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Possible therapeutics: Myokines

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ABSTRACT

Myokines are proteins that participate in various metabolic pathways released by skeletal muscle. They provide cross-talk between organs and muscles, induce muscle atrophy, improve muscle strength, induce muscle hypertrophy, induce glucose uptake, slow cancer progression, and reduce fat mass. Studies have examined the disease mechanisms that myokines may affect depending on the pathways they are involved in. In this review, myostatin, interleukin-6, interleukin-15, decorin, irisin, myonectin, and fibroblast growth factor 21 were examined as potential treatments. In addition, some concerns about myokines as therapeutics were listed.

Keywords: Decorin, IL-6, irisin, myokine, myonectin, myostatin.

Myokines are produced and released by the endocrine organ known as muscle. Communication between muscle and adipose tissue, the liver, the brain, and other organs is mediated by these myokines. They participate in autocrine and paracrine/endocrine regulation of metabolism in muscle via receptors in other tissues and organs such as adipose tissue, liver, and brain.[1,2] Myocytes synthesize and release them during muscle contracts.[2] Among a large number of myokines, the most studied are listed in Table 1.[3]

MYOKINES AS THERAPEUTICS

Myostatin

Myostatin is a member of the transforming growth factor-beta (TGF-β) superfamily. It is also known as growth differentiation factor 8 (GDF-8). Myostatin is a negative regulator of skeletal muscle development.[4]

In mice, myostatin deletion increases the number of satellite cells involved in muscle growth, resulting in improved muscle regeneration, skeletal mass hypertrophy, and decreased total adipose tissue.[5,6]

According to a study, the myostatin/myostatin precursor accumulates in sporadic inclusion body myositis muscles and is associated with amyloid-beta (Aβ) containing aggregates. The expressions of myostatin precursor protein and myostatin dimer are increased, and myostatin precursor protein binds Aβ.[7] Based on these findings, a therapeutic approach to sporadic inclusion body

Table 1. Myokines and their actions in skeletal muscular tissue

Myokine	Action
Myostatin	Stops myoblast proliferation Suppresses satellite cell activation Induces muscle atrophy
IL-6	Enhances glucose uptake, oxidation of fatty acids Increases insulin secretion Decreases cachexia progress
IL-15	Anabolic effect Increases mitochondrial activity Decreases fat mass
Decorin	Antagonist with myostatin Restructuring muscle
Irisin	Improves muscle strength Induces muscle hypertrophy
Myonectin	Induces nutrient storage in adipose tissue
FGF21	Energy metabolism Enhances mitochondrial activity Induces glucose uptake

IL: Interleukin; FGF21: Fibroblast growth factor 21.

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myositis could be myostatin/myostatin precursor reduction.[8]

Myostatin has an indirect effect on adipocytes indirectly.[9] It was found that a major reason for the reduction of body fat in myostatin-null mice was increased muscle mass. Myostatin-null mice develop significant muscle hypertrophy due to accelerated myogenesis and significant adipose tissue loss.[10-12] Cachexia is defined as a decrease in leptin, the "satiety hormone" secreted by adipocytes, in myostatin-deficient mice, although their food intake is not different from control mice.[12,13] Although there have not been many studies on the expression of myostatin in muscle cachexia, specifically as a biomarker and therapeutic target, it is regarded as an excellent research approach in the treatment of cachexia, especially when combined with decorin and leptin.[14]

Satellite cell activation is negatively regulated by myostatin strongly. Increased self-renewal and delayed expression of the differentiation gene (myogenin) result in an increase in the number of satellite cells in myostatin-deficient satellite cells. Myostatin may induce satellite cell quiescence by regulating G1 to S progression.[15]

Interleukin-6

Interleukin-6 (IL-6), a 21–28 kDa glycoprotein, is a pleiotropic prototypic cytokine (a four-helix bundle cytokine) that activates acute immune responses in muscle tissue infection and injury. It mediates both innate and adaptive immune responses.[16,17]

An *in vitro* study in mice lacking the skeletal muscle IL-6 gene revealed that this myokine is a crucial regulator of muscle hypertrophy mediated by satellite cells in normal muscle.[18]

It is obvious that lowering myokine levels can slow the progression of cachexia in cancer patients.[19] High plasma IL-6 levels are evident in patients with advanced or terminal cancer, which correlate with weight loss, anemia, and depression.[20] A clinical trial of tocilizumab, an IL-6 receptor inhibitor that blocks IL-6 binding to its receptor, reduced plasma IL-6 levels in patients with cancer cachexia without affecting tumor growth and improved muscle mass loss.[21-23] Potential side effects of interleukin suppression, such as IL-6, may impair a patient's immune response to infection and should be monitored.[24]

The role of IL-6 was found to be in metabolism rather than inflammation. IL-6 regulates energy metabolism. Mageriu et al.[8] considered that these findings may have similar implications in idiopathic inflammatory myopathy, and it is assumed that more research is needed to define the role of IL-6 in this pathology.

A study showed that IL-6-/- transgenic mouse treated with rabbit myosin-induced idiopathic inflammatory myopathies had no inflammation in myofibers, a complete absence of necrosis and leukocyte infiltration, and no regeneration of myofibers. The muscle infiltrates found in the muscle were macrophages. The conclusion was that a lack of IL-6 prevented chemotactic inhibition of monocyte infiltration into muscle.[25] Blocking the IL-6 signaling pathway could be a potential therapy for idiopathic inflammatory myopathies. This blockage is also approved for the treatment of rheumatoid arthritis.[26]

Bilgic et al.[27] observed a correlation between serum IL-6 levels, a candidate biomarker for adult and juvenile dermatomyositis, and disease activity in dermatomyositis patients. Another study showed that IL-6 has antineoplastic properties by targeting immune cells (Natural killer cells), providing another putative mechanism of action.[28]

Interleukin-15

Interleukin-15 (IL-15) is a myokine released from skeletal muscle following exercise. It has an anabolic effect on muscle protein metabolism.[29] Some studies on the oxidative and fatigue properties of muscle have revealed possible alternative pathways for these topics.[30,31] IL-15 exerts many metabolic actions, inhibiting preadipocyte differentiation and lipogenesis as part of muscle-adipose crosstalk, increasing glucose uptake and fat oxidation in muscle tissue, and stimulating lipolysis.[32]

Changes in plasma IL-15 levels after resistance training yielded inconsistent results. Although a significant increase was observed in one study, no change was observed in another.[33,34]

IL-15 has been shown to reduce white adipocyte size and serum leptin levels in male mice, whereas downregulating anti-inflammatory

and antineoplastic adiponectin can stimulate the production of visceral obesity.[35]

Decreased plasma IL-15 levels are associated with sarcopenia.[36] The elevated serum IL-15 levels of centenarians suggest that high expression of IL-15 confers protection against frailty and age-related diseases.[37,38] Overexpression of IL-15 increases muscle insulin sensitivity, improves mitochondrial function and fatty acid oxidation and protects against obesity and insulin resistance.[39-41] Hence, IL-15 was considered an interesting myokine for treating metabolic diseases such as type 2 diabetes (T2D) and obesity.[42] While there are studies indicating that IL-15 may be a potential treatment for sarcopenia and obesity, there are currently no results confirming the effects of IL-15 regulation on sarcopenic obesity. Therefore, it has been reported that additional scientific and clinical studies are required to better understand whether IL-15 is a vital biomarker and therapeutic role for sarcopenic obesity.[43]

In a study of polymyositis patients and experimentally in a polymyositis rat model, it was reported that the levels of CD163 macrophages were significantly reduced after treatment with the anti-IL-15 antibody, indicating that IL-15 is closely linked to CD163 macrophages and has a significant effect on the pathogenesis of idiopathic myositis. It has also been demonstrated that expression levels of matrix metallopeptidase 9 (MMP9), which has been proven to be involved in the inflammatory process of muscle degeneration, can be regulated by IL-15.[44] Researchers reasoned that IL-15, a key regulator of polymyositis, is a promising therapeutic target and potential treatment for polymyositis.[8]

Decorin

Decorin is a small leucine-rich proteoglycan. It is a component of the extracellular matrix in many tissues and is released by myotubes.[45,46] Decorin is known to suppress tumorigenesis and angiogenesis and prevent the formation of metastatic lesions *in vivo* and *in vitro* in various tumor models.[46] Therefore, decorin is a novel therapeutic candidate for the treatment of patients with solid malignancies.[47]

Decorin binds directly to myostatin, a potent muscle growth inhibitor, and plays a role in muscle restructuring during hypertrophy by acting as an antagonist to myostatin.[12,45] According to this information, it has been said that this myokine can be considered a therapeutic target together with myostatin in cachexia and can modulate the preservation of muscle mass.[3]

Based on the functions of decorin and myostatin being upregulated in inclusion body myositis, it has been reported that decorin can be thought to be downregulated in idiopathic inflammatory myopathies. It is also thought that it can be used as a future therapeutic target in myositis to stimulate muscle regeneration and muscle wasting-related diseases.[8,43]

Irisin

Irisin is a myokine cleaved from the fibronectin type III domain-containing protein 5 (FNDC5) precursor protein induced by peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PPARGC1A) overexpression. It was discovered in 2012.[48] In humans, skeletal muscle is the primary source of irisin, which is also secreted by white adipose tissue, the brain, and other organs.[49]

Irisin promotes the browning of white fat by inducing uncoupling protein 1 (Ucp1) expression, thereby increasing thermogenesis and glucose homeostasis. Muscle-derived irisin exhibits beneficial metabolic effects by increasing energy expenditure, causing minor weight loss, and improving metabolic parameters such as insulin signaling and sensitivity.[48]

Irisin treatment can induce skeletal muscle hypertrophy, improve muscle strength, and reduce necrosis and tissue fibrosis in a murine dystrophy model, implying that irisin may have potential therapeutic value in muscular dystrophy.[50] Several studies have demonstrated that serum irisin levels can be used as a potential biomarker of muscle dysfunction to help predict the development of sarcopenia and provide new strategies for monitoring age-related muscle changes.[51-53]

Since circulating irisin levels increase in obese individuals and decrease in T2D patients, irisin is thought to be important in the development of obesity and T2D.[43,54]

In a study, irisin was shown to reduce breast cancer aggressiveness while also increasing chemotherapy.[55]

The effect of irisin on brain-derived neurotrophic factor-mediated hippocampal neurogenesis was replicated with peripheral irisin administration. Thus, it is recognized that the possible effects of exercise-induced peripheral irisin on neurogenesis are significant.[56] Although clinical studies have shown a transient increase in irisin levels following acute exercise, most studies have yielded conflicting results regarding the effects of chronic exercise training on irisin levels. It was concluded that the level of clinical evidence that exercise-induced irisin production from skeletal muscle directly contributes to neuropsychiatric function in the brain is low, as there is little clinical evidence that it has beneficial effects on neuropsychiatric function.[57,58]

Myonectin

Myonectin is a protein that belongs to the C1q/TNF-related protein (CTRP) family and is also known as CTRP15. It is more abundant in muscle than in circulation. Myonectin expression is stimulated by exercise and nutrients. It promotes fatty acid uptake in cultured adipocytes and hepatocytes and inhibits circulating free fatty acid levels in mice.[59,60] A study has shown that circulating myonectin levels are significantly reduced in T2D patients compared to controls.[61]

In addition, another study found lower serum myonectin concentrations in T2D patients compared to healthy controls. Further studies showed that T2D and serum myonectin were correlated and that T2D patients with diabetic nephropathy had lower serum myonectin than those without diabetic nephropathy. Based on these findings, the researchers concluded that serum myonectin can be used as a biomarker in the diagnosis and classification of diabetic nephropathy and can be used as a therapeutic target or a new drug for the treatment of T2D and diabetic nephropathy.[62]

It was found that dietary control, in addition to exercise, increased the expression level of myonectin in both the soleus and the liver, resulting in an increase in fatty acid transporter levels. This combination has been shown to have a positive effect on lipid metabolism, which is expected to play a therapeutic role in obesity.[63]

Fibroblast Growth Factor 21 (FGF21)

Fibroblast growth factor 21 is a signaling protein found in many tissues induced by stress.[64,65] After an autophagy deficiency, mitochondrial dysfunction increases FGF21 levels to protect against obesity caused by diet and insulin resistance, and also, in mitochondrial respiratory chain deficiency, there is an increase in mitochondrial activity with an increase in FGF21.[66,67]

It was hypothesized that the pharmacological benefits of FGF21 in improving lipid profile, hepatic fat fraction, and markers of liver fibrosis would increase its potential for therapeutic application in obesity-related comorbidities other than hyperglycemia.[68]

In a study in which exogenous FGF21 was administered, the potential application of FGF21 as an antiobesity molecule was shown to work.[69]

CHALLENGES FOR MYOKINE THERAPEUTICS

First, there are some difficulties associated with the discovery phase of myokines. Among these, exercise biology is affected by various factors, and working with small sample amounts can be listed.[70]

Since myokines are released from muscle at concentrations of picomole and femtomole, it was assumed that their concentration in serum could not be determined.[71,72] However, the advancement of modern technologies has prevented these thoughts. Technologies such as gene ontology, cell culture models, stable isotope labeling with amino acids, and immunostaining have provided this.[73,74]

Their protein structure and physiochemical instability hinder the therapeutic application of myokines. Their short half-life in plasma, toxicity, and immunogenicity are also factors to consider.[75] Due to the presence of myokine receptors in various parts of the body, cell and tissue specificity should be ensured in order to prevent possible side effects. Providing drug delivery with nanotechnology can avoid this limitation.[76,77]

In conclusion, it is clear that myokines could

be used in so many conditions due to their actions in metabolic pathways, as long as the effects and consequences are well understood. The usage of myokines as therapeutics looks bright in the future since they regulate lipid metabolism, muscle development, and immune responses. Moreover, they can be used as biomarkers for several diagnoses; myostatin for cachexia, IL-6 for adult and juvenile dermatomyositis, irisin for muscle dysfunction, and myonectin for diabetic nephropathy.

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