


Does iris(in) bring bad news or good news?

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Abstract Irisin, a novel myokine produced in response to physical activity, promotes white-to-brown fat transdifferentiation. The name irisin referred to the ancient Greek goddess Iris, the messenger who delivered (bad) news from the gods. In mice, it has been demonstrated that irisin plays a key role in metabolic regulation, energy expenditure and glucose homeostasis. New findings from various studies carried out in both animals and humans suggest that irisin might also have other favorable effects, such as increasing bone cortical mass, preventing hepatic lipid accumulation, and improving cognitive functions, thus mediating many exercise-induced health benefits. However, data on the role and function of irisin in humans have prompted controversy, due mostly to the only recent confirmation of the presence of irisin in humans. Another strong limitation to the understanding of irisin mechanisms of action is the lack of knowledge about its receptor, which until now remains unidentified in humans and in animals. This review presents an overall analysis of the history of irisin, its expression, and its involvement in health, especially in humans.

Level of Evidence Level V, review.

Keywords Irisin · Adipose tissue browning · Myokine · Exercise · Type 2 diabetes · Obesity · Skeletal muscle

Introduction

Adipose tissue has a key role in energy balance due to its ability to store and release lipids, also contributing to regulating thermogenesis and heat production. It is possible to distinguish at least two types of adipose tissue with very different histological and functional characteristics. The white adipose tissue (WAT) is an energy depot where free fatty acids and triglycerides are stored, while brown adipose tissue (BAT) has thermogenic properties containing specialized mitochondria with uncoupling protein-1 (UCP-1), thus producing heat and, consequently, dissipating energy. Different factors may induce the formation of new BAT [1]. It is now well established that under appropriate stimuli, WAT can transdifferentiate into BAT and vice versa [2], a phenomenon also known as fat browning, and that is of great interest, especially in the field of obesity and diabetes. Much research has been produced in order to understand the mechanisms regulating fat browning. Skeletal muscle seems to play an important role in this context due to its ability to produce cytokines [3], also known as myokines [4], which act as hormones and influence energy homeostasis. Irisin is a recently discovered myokine, and animal studies have demonstrated that it is produced and released in response to physical activity, being able to promote the browning of WAT and improving the overall metabolic status [5]. The name irisin referred to the ancient Greek goddess Iris, the messenger who delivered (bad) news from the gods. Animal studies also suggest that irisin may have additional favorable health effects [6, 7], improving cognitive function and bone metabolism. Irisin may therefore also be a fascinating link between physical exercise and mental faculties, thus confirming the ancient Romans saying *mens sana in corpore sano*. Only recently (2015), has the presence of circulating

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irisin been definitely demonstrated in humans [8], although there are little and conflicting data on its role in humans. Therefore, the aim of this review is to provide a comprehensive overview of studies concerning irisin, from its discovery to its molecular structure and definition of action, with special reference to its possible influences on human health.

Discovery and doubts about irisin

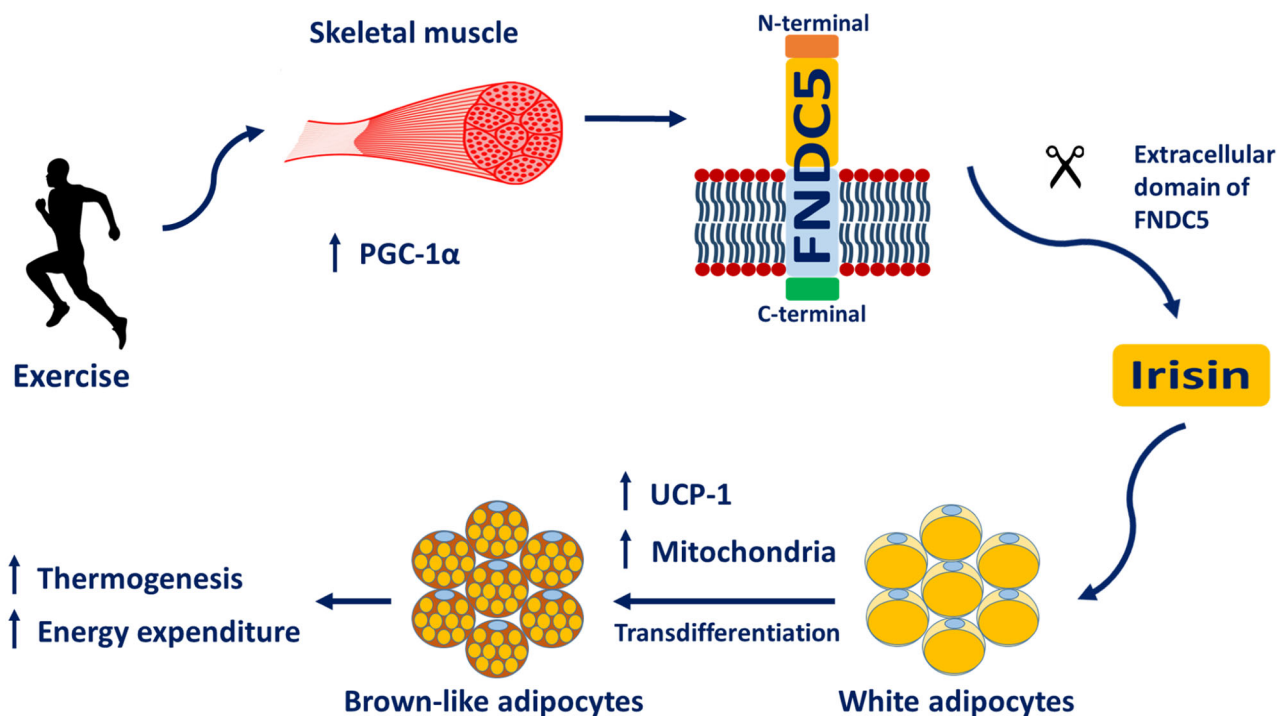
In 2012, Boström et al. [5] first reported that transgenic mice, whose characteristic is an enhanced expression of the muscular peroxisome proliferator-activated receptor gamma coactivator-1 α (PGC-1 α), which is among other things involved in both thermogenesis and biogenesis of BAT [9], exhibited a high production of UCP-1 [5], the biomarker of BAT. In particular, they observed an enhanced mRNA expression of BAT-related genes, and a 25-fold increase in UCP-1 levels in subcutaneous inguinal fat of mice following 3 weeks of wheel running when compared to resting mice. Five target genes whose expression was controlled by PGC-1 α were identified in muscle cells, but only fibronectin type III domain containing 5 (FNDC5), a type I membrane protein, was able to induce a remarkable brown fat gene program. Using Western blot through antibodies against FNDC5 protein, they detected a 32 kDa band that decreased to 20 kDa after deglycosylation. Further analysis by mass spectrometry revealed that FNDC5 protein was cleaved and secreted into the bloodstream as a polypeptide, which they named irisin. In the study, irisin was identified also in human plasma, and healthy adults undergoing 10 weeks of endurance exercise exhibited twofold higher circulating irisin levels than resting individuals, suggesting that this protein was produced by the human skeletal muscle in response to physical exercise [5].

However, following the discovery of irisin by Boström et al., doubts were raised about its effective existence and role in humans. Timmons et al. reported an exercise-mediated increase in muscle FNDC5 expression only in active elderly people, not in young people [10]; they also pointed out that even Boström et al. in their study had included only elderly people, thus raising doubts about irisin effectiveness in human health. Most importantly, Raschke et al. observed that the human encoding FNDC5 gene starts with a non-canonical ATA codon instead of the classical ATG one, claiming that the full-length protein could not be produced [11]. They also found that the first ATG was rather downstream to its ATA codon so that the FNDC5 might likely be translated into a truncated and not functioning protein, proposing that the FNDC5 was a pseudogene. However, contrary to this point of view, in the

previous year it was demonstrated that many encoding genes start with different non-ATG codons, all of them producing complete and functioning proteins [12]. Furthermore, the reliability of certain laboratory tests for detecting irisin using antibodies was questioned [13]. Albrecht et al. analyzed some commercial polyclonal antibody-based ELISA tests used in different studies, and detected a remarkable cross-reactivity with several human serum proteins [14]. They found, using mass spectrometry, an FNDC5 band of \sim 20 kDa that was not detected by any ELISA kit, and concluded that irisin was a myth and not an exercise-regulated myokine. To give a definitive answer to these uncertainties, Jedrychowski et al. used a mass spectrometry validated technique with isotope-enriched peptides as control and gave an adequate and definitive demonstration that irisin exists and circulates in humans [8]. They also ascertained that irisin circulates in its full-length form, and that its production originates from the non-canonical ATA codon. Furthermore, the ELISA kits were validated using both Western blot [15] and mass spectrometry [16] methods, showing remarkable accuracy and reliability.

Structure, expression, and actions

Irisin is cleaved from the extracellular ectodomain of FNDC5 by an unknown protease at the C-terminal, and then released into the bloodstream as a 112 AA polypeptide [5] (Fig. 1). Schumacher et al. characterized irisin structure and biochemical features, demonstrating that this myokine exists as a dimer, and consists of an N-terminal fibronectin type-III-like region, containing a four-stranded β -sheet packed to a three-stranded β -sheet, attached to a small C-terminal tail [17] (Fig. 2). In detail, irisin forms a continuous eight-stranded β -sheet dimer containing each subunit four-stranded β -sheet, probably binding to its receptor just as a preformed dimer. Moreover, the inner 10 H-bonds between the β -sheets, the two salt bridges between Arg-75 and Glu-79' (the prime stands for the second subunit of the dimer), and the tight interaction among the remaining three-stranded β -sheets Trp-90 and Trp-90' gives great stability to the irisin dimer. Shah et al. also demonstrated that the fibronectin type III domain accounts for the thermodynamic stability showed by proteins with this domain, as irisin itself [18]. These findings might contribute to explaining the interesting data reported by Huh et al., who observed no significant differences in detectable circulating levels of irisin in sera that had undergone multiple freezing and thawing cycles [19]. At present, an important limitation is that the irisin receptor has not been identified. However, some studies have shown that irisin promotes fat-browning by activating both the p38 mitogen-activated



PGC-1 α : **peroxisome proliferator-activated receptor gamma coactivator-1 α** ; FNDC5: fibronectin type III domain containing 5; UCP-1: uncoupling protein-1.

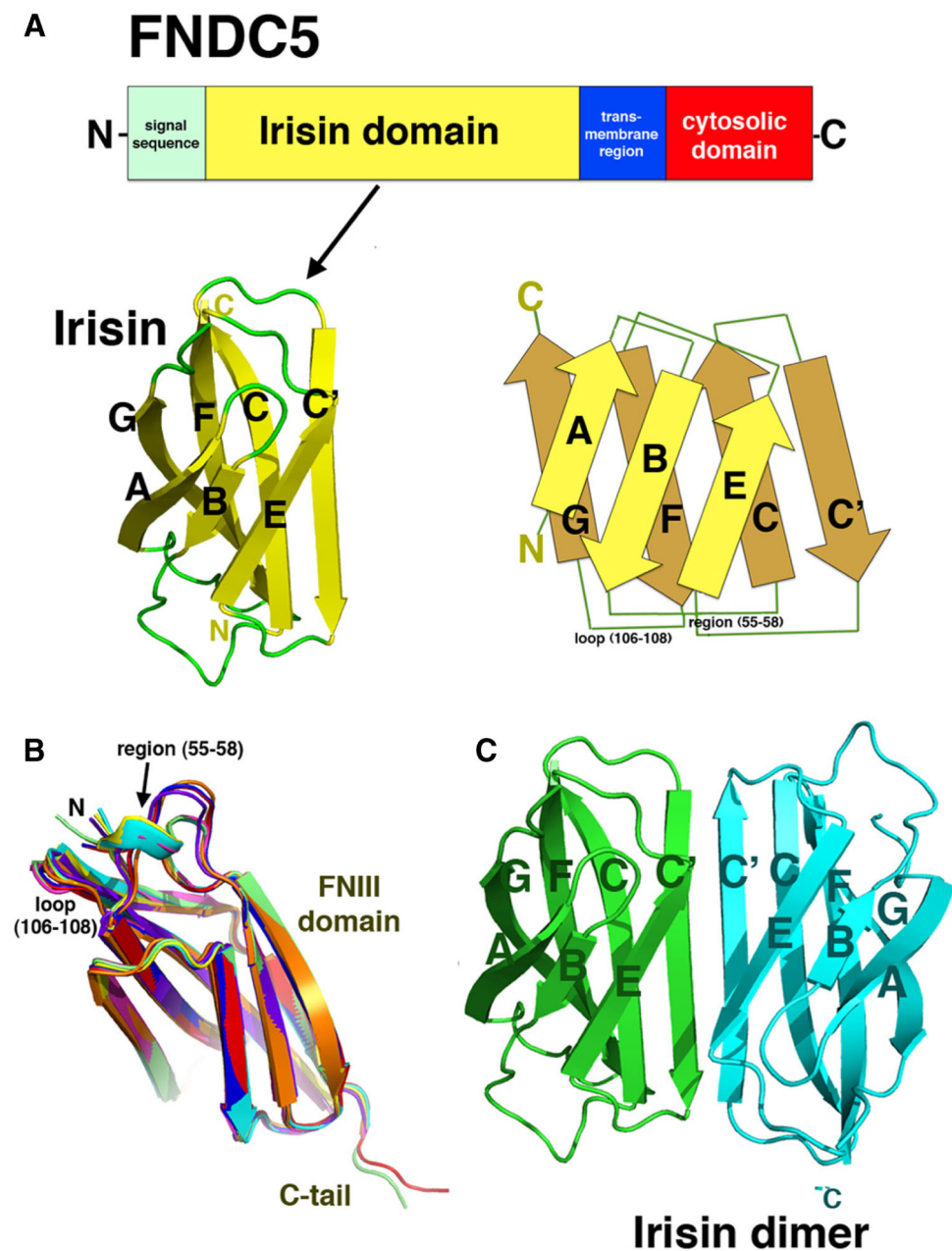
Fig. 1 Mechanism of irisin production and action

protein kinase (p38 MAPK) and the extracellular signal-related kinase (ERK) signaling pathways [20, 21]. Irisin might also act by inducing PPAR α expression [5] and, if confirmed, this effect may suggest that irisin is to some extent able to influence lipid metabolism [22]. Despite the fact that irisin secretion in skeletal muscle following exercise has been described [5, 23], data from several studies focusing on which kind of physical activity is able to promote the secretion of this myokine are conflicting [24] (Table 1). Some studies have found that irisin blood concentrations increased following endurance exercise [5, 25], while studies have reported that only resistance exercise is able to promote irisin expression [26, 27]. Lee et al. provided evidence that both resistance and endurance exercise were able to induce irisin secretion, though the highest peak was reported following endurance exercise [16]. Daskalopoulou et al. also observed higher circulating irisin levels following several kinds of exercise, the greatest peak occurring after maximal workload [28]. Nevertheless, there are data that suggest the lack of a relationship between irisin and exercise [11, 29–31]. A study by Jedrychowski et al., using mass spectrometry, seems to have definitively demonstrated that irisin production is regulated by exercise [8].

Interestingly, it was recently reported that irisin is also an adipokine, its expression having been detected in both mouse [32] and human adipose tissue [33]. Studies in rodents have found the presence of irisin also in cardiomyocytes and in cerebellum Purkinje cells [34]. Aydin et al. observed that the cardiac muscle of rats produced more irisin than skeletal muscle [35], they also identified this myokine both in saliva and in the skin [36], suggesting that even salivary and sebaceous glands may produce irisin. The same authors found irisin immunoreactivity also in the human stomach, liver, pancreas, and spleen, but its role in these organs has yet to be established [37]. While irisin has been isolated and identified in urine [28], lower levels of circulating irisin have been found in patients with renal impairment compared with individuals with normal renal function, thus hypothesizing an exclusive role of the liver in irisin metabolism and elimination [15, 38]. However, Lv et al., using irisin radiolabeled with ^{125}I , found significant radioactivity in the gallbladder, liver, and kidneys in mice, demonstrating that irisin is excreted by both the renal and hepatic route [39].

Irisin exerts its effects mainly on white adipocytes, inducing the brown fat-like gene expression that leads to a phenotypical switch with adipocytes, by which they lose

Fig. 2 Structure of irisin: **a** FNDC5 (fibronectin type III domain containing 5) protein is depicted. The extracellular ectodomain is cleaved to release irisin, consisting of four-stranded β -sheets packed to a three-stranded β -sheets; **b** image showing irisin subunits, highlighted the regions that may constitute the interaction sites amongst protein and protein; **c** picture representing the structure of irisin dimer (Reproduced with permission from Schumacher MA et al. [17] J Biol Chem “© The American Society for Biochemistry and Molecular Biology”)



their single large fat storage, and fill with multiple small lipid droplets, and turn into fat cells with characteristics between white and brown adipocytes that have been called brite or beige adipocytes [40]. Two *in vitro* studies also observed that irisin is able to reduce the differentiation of pre-adipocytes into mature adipocytes [21, 41], thus favoring the transdifferentiation into beige adipocytes. These data seem to indicate that irisin could affect energy metabolism through different, synergetic, mechanisms and its identification in various tissues might suggest irisin is crucial in maintaining cellular metabolic homeostasis.

Clinical data in humans: obesity, insulin resistance, and diabetes

Since its discovery, it has been hypothesized that irisin may have beneficial effects on chronic diseases such as obesity and type 2 diabetes (T2D), as well as protective effects against cardiovascular risk. However, attempts to reproduce in humans the encouraging findings obtained in animal studies have had conflicting results [42]. First, the relationship between irisin and body mass index is still unclear. Although, as expected, an inverse association between irisin concentrations and body mass index has

Table 1 Studies that considered irisin blood concentrations and physical activity

Studies	Participants (<i>n</i>)	Intervention	Change in irisin levels
Boström, 2012 [5]	Healthy adults (8)	10 weeks of aerobic training	Twofold increase vs. non-exercised
Hecksteden, 2013 [31]	Healthy adults: control (39), aerobic training (23), strength training (40)	26 weeks of aerobic training or strength training	No differences between groups
Norheim, 2014 [29]	Inactive men: control (13), hyperglycemic and overweight (13)	12 weeks of combined endurance and strength training 45 min bicycle test at 70% of VO _{2max}	No differences 1.2-fold increase immediately after exercise
Kurdiova, 2014 [30]	Sedentary overweight/obese adults (16)	12 weeks of combined endurance and strength training	No differences
Daskalopoulou, 2014 [28]	Healthy adults: pilot study (4) Main study (35)	Maximal workload on treadmill Three exercise protocols in random order: maximal workload on treadmill; relative workload on treadmill; absolute workload on cycloergometer	35% increase 3 min after exercise Significant increase after each exercise protocol. The greatest peak after maximal workload
Lee, 2014 [16]	Healthy adults (10)	Maximal exercise on cycloergometer Submaximal exercise on cycloergometer at 40% of VO _{2max}	Significant increase acutely after each exercise. The greatest peak after submaximal exercise (3.1 ± 2.8-fold)
Tsuchiya, 2015 [26]	Healthy active men (10)	Three randomized trials: resistance exercise; endurance exercise of pedaling at 65% of VO _{2max} ; combined resistance and endurance exercise	Significant increase 1 h after exercise in resistance (R) trial but not in endurance (E) trial or R + E
Huh, 2015 [27]	Sedentary men: healthy (14), individuals with metabolic syndrome (6)	Four randomized sessions: at rest; high-intensity interval exercise; continuous moderate-intensity exercise; resistance exercise	Significant increase acutely after each exercise session. 1 h post-exercise increase only after resistance exercise (~20%)
Miyamoto-Mikami, 2015 [25]	Healthy adults: control (25), endurance training (28)	8 weeks of endurance training on a leg ergometer	Significant increase in the middle-aged training subgroup vs. middle-aged controls (~20%). No differences in young
Jedrychowski, 2015 [8]	Healthy adults: control (4), aerobic training (6)	12 weeks of aerobic training	Increase after exercise intervention (~4.4 ng/ml) vs. control (~3.6 ng/ml)

been reported by many authors [33, 43, 44], there are studies that have showed either opposite [45–48] or conflicting results [19, 49].

There are also inconsistencies concerning the relationship between irisin, T2D, and insulin resistance [50]. High serum concentrations of irisin have been observed in patients with T2D [51, 52], although the bulk of the studies have reported opposite results [30, 33, 45, 53, 54]. Recently, Khidr et al. [55] confirmed in an Egyptian population that patients with T2D exhibit lower circulating irisin concentrations than non-diabetic people. They also found that the FNDC5 gene rs16835198 G → T polymorphism was a protective factor against T2D, being associated with enhanced irisin glycosylation, a process that favorably influences irisin function [20]. Sesti et al. observed that higher circulating levels of irisin were associated with low insulin-sensitivity [56], and similar

data were also reported by Park et al. [46]. However, Moreno-Navarrete et al. found a positive correlation between irisin concentrations and insulin-sensitivity [33]. Non-alcoholic fatty liver disease (NAFLD) is acknowledged as a classical component of insulin resistance syndrome [57, 58]. Based on animal studies, the relationship between irisin and hepatic steatosis was investigated by Zhang et al., who described a protective effect against hepatic steatosis [59]. Conflicting data were obtained by Polyzos et al., as they observed decreased irisin levels in patients with NAFLD or non-alcoholic steatohepatitis compared with lean controls, although this result was not confirmed in obese patients [43]. An *in vitro* study confirmed the possible protective role of irisin against NAFLD since it reduced the expression of the main regulators of lipogenesis, and prevented lipid accumulation in hepatocytes [60]. Contrary to this report, Choi et al. found a

positive, unexpected, association between irisin and liver steatosis [61]. Even more recently, Petta et al. [62] confirmed a significant association between irisin serum concentration and severity of NAFLD. Petta et al. also found that in patients with NAFLD the FNDC5 gene variant rs3480 A → G was independently associated with protection from fibrosis, probably reducing irisin expression in hepatic star cells. Interestingly, Kim et al. [63] recently found that glucocorticoid receptor activates the transcription of FNDC5 in the liver, an event that is expected to facilitate the occurrence of NAFLD; however, the prevalence of this condition in patients with Cushing's syndrome is about 20%, far below than expected [64]. Therefore, the relationship between irisin and NAFLD has yet to be defined.

Clinical data in humans: cardiovascular risk

Few studies have investigated the relationship between irisin and cardiovascular risk, and much of data do not refer to the global risk, but rather to its association with some of the established cardiovascular risk factors, of which T2D and insulin resistance have already been described above. In a single study that included 151 participants, the overall cardiovascular risk based on the Framingham risk score was investigated; interestingly, higher irisin concentrations were correlated with increased 10-year general cardiovascular diseases [46]. According to Hwang et al., individuals with higher serum irisin levels had lower diastolic blood pressure [65]. Conversely, Liu et al. reported a positive correlation between diastolic blood pressure and irisin [45]. Similar results, also including systolic blood pressure, were reported in a study by Park et al. [46]. Endothelial function has a great impact on cardiovascular risk because it is an independent predictor of cardiovascular events [66–68]. Hou et al. concluded that irisin might have favorable effects on endothelial function in a study of 41 non-hypertensive, non-diabetic, obese people [44]. However, a recent study by Aronis et al. reported higher circulating irisin levels in association with future major adverse cardiovascular events in patients with coronary artery disease who had undergone percutaneous coronary revascularization [69]. Reduced irisin blood levels were reported after myocardial infarction (MI), both in rats [70] and in humans [71], with the studies concluding that it might be a mechanism against energy depletion in critical situations, and proposing irisin as a new marker for an early diagnosis of MI. Moreover, there is evidence [56] of a positive correlation between irisin and carotid intima-media thickness, a well-known biomarker of vascular atherosclerosis that predicts cardiovascular outcome [72]. Interestingly, Rana et al. found in healthy adults a positive correlation between

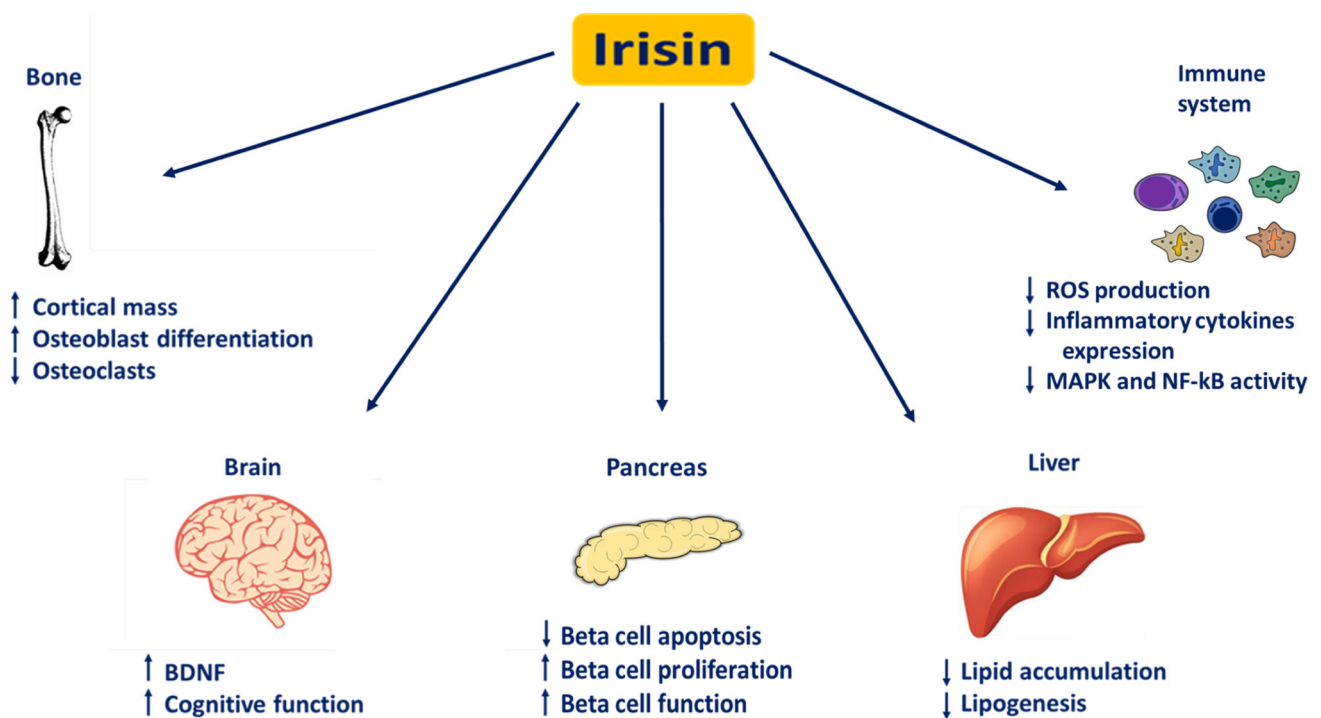
irisin concentrations and telomere length [73], a parameter not only involved in the aging process, but also in predicting premature MI, as previously proposed [74]. Irisin might also influence another important cardiovascular risk factor—serum concentrations of lipids. Some studies have clearly reported a significant association between irisin and a favorable lipid profile [65, 75]. However, both Ebert et al. and Liu et al. found that irisin concentrations were correlated with dyslipidemias [38, 45]; therefore, this interaction needs to be better elucidated. Hyperhomocysteinemia, even when not due to homocystinuria, is another established, though minor, cardiovascular risk factor [76, 77]. Alis et al. found that irisin was negatively correlated with homocysteinemia both in control and diabetic patients [54]. Similar findings were reported by Polyzos et al., who observed an inverse correlation only in individuals affected with NAFLD [78]; the same conclusions were reported by another study that included obese and diabetic participants [49]. However, it is still not clear why irisin should be protective against hyperhomocysteinemia.

Other possible effects of irisin

Both animal and in vitro studies have recently suggested that irisin exerts anti-inflammatory effects modulating the production of cytokines as interleukin-6, interleukin-1 β and tumor necrosis factor- α [79, 80], influencing transcription factors as MAPK and nuclear factor-kappa B [80, 81], or reducing the production of reactive oxygen species [82]. Interestingly, studies in vitro demonstrated that irisin protects pancreatic β -cells from high glucose-induced apoptosis [83]. Irisin has also been shown to protect against palmitic acid-induced apoptosis in hepatocytes [60] or against lipopolysaccharide-induced apoptosis of alveolar epithelial cells in lung [81].

Some favorable effects of irisin on extra-adipose tissue have been reported, mainly concerning bone metabolism and cognitive capacities (Fig. 3). Colaianni et al. observed in mice that irisin improves cortical bone mass by stimulating bone formation [7], reducing the number of osteoclasts [7] and preventing bone loss [84]. In agreement with a possible anabolic effect on bone, it has been demonstrated in vitro that irisin stimulates the differentiation of osteoblasts [85]. If these actions are confirmed, one could hypothesize that irisin promotes changes aimed at making the bone able to support greater loads due to an increased physical activity.

Interestingly, Wrann et al. observed in mice that endurance exercise induced hippocampal expression of FNDC5, the precursor of irisin, and demonstrated that forcing FNDC5 expression in primary cortical neurons promoted brain-derived neurotrophic factor (BDNF)



BDNF: brain-derived neurotrophic factor; ROS: reactive oxygen species; MAPK: mitogen-activated protein kinase; NF-κB: nuclear factor-kappa B.

Fig. 3 Other favorable effects of irisin

expression [6]. Furthermore, Belviranlı et al. found both higher circulating irisin levels and increased plasma BDNF concentrations in trained athletes, reporting a positive correlation between irisin and BDNF, and also between irisin and cognitive function tests [86]. Therefore, these data may indicate that irisin improves cognitive function, and mediates the beneficial effects of physical activity on brain health.

Another noteworthy question concerns irisin levels and impaired kidney function, since some studies have reported, rather surprisingly, decreased irisin circulating levels in individuals with different stages of chronic kidney disease [15, 38]. However, Wen et al. had previously shown that the administration of a specific uremic toxin into myocytes led to a decreased production of FNDC5 [15]. Therefore, uremic toxins might be responsible for the reduced irisin serum levels in patients with reduced renal function.

The relationship between irisin and thyroid function has also been investigated. Animal studies have been inconclusive. In particular, Samy et al. observed in rats affected with hypothyroidism, and in rats with hyperthyroidism, higher circulating irisin levels than in euthyroid ones [87]. In humans, Ruchala et al. observed different serum irisin levels according to thyroid status and reported a negative

correlation between irisin and the thyroid-stimulating hormone, while a positive correlation was observed between irisin and free thyroxine [88]. Similar correlations were reported by Yalcin et al., both in controls and in patients with Graves' disease [89]. However, Panagiotou et al. found no correlation between irisin and thyroid-axis hormones in a cross-sectional study [90]; similarly, they did not observe any change in serum irisin concentrations in two interventional studies in which thyroxine replacement was stopped or recombinant thyrotropin was administered, respectively [90]. Thus, the relationship between irisin and thyroid function remains an intriguing issue to be elucidated.

A complete list concerning all the other possible effects exerted by irisin is reported in Table 2.

Irisin contradictions: a unifying hypothesis

Activation and recruitment of BAT is crucial for modulating energy expenditure and body temperature and hence for survival of many animal species during and post hibernation [91]. Data concerning irisin production and concentrations in animals during the forced inactivity phase of hibernation when BAT is maximally expressed

Table 2 Correlations between blood irisin concentrations and clinical characteristics

	Relationship with irisin concentrations
BMI	No significant correlation (Huh et al. [19]; Sanchis-Gomar et al. [49]) Positive correlation (Stengel et al. [47]; Park et al. [46]; Liu et al. [45]; Pardo et al. [48]) Negative correlation (Moreno-Navarrete et al. [33]; Polyzos et al. [43]; Hou et al. [44])
T2D	↓ Blood concentrations (Moreno-Navarrete et al. [33]; Liu et al. [45]; Choi et al. [53]; Alis et al. [54]; Kurdiová et al. [30]) ↑ Blood concentrations (Al-Daghri et al. [52]; Garcia-Fontana et al. [51])
IS or IR	↑ Blood concentrations in people with ↑ IS (Moreno-Navarrete et al. [33]) ↑ Blood concentrations in people with ↓ IS (Sesti et al. [56]) ↑ Blood concentrations in people with ↑ IR (Park et al. [46])
CKD	↓ Blood concentrations (Wen et al. [15]; Ebert et al. [38])
Lipid profile	Positive correlation with cholesterol and triglycerides (Liu et al. [45]) Positive correlation with cholesterol and LDL-C in people with CKD (Ebert et al. [38]) Negative correlation with blood cholesterol, LDL-C, triglycerides in men and negative correlation with blood cholesterol in women (Oelmann et al. [75])
NAFLD	↓ Blood concentrations in obese adults (Zhang et al. [59]) ↓ Blood concentrations vs. lean individuals and no differences vs obese people without NAFLD (Polyzos et al. [43]) ↑ Blood concentrations (Choi et al. [61])
CV risk	↑ (Based on Framingham risk score) (Park et al. [46])

↑ increased, ↓ decreased, *BMI* body mass index, *T2D* type 2 diabetes, *IS* insulin-sensitivity, *IR* insulin resistance, *CKD* chronic kidney disease, *LDL-C* low-density lipoproteins cholesterol, *NAFLD* non-alcoholic fatty liver disease, *CV* cardiovascular

are not available. However, it was reported that the expression of PGC-1 α , the irisin promoter, is increased in hibernating animals [92]. Therefore, the proposed relationship exercise-irisin-BAT seems contradictory even in animals.

From a teleological point of view, it is also necessary to answer the question of what purpose irisin serves in terms of survival of the human species, beginning with humans who lived thousands of years ago. One of the main purposes, if not the most important, was certainly ensuring energy intake through energy consuming activities such as hunting and fishing. Prehistoric man, much more than today, also had the need to activate thermogenesis (at least in part guaranteed by BAT) for vital needs, an even greater need in the winter when forced to search for food. Interestingly, even Boström et al. asked why exercise should induce a program leading to heat generation and energy consumption [5] when people engage in physical activity in search of food for accomplishing energy intake requests. In that case, it should be considered that muscle contractions produce heat, and muscles themselves use lipids as fuel. Interestingly, Lee et al. demonstrated that exposure to the cold induced irisin secretion proportionally to the intensity of shivering, likely an evolutionary defensive mechanism against hypothermia [16]. We may therefore consider that survival of the human species requires the ability to produce heat for maintaining body homeostasis, particularly when physical activity is undertaken to provide food in adverse cold climatic conditions. It should be considered

that this activity also requires good cognitive function and an adequate bone structure, all aspects that irisin might facilitate. One can also hypothesize that in cases of forced inactivity, as during illness, low physical activity leads to reduced irisin production, decreased thermogenesis from BAT and, consequently, sparing of energy with lower food requirements. This may be a plausible model to explain the role of irisin, a role that today is likely of less importance than yesterday in terms of defense from the cold. On the contrary, today, irisin might be an advantage helping to dissipate energy in less efficient people, thus fighting against excessive fat accumulation. If the actions of irisin are confirmed, we may still imagine a pharmacologic role for this myokine in the treatment of obesity, and diabetes, as well as of cognitive impairment.

Conclusions

Irisin significantly affects energy homeostasis by inducing the browning of white fat, and enhancing heat generation and energy expenditure. Studies also show that irisin is involved in mediating several other exercise-inducible beneficial effects on health. Thus, irisin has undoubtedly generated remarkable interest due to its mechanism of actions that could counteract some diseases characterized by increased cardiometabolic risk, such as obesity and diabetes. Unfortunately, many conflicting results have been reported that do not allow a complete comprehension of the

role of this myokine. Further studies are certainly needed to clarify the conflicting results obtained in humans, and which are probably due to the quite recent demonstration of the existence of irisin. Different confounding factors need to be addressed, first the adequacy of techniques of irisin measurement; also sample size, age, gender, body composition, presence of diseases and kind of exercise need to be carefully analyzed in future studies. Among others, it is likely that the most important gap to fill is the identification of the irisin receptor(s). One might conclude that irisin, despite the origin of its name, is the bearer of good news, proposing a key factor to induce favorable effects on human health.

Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent For this type of study, formal consent is not required.

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