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REVIEW

The role of exercise-induced myokines in regulating metabolism

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Abstract Exercise has beneficial effects in ameliorating metabolic disorders, and a combined therapeutic regimen of regular exercise and pharmaceutical treatment is often recommended. Exercise biology is complex and it involves various metabolic and molecular changes that translate into changes in substrate utilization, enzyme activation, and alternatively, improvement in exercise performance. Besides the effect of exercise on muscle metabolism, it has recently been discovered that contracting muscle can induce secretion of molecules called myokines. In the past few decades, a number of myokines have been discovered, such as interleukin-6, irisin, myostatin, interleukin-15, brain-derived neurotrophic factor, β-aminoisobutyric acid, meteorin-like, leukemia inhibitory factor, and secreted protein acidic and rich in cysteine, through secretome analysis. The existence of myokines has enhanced our understanding of how muscles communicate with other organs such as adipose tissue, liver, bone, and brain to exert beneficial effects of exercise at the whole body level. In this review, we focus on the role of these myokines in regulating local muscle metabolism as well as systemic metabolism in an autocrine/paracrine/endocrine fashion. The therapeutic potential of myokines and the natural or synthetic compounds known to date that regulate myokines are also discussed.

Keywords Myokine · Metabolism · Exercise · Muscle

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Introduction

Exercise is by far an effective way to improve health. In contrast, physical inactivity is associated with development of various diseases such as type 2 diabetes mellitus (T2DM), sarcopenia, osteoporosis, cardiovascular disease, and cancer (Tuomilehto et al. 2001; Monninkhof et al. 2007; Nocon et al. 2008; Wolin et al. 2009; Naseeb and Volpe 2017). Moreover, exercise on a regular basis exerts beneficial effects on metabolic health through not only modifying the traditional risk factors, such as blood glucose and lipid levels, but also by directly regulating glucose transport, insulin utilization, endothelial function, autonomic nervous system etc. (Goodyear and Kahn 1998; Joyner and Green 2009). Therefore, studying the exercise modality can help us discover biomarkers and therapeutic molecules which could underpin numerous physical inactivity-related disorders. However, it is difficult to dissect the mechanisms underlying exercise-induced changes since exercise is a highly complex process which simultaneously involves integrative and adaptive responses in multiple tissues and organs at the cellular and systemic level. Studies have been performed during the past few decades in an effort to elucidate the cellular and molecular mechanisms of acute and chronic exercise, but the majority of exercise biology still remains poorly understood. Anatomically, skeletal muscle is the largest organ which constitutes about 40% of the total body mass, and therefore, it plays a major role in regulation of metabolism. Along with the local effects of skeletal muscle on metabolism, it has recently been discovered that, similar to adipocytes, skeletal muscle is a secretory organ responsible for the production of several hundreds of peptides classified as ‘myokines’ (Bortoluzzi et al. 2006; Yoon et al. 2009; Henningsen et al. 2010). The discovery of myokines has

opened a new door for understanding the biology of exercise, providing evidence that muscles are able to communicate with other organs, such as bone, liver, adipose tissue, brain, etc. In this review, we focus on providing an update on some of the well-known myokines as well as the newly discovered myokines, and study their role in mediating the beneficial effects of exercise on metabolism through either an autocrine, paracrine, or endocrine mechanism.

Exercise physiology

Adaptation to exercise is a complex process as it involves diverse changes in transcriptional and translational responses, mitochondrial function, metabolic regulation, and signaling pathways that govern these changes (Egan and Zierath 2013). In simple terms, the molecular and metabolic responses to exercise can be first categorized into acute exercise (single bout) and chronic exercise training. Exercise training leads to molecular adaptations and these responses can be further classified as adaptation to aerobic (endurance) and resistance exercise. Acute exercise can alter the expression of various genes (Yang et al. 2005) and phosphorylation of proteins (Hoffman et al. 2015) to stimulate the muscle adaptation. However, a transient response to acute exercise is insufficient to alter the muscle phenotype. Rather, phenotypic adaptation in response to chronic exercise training involves accumulation of repeated single bout exercise-induced stimulation. Chronic exercise causes changes in the protein content and subsequently the enzyme function, resulting in improved exercise performance. During acute exercise, the metabolic pathway which provides the energy source is mostly determined by the relative duration and intensity of exercise. If exercise is performed at a low or moderate intensity, glucose derived from the liver or from oral ingestion (Coker and Kjaer 2005), and free fatty acids (FFA) from adipose tissue (Horowitz 2003) primarily provide the fuel needed to the skeletal muscle. If the intensity of exercise is increased, the contribution of circulating FFA is modestly declined while the use of circulating glucose is extensively upregulated (van Loon et al. 2001). If the exercise is continued for more than 1 h at a fixed intensity, the use of energy from lipid oxidation inclines (Romijn et al. 1993). In the case of aerobic exercise, mitochondrial biogenesis is one of the well-known molecular adaptation processes (Howald et al. 1985). Increased mitochondrial ATP production, glucose transport, utilization of fatty acids, and antioxidant capacity all reflect the enhancement of intrinsic oxidative capacity of the muscle after endurance training (Holloszy and Coyle 1984; Powers et al. 1994; Perseghin et al. 1996; Talanian et al. 2010). Among various regulators of skeletal muscle phenotype, peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1α) is a well-defined transcription factor responsible for mitochondrial biogenesis, transformation of muscle fiber type, and regulation of skeletal muscle metabolism (Wu et al. 1999; Lin et al. 2005). On the other hand, resistance exercise is an efficient exercise intervention to improve muscle function in terms of its strength, power, and size through morphological and neurological adaptations (Booth and Thomason 1991; Folland and Williams 2007). The major pathway related to resistance exercise-induced muscle hypertrophy involves p70S6K and mTOR signaling. These pathways combine the nutrient and metabolic stimuli to induce cellular growth and proliferation (Baar and Esser 1999; Bodine et al. 2001). Also, anabolic hormones such as insulin-like growth factor (IGF)-1 can induce mTOR activation and thus adaptive hypertrophy (Adams and McCue 1998). Further details on the molecular mechanisms related to exercise-induced skeletal muscle adaptation have been described elsewhere (Egan and Zierath 2013).

The skeletal muscle as an endocrine organ

More than 50 years ago, there was a notion that skeletal muscle may secrete humoral factors. This was hypothesized based on the fact that when a muscle contracts, the physiology and metabolism of other organs are affected (Goldstein 1961). Later through secretome profiling, numerous myokines were discovered. Myokines are molecules that are expressed, produced, and released by muscle fibers which exert autocrine, paracrine, or endocrine effects (Pedersen et al. 2003). The autocrine and paracrine effects of myokines are mostly involved in the regulation of muscle physiology, such as muscle growth or lipid metabolism, which can provide a feedback loop for the muscle to adapt to exercise training. In contrast, the endocrine effect of myokines is important in mediating the whole-body effect of exercise. To date, the muscle is known to crosstalk with adipose tissue, liver, pancreas, bone, and brain. Among these interactions, the crosstalk with adipose tissue is interesting as adipose tissues are also recently discovered to exert an endocrine effect through secretion of adipokines (Maury and Brichard 2010). During physical inactivity, adipose tissue secretes adipokines, which are mostly pro-inflammatory cytokines, to mediate the pathological process (Fig. 1). It is now well recognized that adipose tissue inflammation can lead to development of metabolic diseases, such as T2DM and atherosclerosis (Iyer et al. 2010). In contrast, myokines are produced during exercise to mediate the health benefits of exercise (Pedersen and Febbraio 2012). Therefore, it is

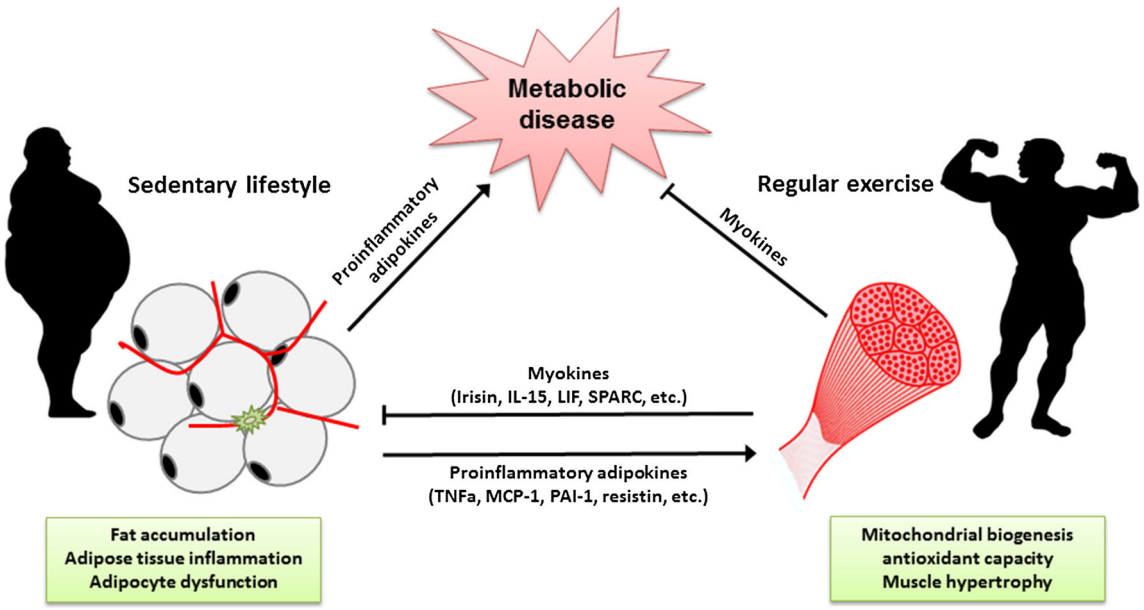

Fig. 1 Relationship between adipose tissue derived adipokines and skeletal muscle derived myokines. In the state of sedentary lifestyle, nutrient overload results in accumulation of fat and subsequent disturbance in adipocyte metabolism, which results in secretion of adipokines which are primarily proinflammatory cytokines. In contrast, contracting muscles in response to exercise secretes myokines, which are suggested to counteract the effects of proinflammatory adipokines. Therefore, the metabolic homeostasis is regulated by balance between adipokines and myokines, and are critical in development of metabolic diseases

hypothesized that myokines may counteract the harmful effects of pro-inflammatory adipokines and maintain the whole body homeostasis. In the following section, we will focus on some of the roles of myokines that have been discovered to date.

Interleukin-6

Interleukin-6 (IL-6) is known as the prototypical myokine induced by contracting skeletal muscle during exercise. During exercise, the circulating IL-6 levels derived from the muscle fibers are elevated up to 100-fold and is correlated with the duration and intensity of exercise (Pedersen and Febbraio 2008; Raschke and Eckel 2013). As early as after 30 min of acute exercise, IL-6 transcription is increased (Fischer 2006), which contributes to the increase in IL-6 secretion. It is confusing that IL-6 is generally classified as a pro-inflammatory cytokine, while as a myokine it is involved in the anti-inflammatory effect of exercise. Specifically, exercise-induced IL-6 is reported to inhibit the production of pro-inflammatory cytokines such as TNFα and IL-1β (Steinbacher and Eckl 2015). Along with its anti-inflammatory effect, myotube-produced IL-6 regulates satellite cell-mediated hypertrophic muscle growth (Serrano et al. 2008), induces glycogen breakdown and lipolysis via AMPK (Kelly et al. 2009), and enhances GLUT4 expression and insulin sensitivity which are canceled by injection of the IL-6 neutralizing antibody before exercise (Ikeda et al. 2016). IL-6 seems to play a dual role in insulin action in myotubes, where short-term insulin exposure shows an additive effect with IL-6 and chronic exposure produces insulin resistance (Nieto-Vazquez et al. 2008). Exercise-induced IL-6 is not only capable of regulating local muscle metabolism but it also exerts beneficial effects on systemic glucose homeostasis and lipid metabolism (Steinbacher and Eckl 2015). Of note, it has been proposed that the skeletal muscle-adipose tissue axis is important for the systemic effects of IL-6 (Pedersen and Febbraio 2012). In humans, IL-6 increases lipolysis and FFA oxidation in adipocytes, which suggests that IL-6 plays a critical role in regulation of fat metabolism (van Hall et al. 2003). Interestingly, IL-6 is involved in exercise training-induced uncoupling protein 1 (UCP1) expression in murine inguinal white adipose tissue (WAT) and thus it participates in adipocyte browning (Knudsen et al. 2014). It has also been recently reported that exercise-induced IL-6 plays a role in protection against myocardial ischemia reperfusion injury (McGinnis et al. 2015). Although numerous studies have discovered that exercise-induced IL-6 has a beneficial role in the regulation of metabolism, understanding IL-6 physiology is still a complex process due to its pro-inflammatory nature in general (Pal et al. 2014; Almuraikhy et al. 2016).

Irisin/FNDC5

Irisin is a PGC1α-dependent myokine suggested to mediate the effect of exercise on adipocyte browning by increasing the expression of UCP1 (Bostrom et al. 2012). In mice overexpressing PGC1α specifically in muscle, PGC1α induces the expression of a membrane protein fibronectin type III domain-containing protein 5 (FNDC5), and exercise triggers the cleavage of FNDC5 to secrete irisin into the bloodstream, which subsequently elevates energy expenditure in the subcutaneous adipose tissue through adipocyte browning (Bostrom et al. 2012). While discovery of irisin has received attention as a candidate for an exercise mimetic, numerous studies that thereafter investigated irisin came to somewhat controversial results, especially with respect to the circulating levels of irisin post-exercise (Bostrom et al. 2012; Huh et al. 2012; Ellefsen et al. 2014; Norheim et al. 2014; Albrecht et al. 2015; Jedrychowski et al. 2015). One possible reason for this discrepancy is the technique used to measure the plasma or serum irisin level. The concern was that human irisin antibodies used in some of the commercial ELISA kits were not able to accurately detect irisin, which may have caused inaccurate measurement or false-positive/false-negative results regarding exercise-induced circulating irisin levels (Perakakis et al. 2017). Recently, circulating human irisin was quantified using mass spectrometry in an antibody-independent manner. Through this technique, circulating irisin levels were detected and were increased by both acute and chronic exercise (Daskalopoulou et al. 2014; Jedrychowski et al. 2015), which concluded the discussion on whether human irisin exists in the circulation and whether it is regulated by exercise. Despite controversies over the effect of exercise on circulating irisin levels, the therapeutic potential of irisin has been proved in numerous reports. The beneficial role of irisin on skeletal muscle metabolism has been proposed by our group and others, and it was shown that irisin stimulates glucose uptake and lipid metabolism via activation of AMPK (Huh et al. 2014a, b; Lee et al. 2015; Rodriguez et al. 2015). Irisin is also involved in muscle growth through induction of IGF-1 and suppression of myostatin (Huh et al. 2014b). In addition to its effects on muscle, exogenous administration of irisin in mice induces adipocyte browning in subcutaneous fat through p38 MAPK and ERK1/2 activation (Zhang et al. 2014). In addition, FNDC5 overexpression in mice stimulates lipolysis via the cAMP-PKA-perilipin/HSL pathway in adipocytes, leading to reduced serum lipid levels (Xiong et al. 2015). In the liver, irisin stimulates glycogenesis while it reduces gluconeogenesis and lipogenesis through regulating GSK3, FOXO1, and SREBP2 (Liu et al. 2015; Xin et al. 2015; Tang et al. 2016). Interestingly, recent reports have suggested that irisin is not only a myokine but also an adipokine, although expressed to a lesser extent (Moreno-Navarrete et al. 2013; Roca-Rivada et al. 2013). Whether the expression of irisin in adipocytes contributes to the local adipocyte or whole body metabolism needs to be further examined. Although the effect of irisin has been implicated the most often in insulin-sensitive tissues, its beneficial effects on other organs such as bone, heart, and blood vessel are being reported (Xie et al. 2015; Fu et al. 2016; Colaianni et al. 2017).

Myostatin

Myostatin is a myokine primarily expressed and secreted by muscle fibers. It is unique in that myostatin is the only myokine reduced in response to exercise (McPherron et al. 1997). Myostatin inhibits satellite cell proliferation and differentiation in an autocrine and paracrine manner, and conversely, genetic deletion of myostatin leads to muscle hypertrophy in humans and mice (McPherron et al. 1997; Lee and McPherron 2001; Schuelke et al. 2004; Rodgers and Garikipati 2008; Relizani et al. 2014). While myostatin activation negatively regulates muscle growth, myostatin expression is downregulated after endurance as well as resistance exercise (Allen et al. 2011). Therefore, it has been proposed that the means of myostatin blockade (antibodies, soluble decoy activin receptor type II B, propeptides) could serve as a therapeutic target for treatment of patients with muscle dystrophies (Lebrasseur 2012). In addition to its local effects on muscle atrophy, myostatin can also modulate metabolic homeostasis through regulation of adipose tissue function (Zhao et al. 2005; Feldman et al. 2006; Guo et al. 2009). In mice fed a high-fat diet, it has been reported that inhibition of myostatin using soluble decoy activin receptor type II B ameliorates the development of obesity and insulin resistance, through mechanisms associated with lipolysis and mitochondrial lipid oxidation in adipose tissue and liver (Zhang et al. 2012). Interestingly, myostatin gene knockout mice show signs of fat browning in the WAT and this effect is thought to be mediated by AMPK activation in skeletal muscle and subsequent induction of PGC1α, FNDC5, and irisin (Zhang et al. 2012; Shan et al. 2013; Dong et al. 2016). On the other hand, in vitro studies have provided evidence that irisin downregulates myostatin gene expression in cultured mouse myocytes and human primary myotubes, suggesting a bidirectional regulation between myostatin and irisin in modulation of muscle growth (Huh et al. 2014a; Rodriguez et al. 2015). These findings highlight the myostatin-irisin pathway as a potential therapeutic target against obesity through adipocyte browning and subsequent induction of energy expenditure. Apart from the effect of myostatin on

muscle and fat, myostatin also strongly accelerates osteoclast formation through SMAD2 and its absence ameliorates rheumatoid arthritis in mice (Camporez et al. 2016). Of note, follistatin is an endogenous inhibitor of myostatin. Follistatin is a hepatokine, which suggests a possible muscle-liver crosstalk in exercise physiology (Hansen et al. 2011). Recently, a phase II clinical trial has been completed using humanized monoclonal myostatin antibody (LY2495655), and it showed improvements such as increase in appendicular lean body mass in patients undergoing elective total hip arthroplasty (Woodhouse et al. 2016) and increased muscle power in older weak fallers (Becker et al. 2015). In addition, the antibody has shown promising results in preclinical models of tumor-induced muscle wasting (Smith et al. 2015).

Interleukin-15

Interleukin-15 (IL-15) belongs to the IL-2 superfamily and is expressed in human skeletal muscle (Quinn et al. 1995). IL-15 is primarily known for its anabolic effects on skeletal muscle. Specifically, it is known to stimulate the accumulation of contractile proteins in differentiated myocytes and muscle fibers (Quinn et al. 1995). IL-15 also modulates glucose uptake in cultured myocytes in vitro and in isolated skeletal muscle ex vivo through activation of the JAK3/STAT3 signaling pathway (Busquets et al. 2005; Krolopp et al. 2016). In addition, IL-15 exerts protective effect against H_2O_2-mediated oxidative stress (Li et al. 2014) and enhances mitochondrial activity through the PPARδ-dependent mechanism in skeletal muscle cells (Thornton et al. 2016). In addition to its effects on muscle, IL-15 downregulates the accumulation of lipids in preadipocytes and reduces the WAT mass, partly through stimulation of adiponectin secretion (Carbo et al. 2001; Quinn et al. 2005), which suggests that IL-15 mediates the exercise-induced muscle-fat crosstalk. Although numerous studies have demonstrated that exercise alters the IL-15 concentration in serum (Riechman et al. 2004; Tamura et al. 2011), there are somewhat conflicting data on the effect of exercise on IL-15 protein expression and secretion from skeletal muscle, which needs to be further studied in the future.

Brain-derived neurotrophic factor

Brain-derived neurotrophic factor (BDNF) is primarily known to be released from the hypothalamus and is a key element in the regulation of neuronal development, plasticity and energy homeostasis (Lapchak and Hefti 1992). In a meta-analysis, blood concentrations of BDNF were increased by acute exercise as well as aerobic exercise training, but not by resistance exercise training (Dinoff et al. 2016, 2017). It is interesting to note that the gene and protein expressions of BDNF are upregulated in human skeletal muscle after exercise, whereas this effect does not seem to translate into its secretion (Pedersen et al. 2009). Therefore, it remains to be elucidated whether skeletal muscle directly contributes to the increased circulating BDNF level. It has recently been reported that exercise induces hypothalamic BDNF and subcutaneous fat browning in mice (Cao et al. 2011). In line with this report, overexpression of FNDC5 using an adenoviral vector in mice upregulated circulating irisin levels, increased hippocampal BDNF expression, and induced subcutaneous fat browning (Wrann et al. 2013), suggesting that there exists an exercise-induced PGC1α/FNDC5/BDNF pathway, which serves as an evidence that irisin mediates the effect of exercise on muscle to brain. In relation to learning and memory, exercise-induced BDNF was shown to reduce the production of toxic amyloid beta peptides, which could be valuable in the treatment of Alzheimer's disease (Nigam et al. 2017). In contrast to the beneficial effect of BDNF in the brain, the roles of BDNF in the periphery are not yet well characterized. Nevertheless, in addition to its role in the regulation of central metabolic pathways, studies have suggested that BDNF may act as a metabolic regulator of skeletal muscle. Specifically, BDNF has been shown to increase the phosphorylation of AMPK and ACC and thus enhance fatty acid oxidation and glucose utilization in skeletal muscle, in an autocrine and paracrine fashion (Matthews et al. 2009). Also, BDNF has been shown to ameliorate insulin resistance in several diabetic mouse models (Tonra et al. 1999; Tsuchida et al. 2001; Yamanaka et al. 2006).

β-Aminoisobutyric acid

β-Aminoisobutyric acid (BAIBA) is formed by the catabolism of thymine, and it has recently been identified in the culture media of myocytes overexpressing PGC1α, through metabolite screening (Roberts et al. 2014). Circulating BAIBA levels have been reported to be significantly increased by 3 weeks of voluntary running exercise training in mice and also by 20 weeks of supervised submaximal aerobic exercise training in humans (Roberts et al. 2014). BAIBA exerts various beneficial effects on muscle metabolism in an autocrine/paracrine manner. First, BAIBA increases mitochondrial FFA oxidation leading to amelioration of insulin signaling, especially the IRS-1/Akt pathway. In addition, BAIBA protects against inflammation in vivo through AMPK-PPARδ-dependent mechanisms (Roberts et al. 2014; Jung et al. 2015). Similar to its

effects on muscle, the endocrine effect of BAIBA includes upregulation of mitochondrial FFA oxidation in adipocytes, resulting in reduced fat accumulation in mice (Maisonneuve et al. 2004; Begriche et al. 2008). BAIBA also interacts with liver, where it reduces hepatic de novo lipogenesis through PPARα activation (Roberts et al. 2014). Also, BAIBA attenuates hepatic ER stress and apoptosis via AMPK, leading to improvement in glucose/lipid metabolic disturbance in mice with T2DM (Shi et al. 2016). Similar to other myokines, BAIBA treatment has shown to induce fat browning through upregulation of thermogenic gene expression in murine WAT (Roberts et al. 2014). Recently, the therapeutic role of BAIBA in renal fibrosis has also been demonstrated, where BAIBA attenuates angiotensin II-induced fibroblast activation and extracellular matrix deposition (Wang et al. 2017).

Meteorin-like

A novel form of PGC1α has been recently discovered, which results from alternative promoter usage and splicing, and was named as PGC1α4. PGC1α4 does not seem to exert most of the known effects of PGC1α, such as regulation of mitochondrial oxidation, but rather is upregulated after resistance exercise, mediating the effect of exercise on muscle hypertrophy and strength in mice and humans (Ruas et al. 2012). Interestingly, mice with muscle-specific overexpression of PGC1α4 produce and secrete a hormone called meteorin-like (also known as subfatin) (Rao et al. 2014). In mice, acute exercise results in upregulation of meteorin-like mRNA expression in muscle after 6 h and circulating meteorin-like levels after 24 h (Rao et al. 2014). Consistently, a single bout of combined resistance and aerobic exercise in young healthy male subjects increases circulating meteorin-like levels at both 1 and 4 h after exercise (Rao et al. 2014). Meteorin-like induced by exercise stimulates upregulation of genes related to adipocyte browning and mitochondrial oxidation as well as anti-inflammatory cytokines. It is interesting to note that whereas other myokines directly induce adipocyte browning through upregulation of thermogenic genes such as UCP1 in adipocytes, meteorin-like has an indirect effect on adipocyte browning through regulation of immune cells. Specifically, meteorin-like stimulates the eosinophils to secrete IL-4 and IL-13, and promotes alternative activation of adipose tissue macrophages which are required for upregulation of thermogenic gene expression as well as anti-inflammatory gene expression in WAT (Rao et al. 2014). A recent study has shown that meteorin-like is not only a myokine, but also an adipokine. However, studies have shown contradicting results regarding its role on adipocytes. One study showed that meteorin-like promotes adipogenesis and controls insulin sensitivity in adipocytes through the PPARγ pathway in mice (Li et al. 2015). On the other hand, another study showed that meteorin-like expression was higher in stromal vascular fraction compared to adipocytes in humans, and that overexpression of meteorin-like inhibits human adipocyte differentiation (Loffler et al. 2017). Therefore, the role of meteorin-like as an adipokine/myokine has yet to be explored.

Leukemia inhibitory factor

Leukemia inhibitory factor (LIF) has previously been reported to have multiple biological functions in platelets, bone, neurons, and liver (Metcalf 2003). Since LIF mRNA expression is increased in human skeletal muscle after resistance exercise and LIF protein is secreted when human cultured myotubes are electrically stimulated (Broholm et al. 2008; Broholm et al. 2011), LIF is classified as a contraction-induced myokine. It is known that LIF plays an important role in skeletal muscle hypertrophy and regeneration by enhancing cell proliferation through the JAK/STAT and PI3K signaling pathway (Alter et al. 2008; Diao et al. 2009). Along with its effects on muscle hypertrophy, LIF acutely increases muscle glucose uptake through the PI3K/mTORC2/Akt pathway (Brandt et al. 2015), suggesting that LIF exerts local effects in muscle in an autocrine and/or paracrine manner. Even before it was classified as a myokine, LIF was shown to stimulate osteoblast differentiation while it was found to inhibit adipocyte differentiation (Aubert et al. 1999; Sims and Johnson 2012). Whether exercise-induced LIF mediates these processes are unclear and yet to be discovered. In terms of measuring post-exercise levels, it is difficult to detect circulating levels of LIF protein, since LIF has a very short half-life of 6-8 min in serum (Hilton et al. 1991). Therefore, the expression and secretion levels of LIF protein after exercise are not well characterized.

Secreted protein acidic and rich in cysteine

Secreted protein acidic and rich in cysteine (SPARC) was initially identified in the bone as osteonectin, but recent studies have shown that it is also found in the muscle, where its level increases during muscle development and regeneration (Termine et al. 1981; Kupprion et al. 1998). SPARC is a matricellular glycoprotein which modulates the interaction between cells and the extracellular matrix (ECM) proteins such as collagen and vitronectin (Bradshaw 2012). Interestingly, it has recently been shown that SPARC directly interacts with actin and plays a critical role in skeletal muscle tissue remodeling (Jorgensen et al.

2017). The ability of SPARC to regulate tissue remodeling also seems to play an important role in adipocyte differentiation and adipose tissue turnover. SPARC inhibits adipogenesis by activating the Wnt/β-catenin pathway (Nie and Sage 2009), whereas higher expression of SPARC in obesity limits the ability of adipose tissue to accumulate lipids (Tartare-Deckert et al. 2001; Kos et al. 2009), leading to metabolic dysregulation in obesity. Distinct from the role of SPARC in regulating the ECM, it has been reported that SPARC directly interacts with AMPK and is involved in glucose metabolism in myocytes (Nie and Sage 2009; Song et al. 2010). Therefore, the relationship between SPARC and metabolic disease is of current interest, which needs to be further examined in detail. Recently, it was discovered that exercise-induced SPARC can also inhibit progression of colon tumor through inducing colon cell apoptosis in mice, suggesting its role in amelioration of cancer (Aoi et al. 2013).

Other myokines

Apart from the myokines discussed above, exercise-responsive myokines are continuously being discovered through global mRNA sequencing and secretome analysis. Apelin is a well-known adipokine upregulated in obese individuals undergoing an 8 week endurance training, and thus, it is identified as a novel exercise-regulated myokine and is suggested to improve muscle metabolism and function (Besse-Patin et al. 2014). IGF-1 and FGF-2 are two well-known osteogenic factors, which are found to be abundant in homogenized muscle tissue and are also secreted from cultured myotubes in vitro (Hamrick 2011), suggesting a muscle-bone crosstalk by exercise. Chitinase-3-like protein 1 (CHI3L1) is another myokine whose gene expression is increased after a single bout of strength and aerobic exercise (Gorgens et al. 2016). Recent evidence suggests that CHI3L1 acts in an autocrine/paracrine manner to stimulate myoblast proliferation and inhibit pro-inflammatory signaling pathways (Gorgens et al. 2014, 2016). CXCL1 (fractalkine) and CCL2 (MCP-1) are well-known chemokines which were induced in muscle by acute exercise (Catoire et al. 2014). Since infiltration of macrophages is important for exercise-induced hypertrophy, CXCL1 and CCL2 are believed to play a role in this process.

The role of myokines in regulating local and systemic metabolism and their therapeutic potential

The identified roles of myokines have proven that myokines are involved in various processes of exercise adaptation, primarily muscle growth and substrate mobilization through regulation of whole body glucose/lipid metabolism. The local effect of myokines on skeletal muscle is summarized in Fig. 2 and Table 1. Many of the discovered myokines mediate exercise-induced muscle growth (IL-6, IL-15, irisin, myostatin, LIF), which implies that these myokines stimulate muscle protein synthesis. Activation of Akt-mTOR-p70S6 K signaling is critical for mRNA translation, ribosomal biogenesis, and nutrient metabolism (Coffey and Hawley 2007; Drummond et al. 2009), and therefore, it is likely that similar pathways are associated with these myokines. Myostatin is unique as it induces muscle atrophy which may counterbalance the other anabolic myokines. Myokines also regulate muscle metabolism through enhancing muscle insulin sensitivity, either by stimulating glucose uptake (IL-6, IL-15, irisin, BDNF, LIF) or lipid metabolism (IL-6, irisin, BDNF, BAIBA). This is in line with the fact that during exercise, ATP synthesis is rapidly activated through substrate utilization (Gaitanos et al. 1993; Parolin et al. 1999), and release of myokines could be a response mechanism against increased glucose demand during contraction.

The mobilization of extramuscular substrates is also critical for maintaining skeletal muscle metabolism during prolonged exercise (van Loon et al. 2005; Wasserman 2009). Therefore, the main target of the secreted myokines in terms of their endocrine effects are insulin-sensitive tissues, such as liver and adipose tissue (Fig. 3 and Table 1). Irisin and BAIBA regulate liver glycogenesis and gluconeogenesis, and a number of myokines have an effect on lipolysis and FFA oxidation in adipocytes (IL-6, IL-15, irisin, myostatin, BAIBA). These effects on adipocytes and liver would potentially enhance whole body insulin sensitivity, which would be beneficial for the treatment of metabolic diseases. The discovery of irisin received attention as it was suggested to mediate the effect of exercise on adipocyte browning. Indeed, the effects of other myokines on adipocyte browning were also shown to be dependent on the action of irisin (BDNF, myostatin). Meteorin-like, BAIBA, and IL-6 can also induce adipocyte browning, but whether this is independent of irisin needs to be investigated further. The myokines that stimulate lipolysis and FFA oxidation in adipocytes usually have an effect on adipocyte browning. However, in terms of myokine-induced adipocyte browning, it is still not known why exercise would induce a process that would reduce the

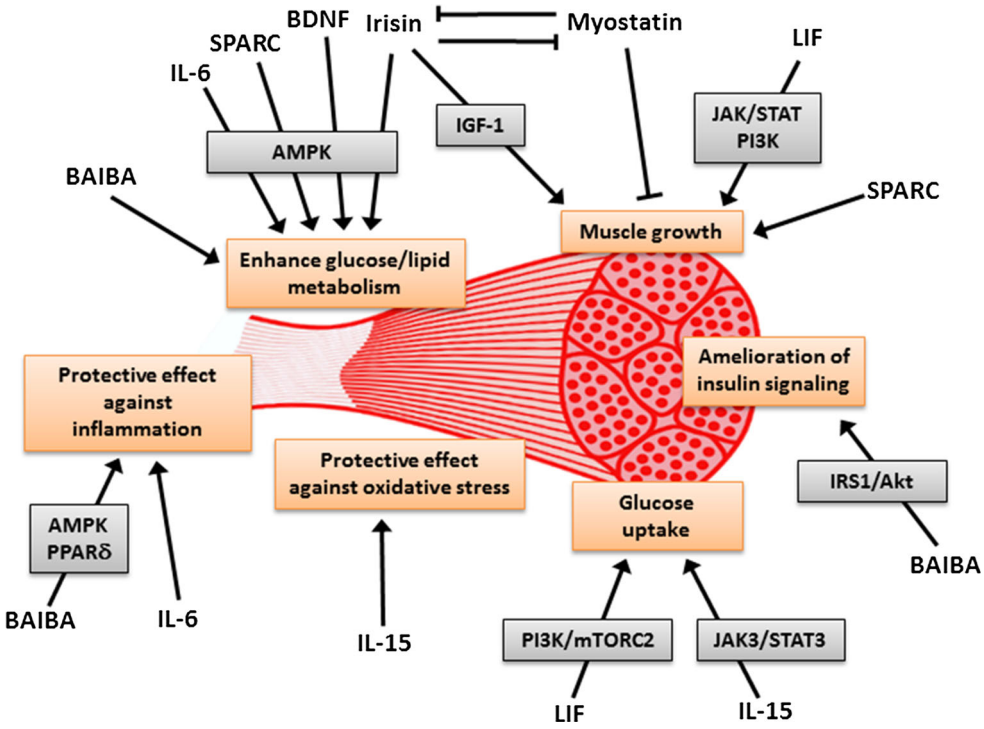

Fig. 2 The local effect of myokines on skeletal muscle. The exercise-induced myokines can regulate muscle physiology in an autocrine and paracrine manner. The figure summarizes the specific roles of each myokines on muscle metabolism and muscle growth. In some cases where the downstream mechanism is known, the signaling pathways which mediate the effect of myokine is shown in the grey box

storage of energy. A potential explanation is that overall metabolism is increased to produce energy, but this point needs to be discussed further in future studies.

Although the identified myokines share a common role in regulating metabolism, how each myokine works and how these myokines work together still remain to be elucidated. It is also important to note that myokines seem to regulate each other, as in the case of myostatin-irisin and irisin-BDNF axis, which implies that myokines may work synergistically to effectively regulate exercise-induced adaptation. The role of myokines in mediating exercise-induced adaptation opens a new door to their pharmaceutical application, where myokines could be used to mimic exercise-induced muscle hypertrophy and substrate mobilization. Understanding the mechanism on how the muscle communicates with other organs will advance the discovery and development of pharmaceutical therapies to support certain disease groups wherein the patients are unable to exercise. Especially, age-related muscle disorders such as sarcopenia could benefit from the myokine-derived drugs. Also, development of anti-obesity and anti-diabetic drugs seems rational based on the metabolic effects of myokines on adipocytes and liver.

Regulation of myokine synthesis and secretion by natural or synthetic compounds

Based on the therapeutic potential of the identified myokines described above, it is important to understand how these myokines are regulated in terms of their expression and secretion. Moreover, it would be valuable to develop natural products or small compounds that regulate the myokines, independent of physical activity. So far, a number of natural or synthetic compounds have been reported to regulate myokines (Table 1). PDX ((10S,17S)-dihydroxydocosa-(4Z,7Z,11E,13Z,15E,19Z)-hexaenoic acid) is produced via sequential lipoxygenation of docosahexaenoic acid and is reported to stimulate the release of IL-6 from skeletal muscle (White et al. 2014). Elocalcitol (a non-hypercalcemic VDR agonist), ionomycin (Ca^{2+} ionophore), and calcineurin (Ca^{2+}-calmodulin–dependent serine/threonine protein phosphatase) also stimulate IL-6 expression or secretion (Holmes et al. 2004; Allen et al. 2010; Antinozzi et al. 2017). AMPK activators AICAR and metformin have been implicated in the upregulation of various myokines including IL-6 (Lauritzen et al. 2013), irisin (Yang et al. 2015), and BDNF (Guerrieri and van Praag 2015). This implies that activation of AMPK signaling is critical to the mechanism of action of myokines in regulating metabolic homeostasis. Leptin also regulates a number of myokines including IL-6, IL-15, and irisin (Nozhenko et al. 2015; Rodriguez et al. 2015), indicating fat-muscle crosstalk. Regulation of irisin by

Table 1 Myokines, their metabolic effects, and compound/drug that affect their expression/secretion

Myokine	Metabolic effects on muscle	Metabolic effects on other organs	Regulation by natural or synthetic compound
IL-6	Induce muscle hypertrophy, glucose uptake, glycogen breakdown, and lipolysis	Increase lipolysis and FFA oxidation in adipocyte, induce adipocyte browning, protect against myocardial I/R injury	Protectin DX (↑), elocalcitol (↑), ionomycin (↑), calcineurin (↑), AICAR (↑), leptin (↑)
Irisin/ FNDC5	Stimulate glucose uptake and lipid metabolism, involved in muscle growth	Induce adipocyte browning and lipolysis, stimulate glycogenesis and reduce gluconeogenesis/lipogenesis in liver	Sodium butyrate (↑), azacytidine (↑), inorganic nitrate (↑), exenatide (↑), metformin (↑), dihydromyricetin (↑), ursolic acid (↑), leptin (↑), myostatin (↓)
Myostatin	Inhibit muscle hypertrophy	Inhibition of myostatin results in adipocyte lipolysis and mitochondrial lipid oxidation, accelerates osteoclast formation	Follistatin (↓), antibody against myostatin (LY2495655, ACE-031, domagrozumab, MYO-029, BMS-986089, 10B3↓), ursolic acid (↓), formoterol (↓), dorsomorphin (↓), LDN-193189 (↓), atomoxetine (↓), ghrelin and its analogue (BIM-28125, BIM-28131↓), fenofibrate (↓), magnolol (↓), epigallocatechin-3-gallate (↓), (-)-epicatechin (↓),
IL-15	Stimulate muscle growth and glucose uptake, enhance mitochondrial activity and exert anti-oxidative effect	Inhibit lipid accumulation in adipose tissue through adiponectin stimulation	Leptin (↑)
BDNF	Enhance fatty acid oxidation and glucose utilization	Induce adipocyte browning indirectly through FNDC5	Resveratrol (↑), loganin (↑), rolipram (↑), AICAR (↑), taurine (↑)
BAIBA	Increase mitochondrial FFA oxidation, ameliorate insulin signaling, anti-inflammatory effect	Increase mitochondria FFA oxidation and browning in adipocytes, reduce hepatic de novo lipogenesis and hepatic ER stress	Inorganic nitrate (↑)
Meteorin-like	Unknown	Induce adipocyte browning indirectly through regulation of eosinophils	None reported
LIF	Induce muscle hypertrophy and glucose uptake	Stimulate osteoblast differentiation, inhibit adipocyte differentiation	None reported
SPARC	Regulate muscle tissue remodeling, enhance glucose metabolism	Inhibit adipogenesis	None reported

small compounds has been examined in various studies, and showed that sodium butyrate, azacytidine, and inorganic nitrate upregulate irisin (Kim et al. 2017; Roberts et al. 2017). Interestingly, treatment with glucagon-like peptide-1 (GLP-1) receptor agonist exenatide markedly increased serum irisin levels (Liu et al. 2016), implying a synergistic action of irisin with the anti-diabetic drug. Whether this effect is directly or indirectly associated with muscle irisin needs to be examined further. In addition, natural product dihydromyricetin and ursolic acid stimulate irisin secretion (Bang et al. 2014; Zhou et al. 2015). In line with this finding, ursolic acid was also shown to decrease the expression of myostatin (Yu et al. 2017), implying its role in maintenance of muscle mass. Myostatin is by far the most extensively studied myokine in terms of its regulation. Small molecules and known drugs such as dorsomorphin, LDN-193189, atomoxetine, formoterol, fenofibrate and ghrelin analogues (Castillero et al. 2011; Busquets et al. 2012; Lenk et al. 2013; Jesinkey et al. 2014; Horbelt et al. 2015; Gomez-SanMiguel et al. 2016), and natural products such as magnolol, epigallocatechin-3-gallate, (−)-epicatechin (Gutierrez-Salmean et al. 2014; Chen et al. 2015; Horbelt et al. 2015) all downregulated myostatin expression and/or secretion, leading to a protective effect against muscle atrophy. In addition, myostatin is the only myokine for which a targeted therapeutic molecule has been developed to date. As mentioned above, there are numerous antibodies against myostatin (LY2495655, ACE-031, domagrozumab, MYO-029, BMS-986089, 10B3) and some of them have been successful in human clinical trials and have proved their potential as novel drugs in the treatment of skeletal muscle atrophy and muscle weakness (Becker et al. 2015; Singh et al. 2016; Woodhouse et al. 2016; Bhattacharya et al. 2017; Wurtzel et al. 2017). With respect to BDNF, there are only indirect evidences which show that BDNF upregulation by resveratrol, loganin, rolipram, and taurine improved brain function (Chou et al. 2013; Tseng et al. 2016; Zhong et al.

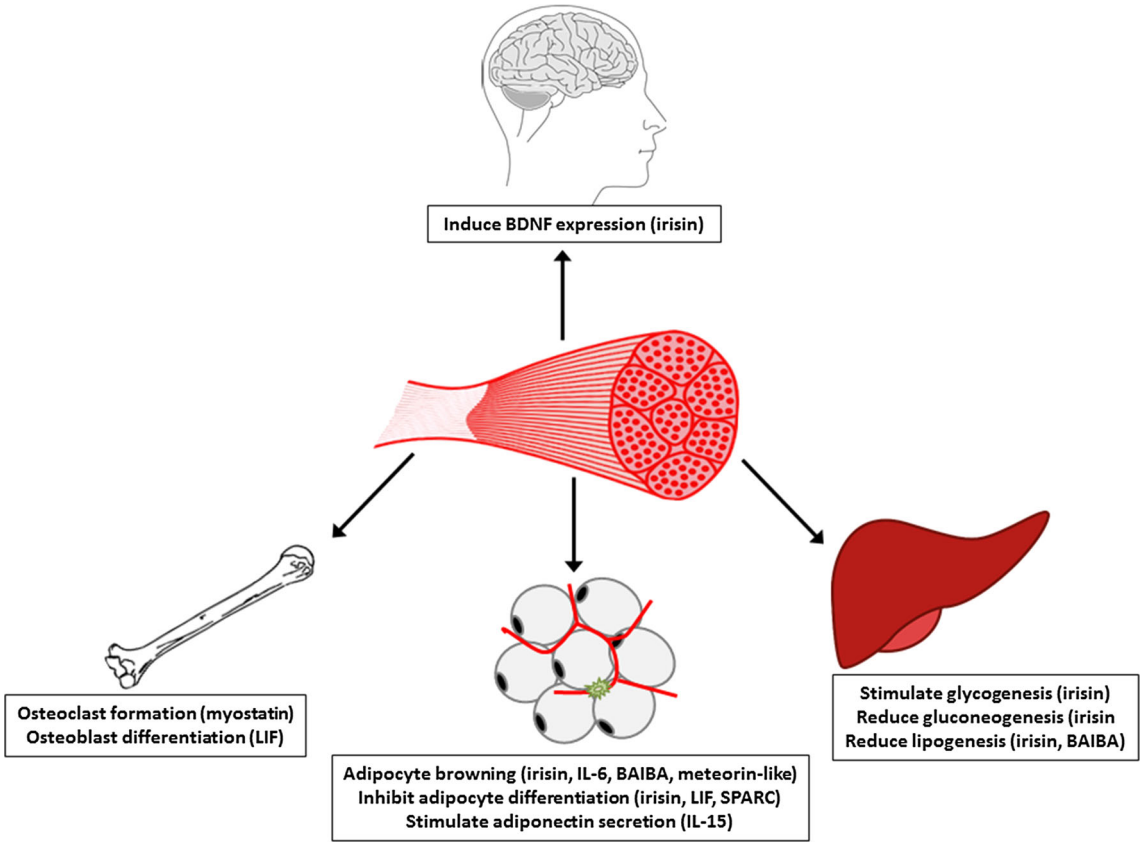

Fig. 3 The endocrine effect of myokines on brain, bone, adipose tissue, and liver. The exercise-induced myokines are capable of mediating the beneficial effect of exercise from muscle to other organs. Among various organs, the crosstalk with the adipose tissue exerts multiple actions including adipocyte browning and inhibition of adipocyte differentiation. Myostatin and LIF have opposite actions on bone. In the liver, irisin and BAIBA modulates glucose and lipid metabolism. Of note, muscle-derived irisin is known to induce BDNF expression in the brain which subsequently results in adipocyte browning

2016; Wicinski et al. 2017). However, it is not known whether these compounds can specifically induce muscle BDNF expression/secretion. Only inorganic nitrate has been reported to stimulate BAIBA (Roberts et al. 2017), and there are no compounds known to date that regulate meteorin-like, LIF, and SPARC. Evidence from previous studies can help us to not only understand the mechanisms underlying the regulation of myokines but also to provide insights into developing therapeutic molecules that target myokines. Since myostatin antibody has shown a good example of myokine as a drug candidate, development of myokine analogue seems promising.

Conclusion

Skeletal muscle is the major organ contributing to the whole body metabolism, and identification of exercise-induced myokines set a new paradigm in exercise biology and metabolic homeostasis. The fact that muscles produce secretory molecules provides the basis for the crosstalk between skeletal muscle and other organs, such as adipose tissue, bone, liver, kidney, brain, etc. Given the complexity and variability among exercise regimens and responses at the metabolic and molecular level, myokines that are sensitive to exercise could serve as prognostic biomarkers which reflect the improvement of whole body metabolism. In the future, expression profiles of the identified myokines could provide means to coordinate individual exercise programs and to maximize the health-promoting benefits of exercise on metabolism. Moreover, based on the role of myokines in fine tuning the metabolic process associated with exercise, development of exercise mimetics or small compounds derived from myokines is a promising field in the treatment of metabolic diseases.

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Compliance with ethical standards

Conflict of interest The author has no conflict of interest.

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