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Review Article

Irisin and its role in the reproductive physiology: a review

Irisina e seu papel na fisiologia reprodutiva: uma revisão

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Abstract

Irisin is a recently discovered hormone produced in various tissues, such as adipose, cardiac, and skeletal muscle tissues. This myokine originates from the cleavage of a protein, FNDC5, and its synthesis and secretion are stimulated in response to skeletal muscle contraction. Recently, our group demonstrated that high-intensity interval training (HIIT) improved follicular development in Wistar rats, possibly through increased mRNA expression for the irisin precursor, the FNDC5 gene. Thus, this study aimed to consolidate topics relevant to the relationship between irisin and fertility in both sexes.

Keywords: fertility, reproduction, FNDC5.

Resumo

A irisina é um hormônio recém-descoberto, produzido em diversos tecidos, tais como adiposo, cardíaco e muscular esquelético. Essa miocina tem sua síntese e secreção estimuladas em resposta a contração do músculo esquelético. Estudo recente do nosso grupo mostrou uma interferência no desenvolvimento folicular após treinamento intervalado de alta intensidade (HIIT), esta foi atribuída a um aumento na expressão de RNAm do FNDC5, precursor da irisina. Este trabalho teve como objetivo conglomerar tópicos relevantes à reprodução e à fertilidade que se relacionam diretamente com a irisina.

Palavras-chave: fertilidade, reprodução, FNDC5.

1. Irisin

Irisin is one of the cytokines produced by skeletal muscles and was recently discovered by Dr. Spielgeman's team at Havard Medical School (Boström et al., 2012). This substance has been called myokine, since it is produced in response to contractile stimuli in the skeletal muscles. Since then, other studies have shown that irisin synthesis can occur in other tissues, such as renal (Huh et al., 2012), adipose (Moreno-Navarrete et al., 2013), cardiac (Aydin et al., 2014a), and hepatic (Aydin et al., 2014b). Its biosynthesis is regulated by the peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α; PPARGC1A), a transcriptional coactivator involved in various metabolic processes, which is activated by muscle contraction (Brenmoehl et al., 2014). In humans, serum irisin levels range from 0.01-2000 ng/mL (Luo et al., 2021). Recently, it was described an irisin detection method from salivary samples that showed correlation (R=0,92) with serum from baseline to 24 hours after exercise (Missaglia et al., 2023). This contributes as a noninvasive method, creating more possibilities of tests.

PGC-1α stimulates the production of the fibronectin type 3 gene containing domain 5 (FNDC5), a precursor of the protein of the same name, in which two extracellular irisin domains are present (Waseem et al., 2022). Physiologically, once cleaved, FNDC5 releases irisin as a bioactive molecule (Figure 1), whose production efficiency can be increased by physical exercise (Boström et al., 2012). Recently, our group observed that the physiological adaptation to high-intensity interval training can be extended to ovarian tissue, since it interferes with follicular development in female rats (Furtado et al., 2021). We believe that this adaptation may have been due to the increase in mRNA expression for FNDC5 after a HIIT session (*data not published*), as well as the production of the protein by skeletal muscle after continuous moderate-intensity exercise (*data not published*). In addition, the presence of irisin in the conditioned medium of skeletal muscle cells was verified by the HPLC method (*data not published*). The mechanism of irisin secretion is still poorly understood, and the cleavage process remains unclear. However,

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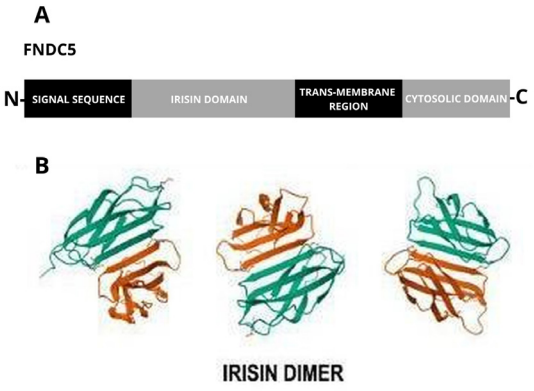

Figure 1. (A) The FNDC5 protein, precursor of irisin, which has several domains and when cleaved releases the irisin domain; (B) Crystallized structure of the irisin dimer (PDB ID: 4LSD; rcsb.org). FNDC5, fibronectin type 3 gene containing domain 5.

disintegrins and metalloproteinases (ADAMs) have emerged as the most promising agents in this process (Azushima and Tamura, 2024).

The peptide sequence of irisin is 100% compatible between rats, mice, humans and cattle (Maak et al., 2021), presenting as a homodimer of 112 amino acids and 25KDa (CH 1). A striking exception in the FNDC5 gene is its initiation codon which, unlike the regular ATG (methionine), starts with ATA (isoleucine) (Raschke et al., 2013). In humans, for example, only 6 genes start with this codon (Maak et al., 2021). This difference in the initiation codon was what supported the hypothesis that irisin was a pseudogene (Raschke et al., 2013). However, Jedrychowski et al. (2015), observed irisin coming from translation via the ATA initiation codon and quantified it using the mass spectrometry technique.

As far as irisin receptors are concerned, they are still poorly understood. Some studies have shown that most of the stimulatory effects of irisin occur through the mitogen-activated protein kinase (MAPK) signaling pathway (Wrann et al., 2013; Song et al., 2014; Zhang et al., 2014; Lee et al., 2015; Qiao et al., 2016; Kim et al., 2018). Already, the inhibitory effects occur through SMAD3, an effector protein of the transforming growth factor beta family (TGFβ; Tiano et al., 2015). The first description of more promising receptors for irisin was made in 2018 by Kim et al. (2018). In this study, the authors found that the receptors for irisin belong to the integrin family, with the subunits αV (ITGαV) and β1 (ITGβ1). In a subsequent study, it was observed that inhibition of αVβ5 blocked the effect of irisin on osteoclasts, thus confirming the receptor family (Estell et al., 2020). On skeletal muscle irisin acts with the receptor αV/β5 (Figure 2); however, it is necessary an activation of this receptor for the heat-shock protein 90α (HSP90α), this protein is stimulated by the muscle contraction (A et al., 2023). On adipose tissue, irisin acts through a two-step mechanism (Figure 3), firstly the protein CD81 forms a complex with the integrins αV/β1 and αV/β5, then this complex activates a focal adhesion kinase (FAK) (Oguri et al., 2020).

The promising results of irisin for weight control through increased energy expenditure and thermogenesis (Bostrom et al., 2012) have led to research into irisin modulating other physiological processes. Fu et al. (2016) observed an increase in glucose uptake, insulin resistance and morbidities related to energy metabolism due to the action of irisin. Given that, regardless of gender, fertility is closely related to energy metabolism, alterations in glucose metabolism and insulin resistance are factors that can lead to reproductive disorders (Luo et al., 2022). Thus, investigating the role of irisin in reproductive tissues, as well as its influence on fertility, is of great importance.

Adipose and muscle tissues play an important role in controlling energy metabolism through the action of hormones such as irisin (Luo et al., 2022). During rest, serum levels of this hormone are higher in women than in men (Zügel et al., 2016) and are even higher in healthy pregnant women (Garcés et al., 2014). In addition, it is well known that obesity (Broughton and Moley, 2017; Craig et al., 2017; Kahn and Brannigan, 2017), as well as malnutrition (Nichols et al., 2003) are risk factors for reproduction. Thus, it is believed that the nutrition-reproduction-physical exercise trinomial is a key point in the importance of irisin for fertility.

2. Irisin and Female Fertility

In ovary, Basini et al. (2021) verified FNDC5 immunolocalization in mural granulosa and interna thecal cells from antral follicles >5mm of diameter (Figure 4) in swine. Moreover, these same authors have shown the expression of mRNA for both, irisin and FNDC5, in granulosa cells (Basini et al., 2021). To our known, Basini`s research team, so far, was the only to confirm the presence of irisin in ovary, although others have observed the effects irisin from exercise or exogenous irisin. Recently, our team observed that the increased production of irisin in the muscle tissue of rats submitted to physical exercise (*data not published*), can block the conversion of testosterone into estradiol, even with a greater distribution of Cyp19A1 in ovarian cells (Furtado et al., 2021). Similarly, irisin from physical exercise or from exogenous injections increased the number of primary and secondary follicles by the reduction of Forkhead box O (FOXO), specifically FOXO1 and FOXO3 (Bastu et al., 2018). These same authors also verified that irisin could promote the secretion of estradiol, follicle stimulating hormone (FSH), and luteinizing hormone (LH) and enhance angiogenesis by the increase of the eNOS expression within the theca cells and oocytes (Bastu et al., 2018). Contrary to Bastu et al. (2018), Ulker et al. (2020) observed a decrease in FSH levels after intramuscular injection of 100 ng/kg of irisin for ten weeks in female rats, impairing the libido of these animals (Ulker et al., 2021). In addition, viral inoculation of FDNC5 in obese female mice increased the number of developing follicles (primary and secondary) (Yuksel Ozgor et al., 2020). In *in vitro* studies, the culture of granulosa cells with irisin at 125, 250 and 500 ng/mL increased the expression of the enzyme CYP19A1, in a concentration-dependent manner (Poretsky et al., 2023). These aspects demonstrate the

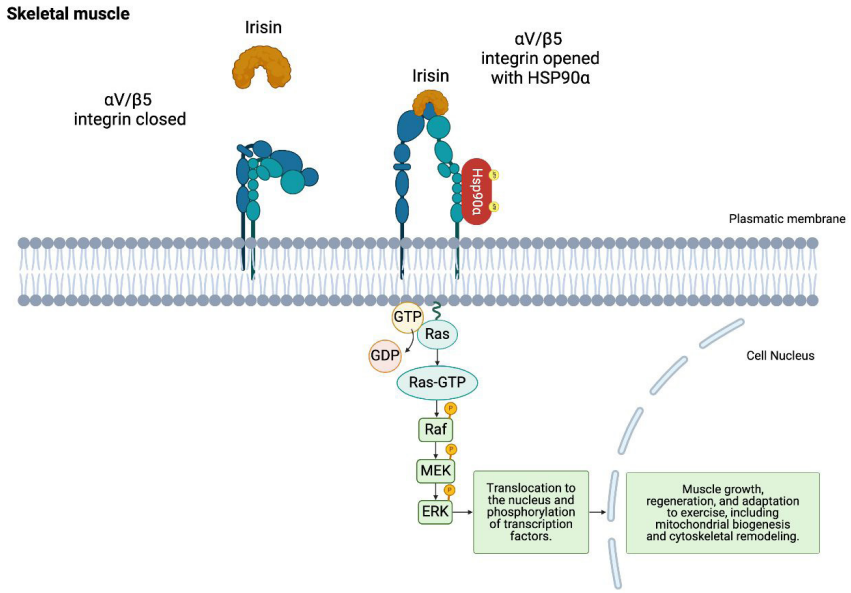

Figure 2. Irisin receptor in skeletal muscle, initially in a closed condition (left) and after activation by heat shock proteins HSP90α (right), a chaperone protein. Extracellularly secreted Hsp90α appears to act as a crucial mediator in the interaction between irisin and integrin αVβ5. This chaperone directly associates with integrin αVβ5, promoting its activation or stabilizing the receptor-ligand complex. For HSP90α to bind and function correctly, it requires two ATP molecules. In skeletal muscle, irisin binding to integrin αVβ5 primarily activates the ERK (extracellular signal-regulated kinase) signaling pathway, also known as MAPK/ERK (Mitogen-Activated Protein Kinase/ERK). Irisin, by activating integrin, stimulates the exchange of GDP for GTP in the Ras protein, activating it. Ras-GTP then recruits and activates Raf kinase, which, upon activation, phosphorylates and activates the second kinase in the cascade, MEK. MEK is a dual-specificity kinase that phosphorylates ERK at two specific residues, threonine and tyrosine, enabling its activation. Once activated, ERK1/2 translocate to the nucleus, where it can phosphorylate various transcription factors and other regulatory proteins.

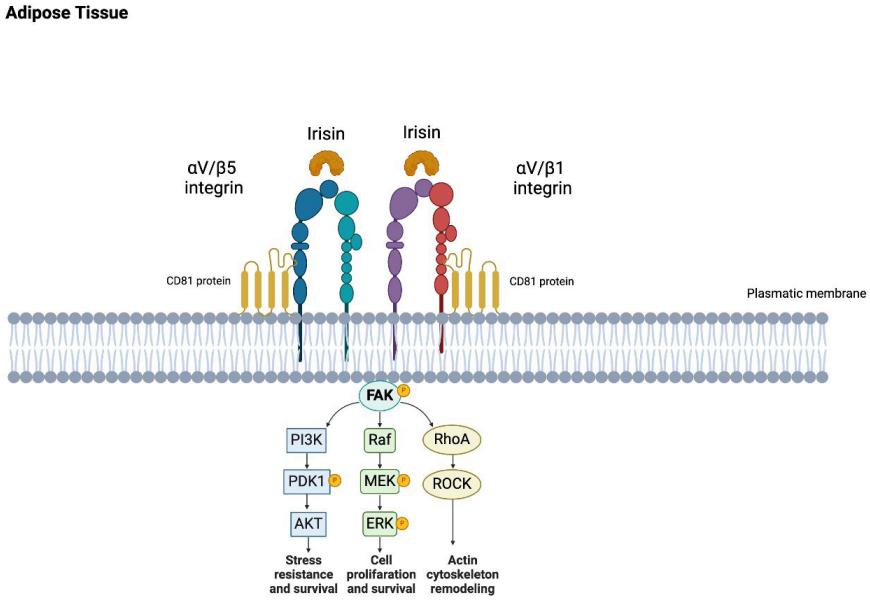

Figure 3. Schematic representation of the importance of the CD81 protein in the signaling of the FAK pathway by irisin. CD81 forms receptor complexes with heterodimeric integrins, composed of α and β subunits, embedded in the lipid bilayer of the cell membrane. Upon complex formation, these receptors promote the activation of intracellular signaling pathways through the phosphorylation of FAK (Focal adhesion kinase), triggering the activation of multiple signaling cascades. These pathways are critical for regulating processes such as cell survival, proliferation, adhesion, and cytoskeletal remodeling, and are essential for the cellular response. Among these pathways, the following are highlighted: PI3K/AKT pathway: The activation of PI3K leads to the phosphorylation of PDK1, which in turn activates AKT. This cascade is crucial for promoting stress resistance and cell survival; Raf/MEK/ERK pathway: The activation of Raf leads to the phosphorylation of MEK and ERK, promoting cell proliferation and survival; RhoA/ROCK pathway: The activation of Ras homolog gene family, member A (RhoA) and Rho-associated protein kinase (ROCK) results in the remodeling of the actin cytoskeleton, regulating cell motility and morphology.

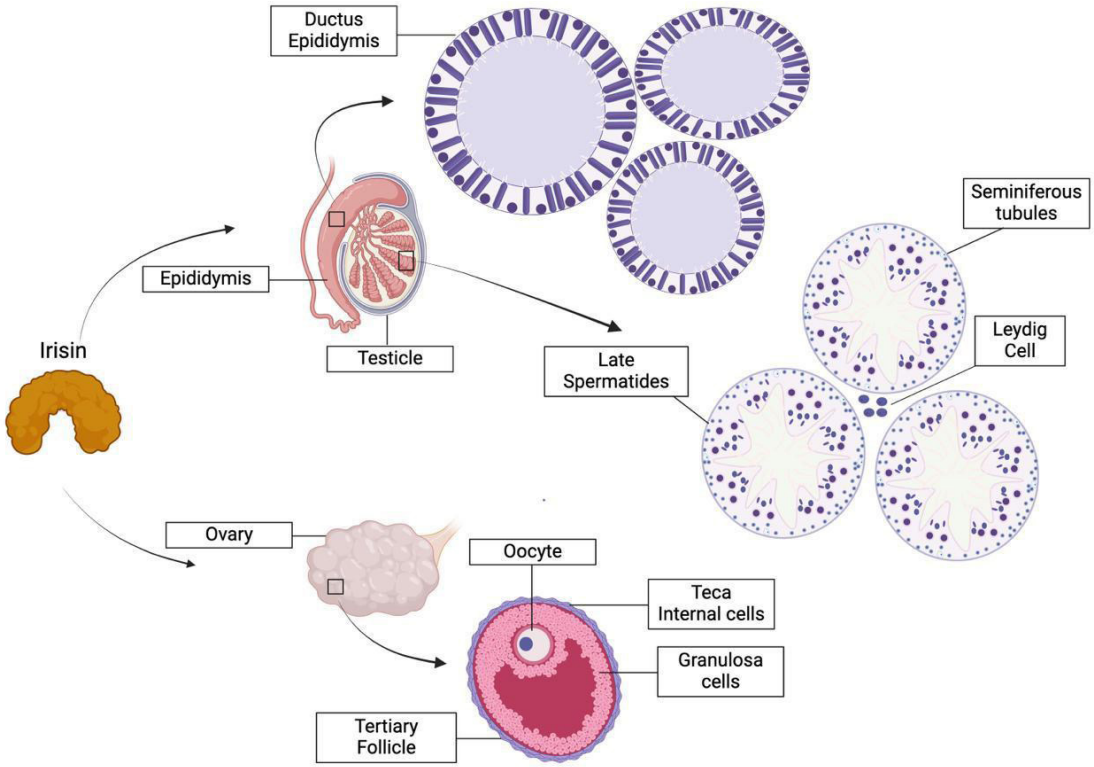

Figure 4. Irisina protein or its mRNA localizations in the male and female reproductive gonads. In the testis, the presence of irisina was detected in Leydig cells and in late spermatids cells, as well as in the epididymal duct. In the ovary, irisin was present in the granulosa and internal theca cells only from tertiary follicles. Adapted from Wahab et al. (2020) and Basini et al. (2021).

importance of knowing the physiology of this hormone and its implication in reproductive physiology in female sex.

In a manner similar to irisin itself, its receptors play crucial roles, and dysfunctions in these receptors can lead to reproductive issues. Zhou et al. (2021) demonstrated that irisin can increase leukemia inhibitory factor (LIF) and αVβ3 expression, thereby enhancing implantation success rates. This may be due LIF is an important growth factor that improve embryo rates (Luz et al., 2012a,b) and ensures a correct implantation of blastocyst on maternal uterus (Zhou et al., 2021). Additionally, irisin may influence puberty timing, as shown by Decourt et al. (2022), where inhibition of the irisin receptor αVβ5 with cilengitide delayed the onset of the first estrous cycle in female mice, suggesting that irisin has a potential role in the regulation of puberty onset. Furthermore, Luo et al. (2021) verified that the complete deletion of the FDNC5 gene promotes morphological abnormalities in the ovarian tissue and irregularities in the ovarian cycle with a reduction in serum levels of both gonadotrophin (FSH and LH), beyond estradiol in adult female mice, as well as a high and down mortality and live birth rates, respectively. All these results together make us believe that irisin could be a promising target for controlling the dynamics of follicular growth.

3. Irisin and Male Fertility

In man, Aydin et al. (2014a) verified irisin immunolocalization in Leydig cells, and spermatogenic cells, especially in late spermatids, as well as in epididymal ducts. In adult non-human primates, irisin was observed in undifferentiated spermatogonia in all stages of the seminiferous epithelium cycle (Wahab et al., 2020). In newborn non-human primates, Wahab et al. (2020) also observed irisin signals, beyond spermatogonia, in interstitial compartment. Considering that spermatozoa production can be influenced by factors related to energy metabolism, the production of gonadal, hypothalamic and pituitary hormones can be altered by exposure to irisin. It was confirmed in rhesus monkeys, in which was demonstrated that irisin interacts with GnRH-producing and -releasing neurons (Wahab et al., 2020).

In recent years, evidence has shown that changes in circulating levels of irisin in the bloodstream during the stages of puberty influence the process of male sexual maturation (Reinehr et al., 2015). Although there is no change in the time at which the separation of the foreskin from the glans occurs (puberty milestone in rats), there is a greater brevity in the formation of the first spermatogenic cycle (Ulker et al., 2020). Furthermore, in tilapia, exposure to irisin at a concentration of 500 ng/g/body weight increased gene expression of the subunit β of both FSH and LH gonadotropins (Jiang et al., 2017).

It is now known that irisin acts by inhibiting appetite and initiating a feeling of satiety which interrupts eating behavior (Yardimci et al., 2023). In obese individuals, irisin is increased and this is because adipose tissue is one of the sites of irisin synthesis (Zügel et al., 2016; Rasool and Khalifa, 2023). This excess adiposity is already known to be harmful to fertility and can reduce the total number of sperm and cause hormonal dysregulation (Katib, 2015). In this context, Ibrahim and El-Malkey (2018) proposed that exogenous administration of irisin would be a promising treatment for infertility caused by obesity, since it improved insulin resistance, lipid profile, as well as hormonal parameters related to fertility (FSH, LH and Testosterone), due to the feedback caused by irisin itself, normalizing the rates of irisin. In addition, these authors also observed that exogenous administration of irisin inhibits the production of reactive oxygen species, the miokyne activates the AMP-activated protein kinase α (AMPK() pathway (Mu et al., 2021), thus protecting the testes from oxidative damage caused by obesity.

4. Final Considerations

Although recent, the evidence obtained to date on irisin has demonstrated its importance for male and female fertility, directly influencing the hypothalamic-pituitary-gonadal axis. Thus, this review provides a novel synthesis of current findings on irisin and its role in reproductive physiology. And it is the first to comprehensively link molecular pathways, hormonal regulation, and fertility outcomes in both sexes. Irisin has been shown to be a potential protector of reproductive tissues from oxidative damage caused, for example, by excess adiposity. The present manuscript presents original data from our research group, including the modulation of ovarian follicular development by exercise-induced irisin expression, adding new insights to a growing field of scientific interest. However, more studies are still needed to further clarify the signaling pathways of irisin, as well as its mechanisms of action and its role in male and female fertility.

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