The truth behind irisin

A DESCRIPTIVE REVIEW ON THE PHYSIOLOGY OF AN EXERCISE-INDUCIBLE WONDER HORMONE

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Abstract

Irisin is a recently discovered so-called wonder hormone that has gained a great deal of attention over the past decade. It has been proposed as the answer to weight loss on social media due to its fat burning properties. The existence of irisin was, however, not immediately accepted and several recent studies still yield rather contradictory results. As an exercise-inducible adipomyokine, irisin is thought to confer a great deal of the health benefits previously attributed to physical activity. While it was first proposed as a novel therapeutic target in metabolic disorders, many researchers now claim its therapeutic potential in numerous additional pathologies. Much less, however, is known about the physiological role of irisin in a healthy state. The current study aims to provide insight into the physiology of irisin as well as its therapeutic promise. As irisin is produced by a variety of tissues, mainly skeletal muscle, and affects an extensive range of bodily systems, it is presumably involved in more than one physiological mechanism. Diverse factors influence circulating irisin levels and there is abundant controversy on which biochemical and/or environmental influences may truly play a role in its regulation. Based on current knowledge regarding the physiology of irisin, the present study hypothesizes that this newly identified hormone fulfils a role in exercise physiology, aiding in whole-body adaptation to physical activity and preventing exercise-induced complications. Besides that, it supports the involvement of irisin in the body's endogenous protection against hypothermia in response to shivering. Further involvement of irisin in other physiological mechanisms, however, is not dismissed considering its wide-ranging effect on the body and the expectation that continuous research may reveal even more of its functions. As a therapeutic target, irisin shows great promise in a variety of malignancies. However, these implications are predominantly based on animal models, and little is known about the pharmacological aspects of irisin or potential risks that could accompany irisin treatment. Before one can reliably apply the suggested 'wonder hormone' in humans, further validation and safety considerations are thus essential.

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Introduction

Ever since its discovery in 2012 (Böstrom et al., 2012), the hormone irisin has received much attention. This so-called exercise hormone is often described using terms such as magic, miracle or wonder hormone. The Pink Dragon studio has advertised with a fitness program that specifically targets irisin generation and release. They mention the hormone irisin, named after a Greek messenger goddess (Böstrom et al., 2012), to be the answer to weight loss. As well as that, irisin is referred to as a youth hormone. These properties render the hormone a hot topic.

Irisin was originally characterized as an exercise-inducible myokine that gives rise to the browning of white adipose tissue (Böstrom et al., 2012). However, recent studies have indicated that irisin exerts a function in many more bodily systems (Mahgoub et al., 2018)(Ma & Chen, 2021). The so-called wonder hormone has been proposed to function as a novel therapeutic target at first mainly in metabolic disorders, but now also in several other malignancies such as neurodegenerative disease or osteoporosis (Chen, J. et al., 2015)(Li, H. et al., 2021)(Pignataro et al., 2021)(Yang et al., 2021).

While a great deal of research is currently directed toward the potential of this newly discovered hormone in therapeutic strategies, it is important to take a step back and wonder why we as humans, and other animals, produce irisin. The present review thus aims to shed light on the underlying physiological role of circulating irisin. It also provides insight on how irisin has earned its status as a wonderhormone.

Discovery of an exercise-inducible myokine

Physical activity is commonly associated with health improvement. However, the underlying mechanism is not yet fully understood (Ma & Chen, 2021)(Motahari Rad et al., 2021). Transcriptional peroxisome proliferator-activated receptor gamma coactivators 1 (PGC-1) are known to induce muscle adaptation in response to physiological demands such as exercise (Arany, 2008). Böstrom et al. (2012) hypothesized that PGC-1α expression may confer health benefits in additional tissues by inducing secretion of signaling molecules from skeletal muscle. They have revealed a function of skeletal PGC-1α in stimulating browning of subcutaneous adipose tissue, involving an upregulation of brown adipose tissue (BAT) marker genes such as UCP1 (Böstrom et al., 2012). Based on this finding, fibronectin type III domain-containing 5 (Fndc5), a target gene of PGC-1α, was identified as likely encoding for a polypeptide to be secreted from skeletal muscle, exerting an effect on adipose tissue (Böstrom et al., 2012). Fndc5 is a known transmembrane protein suggested to undergo proteolytic cleavage, allowing for the release of a peptide fragment. Its proteolytic cleavage has later been confirmed, yet the responsible protease remains unidentified (Nie et al., 2020)(Liu, Y. et al., 2021). Fndc5 mainly resides in the endoplasmic reticulum of a cell. N-linked glycosylation was shown to be required for stabilization of Fndc5 and successful release of its cleavage product from skeletal muscle (Nie & Liu, 2017).

The resulting portion of the Fndc5 protein was named irisin, after the Greek messenger goddess Iris **(figure 1)** (Boström et al., 2012). Irisin is a 112 amino acid polypeptide thought to function as a mediator between muscle and other bodily systems (Böstrom et al., 2012)(Ma & Chen, 2021). The αV class of integrins has recently been suggested to act as irisin receptors in bone and adipose tissue (Kim et al., 2018). Nonetheless, no specific or universal membrane receptor could be identified for this chemical messenger so far (Xie, T. et al., 2020).

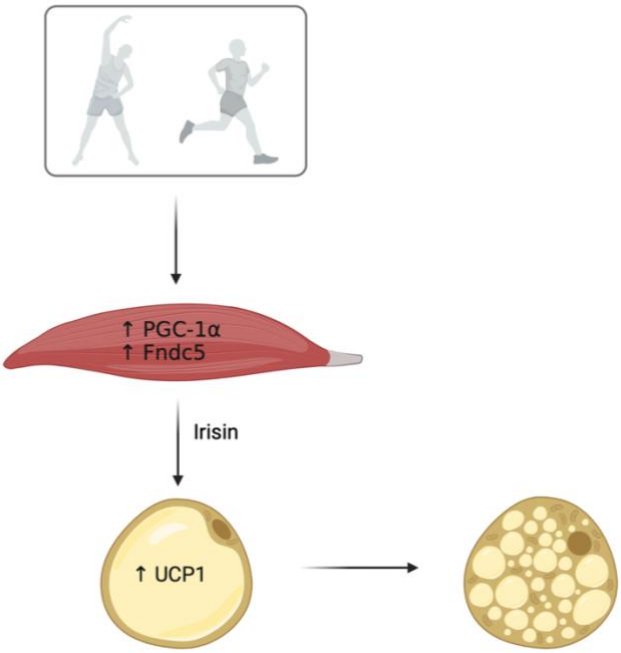

Figure 1: *Schematic overview displaying the functional mechanism of irisin as originally proposed by Böstrom et al. (2012). Muscle contraction during exercise causes the upregulation of PGC-1α in skeletal muscle, which in turn stimulates Fndc5 expression. Increased Fndc5 expression allows for a subsequent upregulation of the release of its cleavage product, irisin. The latter acts on white adipocytes to induce expression of BAT markers, causing a morphological and functional transition towards a more BAT-like program.*

For several years past its discovery, there was substantial controversy regarding the existence of irisin and its role as an exercise-inducible myokine. Multiple researchers deemed its activity in humans rather questionable (Timmons et al., 2012)(Erickson, 2013)(Elsen et al., 2014b). The secreted fragment of Fndc5 is highly conserved between species, with 100% identity between human and mice irisin (Böstrom et al., 2012). Still, it was later revealed that in humans, the gene encoding the irisin precursor Fndc5 contains a non-canonical start codon, ATA rather than ATG (Raschke et al., 2013). This was suggested to underlie a reduced expression of Fndc5 in humans, as the corresponding transcripts were translated into protein with rather low efficiency. Moreover, various studies have indicated inconsistencies when attempting to reproduce the proposed exercise-induced mechanism through which irisin affects adipose tissue (Elsen et al., 2014a). Based on multiple concerns, mainly involving cross-reactivity of commercial ELISA kits typically applied for detection of irisin, Albrecht et al. (2015) concluded irisin and especially its activity as an exercise-inducible myokine in humans to be a myth; three years after its discovery.

Not much later, however, Jedrychowski et al. (2015) have provided proof on the existence of irisin using tandem mass spectrometry. Their method demonstrated the presence of circulating irisin with more specificity than previously achieved. Even while irisin in humans is derived from a transcript with a non-canonical start codon (Raschke et al., 2013), its expression yields detectable circulating levels (Jedrychowski et al., 2015)(Pérez-Sotelo et al., 2017). Furthermore, Jedrychowski et al. (2015) have provided an indication that circulating irisin is truly upregulated by physical activity in young healthy subjects. Their study involved a comparison of irisin levels between sedentary individuals (~3.6 ng/ml) and individuals performing aerobic interval training (~4.3 ng/ml). Additional studies have demonstrated similar upregulations of circulating irisin upon exercise in both rodent models and human participants (Lee et al., 2014)(Huh et al.,

2014b)(Löffler et al., 2015)(Liu, Y. et al., 2021). While the hormone irisin currently appears to be commonly accepted as an exercise-inducible myokine, its precise regulation and physiological role remain a controversial topic.

Irisin secretion

Skeletal muscle is the main source of irisin (Böstrom et al., 2012). Throughout physical activity, muscle contraction causes an elevation in PGC-1α. This subsequently leads to a rise in the expression of Fndc5, the irisin precursor protein and a target of PGC-1α (Böstrom et al., 2012)(Archundia-Herrera et al., 2017). Consistently, artificial silencing of PGC-1α results in reduced Fndc5 expression in skeletal muscle of mice (Liu, Y. et al., 2021). Whether skeletal muscle is truly the most prominent irisin-expressing tissue has been questioned. Based on immunohistochemical staining in human skeletal muscle, Aydin et al. (2014) have suggested that most of the irisin expressed in the muscle tissue is not derived from sarcoplasm, but rather from the nerve sheaths innervating skeletal muscle. Furthermore, complete PGC-1α muscle-specific knockout mice have revealed a reduction in circulating irisin by 72% (Böstrom et al., 2012). Irisin is thus not solely secreted from skeletal muscle.

In fact, irisin secretion from white adipose tissue (WAT) has been detected, rendering the hormone an adipokine as well as a myokine. An in vitro study using murine mesenchymal stem cells revealed that irisin expression increases progressively throughout adipocyte differentiation (Pérez-Sotelo et al., 2017). Moreover, subcutaneous adipose tissue (SAT) deposits account for a larger part of irisin production than visceral adipose tissue (VAT) (Roco-Rivada et al., 2013). Irisin immunoreactivity in tissues other than skeletal muscle or WAT indicates that irisin is produced by various peripheral tissues as well. These include the testis, pancreas, liver, spleen, brain, stomach, cardiac tissues and bone tissue (Aydin et al., 2014)(Zhang, J. et al., 2017). Muscle mass remains, however, one of the main predictors for baseline circulating irisin levels (Huh et al., 2012)(Stengel et al., 2013).

Plasma irisin concentrations are highly variable between studies (Albrecht et al., 2015). Accordingly, there are numerous individual features shown to affect baseline circulating irisin levels. Besides muscle mass, a positive relationship between total body adiposity and Fndc5 expression in skeletal muscle of rats has been identified as well (Roberts et al., 2013). Löffler et al. (2015) have confirmed such a correlation between irisin and BMI in humans. In accordance, baseline circulating irisin is typically higher in obese as compared to normal weight individuals (Stengel et al., 2013)(Löffler et al., 2015). Sex differences also modulate baseline irisin, as men tend to secrete more irisin than women (Ruan et al., 2019). However, this could also be related to accompanying differences in body composition. Further influences involve for instance environmental factors, as area of residence affects circulating irisin levels in humans independent from age, gender, BMI or physical activity (Moreno et al., 2015). Moreover, some extent of maternal heritability has been proposed to determine an individual's baseline circulating irisin concentration (Al-Daghri et al., 2014).

Age is yet another characteristic found to influence baseline circulating irisin levels. Young individuals typically reveal higher irisin concentrations (Stengel et al., 2013)(Löffler et al., 2015)(Ruan e al., 2019). However, it is questionable whether age is an actual predictor for irisin expression. Muscle mass typically undergoes a reduction with age (St-Onge & Gallagher, 2010). A decrease in irisin-releasing tissue could thus be underlying for the age-related changes observed in baseline irisin concentrations. Moreover, ageing commonly lowers the opportunity and extent of physical activity. Assuming exercise to be the most direct stimulator for irisin secretion, a reduction in circulating irisin with age could thus be related to symptoms of ageing rather than the process itself.

Physiological functions of irisin

Over the past decade, a great number of physiological effects of irisin have been identified that cover a variety of organs **(table 1).** In short, irisin stimulates the utilization of lipids and glucose, promoting energy expenditure, it stimulates skeletal muscle activity and growth, it promotes bone remodeling, it confers neuroprotection, it improves cardiovascular function, and it displays anti-inflammatory properties. These are, however, only the effects irisin exerts on a selection of targets. The range of irisin function may thus be even greater.

While brown adipose tissue (BAT) was previously believed to exist only throughout infancy in humans, the presence and activity of BAT has been proven in adults throughout the past decade (Lee et al., 2013). BAT activity provides natural protection against both diet-induced obesity and hypothermia by enhancing energy metabolism and inducing thermogenesis. It does so through the action of the mitochondrial uncoupling protein 1 (UCP1) in brown adipocytes, which contain a relatively high number of mitochondria. UCP1 allows for energy dissipation in the form of heat by disrupting the electron transport chain in mitochondria (Spiegelman, 2013). Irisin is most well-known for its browning effect on WAT, generating so-called 'brite' or 'beige' adipocytes (Rodríguez et al., 2015). It induces upregulation of UCP1 in white adipocytes via activation of ERK and p38 signaling (Zhang, Y. et al., 2016a). Besides, irisin enhances the cellular mitochondrial density of white adipocytes (Castillo-Quan, 2012). The browning effect of irisin on WAT is substantially greater in subcutaneous fat stores than in visceral ones. Contradictory to what was observed for subcutaneous adipocytes, irisin has been shown not to exert an effect on p38 or ERK signaling, nor trigger UCP1 in another way in human visceral adipocytes. Still, it does stimulate mitochondrial metabolism in visceral adipocytes (Li, H. et al., 2019).

The metabolism of skeletal muscle is affected by irisin as well. It acts on myocytes to increase their mitochondrial content and energy expenditure. The latter specifically involves an elevation in oxygen consumption through mitochondrial uncoupling (Vaughan et al., 2015). TNFα and IL6 are known myokines that induce inflammatory cellular stress in myocytes, leading to upregulation of NFkB activity. This subsequently stimulates energy expenditure in the muscle tissue. Irisin, however, simulates skeletal muscle metabolism in a non-inflammatory fashion, without activating the NFkB pathway (Vaughan et al., 2015). Furthermore, the hormone irisin displays pro-myogenic properties. It triggers the expression of muscle growth-related genes in human myocytes (Huh et al., 2014a). In mice, irisin treatment resulted in muscle hypertrophy and was shown to promote muscle regeneration (Reza et al., 2017). Additionally, Y. Liu et al. (2021) recently indicated that static strength training in rats improves the endurance of skeletal muscle via PGC1α-Fndc5-UCP1 signaling. Irisin could thus function in an autocrine or paracrine as well as an endocrine fashion.

As an endocrine factor, irisin also affects a great deal of tissues other than WAT. An example is bone tissue. The muscle-bone axis has only recently become an endocrinological topic. While mechanical interactions between skeletal muscle and bone tissue are widely accepted, biochemical interactions remain largely uncharacterized (Bosco et al., 2021). Irisin is associated with bone health both in vitro and in vivo (Buccoliero et al., 2021). It promotes osteoblast differentiation through induction of osteogenic gene expression in mouse calvaria-derived pre-osteoblast cells (MC3T3-E1) (Yang et al., 2020). Moreover, in bone marrow mesenchymal stem cells (BMSCs), irisin upregulates both autophagy and osteogenesis. Hereby it stimulates osteogenic differentiation (Chen, X. et al., 2020). Consistently, irisin deficiency leads to deranged bone metabolism (Zhu et al., 2021).

Additional functions of irisin have been revealed in literature that target even more bodily systems. According to a review by Ma & Chen (2021), the abundant physiological functions of irisin render it a multi-organ healer. Additionally, in a promotion video for the Pink Dragon studio, irisin is stated to be an answer to weight loss as well as a youth-promoting hormone. The latter was based on a study performed by Rana et al. (2014), which suggested plasma irisin to exert

cellular anti-ageing properties because of its general positive association with telomere length in healthy human subjects. The authors substantiate this hypothesis with the indication that irisin activates signaling pathways involved in cellular proliferation, that have an implication for the regulation of human telomerase reverse transcriptase as well. According to Rana et al. (2014), telomere length is an established predictor of ageing. Conversely, examination in centenarians and their offspring has indicated that telomere length does not predict successful, healthy ageing (Arai et al., 2015). A population-based study performed in Scotland has questioned the predictive quality of telomere length for ageing as well, mentioning that it does not satisfy the criteria of a true biomarker of biological ageing (Der et al., 2012). Furthermore, telomere length is associated with properties of irisin target tissues as well as irisin itself (Rana et al., 2014), which may underlie an indirect relationship between irisin and the biological ageing process. Whether irisin truly confers anti-ageing benefits thus requires further investigation.

Table 1: *Physiological effects of circulating irisin on a selection of target systems*

Target	**Effect**
Lipid and glucose metabolism	↑ Energy expenditure in white adipose tissue - Thermogenesis via UCP1 upregulation (Boström et al., 2012)(Zhang, Y. et al., 2016a) - Enhanced mitochondrial metabolism (Castillo-Quan, 2012) ↓ Adipogenesis (Zhang, Y. et al., 2016a)(Ma & Chen, 2019) ↑ Lipolysis (Xiong et al., 2015) ↑ Fatty acid oxidation (Xin et al., 2016) ↓ Hepatic cholesterol synthesis (Tang et al., 2016) ↓ Plasma glucose (Ozcan et al., 2020) - Reduced hepatic gluconeogenesis (Liu, T. et al., 2015) - Increased glycogen synthesis (Liu, T. et al., 2015) ↑ Glucose tolerance (Roco-Rivada et al., 2013)(Xin et al., 2016) ↓ Pancreatic β-cell apoptosis (Liu, S. et al., 2017)(Xie, T. et al., 2020) ↑ Insulin sensitivity (Xiong et al., 2015) ↓ Body weight (Niranjan et al., 2019)
Skeletal muscle	↑ Energy expenditure (Vaughan et al., 2015) ↑ Regeneration (Reza et al., 2017) ↑ Growth (Huh et al., 2014a)(Reza et al., 2017)
Bone	↑ Osteogenesis (Chen, X. et al., 2020) - Osteoblast differentiation (Yang et al., 2020) ↓ Osteocyte apoptosis (Sorlino et al., 2020)(He et al., 2020) ↑ Bone resorption (Estell et al., 2020) - Osteoclast differentiation (Estell et al., 2020) ↑ Mineralization (Zhang, J. et al., 2017) ↑ Trabecular and cortical bone thickness (Zhang, J. et al., 2017)
Central nervous system (CNS) and behavior	↓ Depression-like behavior (Wang & Pan, 2016)(Sitenski et al., 2018) ↓ Pain threshold (Dameni et al., 2018) ↑ BDNF expression (Wrann et al., 2013)(Natalicchio et al., 2020) ↓ Neuronal injury (Li, D. et al., 2016)(Peng, J. et al., 2017)

Cardiovascular system	↑ Angiogenesis (Liao et al., 2019) ↓ Heart rate (Brailoiu et al., 2015) ↑ Cardiomyoblast differentiation and metabolism (Xie, C. et al., 2015) ↑ Vasorelaxation (Jiang et al., 2015)
Immune system	↑ Macrophage activity (Mazur-Bialy, 2017a) ↓ Inflammation (Askari et al., 2018) - Reduced ROS production in macrophages (Mazur-Bialy, 2017a) - Downregulation of pro-inflammatory cytokines (Mazur-Bialy et al., 2017b)

Exercise-based regulation of circulating irisin

Irisin was originally identified as an exercise-inducible myokine (Böstrom et al., 2012). In relation to its protective function in a variety of organs, Ma & Chen (2021) stated that irisin could provide the previously unknown link between exercise and health. Elevation of circulating irisin concentrations upon acute exercise has been confirmed in some studies (Huh et al., 2012)(Brenmoehl et al., 2014)(Lee et al., 2014)(Löffler et al., 2015), but was not reproducible in others (Elsen et al., 2014a). As mentioned before, the Pink Dragon studio claims to have designed a fitness program specifically targeting maximal irisin secretion. This implies a role of exercise type and length in the regulation of irisin release. Could this be why the exercise-inducibility of irisin remains controversial?

Löffler et al. (2015) showed that in children and young adults, short rounds of intensive exercise induced an elevation of circulating irisin in an acute and transient fashion. The authors compared irisin concentration in blood samples taken directly preceding and immediately after a cycling spiroergometric test of 15 minutes. A study on female adolescents did not reveal any changes in circulating irisin upon a similar duration of high-intensity interval training (HIIT) (Archundia-Herrera et al., 2017). In the latter experimental set-up, however, potential changes were measured based on a baseline sample taken after 48 of abstention from strenuous physical activity and a sample taken 30 minutes past the acute bout of exercise. Moreover, the authors did report an elevation of irisin expression in skeletal muscle 30 minutes after HIIT. The latter may indicate that irisin secretion from skeletal muscle is in fact upregulated during acute exercise, but that changes in circulating irisin are transient.

In the mentioned study on female adolescents, yet another group was asked to perform one bout of moderately intensive, aerobic exercise on a cycle ergometer (Archundia-Herrera e al., 2017). This involved reaching and subsequently sustaining a 65% peak in heart rate for 40 minutes. The authors found that plasma irisin did not increase, nor did the irisin concentration in skeletal muscle; indicating that there was no response of irisin expression upon aerobic exercise of moderate intensity. Another study showed that in healthy male participants, one round of 40-minute aerobic running exercise at 65%-70% of their maximum heart rate induced minimal elevations in plasma irisin concentration (Özbay et al., 2021). An important difference is that in the latter study, blood samples were retrieved immediately after exercise. Thus, these conflicting results may depend on an acute and transient mechanism of irisin upregulation upon exercise. In accordance, Norheim et al. (2014) indicated an acute (~1.2 fold) rise in plasma irisin concentration of healthy men immediately after a 45-minute session of ergometer cycling, followed by a clear decrease upon 2 hours of rest. This irisin response was not dependent on an upregulation of Fndc5 mRNA. Thus, an acute and transient irisin response upon exercise could be initiated through increased translation of Fndc5 mRNA rather than elevated PGC-1α-Fndc5-irisin signaling (Norheim et al., 2014). Exercise intensity was somewhat higher in the latter experimental set-up as compared to the ones mentioned before.

Long-term interventions in physical activity involving a consistent aerobic training program, generally do not cause a chronic elevation of baseline irisin levels (Norheim et al., 2013)(Pekkala et al., 2013)(Löffler et al., 2015). A recent meta-analysis performed by Motahari Rad et al. (2021) has even revealed that circulating irisin undergoes a reduction upon chronic exercise training in randomized controlled trials. On the other hand, the authors also indicated that long-term resistance training does in fact lead to an elevation of baseline irisin levels. A similar result was previously revealed in older male adults by Zhao et al. (2017). The rise of baseline circulating irisin following long-term resistance exercise is likely dependent on changes in body composition. Given that skeletal muscle is the main irisin-producing tissue in the human body, muscle mass gain in response to resistance exercise (Krzysztofik et al., 2019) could underlie baseline changes in plasma irisin not observed following an aerobic training program.

Any discrepancies among studies reporting on circulating irisin levels in response to exercise are presumably dependent on the nature of the performed activity, its intensity and the time in between exercise and sample collection (Norheim et al., 2013). Lee et al. (2014) have for instance revealed that endurance exercise confers a greater effect on irisin levels in healthy individuals than a maximal exercise test. Another study revealed that resistance exercise generates a greater irisin response than endurance exercise (Tsuchiya et al., 2015). Furthermore, in relation to body composition, sex and age differences could establish deviations that may not be ignored when comparing different studies. Huh et al. (2014b) have indicated that while baseline irisin levels are associated with age and fitness level, exercise-induced irisin secretion appears independent from these variables. Still, the involvement of individual subject features that stand in relation to body composition and their effect on the exercise-inducibility of irisin secretion pends further investigation. Environmental influences have even been proposed to specifically affect the exercise-based regulation of circulating irisin as well (Özbay et al., 2021).

Conflicting results on whether exercise directly affects irisin concentrations may also be, at least in part, explainable by the fact that irisin is released from other tissues as well as from skeletal muscle. The mechanism by which physical activity and concurrent muscle contraction induces Irisin expression in skeletal muscle is well established, but this is less clear for other sources. Nonetheless, exercise-inducibility of irisin expression in tissues other than skeletal muscle has been proposed. Fndc5 and irisin expression in murine bone tissue is for instance heightened after a two-week period of voluntary wheel running exercise (Zhang, J. et al., 2017). Besides that, Roco-Rivada et al. (2013) showed that release of irisin from WAT is linked to physical activity. Upon short-term exercise (1 week), the expression and secretion of Fndc5 and irisin, respectively, from WAT displayed an elevation in mice. However, a longer period of exercise (3 weeks) resulted in a significant reduction in Fndc5 and irisin levels. Besides that, the authors revealed that fasting also has an inhibitory effect on irisin secretion from WAT. This response indicates that while exercise may lead to acute irisin production by WAT, prolonged physical activity or reduced energy intake may induce a negative feedback loop on irisin expression (Roco-Rivada et al., 2013). Both factors lead to prolonged elevations in energy expenditure, which could reduce the need for irisin to further promote energy expenditure in fat tissue.

Biochemical interactions and feedback regulation of circulating irisin

Irisin interacts with a large range of bodily tissues and soluble factors (Mahgoub et al., 2018). Therefore, interplay between this recently identified hormone and other, more well-characterized biochemical systems presumably plays an important role in the physiology of irisin. Identification of such interactions may contribute to the discovery of additional, exercise-independent regulatory mechanisms regarding circulating irisin.

For its effects on lipid and glucose homeostasis as well as its capacity to stimulate metabolism in various tissue types **(table 1)**, irisin is deemed a metabolic regulator. A variety of associations,

or lack thereof, found between circulating irisin levels and a selected number of hormones known to play an important role in energy homeostasis are summarized in **table 2.**

The thyroid gland enhances whole-body metabolism by production of hormones that stimulate metabolic activity in nearly all tissues. To regulate the thyroid gland, the anterior pituitary releases thyroid stimulating hormone (TSH). This hormone induces upregulation of the production of thyroid hormones (TH) that in turn affect tissue metabolism in an endocrine fashion (Chiamolera & Wondisford, 2009). Central irisin administration downregulates thyroid releasing hormone (TRH), responsible for stimulating TSH release, serum TSH and circulating thyroid hormone levels in rats (Tekin et al., 2018). Given that both irisin and the thyroid gland are responsible for increasing metabolic activity, such an interaction would indicate some sort of transition between the two systems in the regulation of whole-body metabolism. The association between irisin and TSH in humans, however, remains inconclusive **(table 2)**.

Browning of white adipose tissue is an established function of the messenger hormone irisin. At the time of its discovery, Böstrom et al. (2012) showed that Fndc5, the precursor of irisin, induces drastic changes in gene expression in white adipocytes. These changes correspond not only to the upregulation of UCP1, but also of other known brown fat genes. Moreover, the authors reported that the switch in gene expression program involves a downregulation of certain characteristic white fat genes as well. Specifically, Fndc5 causes a reduction of leptin expression in white adipocytes (Böstrom et al., 2012). Leptin is a hormone secreted by WAT, known for its stimulatory effect on whole-body energy expenditure and its function in reducing appetite (Hegyi et al., 2003). As irisin reduces typical WAT, it thus seems logical that leptin secretion would be downregulated in response to irisin as well. In vivo experiments, however, reveal inconsistent results in rodents and show no such relation in humans **(table 2)**. Similarly, the finding that leptin administration stimulates irisin expression in murine muscle both in vitro and in vivo through NO-dependent upregulation of Fndc5 (Rodríguez et al., 2015), has not been confirmed in humans **(table 2)**.

Insulin is yet another hormone involved in the whole-body energy balance, modulating glucose and lipid homeostasis (Niswender, 2015). Irisin affects the insulin-producing β-cells of the endocrine pancreas **(table 1)**. It has the capacity to suppress β-cell apoptosis along with stimulating β-cell proliferation. Through its interaction with the pancreas, irisin is thought to raise insulin synthesis and release (Xie, T. et al., 2020). Consistently, irisin levels are positively correlated with baseline insulin in humans. However, examination of the effect of irisin on insulin levels in rodents yield contradictory results **(table 2)**. The other way around, exogenous insulin supply, using a hyper insulinemic clamp technique, was found not to exhibit any direct effect of insulin on irisin expression in healthy women (Adamska et al., 2016). Still, insulin was indicated to cause heightened circulating irisin levels in type 2 diabetes mellitus patients (Li, L. et al., 2016). Whether there is in fact a regulatory link between the two hormones thus remains controversial.

The same goes for ghrelin, an established hunger hormone produced by enteroendocrine cells in the gastrointestinal tract, predominantly in the stomach (Latorre et al., 2016). Irisin infusion was shown to increase energy consumption of rats without exerting an effect on body weight (Tekin et al., 2017)(Tekin et al., 2018). This was suggested to be accompanied by heightened ghrelin levels, which could have explained the behavioral change. However, a consistent effect of irisin on ghrelin expression was not identified as several studies yield contradictory results **(table 2)**. Moreover, another study on rats revealed no upregulation of food intake in response to intra-hypothalamic irisin treatment at all (Ferrante et al., 2016).

Table 2: *Overview of studies linking irisin to a selection of other metabolic hormones*

Hormone	**Association with irisin expression**	
	In rodents	***In humans***
TSH	- Irisin reduces serum TSH levels (Tekin et al., 2018)	- No correlation (Stengel et al., 2013)(Panagiotou et al., 2016) - Negative correlation (Ruchala et al., 2014)(Shan et al., 2020) - Positive correlation (Stratigou et al., 2018)
Leptin	- Leptin upregulates irisin expression in murine muscle tissue (Rodríguez et al., 2015) - Irisin does not alter circulating leptin levels (Natalicchio et al., 2019) - Irisin reduces serum leptin levels (Tekin et al., 2017)(Ozgor et al., 2020)(Ozcan et al., 2020)	- No correlation in obese patients (Crujeiras et al., 2014) - Leptin does not alter circulating irisin levels (Gavrieli et al., 2016)
Insulin	- Irisin reduces serum insulin levels (Böstrom et al., 2012)(Ozgor et al., 2020) - Irisin increases serum insulin levels in type 2 diabetic rats (Liu, S. et al., 2017)	- Positive correlation (Stengel et al., 2013) - Positive correlation in obese patients (Crujeiras et al., 2014) - Insulin does not alter circulating irisin levels (Adamska et al., 2016) - Insulin increases circulating irisin in type 2 diabetes mellitus patients (Li, L. et al., 2016)
Ghrelin	- Irisin does not alter circulating ghrelin levels (Natalicchio et al., 2019) - Irisin reduces serum ghrelin levels (Ozgor et al., 2020) - Irisin increases serum ghrelin levels (Tekin et al., 2017)	No correlation (Stengel et al., 2013)

Irisin performs several functions that promote bone remodeling **(table 1)**, which could potentially confer an endocrinological adaptive response to the exercise. Parathyroid hormone (PTH) secretion can be stimulated by exercise as well, partly driven by elevated calcium levels (Gardinier et al., 2015)(Lombardi et al., 2020). PTH is produced by the parathyroid glands, small endocrine glands located directly behind the thyroid gland. It is the main regulator of calcium-phosphate homeostasis (Lombardi et al., 2020). Bone adaptation in response to physical activity has important mechanical implications, preventing fractures under mechanical stress (Turner & Pavalko, 1998). Both dynamic loading and PTH release contribute to bone adaptation upon exercise (Gardinier et al., 2015). An inverse correlation between PTH and circulating irisin has been indicated in women before (Anastasilakis et al., 2014). PTH has a catabolic effect on bone tissue, while the effect of irisin appears in a more anabolic fashion (Colaianni et al., 2015). Besides that, PTH has been suggested to exert an opposing effect as compared to irisin on energy homeostasis (Palermo et al., 2019). The two hormones thus counteract one another in their response to exercise. Recently, a direct regulatory interaction between PTH and irisin has been indicated both in vivo and in vitro, in which either hormone reduces expression of the other

(Palermo et al., 2019). While this interplay still pends further investigation, it provides a novel feedback mechanism that could regulate circulating irisin.

Similarly, a homeostatic feedback loop between irisin and brain-derived neurotrophic factor (BDNF) has been proposed. Wrann et al. (2013) showed that while Fndc5 expression stimulates BDNF production, BDNF potently downregulates Fndc5 expression in murine neurons. The latter effect diminished upon BDNF receptor blockage. The authors hypothesized a negative feedback mechanism to regulate the irisin-induced stimulation of BDNF. Confirmation that circulating irisin increases BDNF expression in the brain of mice has since then been provided (Natalicchio et al., 2019). However, an answer as to whether the proposed feedback mechanism is truly in place awaits subsequent experimental proof.

These and other biochemical factors have been proposed to influence or directly regulate circulating irisin levels (Mahgoub et al., 2018), indicating that exercise is not the sole determinant when it comes to plasma irisin concentration.

Cold-based regulation of circulating irisin

The human body adapts to environmental temperature to maintain a steady body temperature at all times. In response to cold, thermoregulation mechanisms will ensure a heightened energy expenditure to elevate endogenous heat production. This cold-induced metabolic change prevents against hypothermia (Brychta & Chen, 2017). Both muscle and BAT are capable of thermogenesis in response to cold temperatures. To elevate heat production, both tissues induce energy dissipation through futile ATP hydrolysis (Bal et al., 2017). Skeletal muscle can perform such nonshivering thermogenesis (NST) as well as shivering thermogenesis. The latter involves direct heat generation through muscle contractions (Lee et al., 2014). Cold exposure also leads to the generation of beige adipocytes from WAT through activation of a thermogenic program involving UCP1 (Harms & Seale, 2013). This response has been suggested to emerge due to adipocyte transdifferentiation mediated by the β_3-adrenoreceptor (Barbatelli et al., 2010).

The hormone irisin has the capacity to increase energy expenditure and consequential thermogenesis in both adipose tissue and skeletal muscle as well. In adipose tissue it does so via WAT browning (Zhang, Y. et al., 2016a). In muscle tissue irisin also promotes endogenous mitochondrial uncoupling, allowing for increased energy dissipation (Vaughan et al., 2015). Upon its discovery, Böstrom et al. (2012) indicated how the upregulation of energy expenditure seems a counterintuitive response to physical activity. Consequently, the authors hypothesized irisin expression to provide a defense against hypothermia initiated by muscle contraction during shivering **(figure 2)**. Cold exposure indeed increases circulating irisin in humans, and irisin secretion rises proportional to the concurrent shivering intensity (Lee et al., 2014). Consistently, cold exposure stimulates Fndc5 expression in chicken muscle (Li, X. et al., 2015). Examination of the effect of whole-body cryostimulation in middle-aged men has also confirmed cold-induced irisin upregulation (Dulian et al., 2015). Moreover, the authors of the latter study specifically suggested that subcutaneous fat tissue is the major source when it comes to heightened irisin expression in response to cold exposure. Still, recent studies have reported contradictory results on the proposed cold-inducibility of irisin in humans (Dobrodeeva et al., 2020)(Mu et al., 2021).

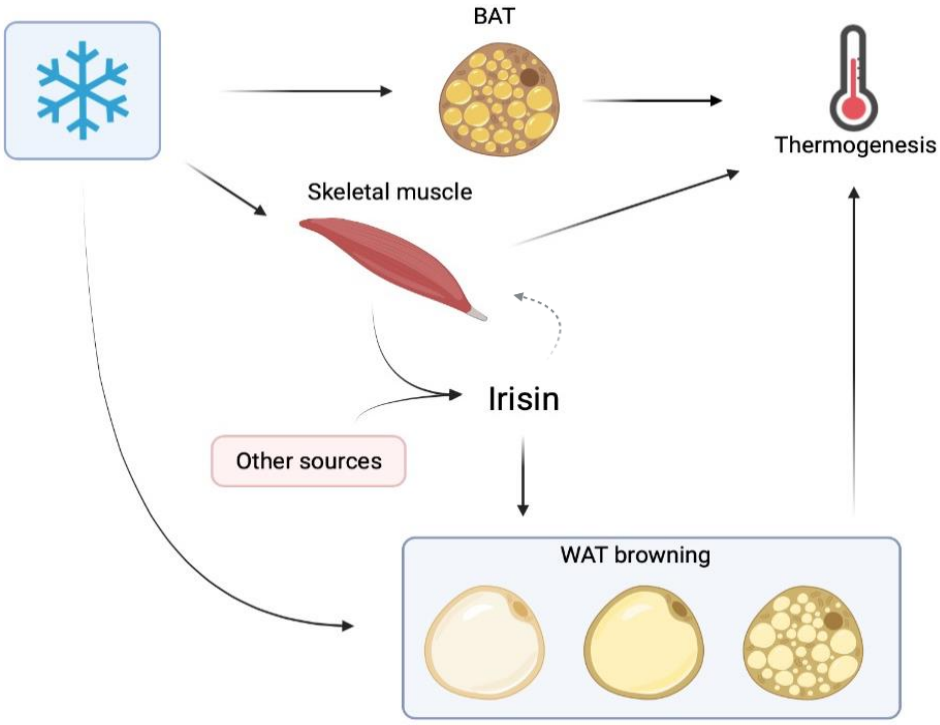

Figure 2: *Cold-induced responses that elevate body temperature via both shivering and nonshivering thermogenesis. Irisin is proposed to provide an additional mechanism that protects against hypothermia through the promotion of WAT browning (Böstrom et al., 2012). The dotted grey arrow indicates that irisin promotes thermogenesis in skeletal muscle as well (Vaughan et al., 2015), adding to the cold-induced thermogenic response of irisin.*

Therapeutic potential of irisin

Regarding its beneficial effects in a variety of organs, irisin has been implicated as a novel therapeutic target in a large range of pathologies. Its potential reaches beyond metabolic disease, in which it was first indicated.

Irisin alleviates diet-induced obesity in mice (Böstrom et al., 2012). This may be attributed to an increased energy expenditure and reduced adipogenesis. Irisin administration does not only reduce body weight and adiposity in obese mice, but it also improves their metabolic profile. Administration or forced overexpression of irisin has shown to attenuate obesity-associated disruptions in lipid and glucose homeostasis (Xiong et al., 2015)(Niranjan et al., 2019). Moreover, irisin treatment leads to a decline of pro-inflammatory markers in both subcutaneous and visceral fat stores (Li, H. et al., 2019). The anti-inflammatory properties in irisin battle chronic low-grade adipose tissue inflammation commonly arising as a result of obesity (Li, H. et al., 2021). Overall, the administration of irisin in a sedentary setting mimics the beneficial alteration of obesity-related metabolic parameters previously observed to be reached by exercise (Yuksel et al., 2020). This indicates that irisin treatment may provide a way to combat excessive weight gain or the detrimental effects of pathological obesity, especially in patients suffering from immobility. Counterintuitively, however, irisin levels are generally already elevated in obese individuals (Stengel et al., 2013)(Löffler et al., 2015). While irisin is known to upregulate thermogenesis via UCP1 expression in mature white adipocytes, it blocks adipogenesis in pre-adipocytes by

inhibiting adipogenic differentiation (Zhang, Y. et al., 2016a). Obese adipose tissue generates more irisin than healthy fat stores, but also secretes factors shown to inhibit PGC-1α and Fndc5 expression in adipocytes undergoing differentiation (Pérez-Sotelo et al., 2017). Hereby, obesity may result in a lack of irisin production by pre-adipocytes leading to overstimulation of adipogenesis and lipid accumulation in WAT. The obesity-related upregulation of irisin production by mature adipocytes may thus be a physiological compensating mechanism, attempting to reduce adiposity through elevated thermogenesis (Pérez-Sotelo et al., 2017). Consistently, Fndc5 expression in skeletal muscle of obese rats is elevated as well, and correlates positively with fat mass (Roberts et al., 2013).

In type 2 diabetes mellitus (T2D), another metabolic malignancy, circulating irisin levels are typically reduced as compared to non-diabetic controls (Liu, J. et al., 2013)(Balaban et al., 2019). The same goes for gestational diabetes mellitus (Li, Y. et al., 2019). Irisin has several favorable effects on glucose homeostasis **(table 1)**. It for instance attenuates insulin resistance via p38-MAPK-PGC-1α signaling and promotes glucose tolerance, stimulating glucose uptake via AMPK signaling pathways (Ye et al., 2019)(Xin et al., 2016). Mice lacking irisin, on the other hand, display a disordered metabolism including reduced insulin sensitivity and other signs of disrupted glucose and lipid homeostasis (Luo et al., 2020). Irisin treatment could thus provide benefits in T2D patients and metabolic derangements in general.

Irisin, however, provides great therapeutic potential beyond metabolic complications. Its protective function against disease-induced tissue damage and dysfunction has been implicated for various organs **(figure 3)**. Irisin improves endothelial function in T2D and it prevents atherosclerosis through stimulation of endothelial proliferation (Zhu et al., 2015)(Zhang, Y. et al., 2016b). Moreover, it prevents cardiomyocyte apoptosis upon myocardial infarction and promotes cardiac remodeling in response to pressure overload (Xin & Lu., 2020)(Peng, Q. et al., 2021). In the liver, irisin prevents hypercholesterolemia by attenuating hepatic cholesterol synthesis (Tang et al., 2016). Besides that, irisin was suggested to ameliorate the progression of hepatic fibrosis by regulating the function of hepatic stellate cells (Dong et al., 2020). Irisin also lessens the impact of disease-induced intestinal injury (Ren et al., 2019)(Bi et al., 2019). Furthermore, irisin prevents acute kidney injury (Zhang, R. et al., 2020). In the case of kidney injury, however, irisin could also potentially be applied to mitigate tubular epithelial cell apoptosis via modulation of reactive oxygen species (ROS) production by the mitochondria (Zhong et al., 2019). Furthermore, irisin was previously mentioned to exert a protective function on neurons of the CNS. It does so via several distinct signaling pathways (Li, D. et al., 2016)(Peng, J. et al., 2017)(Jin et al., 2019). Due to its functions in bone remodeling, irisin can provide protection against osteoporosis as well (Morgan et al., 2021). Similarly, irisin alleviates osteoarthritis via the inhibition of osteocyte apoptosis and prevention of chondrocyte dysfunction (He et al., 2020)(Wang et al., 2020).

Furthering the recently implied therapeutic potential of irisin, the hormone has been suggested to provide therapeutic properties in multiple cancer types as well, including glioma (Huang et al., 2020), osteosarcoma (Cheng et al., 2020), hepatocellular carcinoma (Shi et al., 2017), pancreatic cancer (Zhang, D. et al., 2019), and lung cancer (Shao et al., 2017).

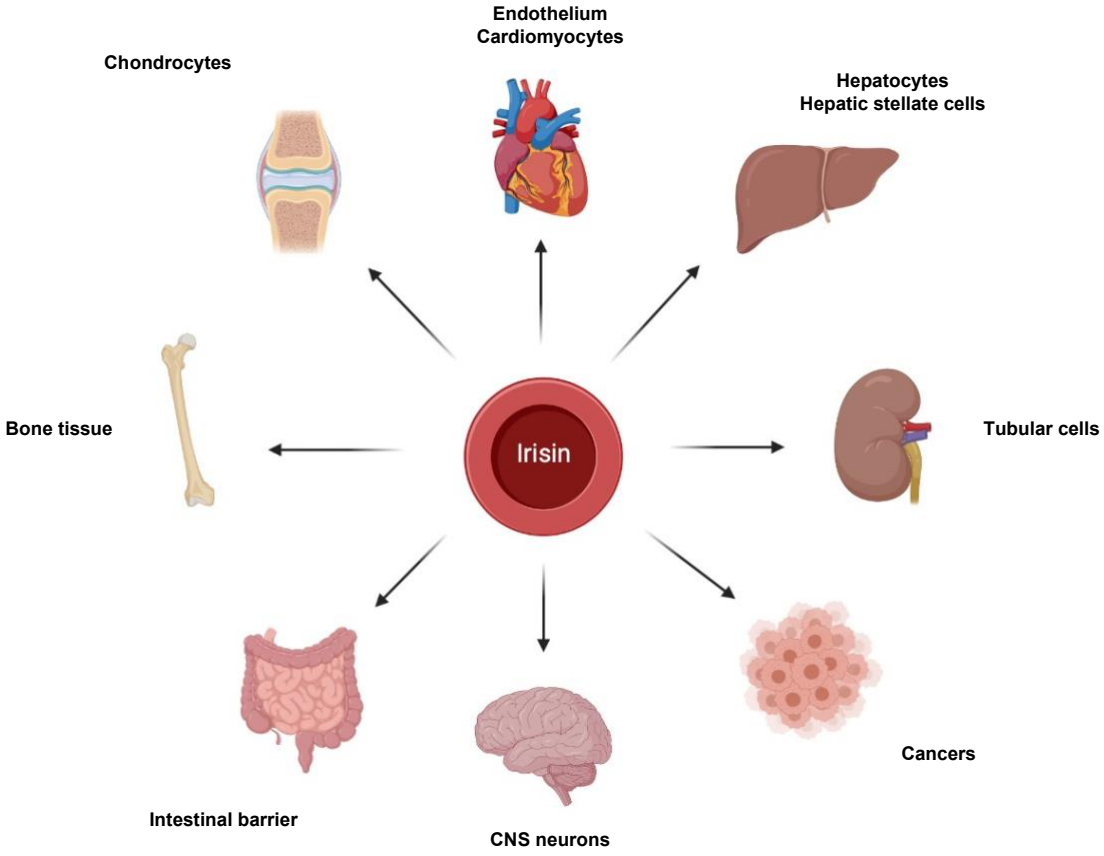

Figure 3: *Selected number of organs and cell types in which irisin has been implicated as a novel therapeutic target for various diseases, showing promise predominantly in mice.*

Much less is known about potential side-effects or other dangers irisin treatment could bring about. Excessive irisin administration for instance results in overproduction of ROS in murine cardiomyocytes, with a corresponding increase in apoptosis (Ho et al., 2018). Besides that, chronic irisin exposure in rats can have adverse effects on the hypothalamus-pituitary-gonadal axis in males as well as the female reproductive system (Tekin et al., 2019)(Ulker et al., 2020). Also, several physiological factors important for the characterization of irisin as a therapeutic option remain largely unidentified **(table 3)**.

Table 3: *Pharmacologically relevant features regarding irisin that remain insufficiently characterized*

Unidentified factor	Current suggestions

Irisin receptor	- The αV family of integrins could act as irisin receptors (Flori et al., 2021)
	  ○ αV class integrins function as irisin receptors in bone and fat tissue (Kim et al., 2018)
	  ○ Irisin mediates gut barrier function via binding to the αVβ5 integrin receptor (Bi et al., 2020)
	- Irisin induces endothelium-dependent vasodilation through activation of the transient receptor potential vanilloid subtype 4 (TRPV4) (Ye et al., 2017)
	- In kidney cells, irisin interacts with the TGF-β type-2 receptor (TGFBR2) to mediate a cellular response (Peng, H. et al., 2017)
	- No specific or universal irisin receptor has been discovered (Mahgoub et al., 2018)(Xie, T. et al., 2020)

Irisin agonist	- No irisin agonist has yet been identified; evidence of its therapeutic potential is typically based on direct exogenous irisin treatment (Askari et al., 2018) - The pharmacological strategy for irisin treatment involves administration of recombinant irisin, but a great deal of alternative interventions have been proposed to raise endogenous irisin secretion (Flori et al., 2021)
Half-life of exogenous irisin	- The in vivo half-life of recombinant irisin is below one hour (Kim et al., 2018) - Metabolic irisin clearance is regulated by the hepatobiliary and renal system (Lv et al., 2015)
Normal range of plasma irisin concentration	- Irisin levels range from 50 pg/mL to over 10 mg/mL and identical samples yield significant differences, rendering it impossible to identify an indicative range of physiological irisin levels (Flori et al., 2021) - The proposed cross-reactivity of commercial ELISA kits (Albrecht et al., 2015), lowers the reliability of precise baseline irisin levels observed in the studies using them

Discussion

Irisin is a recently identified adipomyokine that functions as a chemical messenger predominantly between muscle and various other tissues. The hormone has received much attention in the past decade, leading to the discovery of a great amount of its physiological functions, and more of its effects will likely be characterized in the upcoming years. Regulatory mechanisms affecting irisin expression and secretion remain controversial due to discrepancies between studies with

distinctive experimental designs. While exercise-inducibility is most evident, it is likely that other feedback mechanisms play a role in irisin secretion as well. An extensive interplay between irisin and environmental as well as biochemical factors could be underlying the controversial outcomes of studies attempting to validate a single regulatory mechanism.

Acute and transient changes in irisin levels appear to be induced by acute exercise. Short bouts of intensive exercise as well as longer sessions of aerobic exercise cause an elevation of circulating irisin. Sustained changes in circulating irisin are likely predominantly associated with the results of chronic physical activity, such as changes in muscle mass, rather than exercise directly. Irisin expression is not only exercise-inducible in skeletal muscle, but in certain other tissues as well (Roco-Rivada et al., 2013)(Zhang, J. et al., 2017). Considering the acute and transient fashion in which irisin is upregulated by acute physical activity, deviations in retention time between exercise and sample collection could provide an explanation for some of the reported contradictory results. Moreover, the extent of irisin expression depends greatly on subject features such as body composition and could differ in relation to exercise intensity, providing additional arguments on why exercise-based regulation of circulating irisin is not consistent in its reproducibility.

Irisin drives glucose and lipid homeostasis towards energy mobilization and utilization **(table 1)**. Such features are beneficial for carrying out physical activity, as the contracting muscles require a continuous energy supply to prevent fatigue (Wan et al., 2017). Moreover, the neurological function of irisin in lowering one's pain threshold and reducing depression-like behavior mimic the analgesia and euphoria known to arise during exercise (Fuss et al., 2015). This could indicate the involvement of irisin in such a beneficial mechanism. The body gains from irisin expression throughout exercise in other ways as well. Extensive muscle contraction can lead to exercise-induced muscle soreness and damage (Clarkson et al., 2002). Irisin upregulation upon physical activity may be a way in which the body attempts the counteract this phenomenon, as it promotes muscle regeneration and growth (Huh et al., 2014a)(Reza et al., 2017). As PGC-1 coactivators are established regulators of muscle adaptations to exercise (Arany, 2008), downstream irisin activation could be an additive downstream effector. Similarly, irisin induces bone remodeling **(table 1)**, which is yet another way in which the body adapts to physical activity and concurrent mechanical loading (Turner & Pavalko, 1998). Furthermore, a typical marker for exercise-induced muscle damage is a heightened level of inflammatory factors in both muscle tissue and the circulation (Clarkson et al., 2002). Thus, an additional way via which irisin may be protective against complications arising throughout physical activity are its anti-inflammatory properties. In summary, irisin performs a large range of functions that are beneficial during physical activity and concurrent muscle contraction, it alleviates various exercise-induced complications and aids in whole-body adaptation to exercise.

Exercise-induced muscle damage arises predominantly in people that are untrained or unaccustomed to the specific exercise they are carrying out, and throughout exercise involving eccentric muscle contractions. The latter occurs frequently during resistance training (Da Silva Vasconcelos & Salla, 2018). The exercise-inducibility of irisin is typically not seen upon chronic exercise training, as it often even reveals a reduction in irisin levels (Motahari Rad et al., 2021). However, resistance training displays a greater elevation of irisin levels in an acute setting, as well as in a chronic setting as compared to other modes of exercise (Tsuchiya et al., 2015)(Zhao et al., 2017). While the long-term effect of resistance training could be attributed to changes in body composition, which would require further investigation, the short-term effect still directly implies that irisin secretion is upregulated more throughout resistance training than in other training settings. Such patterns in the exercise-inducibility of irisin secretion substantiate a role of irisin in the prevention of extensive muscle damage. Chronic training allows the body to adapt to the nature of the performed exercise, reducing the risk of exercise-induced muscle damage and attenuating the need for irisin-induced muscle regeneration. Resistance training, on the other hand, remains a risk factor for exercise-induced muscle damage as it involves eccentric muscle

contractions independently of adaptive mechanisms. Thus, such a training mode would demand a greater irisin response.

It is rather unlikely that a hormone affecting a range of bodily systems as great as irisin is solely dependent on exercise-based regulation. It covers a range of functions that goes beyond its beneficial effects during exercise **(table 1)**. Other biochemical and environmental factors are presumably involved in feedback regulation of circulating irisin levels. However, these may affect baseline irisin concentrations irrespectively of its acute exercise-inducibility, as previously discovered to be the case for age and fitness level (Huh et al., 2014b). Research linking irisin to other metabolic hormones remains largely inconclusive. Still, such potential interactions require further attention as they could not only reveal novel regulatory mechanisms for irisin secretion but would also provide further insight into the entire physiology of energy homeostasis.

While direct cold-inducibility of irisin remains somewhat questionable as well, an upregulatory irisin response to shivering seems apparent (Lee et al., 2014). As previously proposed by Böstrom et al. (2012), irisin expression upon this cold-based increase in muscle contraction to prevent against hypothermia may provide a physiological explanation for irisin activity in mammals. Such a physiological role could explain why irisin is upregulated upon muscle contraction in an acute and transient fashion rather than displaying sustained increases, as excessive thermogenesis would not be required anymore once the shivering has passed. Similarly, a protective role of irisin against hypothermia is in line with the observation that irisin levels typically rise in response to acute exercise rather than long-term physical activity. As mentioned, however, irisin is produced by tissues other than skeletal muscle as well (Roco-Rivada et al., 2013)(Aydin et al., 2014)(Zhang, J. et al., 2017). While some have been shown to respond to exercise (Roco-Rivada et al., 2013)(Zhang, J. et al., 2017), this is yet to be linked to muscle contraction or shivering directly. Besides that, the thermogenic effect of irisin predominantly appears in subcutaneous rather than visceral fat deposits (Li, H. et al., 2019). As subcutaneous fat tissue provides an insulating function that protects against hypothermia (Gregory, 1989), it is counterintuitive for irisin to reduce subcutaneous adiposity over visceral adiposity considering a physiological role of protecting against hypothermia. Irisin exerts many more physiological functions than an upregulation of thermogenesis alone **(table 1)**. A function of irisin in the endogenous protection against hypothermia may thus reveal only part of its complete physiological role. It likely involves a more extreme, final preventive mechanism provided by irisin that adds to its other functions. Consistently, higher irisin concentrations are required for it to exert an effect on WAT than on bone tissue (Colaianni et al., 2015).

Given that some exercise modes generate a greater irisin response than others (Lee et al., 2014)(Tsuchiya et al., 2015), an exercise program specifically tailored towards irisin release, such as the Pink Dragon studio has claimed to provide, may be truly achievable. However, it is unlikely that an effective work-out routine maximizing irisin expression can be designed based on current knowledge. Further research into such a specific training program could prove useful in various malignancies. In the case of immobility, irisin treatment appears to be a suitable alternative to exercise. However, its therapeutic potential has been predominantly implied based on rodent models. Whether extrapolation of these results to humans will yield similar promise is yet to be discovered. As much less is known about the potential dangers of (long-term) irisin administration and several of its pharmacologically relevant characteristics remain uncharacterized, a great deal of research still needs to be performed on whether the application of this ‘wonder hormone’ is reliable and safe.

If this were to be the case, irisin may in truth provide a novel therapeutic target for a substantial range of diseases. Obesity is one of the major metabolic disorders for which irisin is proposed to be a solution. However, an obesity-induced elevation of irisin levels has been proposed as a mechanism through which the body attempts to counteract this disorder (Pérez-Sotelo et al., 2017). As this compensatory mechanism does not seem to augment obesity, it is questionable whether exogenous irisin would have an effect. Irisin resistance may be a

pathological state interfering with its therapeutic potential; a possibility that needs to be further explored.

One of the main limitations in current research on irisin is that numerous studies make use of antibody-based commercial ELISA kits for irisin detection, while the specificity of this method has been questioned and cross-reactivity implied (Albrecht et al., 2015). Their reliability is thus arguable. Besides that, most effects of irisin are studied in rodents rather than in humans. Direct implications on both the function and therapeutic potential of irisin are only provided in animal studies. Still, some associations have been validated in human studies.

Conclusion

The so-called miracle hormone irisin plays an important role in exercise physiology, aiding in whole-body adaptation to physical activity and preventing exercise-induced complications. It likely also provides protection against hypothermia, via upregulation of thermogenesis in response to shivering. The large range of effects that the hormone elicits, however, implies that its physiological role may go beyond these mechanisms, pending further investigation. The therapeutic potential of irisin is extensive but requires ample validation in humans.

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