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Responses of Muscle Mitochondrial Function to Physical Activity: A Literature Review

Keyvan Hejazi[1*]

[1] *Physiologist, Department of Exercise and Sport Physiology, Faculty of Sport Sciences, Toos Institute of Higher Education, Mashhad, Iran*

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ABSTRACT

Skeletal muscles play an active role in regulating the metabolic homeostasis through their ability for relating to adipose tissue and endocrine hormones. Contraction of the skeletal muscle leads to increased release of several myokines, such as irisin, which is able to interact with the adipose tissue. Physical activity promotes the irisin mechanism by augmenting the peroxisomes (PGC1-α) in the skeletal muscle. Afterwards, an elevation occurs in the membrane protein of fibronectin type III domain-containing protein 5 (FNDC5) in muscle, ultimately resulting in production of irisin. The expression of irisin and FNDC5 converts white adipose into the brown type and increases energy consumption by the whole body hindering obesity and diabetes. The effects of regular exercise training on preventing obesity, diabetes, and the related complications, as well as improving health have already been proven. However, the point is that these beneficial effects are due to the cellular-molecular mechanisms, which are still under discussion.

In this review, we searched the online databases, including scientific information database (SID), Google Scholar, PubMed, Science Direct, and Scopus. The following keywords were used: training, physical activity, myokine, adipose tissue, PRDM16, PGC-1α, PPARγ, SIRT1, FGF21, bone morphogenetic protein, neurugolin, VEGF, and IL-15. All the articles, including research studies, review articles, descriptive and analytical studies, in addition to cross-sectional researches published during 1998-2017 were reviewed.

According to the obtained results, it seems that expression of irisin and FNDC5 converts the white adipose into brown adipose resulting in increased energy consumption. It has been proven in the literature that regular exercise training prevents obesity, diabetes, and the related complications, as well as improving health.

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Introduction

There are two types of adipose tissue in human body, namely white or single-hollow adipose tissue and brown or multicellular adipose tissue. They are different regarding the metabolic activity, color, and blood vessels (1). White adipose tissue (WAT) is mainly an important center for adjusting energy metabolism and a fuel storage. It also affects other considerable biological processes such as angiogenesis, blood pressure control, blood clotting, and immune system. WAT completes its regulatory functions through secreting the adipokines. Moreover, adipose tissue provides a thermal insulation and protects the internal organs against mechanical damages (2).

On the other hand, brown adipose tissue (BAT) is thermogenic due to existence of exclusive uncoupling protein 1 (UCP1). This

**Corresponding author:* Keyvan Hejazi, Department of Exercise and Sport Physiology, Faculty of Sport Sciences, Toos Institute of Higher Education, Mashhad, Iran. Tel: 05136063044; Fax: 05136063055; Email: keyvanhejazi@gmail.com

protein is located in the mitochondrial internal membrane and producing thermogenesis in the tissue (3). In accordance with cold, the number of brown adipose cells increases and presents as multi-hole cells in WAT. This phenomenon indicates that the new adipose cells result from duplication and differentiation of the pre-existing cells that have been already there. In addition, it might be conducted and affected by transformation in the differentiation mode of white adipose cells (4).

Irisin is known as one of the Myokines speeding up this process. Irisin acts as a bridge between skeletal muscle and other tissues involved in homeostasis and energy metabolism, such as adipose tissue, induced by PGC-1a (5). Irisin is a provoked hormone with regular physical activity secreted by skeletal muscles in mice and human. This hormone stimulates conversion of WAT to brite adipose tissue, improving systematic metabolism by augmenting energy cost (5).

PGC-1a activates the transcription factor PPAR-γ imposing most of its biological effects on energy metabolism (6). It has been also shown to affect and provoke various processes by this factor, such as mitochondrial biogenesis, angiogenesis, the type of fiber change, and muscle atrophy prevention (7). Moreover, PGC-1a regulates the expression of FNDC5 protein (5). This protein is secreted in blood after cleavage and is called as irisin hormone. Then in BAT, it will expression UCP1 gene (8).

There are different theories concerning the effects of exercise on the molecular and cellular mechanisms, as well as related compatibilities to the changes of adipose tissue. One of the newest theories in this regard is irisin hormone. This theory states briefly that a hormone (Myokine) named irisin is secreted from skeletal muscles as the result of exercising. This hormone affects the WAT and conversion into BAT increasing the calorie intake and thermogenesis that finally cause reduction in body weight.

The molecular and cellular mechanisms that arise as responses for compatibility with exercising and the changes of WAT and BAT are among the main parts of thermogenesis regulation, which require further studies. With this background in mind, the present study aimed to evaluate the responses of muscle mitochondria to physical activity, such as stimulating BAT turning it into WAT in order to increase energy consumption and cope with obesity, as well as the related complications.

Materials and Methods

Databases and Search Strategies

In this study, various databases such as Google Scholar, scientific information database (SID), PubMed, Science Direct, and Scopus were searched. We selected the articles published during 1998-2017. The search keywords entailed training, exercise, physical activity, adipose tissue, myokine, PRDM16, PGC-1α, PPARγ, SIRT1, fibroblast growth factor 21 (FGF21), bone morphogenetic protein, neurugolin, vascular endothelial growth factor, and IL-15. Afterwards, the full manuscripts of articles and their methodologies were carefully examined. We omitted the article from our analysis in case of any errors in the study methodology. Moreover, we designed a shorthand form to extract information, which consisted of information about subject, title, journal name, and author.

Results

Development of WAT and BAT

Adipose cells are derived from mesenchymal stem cells that appear on the fetal mesoderm layer. BAT and skeletal muscle tissues arise from the same precursors of myogenic factor 5 (Myf5). It has been determined that several simultaneous activators can affect the process of adipocytes differentiation from transforming white fat cells into brown fat breit cells. Some of these factors are the PR domain containing 16 (PRDM16), CCAAT/enhancer-binding protein β (C/EBPβ), activator of peroxisome gamma multiplicative gamma receptor cofactor alpha (PGC-1α), and growth factors, such as bone morphogenetic protein 7 (BMP7) belonging to transforming growth factor beta (TGFβ) family. Stimulation of WAT with these activators leads to growth of fat cells that might activate the BAT (9).

Adipogenesis process is followed by distinction of white and brown adipocytes resulting in intracellular fat accumulation. A cascade of interactions between several transcription factors control adipogenesis, including the peroxisome activating gamma receptor, PGC-1α, PRDM16, C/EBPβ, Forkhead box protein C2 (FOXC2), and steroid response element-binding protein 1-c (SREBP1c) (10-12).

One of the most important factors in this PPARγ signaling cascade belongs to a large family of nuclear receptors and coordinates the use of adipogenic elements during differentiation of the adipocytes. This receptor is necessary for adipogenesis of both WAT and BAT. Both white and brown adipocytes express high levels of PPARγ (13).

PGC-1α is a protein involved in mitochondrial biogenesis and aerobic metabolism in many cells, such as skeletal muscle and BAT. This protein can upregulate the expression of mitochondrial exothermic genes (14). Another important protein, PRDM16, plays a pivotal role

in regulating the differentiation and evolution of WAT and BAT under the influence of various factors. One of these effective factors is BMP7, which is an essential signal for BAT development and imposes effects by increasing the amount of PRDM16 mRNA in BAT and WAT (15, 16).

Thiazolidinedione (TZD) as an agonist for PPARγ augments the expression of thermogenesis cells in the adipose tissue through the effects of PRDM16. MicroRNA133 also reduces PRDM16 levels, thereby stopping evolution of fat for berit and BAT. The amount of this substance reduces as the result of exposure to cold (16). The evidence suggests that storage area is a part of BAT in the underlying umbilical region and kidney of the rat. Moreover, BAT may appear in the adipose tissue and muscle tissue lacking Myf5 after exposure to chronic cold weather or β-adrenergic stimulation. There are also white and brown fat cells or beige adipose tissue in the WAT containers acting as a kind of precursor to brown fat cells in the adipose tissue, which is currently under discussion (9).

According to the study by Wu et al. (2012), thyroid cells in the adipose tissue are the trigger for expression of non-conjugated protein type 1. In addition, BAT can act in response to stimulation of the cyclic adenosine monophosphate (cAMP) by expressing UCP1 (17). On the other hand, Vegiopoulos et al. (2010) demonstrated that the activities of cyclooxygenase-2 (COX-2) and prostaglandins are among the influential factors that indicate the β-adrenergic downstream signaling pathways in WAT (18).

Boström et al. (2012) showed that stimulating the expression of PGC-1α could stimulate several genes, including the encoded factor of membrane protein gene produced in skeletal muscle fibronectin. The membrane protein of fibronectin, as the irisin protein precursor and its activation agent can be found in the plasma of rats and humans after exercise (19).

Importance of BAT Activation

A potential clinical concept of activating BAT is related to the stimulation of resting energy consumption and the consumption exothermic. In humans, it seems that the exothermic of food consumption is more likely to occur in BAT. In people who have a higher BAT ratio , compared to those with a lower BAT content, the amount of consumed calories in the food that is directly converted to heat is reduced (20). Some examples of BAT activation-related clinical implications encompass stimulation of the basic metabolism, stimulation of the food intake exothermic reactions, increased clearance of glucose and lipids, improved cholesterol metabolism, and positive effects on bone mineral density in women (20).

Vosselman et al. (2013) reported an elevation in glucose uptake of BAT after having consumed a high-calorie meal as carbohydrate-rich foods in adult males. According to Vosselman et al., reported that BAT have an important role in metabolic rate (21). In this regard, Kajimura et al. (2014) estimated that the BAT-dependent energy consumption in cold weather conditions is about 200-400 kcal/day (22).

The amount of active BAT in humans varies and it seems that there is almost 50 g of active BAT in most humans. It is estimated that this 50 g of active BAT may account for about 20% of the energy consumption at rest. Optimistically, about 50 g of active BAT can consume about 5% of the rest energy. A 5% increase in chronic restful energy consumption results in consumption of about 75-100 kcal/day during a year, which may lead to losing 4-5.5 kg of fat per year (20).

Consequently, even in the most optimistic way, activating BAT may affect the process of obesity or body fat reduction. Except for the negative energy balance, BAT activation can also have beneficial metabolic effects. One of these effects is the ability of BAT to oxidize glucose and hypolipidemic and euglycaemic. In case BAT is able to elevate the clearance and oxidation of glucose and excessive fat, it will delay development of insulin resistance (20).

Factors Affecting Adipose Tissue Browning

In addition to the aforementioned factors, some other proteins, hormones, and microRNAs affect the browning process of WAT as summarized in Table 1.

In this context, small molecules, proteins, peptides, and other stimuli play role in inducing the browning process of WAT. The browning process is carried out by nuclear regulator factors, the most important of which being PRDM16, PGC-1α, PPARγ, SIRT1, fibroblast growth factor 21 (FGF21), BMP, neuregulin, vascular endothelial growth factor, and IL-15.

PRDM16

PRDM16 is a determining factor in the development of brown fat, as well as the process of browning. It was shown that upregulating the expression of PRDM16 gene in transgenic rats caused increased energy consumption and glucose intolerance (32). Furthermore, in rats without PRDM16 gene, downregulation of the UCP-1 gene and the brown-fat-specific genes, namely CIDEA, as well as the mitochondrial genes, such as COX-8b are observed in subspecies adiposities (22, 33).

Table 1. factors affecting adipose tissue browning

Agent	Type	Effect	Role	Ref
4E-BPI	Connective protein	Negative	Negative effect on PGC-1α	(22)
BMP7	Secreted protein	Positive	Requirements for the browning process	(23)
ANP	Hormone	Positive	For browning, the white adipose tissue acts through the protein kinase G	(24)
COX-2	Transitional protein	Positive	Essential for browning of WAT through coldness and beta-adrenergic tissue	(18)
FGF21	Secreted protein	Positive	The browning agents of WAT depend on PGC-1α	(25)
miR-133	MicroRNA	Negative	Negative impact on PRDM16	(26)
miR193b-365	MicroRNA	Positive	Requirements for the browning process	(26)
miR196a	MicroRNA	Positive	Preventing Hoxc8 and C/EPBβ	(26)
TRPV4	Ionic channel	Negative	Negative effect on PGC-1α	(27)
C/EPBβ	Transcription factor	Positive	Preventing expression of white fat genes	(28)
EBF2	Transcription factor	Positive	Elimination of the PPARγ steel group leading to connection to PRDM16	(29)
P107 & RB	Transcription factor	Negative	Prevention of PGC-1α gene expression	(22)
SIRT1	Transcription factor regulator	Positive	Elimination of the PPARγ steel group leading to connection to PRDM16	(30)
TIF2 & SRC1	Transcription factor	Negative	Transfusion mice lacking TIF2 showed signs of adipose tissue browning	(31)
TBX15	Transcription	Positive	Essential for production of brown and bean fat cells to increase expression of the UCP1 gene and related genes	(32)
TFAM	Mitochondrial transcription factor	Negative	Reducing TFAM causes increase in the mitochondrial oxidative capacity and the increased activity has a negative effect on UCP1 PRDM16	(32)
TLE3	Transcription factor regulator	Negative	Disrupting PPARγ and PRDM16 interactions	(32)

Peroxisome Proliferator-activated Receptor Gamma Coactivator 1-alpha (PGC-1α)

The PGC-1α protein encoded by the PPARGC1A gene is a transcriptional activator and acts as an activator of PPARγ regulating expression of the UCP1 gene and browning in brown fat. Moreover, in some cases this protein controls the mitochondrial biogenesis and oxidative metabolism in many cells. This protein can cause mitochondrial biogenesis, angiogenesis, and muscle fibers alterations in the skeletal muscle.

In addition, PGC-1α is resistant to dystrophy and muscle atrophy (34). It acts as a mediator in many of the biological mechanisms involved in energy metabolism. PGC-1α was named after identifying the role played by PPARγ activation. Studies have reported an upregulation in gene expression of this protein in a cold environment. This activator controls biogenesis and mitochondrial respiration by UCP1 proteins and the respiratory factors of nucleus (35).

Although this protein is essential for browning of white fat, it does not affect the browning process. However, in various experiments, upregulation of PGC-1α gene in subcutaneous tissue led to a change in the phenotype of adipose tissue to brown fat. This change by upregulation of the UCP1 gene, respiratory chain proteins, and oxidation enzymes has been associated with fatty acids (36).

Body fat of rats is resistant to PGC-1α and expression of mitochondrial genes and exothermic reaction in the subcutaneous fat are slower. However, in rats lacking the PGC-1α gene, expression of mitochondrial biogenic genes in WAT did not depend on PGC-1α. On the other hand, presence of this protein was indispensable for induction of UCP1 and other lipid-specific genes in white fat. This protein may also be involved in controlling blood pressure, regulating cellular cholesterol homeostasis, and developing obesity (37). Despite the important roles reported for PGC-1α in the browning process, there is not sufficient data available regarding PGC-1β and researchers do not consider a significant role for that.

The mechanisms by which PGC-1α activates gene expression is not well known. The results of studies indicate that the CBP/P300 and SRC-1 activate the acetyl transferase. In addition, terminals C include the SR motif and RNA binding region. This region requires expression of specific endogenous genes and interaction with proteins involved in RNA processing, such as Transport Protein Particle (TRAP) complex involved in copy onset (38).

Moreover, PGC-1α is associated with two other transcriptional complexes with acetyl transfer activity, namely GCN5 and TIP60. GCN5 directly secretes PGC-1α in the lysine residue, thereby reducing the PGC-1α transcription activity. In contrast, SIRT1 elevates the function of this cofactor by pseudizing the PGC-1α. SIRT1 controls the mitochondrial biogenesis, free radical production, and fatty acids oxidation by activating PGC-1α (39).

It is assumed that the two factors of nutrition

and hormonal messages affect the levels of PGC-1α (40). Researchers believe that glucose reduction, in addition to rise in glucagon, catecholamine, and glucocorticoid hormones trigger SIRT1 activation, distillation of PGC-1α, and increase the oxidation of mitochondrial fatty acids by activating PPAR (41). Regular long-term exercises seem to positively regulate SIRT1 and PGC-1α indices (42, 43).

SIRT1 can activate PGC-1α, which causes PPAR-γ activation and lipid oxidation. Expression of PGC-1α RNA induces the UCP2 peak in a PPAR-γ-dependent behavior. The effects of IL-15 on glycolic and oxidative muscles are different. Conversion of glycolytic to oxidative fibers may be a factor in lower hypertrophy of oxidation fibers (44). Expression of SIRT1 during overexpression and elevated IL-15 protein are involved in various biological processes, including inhibition of apoptosis, rise in insulin sensitivity, and conversion of glycolytic metabolism to aerobic metabolism.

However, SIRT1 inhibits muscle differentiation and myofibrille protein expression. Therefore, IL-15 and SIRT1 pathways are active in catabolic conditions and have negative effects on hypertrophy and muscle cell production (45). In summary, IL-15 regulates the oxidative metabolism of skeletal muscles instead of regulating insulin sensitivity and individual body composition.

Gurd et al. (2010) reported that following six weeks of intensive periodic exercise, SIRT1 activity augmented by 31% in skeletal muscles (46). One of the cellular changes that occurs due to physical activity is stimulation of AMPK and p38 paths from the SIRT1 pathway, leading to PGC-1α turn on and biogenesis of mitochondria (46).

Activation of AMPK and SIRT1 is strongly associated with induction of PGC-1α and mitochondrial biogenesis. Stimulation of AMPK by PGC-1α depends on SIRT1 triggered by RSV, metformin, and Nitrophenol A-769662. These effects result from AMPK ability to increase the levels of SIRT1 activating cells, as well as NAD^+, which triggers the activation of SIRT1 and allows PGC-1α to be distilled and affect other downstream pathways in rat muscle. AMPK subunit genetic damage Gamma-sensitive AMP in the muscle damages NAD^+. Therefore, activation of the PGC-1α pathway to AMPK is dependent on stimulation of SIRT1 through sensitive AMP in NAD^+ (47).

When turned on by AMPK, SIRT1 not only regulates PGC-1α, but also positively expresses the PGC-1α gene. This is performed in conjunction with MyoD by forming the SIRT1-MyoD-PGC-1α complex on the PGC-1α promoter in muscle tissue, providing a self-regulating loop for expression of PGC-1α. This result was not expected because SIRT1 is known to suppress MyoD impact on the target gene.

However, this discovery helps to describe the important relationship between the coordinated adjustment of specific muscle adaptation changes in gene expression and metabolism. Moreover, it contributes to adjusting PGC-1α to the downstream AMPK and SIRT1. Transcription activation adjusted by binding of the SIRT1-MyoD-PGC-1α complex to DNA is terminated by any reduction in the NAD^+/NADH ratio or by the PGC-1α distillation via GNC5. Consequently, SIRT1 and MyoD are released allowing PGC-1α to be coupled with its transcriptional inhibitor, RIP140. It describes this dynamic interaction between PGC-1α and SIRT1, which can regulate the expression and activation activity (47, 48).

PGC-1α Function in Skeletal Muscle

It has been shown that high contractile activity, such as in exercise changes the phenotypic adaptations of skeletal muscle to a more oxidative phenotype. Specifically, exercise activity leads to alterations in the type of blur, mitochondrial biogenesis, and other adaptive changes in humans (49-51). The coordinated adjustment of these processes is very interesting, and the available findings suggest that PGC-1α is the main actor of these adaptations. The genetic model of cell, with a change in expression of the PGC-1α gene, provided much information on the role of PGC-1α in altering the type of blur, mitochondrial biogenesis, angiogenesis, expression of GLUT4, and ultimately improving exercise performance (52).

PGC-1α Adjustment in Response to Physical Exercise

There are various signaling pathways in skeletal muscle for adjusting PGC-1α that have been tested on normal treadmill exercise for normal induction during a six-week running at 60 min/day (52). And given the positive effects of physical exercise on body composition and weight loss that has recently been taken into consideration, further evaluations are needed during other sports exercises.

PPARγ

PPARγ is typically coupled with transfusional modulators, such as SIRT1, which regulates the distilling of PPARγ as an essential part for using PRDM16 in PPARγ, PRDM16, and PGC-1α trials. Moreover, PPARγ is a necessary transcription factor for differentiation and Preservation of both white and brown adipocytes (32). In fact, PPARγ has two distinct roles in differentiation of adipose tissue. When PRDM16 is low, PPARγ induces white fat cell differentiation, but when the

PRDM16 protein level increases, PPARγ activity induces the white adipose tissue to the browning adipose tissue (53).

SIRT1

A family of proteins (expressed by genes with the same name) that has both mono- ADP-Ribosyl-Transferases deacetylase activity. This protein family consists of seven members of SIRT1-7 in the mammalian cells (54). SIRT1 is known as an essential protein in antioxidant defense and hemostasis control. In fact, SIRT1 plays role in many vital functions, including controlling free radicals production and fat oxidation through structural histones and many transcription factors (55). SIRT1 induces potential metabolic reactions that delay aging with metabolic changes. These mechanisms involve the two following aspects (56): 1) increasing stress through adjusting pro-apoptosis factors, such as P53 and FOXO and 2) providing a series of endocrine responses that might inhibit fat synthesis and insulin secretion by beta-Langerhans cells through regulating key genes associated with metabolism such as PGC-1α.

Fibroblast Growth Factor 21 as a Myokine

Fibroblast growth factor 21 (FGF21), a hormone involved in metabolic procedures, is mainly produced by liver. Stimulating PGC-1α expression is the key role of this factor in mediating gluconeogenesis and fatty acid oxidation in the liver, in addition to mitochondrial biogenesis in the adipose tissue (57). The PI3K/Akt pathway is of importance in insulin signaling and cellular volume increase. It should be noted that FGF21 is mainly expressed in muscles. Serum FGF21 levels augment in Akt-transgenic mice (58). Therefore, skeletal muscle is also considered as a source of FGF21 and expression of this factor is regulated by a mechanism dependent on PI3K/Akt signaling pathway.

Furthermore, FGF21 due to the production of various types of stress, is known as a mayokine (59). The amino acids generated by autophagy are used for energy production or other purposes during nutrient deficiencies. Mitochondrial dysfunctions in mice lacking autophagy-related 7 (Atg7) cause upregulation of FGF21 by triggering the transcription factor 4 (TCF4). This agent is an important regulator of integrated stress response. Lack of autophagy and subsequent mitochondrial dysfunction increases production of FGF21 as myokine. The latter changes lead to higher protection against obesity and insulin resistance caused by diet.

FGF21 as a myokine shows the effects that cause browning of WAT (60). Physical activities are supposed to raise the levels of FGF21. However, the results obtained by different studies are contradictory and require further study (61-64). It was reported in a study that trainings with three-week intervals may be associated with decline in plasma FGF21 levels (64). On the other hand, two weeks of intense aerobic activity increased serum levels of FGF21(62). Another study revealed that insignificant FGF21serum levels could be attributed to eight weeks of endurance training as three sessions weekly (65).

Bone Morphogenetic Protein

This factor belongs to a family of growth factors that have multiple roles in different tissues and physiological processes. In the adipose tissue, BMP types 2 and 4 encourage commitment of mesenchymal cells to the adipocyte lineage and differentiation of mature adipocyte precursors into white adipocytes (66). The existing data are not complete in this regard, but it has been shown that BMP7 in adipose tissue promotes the distinction between white adipocytes and brown adipocytes (67).

BMP8 enhances browning of brown and beige adipose tissue through the central and peripheral nervous system and is responsible for regulating energy balance. In addition to the activity in signaling pathway of non-mature cells, BMP plays role in differentiation of adult neoplasms and adipocytes (67).

Neuregulin 4

BAT is of value in energy balance and metabolism. Neuregulin 4 (Nrg4) is a quaternary epidermal growth factor secreted from brown fat and plays role in liver cells. Nrg4 is effective in inducing differentiation of adipocytes. Moreover, directly affects liver and by binding to the ErbB receptor in liver and reducing liver lipogenesis maintains a metabolic balance regarding obesity (29).

Vascular Endothelial Growth Factors A and β1

These factors are expressed at high levels in brown fat and have considerable roles in regulation of angiogenesis, exothermic reactions, and function of macrophages. Upregulation of vascular endothelial growth factor (VEGF) gene in the adipose tissue of mice increases the BAT mass, stimulates the browning process, and enhances the metabolic profile (68).

IL-15 and White Fat

IL-15 is a myokine secreted from muscles and contributes to the relationship between muscle and fat (69). It has been reported that IL-15 has a reducing effect on WAT. This interleukin

triggers fat cell apoptosis and decomposition. In addition, it turns on beta-oxidation and lipolysis leading to degradation of triglyceride and VLDL. This myokine has been observed to inhibit lipogenesis (69).

The molecular mechanisms of IL-15 impact on adipose tissue include the MAPK P42/44 STAT5, and SAPK/JAK pathways. The first one seems to be accompanied by a reduction in IL-15-induced differentiation. The latter pathway results in augmented fat cell apoptosis. Therefore, this myokine reduces body fat mass through the mentioned pathways (69).

IL-15 and IL-6 in Skeletal Muscle

Regarding intracellular signaling, many of the new observations have shown that the PPAR-α transcription factor may play role in protein synthesis (70). Therefore, IL-15 activates this transcription factor and regulates expression of various genes associated with the metabolism of protein and fat. Increases expression of PPAR-α mRNA in the skeletal muscles and liver leads to altered metabolism of proteins and lipids both in liver and muscles. In addition, some studies have shown that IL-15 is an important regulator of muscle mass in response to resistance training (71). This interleukin augments the GLUT4content in muscle cells. Therefore, this myokine regulates the metabolism of proteins and carbohydrates (69).

Mayokin IL-15 reduces the protein breakdown in cancer by interfering with the Ubiquitin-ATP proteolytic system. Protein decomposition is accompanied by DNA fragmentation and apoptosis in catabolic conditions. The use of IL-15 decreases muscle apoptosis and maintains muscle mass through a mechanism related to stimulation of UCP3. UCP3 is associated with mitochondrial thermogenesis and prevents free radical production in mitochondria which could be attributed to apoptosis.

TNF-α is also a factor involved in apoptosis and muscle proteolysis. Myokine IL-15 can diminish expression of TNFR1 and TNFR2. As a result, maintains skeletal muscles in catabolic conditions (69). In fact, IL-15 is highly expressed in normal skeletal muscles, but its mRNA decreases in cancer. This myokine has a positive effect on all types of cancer and improves the function and pathology of muscle. This suggests that this myokine has a therapeutic impact on neuromuscular disorders (72). In other atrophic conditions, such as age-related atrophy and atrophy due to lack of skeletal muscle, there is a significant positive correlation between this myokine mRNA and atrophic inhibition. This can hinder the reduction of musculoskeletal musculature in aging (73).

In addition, IL-15 elevates lipid oxidation by increasing the expression of CPT1 and CPT2 in liver. This myokine upregulates UCP3 and UCP1 genes in BAT. Furthermore, it stimulates the expression of FAT IL-15 and FATP by upregulating PPAR-α and PPAR-γ. This suggests that FAT and FATP may interfere with the function of this myokine in BAT (69).

Myokine Levels rise during endurance and resistance exercise activities and affect the responses of skeletal muscles during exercise. In addition, the myokine contributes to muscular adaptations as the result of endurance and resistance exercises by influencing the receptors on cell surfaces and initiating intracellular signaling cascades. For example, IL-6 acts in muscle hypertrophy in resistance exercises, while elevates glucose uptake and promotes insulin sensitivity in endurance exercises. Myokine IL-15 similar to IL-6 helps with resistance training to muscle hypertrophy, although the signaling paths and molecular adaptations of these two myokines are different. In addition, IL-15 increases fat metabolism as a result of endurance exercises (8).

Myokine IL-6 augments lipid oxidation activity via IL-6R and gp130 receptors, as well as the PI3K/AKT pathway leading to increased insulin sensitivity. IL-6 also raises muscle mass by IL-6/STAT3, ciclin DI, and MyoD. Moreover, IL-15 boosts metabolism through SIRT1 during exercise and increases muscle mass and myosin heavy chain (MHC) in type IIa and IIb strands through its effect on IGF-1 (74, 75).

IL-6 plays role in oxidation of adipose tissue and suppresses the pre-inflammatory cytokines. It has been well documented that myokine IL-6 contributes to the reduced metabolic diseases, such as type 2 diabetes. In addition, IL-6 can be useful in preventing diabetes mellitus by enhancing the neurological and axonal regeneration. This interleukin improves nerve conduction velocity. It has been demonstrated that IL-15 causes the bone density and net mass to augment (76).

Conclusion

There is generally much persuading information indicating that exercise can activate BAT to prevent and treat obesity. However, contradictory results might be found in the literature. Both significant and insignificant relationships have been reported between the study indices with physical activity and exercising. The contradiction of results may be because of different methodologies, severity, duration, iteration, used program, and the technique of measuring indicators or different participants (i.e., human, non-human, young, old, diseased, and healthy).

Irisin seems to be affected by different types of sport activities and have role in converting WAT to BAT. Moreover, the mechanisms related to it can cause weight reduction and increase in body temperature. The response of Irisin to other exercises with different intensities is still unknown. Therefore, more studies are recommended in this field.

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Conflict of Interest

The Author declares no conflicts of interests for the present study.

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