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Myokines and adipokines: Involvement in the crosstalk between skeletal muscle and adipose tissue

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ABSTRACT

Skeletal muscle and adipose tissue are the two largest organs in the body. Skeletal muscle is an effector organ, and adipose tissue is an organ that stores energy; in addition, they are endocrine organs that secrete cytokines, namely myokines and adipokines, respectively. Myokines consist of myostatin, interleukin (IL)-8, IL-15, irisin, fibroblast growth factor 21, and myonectin; adipokines include leptin, adiponectin, resistin, chemerin, and visfatin. Furthermore, certain cytokines, such as IL-6 and tumor necrosis factor-α, are released by both skeletal muscle and adipose tissue and exhibit a bioactive effect; thus, they are called adipo-myokines. Recently, novel myokines or adipokines were identified through the secretomic technique, which has expanded our knowledge on the previously unknown functions of skeletal muscle and adipose tissue and provide a new avenue of investigation for obesity treatment or animal production. This review focuses on the roles of and crosstalk between myokines and adipokines in skeletal muscle and adipose tissue that modulate the molecular events in the metabolic homeostasis of the whole body.

Contents

Abbreviations: ACC, acetyl-CoA carboxylase; Akt, protein kinase B; AMPK, AMP-activated protein kinase; ERK, extracellular-signal regulated kinase; FABP, fatty acid binding protein; FAT/CD36, fatty acid translocase; FATP, fatty acid transport protein; FGF21, fibroblast growth factor -21; FNDC5, fibronectin type III domain-containing 5; GLUT, glucose transporter type; IGF, insulin like growth factor JAK Janus-activated kinase; MCP-1, monocyte chemotactic protein-1; NF-κB, nuclear factor-kappa B; PGC-1α, peroxisome proliferator-activated receptor γ co-activator 1α; SIRT1, silent information regulator 1; STAT, signal transducer and activator of transcription; SVF, stromal vascular fraction; UCP2, uncoupling protein 2; WAT, white adipose tissue.

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1. Introduction

The prevalence of obesity has reached pandemic proportions, becoming a major public health problem in numerous developed countries where being overweight and obese results in more deaths than malnutrition. In 2014, ~39% of adults worldwide aged ≥18 years were overweight, and 13% were obese [1]. One of the major advances in obesity research over the past decades is the discovery that adipose tissue, especially white adipose tissue (WAT), acts as an endocrine organ and modulates metabolism by signaling other organs [2].

An extensive body of *in vivo* and *in vitro* research has explored the capacity of skeletal muscle and adipose cells to produce cytokines [3–6]. The concept of adipocytes as major secretory cells that release "adipokines" has more recently received greater attention owing to the development of a parallel concept in skeletal muscles. Identification of muscle as a "myokine"-producing organ has laid the foundation for a new field of research. Unfortunately, very few studies have considered the interrelation between skeletal muscle and adipose tissue, although a direct relationship between skeletal muscle mass or activity and adipose tissue mass has been indicated in some studies [4,5,7,8]. Multiple determinants play a key role in this complex process. In this review, we address the effects of only myokines and adipokines on skeletal muscle and/or adipose tissue. Furthermore, particular emphasis is placed on protein and energy metabolism in myocytes and/or adipocytes.

2. Skeletal muscle and adipose tissue

2.1. Skeletal muscle

Skeletal muscle, the largest organ in the human body, is a major metabolic tissue that is responsible for approximately 85% of the insulin-stimulated glucose uptake via glucose transporter type 4 (GLUT4)-mediated transport and for lipid metabolism [9,10]. More than a decade ago, contracting human skeletal muscle was elucidated to release significant amounts of interleukin (IL)-6 into the circulation during prolonged single-limb exercise [11,12]. The identification of muscle as a myokine-producing organ consequently provided a conceptual basis to explain how muscles communicate with other organs, even *in vitro*. During proliferation, myocytes tend to secrete myokines that suppress neurogenesis and adipogenesis; during differentiation, myocytes release myokines that specifically promote myotube formation, vascularization, and neurogenesis [5]. It has been suggested that the cultured muscle cells secrete different types and amounts of myokines at different developmental stages to communicate with various types of cells.

2.2. Adipose tissue

Adipose tissue functions not only as an energy reserve organ but also as a major endocrine organ, secreting adipokines involved in maintaining homeostasis. Adipose tissue includes two fractions: mature adipocytes and stromal vascular fraction (SVF). The SVF includes preadipocytes and shares numerous phenotypic features with pro-inflammatory macrophages, including the capacity to secrete factors such as IL-6, tumor necrosis factor (TNF)-α, and monocyte chemotactic protein-1 (MCP-1). Adipocytes in adipose tissue secrete a wide range of factors, considered adipokines, similar to myokines released from skeletal muscle. However, there has been uncertainty over whether this concept should also be applied to other forms of adipocytes, such as brown and brite tissue. Specifically, the different forms of adipocytes could interconvert. Although brown adipocytes definitely secrete specific proteins [13], the extent of the secretory protein profile of brown adipocytes, as well as brite adipocytes, is currently unclear. The wide spectrum of molecules secreted by adipose cells indicates that this tissue is very important for the regulation of energy homeostasis.

2.3. Muscle-adipose axis

There are multiple adipose tissue sites (locations) or depots within an organism, and skeletal muscles also share the key characteristics required to secrete cytokines that have endocrine or paracrine functions [14]. Because adipose tissue is adjacent to the muscle, it can induce different signaling pathways. Therefore, location plays a key role in the physiological interactions between adipose tissue and closed muscle, depending on whether it is subcutaneous, intermuscular, or intramuscular fat. Skeletal muscle is also located in different areas and has various muscle fiber types including type I and type II (a, b, x) [15]. Crosstalk between myogenic cells and adipocytes might play a significant role in the rate and extent of myogenesis, adipogenesis, protein turnover, and lipogenesis/lipolysis [16–18]. Furthermore, crosstalk between myocytes and adipocytes has been supported by co-culture models using both cell types [4,19]. Myokines and adipokines secreted from corresponding tissues have an important effect in maintaining a balanced ratio of skeletal muscle to fat and thus, may play a key role in the modulation of body composition and even in the production of muscle in animals (Fig. 1).

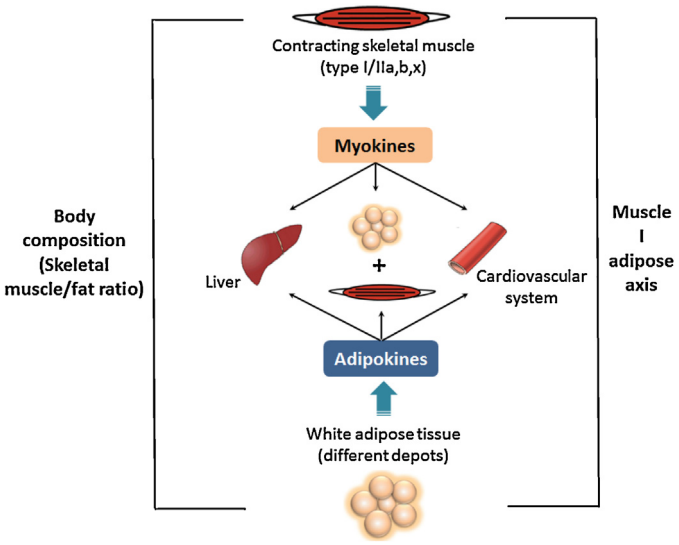

Fig. 1. Skeletal muscle-derived factors "myokines" and adipose tissue-derived factors "adipokines" exert their effects mainly in the organs of adipose tissue and/or skeletal muscle.

3. Myokines and their roles in skeletal muscle/adipose tissue protein and energy metabolism

Myokines have been explored to a lesser extent than adipokines. Previous studies of cytokines secreted from myocytes focused mainly on IL-6, IL-8, and IL-15 [20]. The classic and best-described member of this family is IL-6. However, during recent years, other myokines (e.g., irisin, myonectin) have been identified, revealing new scientific and technological horizons. These studies have highlighted the potential roles of myokines in mediating tissue crosstalk to control integrated physiology and in modulating human health and livestock production. Therefore, we believe the characteristics and biological effects of the known and unknown muscle-secreted myokines will dominate obesity research in the coming decade.

3.1. Myostatin

Myostatin belongs to the transforming growth factor-β superfamily and is the first recognized myokine involved in suppressing satellite cell activation and myoblast proliferation [21]. Furthermore, myostatin induces skeletal muscle fiber-type switches, facilitates slow and inhibits fast myosin heavy-chain expression during myogenic differentiation [22], and regulates glucose disposal [23]. Myostatin also plays a critical role in muscle-to-fat shift events. Gene expression of myostatin and its associated binding proteins can be modulated in skeletal muscle and adipose tissue of obese mice, demonstrating that alterations in their expression contribute to changes in the growth and metabolism of lean and fat tissues during obesity [24,25]. A loss of function mutation in myostatin in humans or the absence of myostatin in knockout ($Mstn^{-/-}$) mice leads to a striking doubling of muscle mass [26,27] and drives browning of WAT indirectly through the signaling of AMP-activated protein kinase- peroxisome proliferator-activated receptor γ co-activator 1α-fibronectin type III domain-containing 5 [28]. Furthermore, $Mstn^{-/-}$ mice show a dramatic increase in insulin sensitivity and glucose uptake and a reduction in adipose tissue mass [29], which may be an indirect result of metabolic changes in skeletal muscle. The myokines of myostatin also induce muscle atrophy via well-recognized pathways, by inhibiting myoblast proliferation, downregulating activity of the insulin-like growth factor-protein kinase B pathway, and increasing ubiquitin-proteasomal activity [30,31]. Thus, a basal level of autophagy occurs in response to the presence of myostatin activity, to balance skeletal muscle metabolism.

3.2. IL-8

IL-8 belongs to the cysteine-X-cysteine family of chemokines. Exercise induces a marked increase in IL-8 mRNA and protein expression within muscle fibers without any changes in the plasma IL-8 concentration [32], indicating that muscle-derived IL-8 probably plays a local role. Elevated levels of secreted IL-8 are an intrinsic property of skeletal muscle in type 2 diabetes, creating a microenvironment that limits glucose disposal [33]. Visceral adipose tissue releases higher amounts of IL-8 than subcutaneous adipose tissue. The high levels of IL-8 released from adipose tissue and the accumulation of this tissue account for some of the increased circulating IL-8 in obese subjects [34]. Thus, adipose tissue is another IL-8 generating organ. Furthermore, AMPK activator AICAR can reduce IL-8 secretion in human adipose tissue and skeletal muscle cells [35]. Therefore, the AMPK signaling pathway is involved in myokine IL-8 production.

3.3. IL-15

IL-15 is constitutively expressed by skeletal muscle and modulated by exercise [36]. It exerts an anabolic effect on skeletal muscle *in vitro* and *in vivo*, decreases muscle protein degradation but does not increase protein synthesis, and reduces adipose tissue mass, suggesting that IL-15 plays a key role in the muscle-fat interaction [4,37–40]. The pleiotropic myokine IL-15 also regulates oxidative skeletal muscle fiber metabolism, consequently modulating body composition and insulin sensitivity. Transgenic mice that overexpress skeletal muscle-specific IL-15 have lower body fat following high-fat feeding and greater insulin sensitivity without changes in overall lean body mass; however, the oxidative soleus muscle mass is increased in these mice, accompanied by alterations in the expression of genes associated with fatty acid metabolism including silent information regulator 1 (SIRT1), SIRT4, and uncoupling protein 2 (UCP2) [41]. Furthermore, IL-15 treatment increases mitochondrial membrane potential and decreases lipid deposition in cultured adipocytes; overexpression of muscle-specific IL-15 elevates mitochondrial activity and mass in adipose tissue [42]. These findings indicate that IL-15 is linked to altered mitochondrial function in myocytes and adipocytes and plays a key role in the crosstalk between skeletal muscle and adipose tissue.

3.4. FGF21

Fibroblast growth factor-21 (FGF21) is a member of the FGF super-family. FGF21 has a direct effect on glucose uptake by skeletal muscle. It increases basal and insulin-stimulated glucose uptake in myotubes accompanied by enhanced GLUT1 mRNA abundance at the plasma membrane, and potentiates insulin-stimulated glucose transport of isolated extensor digitorum longus muscle without altering phosphorylation of Akt or AMPK [43].

Mitochondrial respiratory chain deficiency raises a compensatory response in the skeletal muscle via increased expression of FGF21 mRNA and protein in muscle, resulting in enhanced mitochondrial function through a PGC-1α dependent pathway [44]. Mice without FGF21 fail to fully induce PGC-1α expression in response to a prolonged fast and have impaired gluconeogenesis and ketogenesis [45]. There may be a relationship between FGF21 and PGC-1α factor. Moreover, FGF21 has many functional similarities to adiponectin, which acts as a downstream effector

of FGF21, controlling systemic glucose and lipid homeostasis in skeletal muscle and the liver in an endocrine manner. Meanwhile, adiponectin regulates the effect of FGF21 on energy metabolism and insulin sensitivity in these tissues; thus, the FGF21-adiponectin axis may be involved in these events [46,47].

FGF21 is also an important endogenous regulator for integrated energy and lipid metabolism and inhibits lipolysis during fasting [48]. Increased secretion of myokine FGF21 from muscle is associated with disturbance in mitochondrial function and integrated stress response activation in skeletal muscle. FGF21 also has endocrine effects leading to increased browning of WAT, with up-regulation of the UCP1 gene and PGC-1α protein [49–51], suggesting that crosstalk between muscle and adipose tissue is mediated by this myokine; this may explain the fat or weight loss observed post-FGF21 treatment *in vivo*. FGF21 gene is also a direct target of PPARγ, and the synergy between FGF21 and PPARγ pathways is demonstrated in 3T3-L1 adipocytes [52].

3.5. Irisin

In 2012, a new muscle tissue-secreted peptide FNDC5/irisin was identified [8]. FNDC5 is synthesized as a type I transmembrane protein and its soluble form, irisin, is released into circulation during proteolytic processing. It is speculated that FNDC5 activity and/or expression might be mediated by a cell surface receptor, but the identity of such a receptor is not yet known.

Irisin acts on skeletal muscle, resulting in increased energy expenditure and oxidative metabolism through the induction of metabolic genes associated with the regulation of cell energetics. FNDC5 mRNA expression and irisin secretion, as well as PGC-1α and myogenic gene expression, are increased during myogenic differentiation, in addition to the extracellular-signal regulated kinase (ERK) pathway in human myocytes. Moreover, irisin induces glucose uptake via the reactive oxygen species-mediated AMPKα2 pathway accompanied by p38MAPK-GLUT translocation in differentiated skeletal muscle cells [6,53].

In obese subjects, FNDC5 expression in skeletal muscle and circulating irisin levels are reduced and are related with insulin sensitivity [54]. Irisin improves glucose homeostasis with up-regulation of UCP1 and activation of p38MAPK and ERK signaling pathways, increases adipocyte energy expenditure, and modulates the expression of metabolic enzymes and intermediates; this inhibits lipid accumulation and reduces body weight in mice [55,56], demonstrating that irisin can potentially prevent obesity and obesity-associated type 2 diabetes. Irisin also promotes UCP2 protein expression in adipocytes with multilocular lipid droplets and a higher density of mitochondria, a characteristic feature of brown adipocytes [8]. These studies show that FNDC5/irisin is a myokine with a pleiotropic role in muscle and is involved in the improvement of adipocyte metabolism.

Our knowledge of the regulation of irisin has greatly expanded over the past three years; however, several questions remain, such as (1) identification of the irisin receptor; (2) elucidation of the molecular pathways modulating the cleavage of FNDC5 into irisin; and (3) identification of other functions of irisin based on its effect on energy metabolism in skeletal muscle and adipose tissue.

3.6. Myonectin

Myonectin, a recently identified novel myokine, is expressed mainly in skeletal muscle. Myonectin is a nutrient (carbohydrate or lipid) regulator secreted by skeletal muscle in response to changes in the cellular energy state resulting from glucose or fatty acid fluxes. It promotes fatty acid uptake in cultured adipocytes and hepatocytes by up-regulating the expression of genes that are involved in lipid uptake, such as fatty acid translocase (FAT/CD36), fatty acid transport protein 1 (FATP1), fatty acid binding protein 1 (FABP1), and FABP4. Myonectin expression may be regulated differentially depending on the muscle fiber type. Within skeletal muscle, a predominantly slow-twitch, oxidative muscle fiber type (e.g., soleus) tends to have a higher level of myonectin transcript expression relative to a glycolytic, fast-twitch fiber type (e.g., plantaris). Exercise and nutrients are the primary stimulators of myonectin expression. The level of myonectin transcript expression can be up-regulated in cultured mouse myotubes with the addition of glucose or free fatty acids, demonstrating that myonectin may be responsive to a nutrient flux, to inform other tissues of the nutrient status and promote nutrient uptake and storage [57,58].

4. Adipokines and their roles in adipose tissue/skeletal muscle protein and energy metabolism

Adipose tissue is not only an energy reserve providing free fatty acids to different tissues (e.g., skeletal muscle, liver, and heart) but also an endocrine organ with autocrine and paracrine functions due to the secretion of adipokines, such as leptin and adiponectin (Fig. 2). The different fat depots (subcutaneous *vs*. visceral) are heterogeneous not only in terms of metabolic capacity but also in the adipokine secretion pattern. The term adipokine is used to describe all proteins secreted from any type of adipocyte that play a central role in energy homeostasis and immunity. Although certain adipokines have been identified and extensively studied, the identification and functional studies of new adipokines and their regulation of integrative physiologic responses are essential for further understanding.

4.1. Leptin

Leptin, the first identified adipokine [59], is a hormone produced primarily by WAT as well as numerous other tissues and cells including brown adipose tissue [60]. Subsequent research

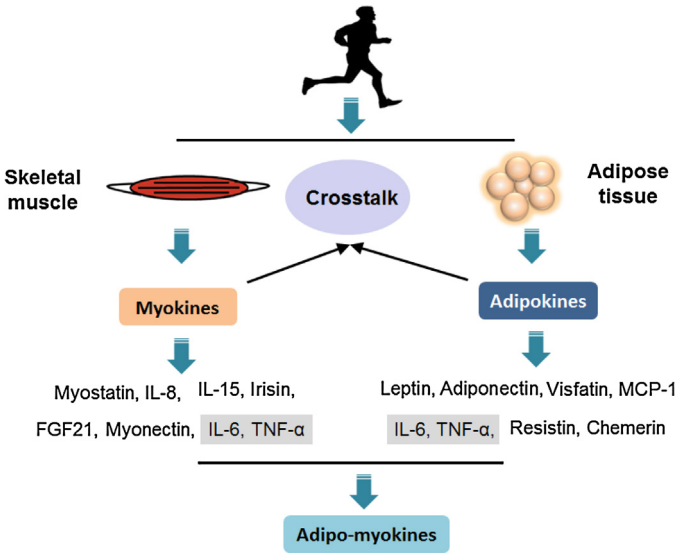

Fig. 2. Known secretory factors from skeletal muscle and adipose tissue. Adipocytes/adipose tissues secrete adipokines including interleukin (IL)-6, tumor necrosis factor (TNF)-α, leptin, adiponectin, resistin, chemerin, visfatin, and monocyte chemotactic protein-1 (MCP-1). Skeletal muscle secretes myokines including IL-6, TNF-α, myostatin, IL-8, IL-15, irisin, fibroblast growth factor 21 (FGF21), and myonectin. Some of the adipo-myokines (e.g., IL-6, TNF-α) are secreted from both adipocytes and myocytes and are involved in the crosstalk between adipose and skeletal muscle tissue.

identified an association between leptin and adipocyte volume and that subcutaneous adipocytes are larger than omental adipocytes [61]. Skeletal muscle also releases leptin [62]; however, the pattern of release is different from that of subcutaneous adipose tissue [63,64], suggesting that leptin may contribute to whole body leptin production and metabolism. Leptin and the branched-chain amino acid leucine synergistically regulate protein metabolism in skeletal muscle *in vivo* and myocytes *in vitro* [65]. We speculate that leptin production is likely modulated by nutrients, including various amino acids. The MEK-ERK pathways in the ventromedial hypothalamus play an important role in leptin-induced glucose uptake in red-type muscle, as well as in whole-body glucose utilization [66]. It provides important insight into the mechanism of the antidiabetic effects of leptin in humans and rodents.

4.2. Adiponectin

Adiponectin was initially identified as a factor secreted by WAT and later by brown adipose tissue [67–69], playing a critical role in energy homeostasis and the insulin signaling pathway. Its actions are modulated via binding to receptors, especially adiponectin receptor 1. The location of adipose depots differentially influences circulating adiponectin concentrations, which are positively associated with lower extremity fat and negatively correlated with truncal fat [70]. Triglyceride clearance is enhanced by increasing lipoprotein lipase expression in WAT in adiponectin transgenic mice [71].

AMPK is the downstream protein in the adiponectin signaling cascade, and activation of AMPK likely plays a critical role in mediating the simulative effects of adiponectin on fatty acid oxidation in skeletal muscle [72,73]. However, it is still unclear whether adiponectin modulates intramyocellular triglyceride mobilization. Adiponectin regulates mitochondrial biogenesis and improves lipid metabolism in skeletal muscle through two pathways: AMPK/SIRT1/PGC-1α dependent mechanisms [74] and the p38 MAPK/PGC-1α signaling pathway [75,76]. However, it is still largely unknown how exactly adiponectin increases mitochondrial oxidative metabolism. Additionally, a recent study indicated that adiponectin induced autophagy and reduced oxidative stress, especially under pathological conditions [77]. In future studies, we should try to understand if the local pool of adiponectin in skeletal muscle or adipose tissue acts in the same or in a different manner compared with the circulating pool of adiponectin.

4.3. Resistin

In skeletal muscle cells, chronic incubation with resistin decreases fatty acid uptake and metabolism via a mechanism involving reduced cell surface FAT/CD36 content, FATP1 expression, and phosphorylation of AMPK and acetyl-CoA carboxylase (ACC), without altering cell viability [78]. It also reduces basal and insulin-stimulated glucose uptake, oxidation, and glycogen synthesis independent of AMPK by altering insulin receptor substrate-1 and Akt1 function and decreasing GLUT4 translocation [79,80]. All of these observations highlight the potential role of resistin in obesity and impaired glucose homeostasis. In cultured human visceral adipose tissue, resistin stimulates lipolysis via protein kinase A and ERK signaling pathways and promotes fatty acid and glycerol efflux from adipocytes to plasma, indicating a central role of resistin in obesity-related pathologies via its effect on adipose tissue [81]. Moreover, a calculation was recently developed to indicate the close relations among leptin, adiponectin, and resistin [82].

4.4. Chemerin

Chemerin is expressed at its highest levels in WAT and the liver [83]. The research conducted in our lab showed increased mRNA expression by chemerin in conjunction with skeletal muscle cell differentiation; moreover, incubation with chemerin promotes proliferation and suppresses differentiation of muscle cells through ERK1/2 and mTOR signaling pathways [3]. Chemerin induces insulin resistance in adipocytes and skeletal muscle cells. Accumulated abdominal visceral fat, elevates blood pressure, and an abnormal lipid profile are significantly associated with serum chemerin concentrations [84]; thus, chemerin may be used as a mediator linked to visceral obesity. The expression of chemerin, its receptor CMKLR1, and G protein-coupled receptor 1 are altered in WAT and skeletal muscle in the obese/diabetic mouse model [85], indicating that chemerin influences glucose homeostasis and may contribute to the metabolic derangements that are characteristic of obesity and type 2 diabetes.

4.5. Visfatin

Visfatin and leptin have a coordinated role in various functions. The pleiotropic effects of leptin may be partially mediated by visfatin. The production of visfatin is increased by leptin in adipose tissue *in vivo* and *in vitro* through MAPK and PI3 K pathways [86]. It also stimulates glucose uptake in muscle cells through Ca^{2+}-mediated phosphorylation of AMPKα2 [6]. Findings from a previous study indicated that visfatin was produced at higher levels in skeletal muscle than in visceral adipose tissue [7]; therefore, visfatin might further function as a myokine that affects skeletal muscle growth and metabolism.

4.6. MCP-1

MCP-1 is expressed by adipocytes and a number of other cell types [87,88]. Basal adipose tissue MCP-1 mRNA level is significantly higher in *ob*/*ob* mice than in lean mice [89]. Insulin increases expression and secretion of MCP-1 in murine adipocytes *in vitro* and in *ob*/*ob* mice *in vivo* [90]. It reduces insulin-stimulated glucose uptake in the myocytes at concentrations even below that found in the circulation, which is accompanied by the activation of the ERK1/2 but not the NFκB pathway [91]. Thus, MCP-1 opens a completely novel but important window in modulating adipocyte metabolism and insulin sensitivity. In addition, conditioned media from differentiated human adipocytes impair insulin signaling in human skeletal muscle cells *in vitro*; regeneration of myotubes for 24 or 48 h after stimulation of insulin resistance restored normal insulin signaling and secretion of IL-6, but not the normal release of MCP-1 [92], indicating different functions and regulation mechanisms between MCP-1 and IL-6.

5. Adipo-myokines

Recent studies revealed that there is considerable overlap between myokines and adipokines. A number of cytokines (called "adipo-myokines") secreted from skeletal muscle cells are also secreted by adipocytes [93]. The classic and best described members of this family are IL-6 and TNF-α (Table 1, Fig. 3).

5.1. IL-6

IL-6 is a cytokine produced by multiple tissues in the body, including skeletal muscle, adipose tissue, and immune cells. The myokine IL-6 is of critical importance for muscle performance during contraction, while the adipokine IL-6, if chronically elevated, can induce muscle insulin resistance. The concepts and

Table 1
Reciprocal metabolic effects of adipo-myokines interleukin (IL)-6 and tumor necrosis factor (TNF)-α in skeletal muscle and adipose tissue (increase: ↑; decrease: ↓).

	IL-6	TNF-α
Skeletal muscle		
Differentiation	↑	↓
Protein synthesis	↓	↓
Protein degradation	↑	↑
Lipid storage	↓	↑
Lipid oxidation	↑	↓
UCP3 expression	↑	↑
Glucose transport	↑	↓
Glucose synthesis	↑	↓
Adipose tissue		
Differentiation	↓	↓
Lipid storage	↓	↓
Lipid oxidation	↑	↑
UCP2 expression	↑	↑
Glucose transport	↑	↑

UCP, uncoupling protein.

approaches derived from studies of IL-6 may serve as a valuable model for studies of other myokines or adipokines.

IL-6 exerts its biological effect by binding to the IL-6 receptor and activating the Janus-activated kinase-signal transducer and activator of transcription signaling pathway [94]. The role of IL-6 in living systems is ambiguous or even contradictory because of its dual effect, since it sometimes functions as a pro-inflammatory cytokine and sometimes as an anti-inflammatory factor, depending on the environment (muscle cell *vs.* immune cell) [12].

IL-6 works as an energy sensor and exerts beneficial effects on metabolism. When muscle glycogen content is low, the IL-6 gene expression level and protein release are enhanced [95], indicating that IL-6 is involved in an energy-sensing pathway. Following release from both type I and type II muscle fibers, IL-6 acts in an endocrine manner through the gp130Rβ/IL-6Rα receptor, causing subsequent activation of AMPK and/or PI3K pathways and increasing glucose uptake and fatty acid oxidation [12]. The expression of IL-6 is more prominent in type I skeletal muscle fibers, whereas type II fibers solely express TNF-α [96], demonstrating a difference in the response to the two adipo-myokines. IL-6 deficiency raises the levels of skeletal muscle free fatty acid transporters and intramuscular lipid content in type I but not in type II muscle fibers in mice [97]. The specificity of adipo-myokine expression in different muscle fiber types demonstrates that these factors may play specific regulatory roles in normal muscle physiology and enhance their established endocrine effect in muscle.

However, the exact mode of action of IL-6 in adipocytes is far from clear. A high local IL-6 concentration increases lipolysis and fatty acid oxidation, likely via the activation of the AMPK signaling pathway, and modulates leptin production in human adipose tissue [98–100]. Muscle-specific IL-6 knockout mice had lower inguinal adipose tissue mass and reduced GLUT4 protein content, AMPK phosphorylation, and fatty acid synthase mRNA expression in the tissue [101]. Skeletal muscle IL-6 might affect WAT mass through regulation of glucose uptake capacity as well as lipogenic and lipolytic factors.

5.2. TNF-α

TNF-α is secreted by adipocytes and linked to the development of insulin resistance in adipose tissue [102]. In fact, TNF-α is secreted by various cell types including skeletal muscle.

In skeletal muscle tissue, TNF-α inhibits myoblast differentiation *in vitro* by decreasing myoD and myogenin expression [32] via nuclear factor-kappa B (NF-κB) activation and impairment of the IGF-1 signaling pathway [103]. Through TNF receptor 1, TNF-α signaling suppresses AMPK activity and consequently reduces ACC phosphorylation and fatty acid oxidation and increases intramuscular diacylglycerol accumulation causing insulin resistance in skeletal muscle [104]. Recent work from our laboratory demonstrated that different n-6:n-3 polyunsaturated fatty acid ratios can mediate the transcription rate of IL-6 and TNF-α in skeletal muscle

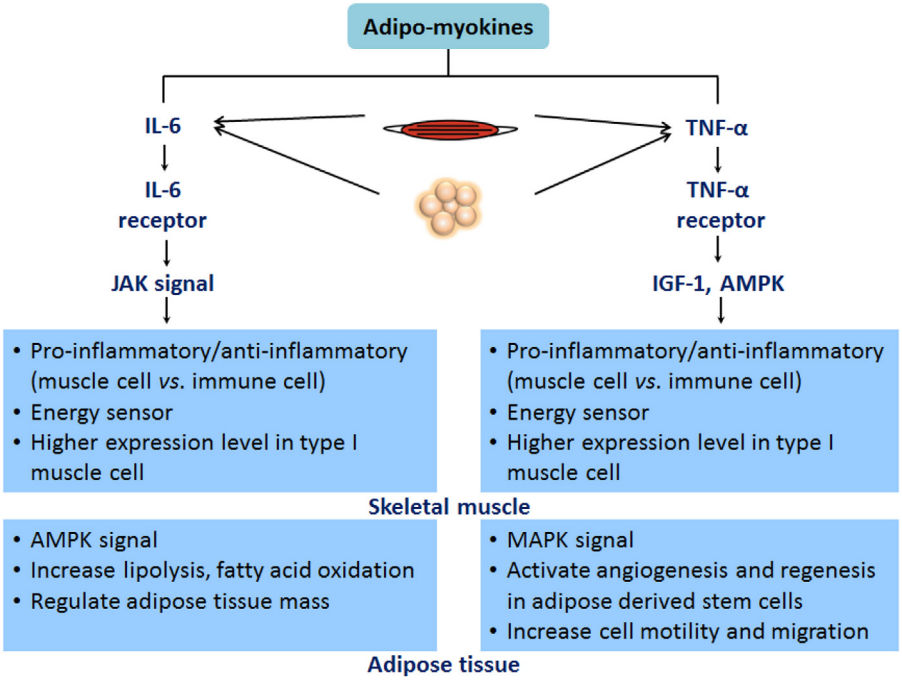

Fig. 3. Biological effects of adipo-myokines IL-6 and TNF-α on skeletal muscle and adipose tissue.

and subcutaneous adipose tissue in finishing pigs as an animal model [105].

TNF-α can limit adipose tissue mass by increasing total glucose metabolism, accelerating lactate production, and enhancing lipolysis in adipocytes in a direct paracrine fashion [106]. In human preadipocytes, TNF-α activates the MAPK signaling pathway, including ERK1/2 and JNK but not p38, in a distinct time- and concentration-dependent manner, which is mediated by the TNF receptor [107]. Furthermore, the adipo-myokine TNF-α plays a role in activating the angiogenic and regenerative potency in adipose-derived stem cells. Treatment with TNF-α enhances adipose-derived stem cell proliferation and F-actin microfilament assembly, increases cell motility and migration through the extracellular matrix, and up-regulates the mRNA expression of proangiogenic factors [108].

6. Crosstalk between myokines and adipokines

Certain myokines and adipokines interact with each other. IL-6, TNF-α, and leptin are the three hormones that are modulated in a similar manner, and their communication has a further layer of complexity as TNF-α also stimulates leptin production [17]. Administration of the adipokine leptin promotes irisin-induced myogenesis, but represses the subcutaneous fat browning induced by this myokine in wild-type and *ob*/*ob* mice. Leptin administration also induces an increase in FNDC5 expression in skeletal muscle of wild-type and *ob*/*ob* mice in a PGC-1α and inducible nitric oxide synthase-dependent manner, but reduces the expression of this myokine in subcutaneous fat by decreasing PGC-1α expression [109]. FNDC5 expression level in subcutaneous tissue is higher in non-obese than in the obese subjects, and leptin decreases FNDC5 mRNA expression in the subcutaneous adipose tissue of non-obese subjects [110]. Compared with wild-type littermates, transgenic over-expression of myostatin propeptide in mice fed a high-fat diet enhances muscle mass and circulating adiponectin and increases epididymal adiponectin mRNA expression [111], suggesting that there is crosstalk between myokines and adipokines as well as the positive effects of enhanced muscle growth on fat metabolism. Therefore, the interaction of myokines and adipokines lay foundation of the crosstalk between skeletal muscle and adipose tissue.

7. Proteomics/secretomics used to identify novel myokines or adipokines

Myokines and adipokines work in a hormone-like fashion, and an increasing body of evidence implies that myokines and adipokines play a critical role in body homeostasis. However, the major challenge now is to determine the characteristics of new cytokines and relate them to *in vivo* conditions.

Advances in proteomics have allowed for more comprehensive analyses of proteins secreted from skeletal muscle and adipose tissue. Recently, proteomic studies focusing on the secretomics (the entire complement of secreted proteins) of cultured mouse or human myotubes have revealed a large number (approximately 300 in humans and 600 in mouse) of muscle cell-derived secretory myokines with potential autocrine, paracrine, and/or endocrine functions [5,112,113]. These findings also suggest that muscle cells secrete different types of myokines under different conditions in order to communicate with various types of cells.

The first study of human adipose tissue, rather than the adipocyte cell secretome, was reported in the year 2007. Human visceral adipose tissue explants were cultured in media containing L-[^{13}C6,^{15}N2]lysine to validate the origin of the identified proteins (adipose- or serum-derived), and the obtained proteins were categorized based on function [114]. Visceral, subcutaneous, and gonadal fat of rats differentially secrete proteins depending on their anatomical localization [115]. Using separate filtering methods, approximately 28 TNF-α modulated secretory proteins were identified based on comparative analysis of levels of proteins released in the media from L6 skeletal muscle cells [116].

However, secretomics for skeletal muscle and adipose tissue is still in its infancy. A comprehensive profiling of the secretome will expand our knowledge of the composition of the myokinome and adipokinome and may contribute to a better understanding of the role of novel secreted factors in the ontogeny, physiology, and pathology of muscle and adipose tissue. This knowledge will ultimately help us improve the diagnostic and therapeutic approaches for diseases related to muscle and adipose tissue.

8. Concluding remarks and future perspectives

The evidence collected so far clearly indicates that skeletal muscle and adipose tissue function as endocrine organs producing a variety of factors to fine-tune metabolism. It is essential to further clarify the interactions among adipose depots, such as inter- and intra-muscular fats, muscles of different fiber types (types I and II), and associated signaling pathways. In this rapidly advancing age of "-omics" technologies, future studies will define new myokines and adipokines released from skeletal muscle or adipose tissue cells.

It is also warranted to identify the crosstalk mechanisms that govern myokine or adipokine synthesis in skeletal muscle or adipose cells: (a) the mechanisms that are most critical, (b) how myokines and adipokines interact with each other, and (c) how myokines and adipokines are induced and regulated by various nutrients, such as amino acids, fatty acids, and plant extracts. It is also pivotal to examine the *in vivo* effects of myokines and adipokines by direct administration in animal models, which is the current research focus in our laboratories. Understanding the complexity of crosstalk between skeletal muscle cells and adipocytes will allow the development of new strategies to improve human health and to sustain the production of high-quality meat in livestock. Finally, myokines and adipokines could be developed into biomarkers for diagnosis, prognosis, and therapeutic targets in diseases such as obesity and metabolic syndrome.

Conflict of interest

The authors have no conflicts of interest to declare.

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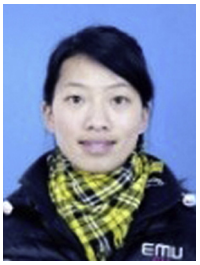

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