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REVIEW

An Updated Mini Review of Acute and Chronic Responses to Exercise Training-induced Irisin in Browning of White Fat

Sílvia Rocha-Rodrigues[1,2*] Bruno Silva[1,3]

1. Polytechnic Institute of Viana do Castelo, School of Sport and Leisure, Melgaço, Portugal
2. Laboratory of Metabolism and Exercise, Research Centre in Physical Activity, Health and Leisure (CIAFEL), Faculty of Sport Sciences, University of Porto, Portugal
3. Research Center in Sports Sciences, Health and Human Development (CIDESD), Vila Real, Portugal

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ABSTRACT

Nowadays, is well established that the benefits induced by exercise training (ET) affects not only skeletal muscle, but also other non-contractile organs over time. One potential mechanism underlying this crosstalk is the synthesis and secretion of several biological active factors, such as irisin, by muscle contractile activity. This hormone has been described to be able to induce a brown adipocyte-like phenotype in white adipose (WAT), increase whole-body metabolic rate, and therefore prevent and/or treat obesity-related metabolic diseases. Thus, the modulatory impact of ET on WAT may also occur through skeletal muscle - adipose organ axis. In this review, we summarize the acute and chronic adaptations to ET-induced irisin synthesis and secretion on the development of browning of white fat and, thus, providing an overview of the potential preventive and therapeutic role of ET on the obesity-related underlying pathways.

1. Introduction

Exercise training (ET) represents an important part in the increase of energy expenditure in active humans, stimulates fat mass loss and helps to maintain lean mass, besides promoting positive effects on the physiological function of hormones [1]. Accumulating evidence show that distinct ET modalities, such as endurance, strength and high-intensity interval training (HIIT), have a significant effect on reducing visceral fat accumulation [2-5] as well as adipocyte disturbances induced by obesity. Thus, contributing to systemic metabolic improvements through a favorable dynamics changes in white adipose tissue (WAT) morphology and metabolism [6-9], including a brown adipocyte-like phenotype [10-12]. This phenotype has been characterized by a greater capacity for thermogenic stimulation, as demonstrated by elevated uncoupled protein 1 (UCP1) expression and other brown adipocyte-specific genes [10-11, 13], converting these cells into more metabolically active cells, which in turn, burn more calories[14]. The presence of this type of cells opens attractive perspectives to treat obesity and related metabolic disorders.

Based on current state of knowledge, ET stimulates the production and secretion of several biological factors in skeletal muscle, such as irisin, whose effects can be local and/or far-reaching organs/tissues, like white adipose tis-

**Corresponding Author:*
Sílvia Rocha-Rodrigues,
Escola Superior Desporto e Lazer; Complexo Desportivo e de Lazer Comendador Rui Solheiro, 4960-320 Melgaço, Viana do Castelo, Portugal;
Email: silviadarocharodrigues@gmail.com

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sue (WAT), liver, heart, and brain in distinct animal models [15-17]. Thus, skeletal muscle has been recognized as endocrine organ. The present review highlights the prominent role of skeletal muscle-induced irisin in browning of white fat in response to acute and chronic adaptations induced by ET to better understand its regulation in skeletal muscle and its possible systemic and tissue modulatory effects on WAT and its potential application in combating metabolic diseases.

2. Exercise Training-regulated Myokines to Induce Browning of White Fat

Mechanistically, muscle contractile activity induces local paracrine-mediated actions on several signaling pathways involved on its structure and metabolism and also produces and secretes myokines, which act in an endocrine-like fashion on distant organs and tissues, including WAT [18]. Particularly, some myokines alter the metabolic phenotype of WAT by inducing browning, fatty acid oxidation and improving insulin sensitivity [10, 12-13, 19-20]. Therefore, myokines likely provide a conceptual basis to understand, at least in part, the modulatory impact of ET on WAT, e.g. the cross-talk between skeletal muscle and adipose organ axis, which is of particular interest in the context of obesity and metabolic disorders. Evidence have been supported that ET stimulates several myokines secretion by skeletal muscle, including β-aminoisobutyric acid (BAIBA) [21], brain-derived neurotrophic factor (BDNF) [22], IL-6 [17], meterion-like [23] or irisin [10]. Once released into the bloodstream, they can operate upon distant organs in a hormone-like fashion and may drive important *stimuli* ultimately leading to browning of white fat. Roberts and colleagues [21] identified BAIBA as a myokine able to increase the expression of brown adipocyte–specific genes in white adipocytes *in vitro* and *in vivo* by a peroxisome proliferator-activated receptor α-dependent mechanism. This myokine also improved glucose homeostasis in mice and induced a brown adipose–like phenotype in human pluripotent stem cells [21]. Meteorin-like is mainly induced in response to strength training and peroxisome proliferator-activated receptor gamma coactivator 1α (PGC-1α)4 overexpression, which promotes activation of M2 macrophages and catecholamines production from these cells to induce browning effects [23] and sustain adaptive thermogenesis [24]. An overexpression of the *Il6* mediated by ET increased the UCP1 gene and protein expression in rat brown and white adipose tissue [17, 25]. Moreover, the ET-induced increase in skeletal muscle IL-6 levels was strongly correlated with brown adipocyte-like phenotype markers expression and its regulators in obese rats [26]. Despite de potential role of these myokines mediating the beneficial effects of ET, irisin is the one that has received more attention in literature due to its physiological functions and potential applications in health and in a variety of metabolic diseases. Irisin is derived from fibronectin type III domain-containing protein 5 (FNDC5), membrane-spanning protein highly expressed in skeletal muscle, proteolytically cleaved and released into circulation as a powerful messenger reaching other distant organs, such as WAT [15-16]. Indeed, several studies have been supported that irisin induces skeletal muscle hypertrophy [27], energy expenditure by stimulating the brown-like phenotype in WAT [11-12], and improved glucose homeostasis by reducing insulin resistance [28-29]. In the original study, Bostrom *et al*[10] reported that *in vivo* and *in culture* brown adipocyte-like phenotype were mediated *via* the activation of the main metabolic regulator, PGC-1α, a well-known player on skeletal muscle adaptive response to ET [30-32]. As an important transcriptional coactivator involved in energy metabolism, elevated levels of PGC-1α has been associated with an increased mitochondrial content [11], fatty acid oxidation as well as brown adipocyte-like phenotype development in WAT [12, 33]. Moreover, the Sirtuin 1 (SIRT1), a NAD^+-dependent type III metabolic sensor, also seems to be closely involved in the regulation of these processes [30]. The SIRT1 binds to PPARγ and represses the transcriptional activation of PPARγ by binding to nuclear co-receptor/silencing mediator of retinoid and thyroid hormone receptor complex, resulting in the reduction of fat accumulation in WAT and higher level of non-esterified fatty acids (NEFA) in blood [34]. SIRT1-dependent deacetylation of Lys268 and Lys293 is required to recruit the brown adipose tissue (BAT) program activation and repression of visceral WAT genes associated with insulin resistance [35]. In response to 8-wks of ET, higher levels of SIRT1 was found associated to a brown-like phenotype development in WAT from obese rats [36].

2.1 Acute Skeletal Muscle Adaptations

Animal-based studies reported an increased skeletal muscle FNDC5 expression in response to acute bout of exercise [10, 37-38] while some found no alterations [39-42]. The study of Dehghani and colleagues [37], whose objective was to analyse the distinct types of muscle contractions, demonstrated that one bout of both concentric and eccentric exercises increased skeletal muscle PGC-1α and FNDC5 mRNA expression in skeletal muscle of BALB/C mice. Moreover, the eccentric exercised group benefited from a greater impact on PGC-1α and FNDC5 genes than the concentric exercised group, suggesting that a single bout of eccentric exercise has a notable impact

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on myokines secretion and their regulators. This effect was attributed to muscular microscopic damage and the greater production of reactive oxygen species, in comparison with the concentric exercises [43]. After an acute exercise session, was reported no changes immediately and after 3h from acute submaximal bout of exercise at 70% maximal running velocity in *tibialisanterior* muscle [39]. While [40] and [42] showed that *gastrocnemius* FNDC5 mRNA expression decreased immediately after exercise session and remained unchanged 3h after submaximal and maximal treadmill running. On the other hand, mice *quadriceps femoris* and *triceps surae* muscles FNDC5 values displayed high levels 24 hours after cessation of ET bout [37]. Czarkowska-Paczek and colleagues [40] showed an increase of circulating irisin levels 3h after the end of treadmill running session with no alterations on FNDC5 levels. Other studies with rodents supported this idea revealing that circulating irisin levels were acutely overexpressed immediately after one bout of exercise [41, 44]. This acute response was possibly attributed to the commonly described ET-induced oxidative stress. Oxidative stress is known to stimulate p38 MAPK and the extracellular regulated protein kinase (ERK) [45-46], which in turn activates PGC-1α in skeletal muscle, an important regulator of FNDC5.

Evidence from human studies showed that FNDC5 mRNA expression was increased in endurance-trained athletes males with maximal oxygen consumption (VO_2 max) higher than 55 $mL^{-1}.kg^{-1}.min^{-1}$[47]. In response to an acute bout of high-intensity exercise [48] and strength exercises (5 sets of 10 repetitions until failure) [49], skeletal muscle FNDC5 and PGC-1α mRNA levels increased in healthy individuals.Although an increased FNDC5 has been detected without any changes in circulating irisin after ET [47, 49], acute increases in irisin levels have been widely reported in physically inactive individuals[10, 50-56]. In this line, Kraemer *et al* [54] found that plasma irisin levels increased during the course of a 90 min (60% of VO_2 max) treadmill running, reaching the peak values at 54 min while returned to baseline levels immediately post-exercise. Moreover, Norheim *et al*[56] reported a peak concentration of irisin after 45 min cycling without a concomitant increase in *Fndc*5 gene expression, which suggests that increases on irisin levels during acute exercise may be associated with protein *post-translational* modifications. Actually, the type, duration, and particularly the intensity of the ET sessions seems to influence the expression of circulating irisin. In fact, high-intensity exercise at 80% VO_2max for 20 min promoted greater irisin response comparatively to low-intensity exercise at 40% VO_2max for 40 min under similar energy consumption conditions [50]. Thus, circulating irisin levels increased when the muscle adenosine triphosphate (ATP) levels acutely dropped, but remain unchanged when muscle ATP content is restored, suggesting that irisin may contribute to ATP homeostasis [57]. Based on this hypothesis, the lack of irisin changes in some studies may be explained by the intensity as short-term low-to-moderate intensity ET induces low ATP depletion [57]. In this line, plasma irisin levels seem to be progressively elevated in response to increasing ET workloads as physically active individuals with higher VO_2max showed greater concentrations of irisin during maximal workload ET [50, 53, 55]. Collectively, data suggest that circulating irisin levels seem to be increased in response to acute intense ET in humans; however new insights into irisin regulation during ET are clearly needed. However, some inconsistencies may be related to interactions between irisin and other cytokines and hormones, for example IL-6, BDNF or adiponectin [58-60]. Moreover, other tissues, such as cardiomyocytes and purkinje cells of cerebellum [13, 59, 61], have been described to interfere with irisin metabolism/regulation, and should also be considered in future studies.

2.2 Chronic Skeletal Muscle Adaptations

In animal models, several studies have confirmed that chronic ET programs induced FNDC5 synthesis and subsequently release irisin into circulation that have impact on browning of white fat [10-13, 62]. Whereas some studies have not been able to recognize a consistent increase in the expression of FNDC5 mRNA [63] or plasma irisin levels [49, 64] after long-term ET program. Tiano et al 2015 [12] studied the contribution of distinct models of exercise, such as running, countercurrent swimming and voluntary running wheel, on irisin secretion and browning of white fat. For the treadmill and swimming models, mice showed a ~35% increase in serum irisin levels at 2nd week along with an increase in the area under the curve (AUC) over the 3rd week; however a voluntary running wheel model had no impact on irisin concentration. In the same study, only the treadmill-exercised mice showed an increased FNDC5 mRNA and protein expression in skeletal muscle. In response to 2-wks of treadmill running [12], the browning-related markers, such as PGC-1α; its downstream target UCP1, the major protein responsible for nonshivering thermogenesis; and PR domain containing 16, the transcriptional regulator of BAT differentiation [65] were increased in both subcutaneous and visceral fat depots. Moreover, a strength exercise program increased serum irisin and *soleus* FNDC5 levels in mice performed ladder climbing with tail weight 3 days *per* week for 12 weeks [66]. Xiong and colleagues [67] created a mouse model of *Fndc*5 mutation through transcription activator-like effec-

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tor nuclease-mediated DNA targeting. In response to 8-wks of treadmill running (60min.day^{-1}, 10% slope at constant 18min.m^{-1} velocity), the *Fndc*5 mutant mice exhibit lower VO_2max and attenuate ET-induced browning of white fat when compared with exercised wild-type mice, providing genetic evidence that *Fndc*5 is required for exercise-induced browning of WAT in mice.

Several studies reported that irisin remained stable after an ET program, but the duration of high levels after exercise remains unresolved [38, 40, 68]. Another aspects that need further investigation are the effects of different types and intensities of exercise on muscle metabolism and disruption at distinct ways, and in turn, on irisin concentrations [69-70]. Nevertheless, data from studies performed with humans are not so consistent. Some studies showed that chronic ET, strength or the combination of both models did not affect skeletal muscle FNDC5 [48-49] or circulating irisin [49, 63, 71] levels in sedentary healthy individuals or in children with obesity [72]. In contrast, other studies revealed an increased FNDC5 and PGC1α expression in response to 12-wks of combined endurance and strenght exercises [56]. A study using Gene Set Enrichment Analysis method showed that ET promoted several alterations on genes involved in metabolism, mitochondrial biogenesis, oxidative stress and signaling, membrane transport, cell stress, proteolysis, apoptosis, and replication [33], underlining the degree of plasticity of WAT and its prominent role in physiological whole-body adaptions to ET. Moreover, ET-induced browning of white fat is possibly associated with other myokines synthesis and secretion, including IL-6, BAIBA, BDNF, meteorin-like and others. Altogether, data suggest that irisin levels seem to be increased acutely and chronically in response to ET; however new understandings into irisin regulation during ET are clearly needed.

3. Conclusions

In summary, acute and chronic response to ET seems to have a crucial role in the synthesis and secretion of irisin from skeletal muscle to stimulate the browning of white fat and its main regulators (figure 1), which are determinant for improving metabolic function and energy expenditure, and, thus, preventing and/or counteracting obesity-related metabolic disorders.

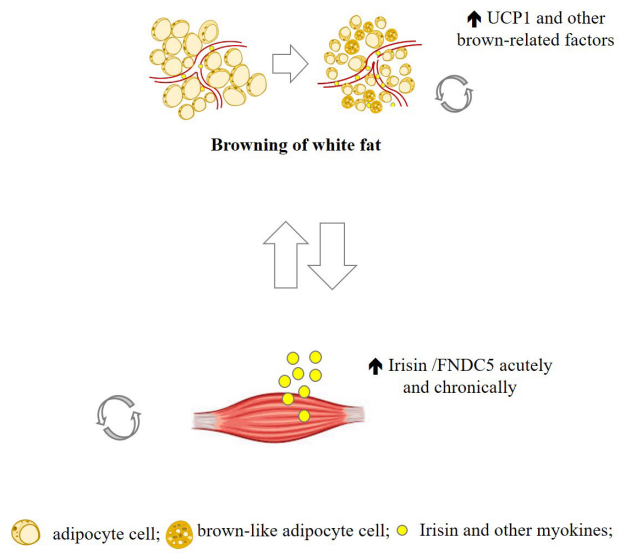

Figure 1: Summary of acute and chronic adaptations to ET-induced irisin secretion in browning of white fat.

Legend: FNDC5, fibronectin type III domain-containing protein 5; UPC1, uncoupled protein 1; © increase

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