Role of interleukin-6 and interleukin-15 in exercise

Abstract

Cytokines are released by numerous body tissues to control and coordinate immune responses. However, the role of these molecules in the skeletal muscle has received growing interest. Researchers have demonstrated that contracting skeletal muscle may synthesize and release interleukin-6 (IL-6) and interleukin-15 (IL-15) in response to the exercise. These cytokines potentially have anabolic effects in human skeletal muscle and can be associated with hypertrophic processes.

Keywords: interleukin-6, interleukin-15, hypertrophy, skeletal muscle

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Introduction

Cytokines are key modulators of inflammation, participating in acute and chronic inflammation via a complex and sometimes contradictory network of interactions.[1] The cytokines and other peptides that are produced, expressed and released by muscle fibers, and exert autocrine, paracrine or endocrine effects, are classified as myokines. Skeletal muscle contains resident immune cell populations and their abundance and type are altered in inflammatory myopathies, endotoxemia or other different types of muscle injury.[2] The interleukins (ILs) correspond to class of cytokines released by numerous body tissues to control and coordinate immune responses. There are several isoforms and the most known is interleukin-6 (IL-6), an early-stage myokine that might play important role in exercise-induced muscular growth. IL-6 was first cloned and characterized in the mid-1980s by several independent groups, by assessing immunoglobulin production and acute-phase protein responses in different cell lines.[3] IL-6 is a pleiotropic cytokine associated with the control and coordination of immune responses, inflammation, hematopoiesis, and oncogenesis, which regulates cell growth, survival, and differentiation.[4] Skeletal muscle cells are a further important source of IL-6 and this cytokine is detected locally at elevated concentrations in actively contracting muscle fibers and after increased workload. Exercise is known to cause major physiological, hormonal, metabolic, and immunological effects. The resistance training acutely upregulates IL-6 by up to 100-fold, and the peak of IL-6 level is reached at the end of the exercise or shortly after, about 30 minutes after the exercise, followed by a rapid decrease towards pre-exercise levels.[5] Exercise-induced metabolic stress may further stimulate its production.[6,7] However, there is a low interaction between muscle damage and increased levels of IL-6, and studies found a low correlation in the time course of IL-6 and creatine kinase.[8,9] Therefore, researchers found that muscle tissues during the contraction are the predominant source of IL-6.[5] Thus, muscle damage is not required in order to increase plasma IL-6 during exercise.

The IL-6 response is sensitive to the exercise intensity, so exercise involving a limited muscle mass, e.g. the muscles of the upper extremities, may be insufficient to increase plasma IL-6 above pre-exercise level. Therefore, intensity and duration of the exercise are fundamental to determine the magnitude of the exercise-induced increase of plasma IL-6.[5] Exercise duration is the most important factor to determine the post-exercise plasma IL-6 amplitude. More than 50% of the variation in plasma IL-6 following exercise can be explained by exercise duration alone. Increases of plasma IL-6 only occur if the exercise involves a considerable muscle mass working for a long time at a considerable intensity. Thus, regardless of the mode, the exercise for less than one hour induces a peak of plasma IL-6 concentration below 10 pg/ml (< 10 fold increase from pre-exercise level).[5] Additionally, IL-6 is important in energy homeostasis, facilitating the mobilization of glycogen and free fatty acid during intense exercise. This mobilization from the liver to the circulation may result in enhanced substrate uptake by other tissues, e.g., the contracting skeletal muscle. Thus, reduced availability of the fuel substrates of the contractile muscle activity appears to be one of the main triggers of IL-6 production.[5–10] Therefore, low physical activity results in elevated basal IL-6 levels, while a high level of physical activity results in low basal IL-6 levels. In addition, the IL-6 released from the contracting muscle may induce an anti-inflammatory response. This is reflected by an increase of IL-1ra, IL-10, CRP, and cortisol without concomitant increases in pro-inflammatory mediators.[5] 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, satellite cells enter into the cell cycle, (i.e. are activated) to provide the precursors needed for new muscle formation in growth and repair.[8] 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 damage within the contractile and cyto skeletal proteins of the myofiber. This myotrauma initiates the release of growth factors that influence satellite cells in a cascade of regenerative events which ultimately lead to myofiber hypertrophy.[11]

[12]have found that an increase in the area of muscle fibers can occur without the addition of new myonuclei, however, myonuclear addition is required when hypertrophy reaches 26%. Thus, these new myonuclei are able to increase their protein synthesis and support an enhancement of cytoplasmic area.

The immune inflammatory response plays an important role in skeletal muscle hypertrophy, and after the muscle damage induced by exercise, the ratio of IL-6 in myofibers immediately increases, with a peak in 12 hours. Simultaneously, neutrophils from the blood increase in number in the area of the myotrauma and the agents that stimulate and attract macrophages and lymphocytes are released. In the following, macrophages are attracted to the injury site where they phagocytose cellular debris and chemotactically attract satellite cells. The interaction between the satellite cells and the macrophages is mediated by cytokines such as IL-6. Thus, this cytokine is also involved in enhanced protein degradation, proliferating satellite cells which may support muscle regeneration.[11–13] Once active, the satellite cells follow an ordered set of events, including proliferation, migration, and incorporation into the adult overloaded myofibers, leading to myofibers growth.[12]

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 mediator 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, transcriptionally activating key mediators of the cell cycle regulation.[14,15]

[16]have found in mice (*IL-6*-deficient) that genetic loss of IL-6 blunted muscle hypertrophy and IL-6 deficiency abrogated satellite cell proliferation and myonuclear accretion in the preexisting myofiber by impairing STAT3 activation and expression. Therefore, IL-6 emerges as an important molecule for muscle hypertrophy by controlling satellite cell proliferation and myonuclear accretion. Moreover, it plays a role in the STAT3 activation pathway by mediating these effects.Another myokine that has received considerable interest for its potential role in skeletal muscle growth is interleukin-15 (IL-15). This cytokine may be secreted from skeletal muscle and function as an endocrine regulator of adipose tissue, thus acting as a myokine. Interleukin-15 mRNA is widely distributed among tissue and cell types, including heart, brain, lung, liver, kidney, pancreas, skeletal muscle, and macrophages. Additionally, among the cytokine mRNAs expressed within the skeletal muscle, IL-15 mRNA has been reported to be the most representative.[17,18] In mouse, IL-15 stimulated protein synthesis and inhibited protein degradation in cultured skeletal myotubes.[19] In human skeletal myogenic cultures, IL-15 induces the accumulation of myosin of heavy chain in differentiated muscle cells, which suggests that IL-15 acts as an anabolic factor in muscle growth. In mouse, the over expression in skeletal myogenic cell lines induced 5-fold higher levels of sarcomeric myosin of heavy chain and α-action accumulation in differentiated myotubes.[20]

In humans, circulating IL-15 was elevated in response to a single session of resistance exercise in untrained and trained states.[18] found a significant increase in plasma IL-15 after resistance exercise. Recently,[21] found an increase in serum IL-15 by ~5.3-fold immediately post-exercise. In addition, systemic IL-15 levels and IL-15 mRNA in skeletal muscle are markedly elevated after eccentric (but not concentric) exercise, suggesting that these elevations are contingent on damage to fibers.[18] On the other hand, no change was found in endurance exercise.[22,23] 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[20]. Moreover, IL15 binds to the endothelial cells with high affinity and stimulates angiogenesis. Thus, acute changes in IL-15 with exercise may be associated with the changes in the blood supply requirements and neo vascularization that occur with training.[24] Tumor necrosis alpha-factor (TNF-α) is a catabolic cytokine and it has been shown to be elevated in inflammatory tissue. Higher levels of TNF-α is often associated with lower muscle mass in elderly, and this cytokine stimulates an important pathway in apoptosis signaling. IL-15 can potently inhibit this process, as the IL-15 receptor can specifically block the TNF-α mediated apoptosis by recruiting the TNF receptor-associated factor (TRAF2) and preventing TNF signaling.[18]

[21]show that a higher alpha-receptor IL-15Rα protein expression, at 4 hours post-exercise, performed a greater volume of resistance exercise and had a higher force production. Additionally,[18] found that a single nucleotide polymorphism in exon 7 and 4 of IL-15Rα was able to explain a ~11% of the hypertrophy after 10 weeks of resistance exercise training in young men and women. Regarding the expressions,[25] it has been demonstrated that the levels of IL-15 mRNA were enhanced in many muscle groups, dominated by type II fibers and that resistance exercise-induced increased muscular IL-15 mRNA levels 24 h post-exercise. Although the expression of IL-6 is uncertain, [26] found that type 1 fibers show a greater increase when compared with type 2 fibers. On the other hand, [23]reported higher expression of IL-6 in type 2 fibers compared with type 1 fibers. In addition, IL-6 and IL-15 can decrease body fat.[19] found in pig that IL-15 dose-dependently stimulated lipolysis and had a small inhibitory effect on lipogenesis. IL-6 also showed lipolytic effect observed in cultured adipocytes, suggesting a direct effect of IL-6 on adipose tissue. Increased IL-6 mRNA content in the adipose tissue is observed in response to exercise, and this increase appears to be mediated by catecholamines.[5] In summary, IL-6 and IL-15 are cytokines released by numerous body tissues to control and coordinate immune responses. These molecules are activated in skeletal muscle in response to exercise and play an important role in training adaptation and in hypertrophy muscle growth. The knowledge of these factors their consequences in the organism are of great relevance, from the application in studies of muscular strengthening and hypertrophy to possible applications in therapies and treatments. Although studies have been growing in this sense, much research is still necessary to determine the full extent and mode of action of these factors.

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Conflict of interest

The authors declare no conflicts of interest.

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