is necessary for the regulation of cell growth and phenotypic adaptation. From all the multiple STAT isoforms, STAT3 is critical for satellite cell proliferation and differentiation, and it is responsible to transcriptionally activate key mediators of the cell cycle regulation [8,9]. The genetic knockout of IL-6 has been shown to result in diminished satellite cell proliferation by impairing STAT3activation and the expression of its target gene cyclin D1.Complementing this result, IL-6 treatment in rats increased the phosphorylation of STAT3, increased cyclin D1 expression and the satellite cell proliferation. Additionally, in human serum, IL-6 has increased rapidly following eccentric exercise, and remained elevated similar to the time course for satellite cell expansion, with a peak in IL-6 occurring a few days post-exercise. Collectively, these data indicate that IL-6 plays an important role in regulating satellite cells during post-exercise recovery [10]. In addition, show that IL-6 is involved in the collagen synthesis, which supports the hypothesis that IL-6 is an important growth factor of the connective tissue in healthy human tendons [11].

Interleukin-15

Another myokine that has received considerable interest for its potential role in skeletal muscle growth is interleukin-15 (IL-15).This cytokine is one of the most abundantly released in skeletal muscle [2]. In animals, IL-15 stimulates protein accretion and leads to myosin heavy chain (MHC) accumulation in differentiated myocytes and myotubes, while reducing protein degradation. This ability of IL-15 to inhibit myotube protein degradation suggests that it may be of great utility in treating muscle wasting characteristics of some cases of cachexia cancer, muscular dystrophies, or aging (i.e. sarcopenia) [12].

In humans, plasma IL-15 increased significantly in response to acute resistance exercise, and in human skeletal myogenic cultures, IL-15 induced the accumulation of myosin of heavy chain in differentiated muscle cells; which suggests that IL-15 acts as an anabolic factor in muscle growth [13,14]. Recently, found an increase in serum IL-15 by ~5.3-fold, immediately post-resistance exercise. Moreover, the myofibrillar protein synthesis increased by ~2-fold above, raising their values from 0-4 hours post-exercise, which was associated with the alpha-receptor IL-15Rα mRNA levels. On the other hand, no change was found in endurance exercise [15-17]. This data demonstrate that IL-15 levels are upregulated in human skeletal muscle following strength training, and the main mechanism involved in the anabolic effects of IL-15 relies on a decrease in the proteolytic rate [14].

The IL-15 receptor-α gene (IL-15Rα)is expressed in a variety of immune and non-immune cell types and tissues, including T cells, B cells, NK cells, macrophages, thymus and bone-marrow cells, in the brain, intestine, liver, skeletal muscle, lung, heart and kidney. Thus, the IL-15/IL-15Ra signaling system acts at various levels of bioregulation throughout the organism, and it is not only recruited to modulate cellular functions in many different systems, but it is also capable of functionally linking these systems with each other [18]. Show that the genetic variation inthe IL-15 receptor-α gene (IL-15Rα) explains the proportion of the variability for the response to muscle hypertrophy [2]. Indeed, found that IL-15 administration induces a 33% reduction of adipose tissue in growing rats, with no reduction in food intake, and this anti-adipose effect ofIL-15 depends on the expression of IL15Rα on adipocytes [18].

Others interleukins

Up to now, there are few studies with other myokines. found in mice that IL-10 is an important mediator to promote muscle growth and regeneration [19]. Investigated IL-7 in vitro and in vivo [20]. These authors found that this interleukin is produced and secreted by human skeletal muscle cells, and they can stimulate satellite cells proliferation, induce myogenesis and migration, and regulate muscle cell development. In addition, muscle biopsy samples show that the expression of IL-7 mRNA increased threefold in musculus vastus lateralis and fourfold in musculus trapezius from male individuals undergoing a resistance training program.

Another interleukin expressed in skeletal muscle is IL-8. This interleukin belongs to a large family of chemokines and it is involved in the processes of angiogenesis [21]. Reported a small release of IL-8 from working muscle after knee-extensor exercise, and the plasma concentration of IL-8 was very low [22]. These findings show that a high local IL-8 expression takes place in working muscle, which is accompanied by only a small and transient release, which indicates that muscle-derived IL-8 exerts its effect locally. In addition, the authors suggest a possible role of the skeletal muscle-derived IL-8 in the stimulation of neovascularization. Studied eight male volunteers that performed 60 min of bicycle exercise, with either a normal or reduced glycogen intramuscular content [23]. The authors found that IL-6 and IL-8 mRNA increased during contraction. Furthermore, the levels of IL-6 and IL-8 mRNA were significantly greater with reduced intramuscular

glycogen. Thus, the mRNA of IL-6 and IL-8 appears to be influenced by glycogen availability in the contracting muscle.

Aging is associated with increased levels of circulating cytokines, proinflammatory markers, and increased secretion of cytokines by adipose tissue, which represents the major causes of chronic inflammation. High levels of IL-6, IL-1, tumor necrosis factor-α (TNF-α), and C-reactive protein are associated in the older subject with increased risk of morbidity and mortality. TNF-α causes increased muscle catabolism and, in murine models, the inhibition of inflammation pathways promotes muscle regeneration. The decrease in myofibrillar contractility is partly mediated by the increase in oxidative stress and nitric acid production, both of which are promoted by the increase in TNF-α levels. On the other hand, muscle training promotes the decrease of TNF-α levels [24].

Conclusions

In summary, exercises how an inverse correlation with low-grade systemic inflammation, and the acute elevation of ILs enhances anabolism, whereas the suppression of chronic ILs production mitigates the catabolic processes. Thus, the acute effects of resistance training on ILs must be differentiated from chronic training. This review enhances the roles of ILs released by skeletal muscle in response to exercise, and how these proteins play an important role in training adaptation and in hypertrophy muscle, which significates great acknowledgement to research and medical applications.

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