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Artigo Revisão

Irisin: A Bright or a Dark Future?

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A B S T R A C T

Seven years ago, irisin was first announced as a new and exciting myokine, which was secreted by the skeletal muscle in response to exercise and contributed for some of the health benefits promoted by physical activity. It was suggested that exercise stimulates the increase of the amount of the coactivator PGC-1α, which subsequently increases the expression of FNDC5, a membrane protein that is proteolytically cleaved to form irisin. Once released into the bloodstream, irisin connects to a yet unknown receptor on the surface of white fat cells and promotes a special process known as "browning" of white adipose tissue, which increases thermogenesis and the energy expenditure. Since its discovery, great hopes have been raised, and the association between irisin and these abovementioned functions led this myokine to be considered a potential therapeutic weapon in the fight against obesity and other related metabolic disorders, such as diabetes. However, concerns about its presence, regulation and the yet-to-be fully understood functions associated with inconstant results, put the future of irisin in doubt. Therefore, caution needs to be taken in expressing optimism, and the near future will be a challenge for irisin's ability to survive as a useful tool in the treatment of metabolic diseases. Meanwhile, new associations between irisin, neoplastic, cardiovascular and neurodegenerative diseases are being deduced and further studies will help to clarify the role of irisin in humans.

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Irisina: Um Futuro Brilhante ou Escuro?

R E S U M O

Há 7 anos atrás, a irisina foi apresentada como sendo uma nova e excitante miocina, segregada pelo músculo esquelético em resposta ao exercício físico e que contribuiria para alguns dos benefícios promovidos pela atividade física. Foi sugerido que o exercício estimularia a produção do co-ativador PGC-1α, o qual subsequentemente aumentaria a expressão de FNDC5, uma proteína de membrana que por sua vez daria origem à irisina. Uma vez libertada na corrente sanguínea, a irisina ligar-se-ia a recetores ainda não completamente identificados na superfície das células do tecido adipose branco e desencadearia um processo conhecido como "acastanhamento" do tecido adiposo branco, o que levaria a um aumento da termogénese e a um maior dispêndio de energia. Desde a sua descoberta, grandes esperanças foram criadas, e a associação entre a irisina e as funções descritas anteriormente levaram a que esta miocina fosse considerada uma potencial arma terapêutica no combate à obesidade e às doenças metabólicas relacionadas como a diabetes. Contudo, preocupações acerca da sua presença, regulação e funções ainda não completamente esclarecidas, associadas a resultados inconstantes, puseram o futuro da irisina em causa. Assim, todo o optimismo deve ser expresso com cautela, e o futuro próximo será um desafio para a capacidade da irisina sobreviver enquanto ferramenta útil no tratamento de doenças metabólicas. Entretanto, novas associações entre a irisina e doenças neoplásicas, cardiovasculares e neurodegenerativas foram sendo propostas, sendo que estudos futuros ajudarão a clarificar o papel da irisina nos humanos.

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Introduction

Skeletal muscle represents the largest organ of the body in normal-weight individuals, and it is actually considered to be an endocrine organ with the ability to communicate with other tissues via myokines, which are released into the bloodstream during physical activity. These myokines are the messengers of a complex network responsible for the communication between skeletal muscle and other organs, such as adipose tissue, brain, liver and pancreas and mediate some of the beneficial effects of exercise.[1]

Boström *et al* reported that a transcriptional coactivator called PGC-1α (peroxisome proliferator-activated receptor gamma coactivator 1α) stimulates the expression of the membrane protein FNDC5 (fibronectin type III domain containing protein 5) in response to exercise, which is proteolytically cleaved and releases the extracellular part into the bloodstream. This smaller and soluble protein is the newly discovered myokine named irisin, in honour of Iris, the Greek messenger Goddess.[2] In this initial study, it was suggested that irisin is released into the circulation after physical activity and promotes a special process knowing as "browning" of white fat cells into brite cells, also known as beige cells (white fat cells with a similar phenotype to brown fat cells), by increasing cellular mitochondrial density that contains the uncoupling protein 1 (UCP1).[2] This change is characteristic of brown adipose tissue and results in an increase of energy expenditure, modest weight loss and improvements in glucose homeostasis.[3]

The discovery of irisin as an exercise-regulated myokine capable of inducing "browning" of white adipose tissue, led this protein to be recognized as a potential new treatment for obesity and other related disorders, such as type 2 diabetes mellitus (T2DM). At the same time, new functions of this hormone began to be studied, and the association between irisin, cardiovascular, neurodegenerative and neoplastic diseases have a promising future, regarding many questions that need to be answer, discussed later on this review.

This paper aims to summarize the major findings and developments about irisin, since it was first announced, seven years ago. Based on the evidence published to date, the association between this myokine and physical activity will be carefully analysed, as well its association with metabolic diseases. Finally, recent papers on this topic and what science can expect from irisin in the near future will be discussed.

Methods

The PubMed bibliographic database was used to search for all papers published up to the 31st December of 2018, using the following keywords: irisin, exercise, obesity and diabetes.

Inclusion criteria were studies performed preferentially in humans that investigate irisin's regulation by exercise and/or its association with obesity and/or diabetes. Only studies in English were considered. The full texts of the selected papers were retrieved and read in full. Additional papers were identified in the reference lists of selected papers.

Overall, 74 papers were considered to be relevant and were included in this review.

FNDC5 gene, FNDC5 protein and irisin. Expression and regulation by exercise

In the original study by Boström *et al*, the main goal was to investigate how PGC-1α expressed by skeletal muscle in response to physical activity affected the white adipose tissue. The authors identified irisin as a myokine dependent on PGC-1α, which was responsive to exercise. Evidence from in vitro and animal studies suggested that irisin stimulated the expression of the uncoupling protein 1 (UCP1), which was responsible for the "browning" of white adipocytes. These conclusions were supported by the fact that FNDC5 and irisin were both induced by the overexpression of PGC-1α and the physical activity in mice. Moreover, levels of circulating irisin increased in humans after a 10-week endurance exercise programme (twofold increase).[2]

It needs to be pointed out at this stage that the term irisin and FNDC5 are often used as synonyms, but they are not the same: FNDC5 is a trans-membrane protein encoded by the *FNDC5* gene and it is the precursor of irisin, a blood-circulating protein which is produced by proteolytic cleavage of FNDC5.[2] On the other hand, PGC-1α is a transcriptional coactivator which regulates gene expression, including the *FNDC5* gene.[3] Before irisin was first discovered, PGC-1α was known for being responsible for many of the downstream molecular events that were induced by exercise, such as increasing the oxidative metabolism.[4]

Most of the findings of Boström and his team were obtained in animals. They reported that mouse's and human's irisin were 100% identical, implying a highly conserved function across species.[2] These results were first put in doubt by Raschke *et al*, suggested that the *FNDC5* gene in humans differs from that of mice by a mutation in the start codon (ATA in humans and ATG in mice), which would lead to a different protein.[5] Boström and other researchers replied later, enumerated evidence and demonstrated that irisin was expressed and metabolically regulated by exercise in humans as well in mice, despite the mutation in the start codon.[6-9]

Besides this question, since the beginning, some clinical studies investigated the influence of exercise on *FNDC5* mRNA expression both in skeletal muscle and also in circulating irisin levels. The results were controversial and some of the studies performed on humans could not reproduce an increase of *FNDC5* mRNA expression or irisin after exercise.[5,10-16] The ones that did it, demonstrated an increase in circulating irisin levels more often associated with acute exercise[17-27] rather than long training sessions.[2] A fascinating fact reported by some of these papers was that irisin returns to its baseline values in a short amount of time after exercise, normally in a period between 10-60 minutes.[18,24,25,27] Recent data also shows that the irisin's response to acute exercise does not depend on the individual training status, but it could depend on the training mode.[27,28]

Analysing all of the evidence on irisin, information seems to be heterogeneous, and in some cases even contradictory. Explanations for this inconsistency started to appear, and besides the different studies performed, the different populations analysed and the different exercise protocols, methods used for the detection of *FNDC5* mRNA in skeletal muscle and irisin in plasma began to be criticized. In Boström *et al* research, the presence of irisin in plasma was quantified based on western blots, using an antibody against the trans-membrane segment of FNDC5 (non-secreted portion), which would fail to detect the secreted irisin's fragment.[5] Later on, several enzyme-linked immunosorbent assays (ELISA) were validated and became commercially available to measured irisin concentrations easily and quickly.[29] Once again, even with the standardization of methods using ELISA assays the results were not consistent, and Jedrychowski *et al* tried to put an end on this discussion, using for the first time mass spectrometry to quantify irisin after physical activity in humans. With this accurate and antibody-independent technique, irisin levels were detected and

increased in human's plasma by both short and long time exercise protocols.[9] Until to date, these results were not been challenged yet. Since this represents one of the hot topics on irisin's, it will be discussed later on this review.

Irisin and metabolic diseases

Despite the initial controversy over irisin's existence and its regulation in humans, this myokine was proposed to be partly responsible for some of the beneficial effects of exercise on obesity, diabetes and associated metabolic diseases, by inducing "browning" of white adipose tissue, which leads to an increase in energy expenditure, reducing body weight and improving glucose homeostasis.[2]

Regarding obesity, a negative correlation was reported between irisin and BMI (body mass index) in several studies.[11,30-34] These results were in line with the irisin's anti-obesity effect defended by Boström *et al*.[2] However, controversy existed, as other studies founded no correlation,[17,35,36] or either a positive correlation.[25,37-45] Roca-Rivada *et al* proposed that irisin was not only a myokine, but it was also an adipokine.[46] Thus, 72% of the circulating irisin was originated from the skeletal muscle and acted as a myokine,[2] while the remaining percentage, 28%, which could be higher in cases of obesity, derived from the white adipose tissue.[46] This fact could explain the "unpredictable" positive correlation observed in some of these studies.

It was proposed that irisin, via AMP-kinase activation, promoted the translocation of GLUT 4 (glucose transporter 4) to the skeletal muscle cells membrane and consequently increased glucose uptake in an action similar to insulin.[23,24,47] The majority of the studies showed that circulating irisin levels are lower in patients with T2DM.[13,30,31,38,42,48-50] T1DM51 and also in mothers with gestational diabetes.[52,53] Reduced plasma levels of irisin during the first pregnancy trimester were identified as a risk factor for gestational diabetes.[54] In line with these findings, other studies showed a positive correlation between irisin and insulin resistance, which was assessed by the homeostasis model of assessment of insulin resistance (HOMAR-IR) index.[35,39,41,50,55-57] All of these results were in line with Boström *et al*, who proposed a protective effect of irisin against insulin resistance.[2]

When analysed the association between irisin and metabolic syndrome (MetS), a combination of various medical disorders including obesity and insulin resistance, higher circulating irisin levels in patients with MetS were also reported, when compared with patients without MetS.[25,39,58,59]

Once again, caution needs to be taken in the analysis of these results; besides the controversy around irisin's detection methods, different studies protocols were performed and heterogeneous populations analysed, some of them with co-morbidities associated and others not.

Irisin and new associations

Irisin was primarily identified as a myokine, which was produced in skeletal muscle and released in human plasma.[2] It was reported that *FNDC5* mRNA was also expressed in other tissues besides the skeletal muscle, such as the heart, kidney, brain, liver and adipose tissue[14,17,46] Irisin has also been detected in saliva,[11,60] breast milk,[52] and cerebrospinal fluid.[53,61] Therefore, in addition to the first and well-known function of this myokine, which is related to the expenditure of energy and "browning" of white adipose tissue, irisin has been associated with other actions in different organs and systems.

The benefits of exercise on the brain are already known and, surprisingly, an association between physical activity, irisin and neurodegenerative diseases has been put forward. It was reported that, in response to endurance exercise, irisin promotes the expression of brain-derived neurotrophic factor (BDNF) in the dentate gyrus of hippocampus, a part of the brain responsible for learning and memory. This could represent a great advance in the understanding of neurodegenerative diseases, such as Alzheimer's disease, and could open the door for future therapeutic approaches in the management of these disorders, leading to an improvement of brain function.[8,62-65]

Irisin has already been studied as a molecular diagnostic marker for cardiovascular diseases. Decreased circulating irisin levels are associated with increased cardiovascular risk.[66,67] Recent studies demonstrated decreased irisin levels in the saliva and serum of patients with acute myocardial infarction (AMI), adding new diagnostic and prognostic information to the usual biomarkers.[60,66,68,69]

Irisin has also been associated with the aging process.[66,70] It is accepted that telomere length decreases over the years, and unexpectedly, a positive correlation was found between irisin and telomere length. Therefore, besides irisin could be used for predict telomere length in healthy subjects, it was proposed that this myokine had anti-aging properties. However, the mechanism through which irisin improved life expectancy is yet unknown.[70]

At last, an association between irisin as a diagnostic marker in breast,[71] pancreatic[72] and colorectal cancer[73] is already been proposed, but further investigation on this issue is required.

Irisin and its future

Since irisin's discovery, seven years ago, many advances regarding the knowledge about this myokine occurred. Despite the future that looked bright for these years, there are some questions that need to be answered.

A weakness regarding this myokine is related to its physiology. Irisin's secretion mechanism by the cleavage of FNDC5 is not completely understood, neither the responsible protease for that. However, after irisin is released from the skeletal muscle cells, it is detectable in both human and mice plasma and by an unknown mechanism, increases the expression of UCP1 and other brown adipose tissue related genes.[2] Boström and his team proposed a hypothetical existence of a cell surface receptor,[2] but until recently there was no evidence in support of this. Only in 2018, for the first time, Kim *et al* proposed that irisin mediated effects both on bone and fat cells via αV integrin receptors *in vitro* and in animal studies.[74] This fact needs to be validated for humans and is probably one of the most important issue that requests to be investigated in future research: to identify irisin's receptor in humans, maybe not only on the surface of white fat cells, but hopefully on other tissues too.

Another point of disagreement is related with the methods used to detect and quantify irisin in human plasma. Despite the validated ELISA kits that are been used for this propose, results still appear to be a little inconsistent and maybe mass spectrometry will have a word to say. Expectation exists that an accurate method will bring clear results in a near future.

The regulation of FNDC5/irisin by exercise is another topic that needs to be clarified. Increased circulating irisin levels have been found more often associated with acute exercise rather than with long term protocols. It is crucial to clarify the exact timing of irisin's increase after physical activity, as well as which type of exercise and intensity are responsible for the largest increases. Until now, there is not enough data to generalize results.

In line with all that has already been proposed, a better understanding about the association between irisin and metabolic diseases is highly desirable, as this would help to clarify the role of irisin in diabetes and obesity, and would also explain how it can or cannot be a useful therapeutic tool for the management of these health problems in the near future. Maybe a simple "irisin pill" will never replace the benefits of a complete workout, but it could possibly help patients with medical conditions which prevent them from taking exercise.[3]

Meanwhile, further studies are needed, and an answer to all of these gaps of knowledge is crucial for irisin's survival. Let us hope that this journey is just the start of a bright new era with regards to the health of humans.

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