Edward F. Adolph Distinguished Lecture: Muscle as an endocrine organ: IL-6 and other myokines

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Pedersen BK. Edward F. Adolph Distinguished Lecture: Muscle as an endocrine organ: IL-6 and other myokines. J Appl Physiol 107: 1006–1014, 2009. First published August 20, 2009; doi:10.1152/japplphysiol.00734.2009.—Skeletal muscle is an endocrine organ that produces and releases myokines in response to contraction. Some myokines are likely to work in a hormone-like fashion, exerting specific endocrine effects on other organs such as the liver, the brain, and the fat. Other myokines will work locally via paracrine mechanisms, exerting, e.g., angiogenic effects, whereas yet other myokines work via autocrine mechanisms and influence signaling pathways involved in fat oxidation and glucose uptake. The finding that muscles produce and release myokines creates a paradigm shift and opens new scientific, technological, and scholarly horizons. This finding represents a breakthrough within integrative physiology and contributes to our understanding of why regular exercise protects against a wide range of chronic diseases. Thus the myokine field provides a conceptual basis for the molecular mechanisms underlying, e.g., muscle-fat, muscle-liver, muscle-pancreas, and muscle-brain cross talk.

adipose tissue; cytokines; insulin resistance; skeletal muscle

ONE DECADE AGO we identified a humoral factor (a cytokine) that was produced and released from contracting muscle cells and appeared to have major metabolic effects. Given that skeletal muscle is the largest organ in the human body, our discovery of contracting muscle as a cytokine-producing organ opened a whole new paradigm: Skeletal muscle is an endocrine organ, which by secretion of hormone-like factors may influence metabolism in tissues and organs. In continuation, we suggested that cytokines and other peptides that are produced, expressed, and released by muscle fibers and exert either autocrine, paracrine, or endocrine effects should be classified as “myokines” (86).

Adipose tissues have been regarded as the major sources of cytokines (adipokines); however, the finding that muscles produce and release cytokines (myokines) suggests that working skeletal muscle in addition to adipose tissue may be a major source of secreted molecules. Myokines provide a conceptual basis to explain how muscles communicate to other organs. Thus our overall idea is that contracting skeletal muscles release myokines, which work in a hormone-like fashion, exerting specific endocrine effects on other organs or which work locally via paracrine mechanisms.

STATE OF THE ART

For half a century, researchers sought a link between muscle contraction and changes in peripheral organs in the form of an “exercise factor,” which could be released from skeletal muscle during contraction and mediate some of the exercise-induced metabolic changes in other organs such as the liver and the adipose tissue. The idea that signaling pathways from contracting muscles to other organs were not solely mediated via the nervous system was supported by the findings from electrical stimulation of paralyzed muscles in patients with spinal cord injuries (45).

It was obvious that one or more muscle-derived humoral factors existed. For lack of more exact knowledge, these humoral factors were called the “work stimulus” or the “work factor.” In this context, our identification of muscle as a cytokine-producing organ was kind of a breakthrough. In year 2000, it became clear that contracting human skeletal muscle releases significant amounts of interleukin (IL)-6 into the circulation during prolonged single-limb exercise (108). Research during the subsequent years highlighted the fact that muscle-derived IL-6 is an important player in metabolism (86). Today, it appears that skeletal muscle has the capacity to express several myokines. The list includes IL-6, IL-8, IL-15, brain-derived neurotrophic factor (BDNF), and leukemia inhibitory factor (LIF) (86). Through other strategies, Kenneth Walsh and colleagues (Boston, MA) identified the myokines fibroblast growth factor 21 (FGF21) and follistatin-like-1 (35, 77). Thus, although the idea of an “exercise factor” can be traced back many years, our identification of muscle as a myokine-producing organ opens for a whole new field of research.

IL-6: THE MYOKINE PROTOTYPE

The fact that the plasma concentration of IL-6 increases during exercise has been a consistent finding (86). The increase in IL-6 is followed by the appearance of IL-1 receptor antagonist (IL-1ra) and the anti-inflammatory cytokine IL-10. Con-
centration of the chemokines IL-8, macrophage inflammatory protein-α (MIP-1α), and MIP-1β are elevated after strenuous exercise. Of note, the cytokine response to exercise and sepsis differs with regard to TNF-α. Thus the cytokine response to exercise is not preceded by an increase in plasma-TNF-α. Although there may be a moderate increase in the systemic concentration of these cytokines, the underlying fact is that the appearance of IL-6 in the circulation is by far the most marked and that its appearance precedes that of the other cytokines (86).

Exercise-induced plasma IL-6 concentrations increase in an almost exponential manner. The peak IL-6 level is reached at the end of the exercise or shortly thereafter, followed by a rapid decrease toward preexercise levels. The basal plasma IL-6 concentration may increase up to 100-fold after exercise (83). Because IL-6 is a classical inflammatory cytokine, it was first thought that the IL-6 response was related to muscle damage. However, it has become evident that muscle damage is not required to increase plasma IL-6 during exercise. Rather, eccentric exercise may result in a delayed peak and a slower decrease of plasma IL-6 during recovery (86).

Sources of contraction-induced IL-6. As with many paradigm-shifting studies, our initial findings that led to the identification of IL-6 as a myokine were somewhat serendipitous. A decade before, we had initiated the very first studies using exercise as a tool to study the immune system (85). This research soon opened a new research field called “exercise immunology,” leading in 1993 to the foundation of the International Society of Exercise and Immunology (84). It was while looking for a mechanistic explanation to exercise-induced immune changes that we came across IL-6, which we later identified as the first “exercise factor.” With this in mind, it was obvious that we first focused on immune cells as the source of IL-6 (72).

However, it soon became clear that the contracting skeletal muscle per se is the main source of the IL-6 in the circulation in response to exercise. In resting human skeletal muscle, the IL-6 mRNA content is very low, although small amounts of IL-6 protein predominately in type I fibers may be detected using sensitive immunohistochemical methods (93). In response to exercise, an increase of the IL-6 mRNA content in the contracting skeletal muscle is detectable after 30 min of exercise, and up to 100-fold increases of the IL-6 mRNA content may be present at the end of the exercise bout (42, 107). By obtaining arterial-femoral venous differences over an exercising leg, we found that exercising limbs released IL-6. In an attempt to determine which cells produce the IL-6, Keller et al. (42) isolated nuclei from muscle biopsies obtained before, during, and after exercise. Using RT-PCR, it was demonstrated that the nuclear transcription rate for IL-6 increases rapidly and markedly after the onset of exercise (42). This suggested that a factor associated with contraction increases IL-6 transcriptional rate, probably in the nuclei from myocytes, given the observation that IL-6 protein is expressed within muscle fibers (63). Further evidence that contracting muscle fibers themselves are a source of IL-6 mRNA and protein has been achieved by analysis of biopsies from the human vastus lateralis using in situ hybridization and immunohistochemistry (33, 88). Contracting skeletal muscles may account for most of the IL-6 found in the circulation; however, other studies have demonstrated that skeletal muscle is not the sole source of exercise-induced IL-6. Fischer et al. found that the IL-6 net release from the exercising legs was almost completely blocked when subjects were pretreated with vitamins C and E for 4 wk, yet the systemic increase of plasma IL-6 was only reduced by 50% (24). Other sources of IL-6 include connective tissue (57), the brain (74), and adipose tissue (40, 62).

Muscle-derived IL-6, muscle glycogen, and carbohydrate ingestion. By manipulating muscle-glycogen content, both intramuscular IL-6 mRNA expression (42) and protein release (105) were exacerbated when intramuscular glycogen was compromised, suggesting that IL-6 worked as an energy sensor. In addition, a number of studies show that glucose ingestion during exercise attenuates the exercise-induced increase in plasma IL-6 (86) and totally inhibits the IL-6 release from contracting skeletal muscle in humans (21).

IL-6 upstream signaling in skeletal muscle. Skeletal muscle cells are capable of producing IL-6 in response to various stimuli such as lipopolysaccharide, reactive oxygen species (ROS), and inflammatory cytokines as well as during contraction (86). The neuronal nitric oxide (NO) synthase isoform is abundantly expressed in human skeletal muscle (26), and a number of observations provide evidence that NO production is significantly increased within contracting skeletal muscle (3, 31, 59, 60, 98, 103). In vitro studies suggest that NO (6) may alter signaling networks by redox-sensitive modification, by nitration of proteins within the cytoplasm or nucleus (32), or it may exert effects on transcription via an increase in cGMP (92).

A human exercise study convincingly demonstrated that NO production within contracting skeletal muscles is a key regulator of pretranslational signaling events leading to muscle IL-6 production. Pharmacological inhibition of NO production during exercise attenuated the increase in IL-6 mRNA levels in human skeletal muscle and intra-arterial infusion of an NO donor was accompanied by increases in IL-6 mRNA content in resting skeletal muscle. Moreover, the drug-induced changes of IL-6 mRNA expression were accompanied by similar alterations in IL-6 protein release supporting the functional significance of the IL-6 mRNA change (109).

In cultured skeletal muscle cells, inflammatory stimuli may elicit the production of IL-6 via signaling pathways that involve c-Jun NH2-terminal kinase (27) and the transcription factor NF-κB (52). NF-κB represents a major pathway by which IL-6 is transcribed in immune cells, and this pathway may potentially play a role in exercise-induced IL-6 production. Increased ROS formation in skeletal muscle after exercise has been demonstrated directly in animals (18, 36) and indirectly in humans (2). NF-κB is a redox-sensitive transcription factor (100) that may be activated by ROS. Murine skeletal myotubes release IL-6 when exposed to oxidative stress in an NF-κB-dependent way (52). In addition, supplementation with different antioxidants attenuates the systemic increase of IL-6 in response to exercise (24, 112, 116). The observation that nonsteroidal anti-inflammatory drugs, which inhibit NF-κB activity, reduce the exercise-induced increase of IL-6 further supports the idea that NF-κB represents a link between contractile activity and IL-6 synthesis (51, 97). On the other hand, a number of stimuli, including oxidative stress, low glucose availability, low glycogen content, catecholamines, and hyperthermia, which are all features of exercise, are capable of...
inducing heat shock proteins (5, 15, 22, 78, 117, 122), which may in turn activate IL-6 synthesis (95).

However, the importance of the NF-κB signaling pathway in contraction-induced activation of muscle-derived IL-6 is yet not understood as this pathway is activated by contraction in rodent skeletal muscle (34, 37) but not in humans (16, 109). Moreover, the IκB kinase-β does not increase the transcription of IL-6 (13), suggesting that it is less likely that IL-6 gene transcription in skeletal muscle is dependent on activation of the IκB kinase-β/NF-κB signaling pathway.

Membrane depolarization activates voltage-dependent Ca²⁺ channels and induces Ca²⁺ release, which is obligatory for skeletal muscle contraction. A low sustained intracellular concentration of Ca²⁺+ has been shown to activate nuclear factor of activated T cell (NFAT) through the action of calcineurin and IL-6 gene expression in cultured human muscle cells. Thus, whereas the Ca²⁺+/NFAT pathway represents one arm of the IL-6 gene regulation, intramuscular glycogen content has also been shown to play an influential role in this process. It appears that, unlike IL-6 signaling in macrophages, which seems entirely dependent on activation of the NF-κB signaling pathway, intramuscular IL-6 expression is regulated by a network of signaling cascades that among other pathways are likely to involve cross talk between the Ca²⁺+/NFAT and glycogen/p38 MAPK pathways (reviewed in Ref. 86).

IL-6 and AMP-activated protein kinase. Skeletal muscle displays a high degree of metabolic flexibility, which allows the myofibers to adapt to various physiological demands by shifting energy substrate utilization. Transcriptional events play a pivotal role in the metabolic adaptations of skeletal muscle. The expression of genes essential for skeletal muscle glucose and lipid metabolism is tightly coordinated in support of a shift in substrate utilization. AMP-activated protein kinase (AMPK) regulates skeletal muscle metabolic gene expression programs in response to changes in the energy status (61). Although AMPK may influence the transcription of metabolic genes, AMPK exerts most of its effects via its role as a protein kinase that regulates the activation of key metabolic enzymes by phosphorylation.

AMPK exerts an acute regulatory role on numerous metabolic processes, including fatty acid oxidation (68). It does so because activation of AMPK phosphorylates acetyl CoA carboxylase β (ACCβ), resulting in inhibition of ACC activity, which in turn leads to a decrease in malonyl CoA content, relieving inhibition of carnitine palmitoyl transferase 1 and increasing fatty acid oxidation (38). Acute treatment of muscle cells with IL-6 increased both basal glucose uptake and translocation of the glucose transporter GLUT4 from intracellular compartments to the plasma membrane (14). Moreover, IL-6 increased insulin-stimulated glucose uptake in vitro, whereas infusion of recombinant human IL-6 into healthy humans during a hyperinsulinemic, euglycemic clamp increased glucose infusion rate without affecting the total suppression of endogenous glucose production (14). The effects of IL-6 on glucose uptake in vitro appeared to be mediated by activation of AMPK, since the results were abolished in cells infected with an AMPK dominant-negative adenovirus (14). Apart from the effects of IL-6 on glucose metabolism, several studies have reported that IL-6 may increase intramyocellular (8, 14, 91) or whole body (115) fatty acid oxidation. This effect is also mediated by AMPK (14, 38). A recent study suggests that IL-6 activates AMPK in skeletal muscle by increasing the concentration of cAMP and secondarily the AMP-to-ATP ratio (43).

Work from several groups (69, 110, 120) has demonstrated that leptin, signaling through the leptin receptor (LRb), may activate AMPK in peripheral tissues such as skeletal muscle. Thus it appears that IL-6 acutely mediates signaling through the gp130 receptor and exhibits many “leptin-like” actions such as activating AMPK and insulin signaling (111). Although most studies point to an effect of IL-6 on AMPK, Glund et al. (30) provided evidence that AMPK-dependent pathways regulate IL-6 release from isolated oxidative skeletal muscle.

A number of studies both in vitro (56, 99, 101, 102) and in rodents in vivo (44, 46, 47) demonstrate that IL-6 is capable of inducing insulin resistance. In the latter studies, IL-6 appears to induce insulin resistance via adverse effects on the liver. The IL-6-induced insulin resistance appears due to increased suppressor of cytokine signaling-3 (SOCS-3) expression (102), since SOCS-3 may directly inhibit the insulin receptor (114). However, it is quite clear that in healthy skeletal muscle, not least in humans, the IL-6-induced activation of AMPK overrides the IL-6-induced activation of SOCS-3. Of note, IL-6 knockout mice develop mature onset obesity and glucose intolerance (118), supporting the notion that IL-6 may exert beneficial effects on metabolism; however, even this observation is unclear (19).

The anti-inflammatory effects of exercise and IL-6. Systemic low-level inflammation is defined as two- to fourfold elevations in circulating levels of proinflammatory and anti-inflammatory cytokines, naturally occurring cytokine antagonists, and acute-phase proteins, as well as minor increases in counts of neutrophils and natural killer cells (10–12). A recent number of papers have documented that self-reported physical activity or physical performance is correlated inversely with systemic low-level inflammation, suggesting that the anti-inflammatory activity induced by regular exercise may exert some of the beneficial health effects of exercise in patients with chronic diseases [reviewed previously (64, 79, 89, 90, 123)].

As said, IL-6 is the first cytokine present in the circulation during exercise; the appearance of IL-6 in the circulation is by far the most marked, and its appearance precedes that of the other cytokines. The fact that the classical proinflammatory cytokines, TNF-α and IL-1β, in general do not increase with exercise, whereas exercise provokes an increase in circulating levels of well-known anti-inflammatory cytokines and cytokine inhibitors such as IL-1ra, IL-10, and soluble TNF receptor (sTNF-R) (75, 76), suggests that exercise provokes an environment of anti-inflammatory cytokines. Importantly, we showed that rhIL-6 infusion as well as exercise inhibited the endotoxin-induced increase in circulating levels of TNF-α in healthy humans (104). The anti-inflammatory effects of IL-6 are also demonstrated by IL-6 stimulating the production of the classical anti-inflammatory cytokines IL-1ra and IL-10 (106).

The role of training adaptation. Several epidemiological studies have reported a negative association between the amount of regular physical activity and the basal plasma IL-6 levels: the more physically active, the lower the basal plasma IL-6 (83). Although plasma IL-6 appears to be downregulated by training, the muscular expression of the IL-6 receptor appears to be upregulated (41). Accordingly, it is possible that the downregulation of IL-6 is partially counteracted by an enhanced expression of IL-6R, whereby the sensitivity to IL-6...
is increased. This finding has made us speculate that IL-6 resistance exists as a biological phenomenon. If the amount of IL-6 receptor on the surface of muscle fibers reflects enhanced IL-6 signaling, it appears that healthy, well-trained humans are more sensitive to IL-6, whereas untrained people have impaired IL-6 signaling and compensatory high circulating IL-6 levels. The latter would be in line with what is known for leptin resistance and insulin resistance.

**IL-6: a true myokine with endocrine and paracrine effects.** From a rather unexciting existence as a player in the textbook version of the inflammatory response, IL-6 has recently been taken to center stage in the search for culprits underlying the inflammatory component of the metabolic syndrome (55). The findings suggesting that IL-6 is yet another proinflammatory cytokine are in contrast to the numerous studies showing that IL-6 has beneficial effects on muscle metabolism [reviewed previously (29, 80, 86)].

Chronically elevated IL-6 levels lead to inappropriate hyperinsulinemia, reduced body weight, and impaired insulin-stimulated glucose uptake by the skeletal muscles (25). In contrast, IL-6 knockout mice develop obesity and insulin resistance, providing evidence against a causative effect of IL-6 in insulin resistance (118). Numerous explanations for the two divergent opinions have been put forward, including differences in model systems, chronic vs. pulsatile exposure, and in vitro vs. in vivo effects (29, 82). Of note, in resting healthy humans, plasma IL-6 is normally about 1–2 pg/ml or less (49).

Although exercise itself leads to an acute increase in IL-6 production and release by the working muscle, exercise training leads to reduced circulating IL-6 levels (23) and, according to changes in levels of IL-6 receptor expression, to an increased IL-6 sensitivity in skeletal muscle (41). In patients with type 2 diabetes or in elderly people (9, 87), circulating levels of IL-6 are about two- to threefold higher than those measured in healthy individuals. This represents a low, but chronic IL-6 exposure, contrasting the situation in exercise, where IL-6 levels increase acutely up to 100-fold. As recently pointed out by Anna Krook (55), the IL-6 levels achieved after electrotransfer by Franckhauser et al. (25) was ~800 pg/ml, corresponding to many 100-fold above both normal and diabetic values and ~5-fold higher than those seen after strenuous exercise. In fact, concentrations are equivalent to those noted in the context of severe infections. Therefore, caution should be taken before extrapolating these findings to what is seen in patients with chronic disorders or in normal physiology, such as exercise.

Although the effects of IL-6 is highly dependent on the tissue and although both dose and time appear to be determining factors for the biological role of exercise, the role of IL-6 in contracting muscle is, as a matter of fact, very clear. In response to muscle contractions, both type I and type II muscle fibers express the myokine IL-6, which subsequently exerts its effects locally within the muscle (e.g., through activation of AMPK). In skeletal muscle, IL-6 acts in an autocrine or paracrine manner to signal through a gp130R/IL-6R homodimer, resulting in activation of AMPK and/or phosphatidylinositol 3-kinase to increase glucose uptake and fat oxidation (14). IL-6 is also known to increase hepatic glucose production during exercise (20) and induces whole body lipolysis in humans (115) (Fig. 1).

**IL-15: A ROLE IN MUSCLE-FAT CROSS TALK**

IL-15 is expressed in human skeletal muscle (81). It possesses anabolic effects on skeletal muscle in vitro and in vivo and may also take part in reducing adipose tissue mass (81). Therefore, IL-15 has been suggested to be involved in muscle-fat cross talk. Recently, we demonstrated that IL-15 mRNA levels were upregulated in human skeletal muscle after a bout of strength training (71), suggesting that IL-15 may accumulate within the muscle as a consequence of regular training.

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Fig. 1. Biological role of contraction-induced interleukin (IL)-6. Skeletal muscle expresses and releases myokines into the circulation. In response to muscle contractions, both type I and type II muscle fibers express the myokine IL-6, which subsequently exerts its effects both locally within the muscle [e.g., through activation of AMP-activated protein kinase (AMPK)] and, when released into the circulation, peripherally in several organs in a hormone-like fashion. Specifically, in skeletal muscle, IL-6 acts in an autocrine or paracrine manner to signal through a gp130R/IL-6R homodimer, resulting in activation of AMP kinase and/or phosphatidylinositol 3-kinase to increase glucose uptake and fat oxidation. IL-6 is also known to increase hepatic glucose production during exercise or lipolysis in adipose tissues. Previously published in Pedersen and Febbraio (86).
We further demonstrated a negative association between plasma IL-15 concentration and trunk fat mass, but not limb fat mass, in humans. In support of this finding, we demonstrated a decrease in visceral fat mass, but not subcutaneous fat mass, when IL-15 was overexpressed in murine muscle (70).

Quinn et al. (96) found that elevated circulating levels of IL-15 in mice resulted in significant reductions in body fat and increased bone mineral content, without appreciably affecting lean body mass or levels of other cytokines. Although the latter model represented an artificial system, the findings lend some support to the idea that IL-15 secretion from muscle tissue may modulate visceral fat mass specifically via an endocrine mechanism.

**IL-8: A ROLE IN EXERCISE-INDUCED ANGIOGENESIS?**

IL-8 is a known chemokine that attracts primarily neutrophils. In addition to its chemokine properties, IL-8 acts as an angiogenic factor. The plasma concentration of IL-8 increases in response to exhaustive exercise such as running, which involves eccentric muscle contractions, whereas we and others found no increase in plasma-IL-8 in relation to concentric exercise (86).

However, when measuring the arteriovenous concentration difference across a concentrically exercising limb, our group (1) detected a small and transient net release of IL-8, which did not result in an increase in the systemic IL-8 plasma concentration. The fact that a high local IL-8 expression takes place in contracting muscle with only a small and transient net release may indicate that muscle-derived IL-8 acts locally and exerts its effect in an autocrine or paracrine fashion (1). It is not likely that muscle-derived IL-8 would work as a chemoattractant of neutrophils and macrophages when, in fact, in concentric exercise there is little or no accumulation of neutrophils or macrophages in skeletal muscle. However, a more likely function of muscle-derived IL-8 is to stimulate angiogenesis. It induces its chemotactic effects via CXCR1, whereas CXCR2, which is expressed by human microvascular endothelial cells, is the receptor responsible for IL-8-induced angiogenesis (4, 48, 73). The expression of the IL-8 receptor CXCR2 is enhanced in human skeletal muscle biopsies after concentric exercise, and the increase in CXCR2 protein is seen not only in the muscle fibers but to a greater extent in the vascular endothelium, suggesting that it may play a role in angiogenesis (28). IL-8 signaling promotes angiogenic responses in endothelial cells, increases proliferation and survival of endothelial and cancer cells, and potentiates the migration of cancer cells, endothelial cells, and infiltrating neutrophils at the tumor site. Accordingly, IL-8 expression correlates with the angiogenesis, tumorigenicity, and metastasis of tumors in numerous xenograft and orthotopic in vivo models (121).

The finding that a high local IL-8 expression takes place in contracting muscle with only a small and transient release that does not contribute to the plasma levels of IL-8 underscores the fact that muscle-produced IL-8 has no systemic effects. However, it is likely that IL-8 produced by contracting myofibers exerts its effect locally and plays a role in exercise-induced angiogenesis.

**BDNF: A ROLE IN NEUROBIOLOGY AND METABOLISM**

BDNF is a member of the neurotrophic factor family, which plays a key role in regulating survival, growth, and maintenance of neurons (67), and BDNF plays a role in learning and memory (113). Hippocampal samples from donors with Alzheimer disease show decreased BDNF expression (17), and individuals with Alzheimer disease have low plasma levels of BDNF (58). Also, patients with major depression have lower levels of serum BDNF than normal control subjects (39). Other studies suggest that plasma BDNF is a biomarker of impaired memory and general cognitive function in aging women (50), and a low circulating BDNF level was recently shown to be an independent and robust biomarker of mortality risk in elderly women (53). Interestingly, low levels of circulating BDNF are also found in individuals with obesity and Type 2 diabetes (54). In addition, we demonstrated that there is a cerebral output of BDNF and that this is inhibited during hyperglycemic clamp conditions in humans. The latter finding may explain the concomitant finding of low circulating levels of BDNF in individuals with Type 2 diabetes and the association between low plasma BDNF and the severity of insulin resistance (54). BDNF appears to play a role in both neurobiology and metabolism. Studies have demonstrated that physical exercise may increase circulating BDNF levels in humans (65). We studied whether skeletal muscle would produce BDNF in response to exercise (66). It was found that BDNF mRNA and protein...
expression were increased in human skeletal muscle after exercise; however, muscle-derived BDNF appeared not to be released into the circulation. BDNF mRNA and protein expression were increased in muscle cells that were electrically stimulated. Interestingly, BDNF increased phosphorylation of AMPK and ACC and enhanced fat oxidation both in vitro and ex vivo. Thus we have been able to identify BDNF as a novel contraction-induced muscle cell-derived protein that may increase fat oxidation in skeletal muscle in an AMPK-dependent fashion (Fig. 2). The possibility exists that BDNF may be classified as a myokine, which works in an autocrine or paracrine fashion.

OTHER MYOKINES

Through other strategies, Kenneth Walsh (Boston, MA) (119) discovered other new myokines. He developed the so-called myomouse. The myomouse demonstrates that substantial increases in muscle fiber hypertrophy, weight, and strength occur on induction of Akt signaling in skeletal muscle. The increase in muscle mass caused by myogenic Akt induction results in diminished fat deposition and improvements in whole body metabolism. Based on these findings, Walsh devised a protocol to identify novel muscle-secreted proteins (myokines) that confer the phenotypic changes brought on by myogenic Akt induction. One of these newly discovered factors, referred to as follistatin-like 1, functions to promote endothelial cell function and stimulates revascularization in response to ischemic insult through its ability to activate Akt-endothelial nitric oxide synthase signaling (77). Using the myomouse model, Walsh and colleagues (35) further identified FGF21 to be produced by skeletal muscle. FGF21 has been known to be a hormone that is induced in liver by fasting. A recent study demonstrated that FGF21 induces hepatic expression of peroxisome proliferator-activated receptor gamma coactivator protein-1α (PGC-1α), a key transcriptional regulator of energy homeostasis, and causes corresponding increases in fatty acid oxidation, tricarboxylic acid cycle flux, and gluconeogenesis without increasing glycogenolysis. Mice lacking FGF21 fail to fully induce PGC-1α expression in response to a prolonged fast and have impaired gluconeogenesis and ketogenesis (94). The latter results reveal an unexpected relationship between FGF21 and PGC-1. However, the precise biological function of muscle-derived FGF21 is not known.

LIF belongs to the IL-6 cytokine superfamily and is constitutively expressed in skeletal muscle. We have demonstrated that endurance exercise in humans increases the expression of LIF in skeletal muscle (7). Ongoing research in our group suggests that also LIF may be classified as a true myokine (7).

NEW HORIZONS

Skeletal muscle has the capacity to produce and express cytokines belonging to distinctly different families. To date, the list includes IL-6, IL-8, IL-15, LIF, BDNF, follistatin-like 1, and FGF21 and contractile activity plays a role in regulating the expression of these cytokines in skeletal muscle. The finding that muscles produce myokines creates a paradigm shift and opens new scientific, technological, and scholarly horizons. We are convinced that the characterization of the biological effects of known and unknown peptides, constituting the muscle secretome, will dominate the coming decade, just as the discovery of adipose tissue as a secretory organ in the mid-1990s was a dominating research area in the past decade, giving rise to the identification of new regulatory peptides (e.g., leptin and adiponectin) and their receptors.

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