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Review

A glance at the therapeutic potential of irisin against diseases involving inflammation, oxidative stress, and apoptosis: An introductory review

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ABSTRACT

Irisin is a hormone-like molecule mainly released by skeletal muscles in response to exercise. Irisin induces browning of the white adipose tissue and has been shown to regulate glucose and lipid homeostasis. Keeping its energy expenditure and metabolic properties in view, numerous studies have focused on its therapeutic potential for the treatment of metabolic disorders like obesity and type 2 diabetes. Recently, the anti-inflammatory, anti-apoptotic and anti-oxidative properties of irisin have received a great deal of attention of the scientific society. These pathogenic processes are often associated with initiation, progression, and prognosis of numerous diseases like myocardial infarction, kidney diseases, cancer, lung injury, inflammatory bowel diseases, atherosclerosis, liver diseases, obesity and type 2 diabetes. In the current review, we present evidence regarding the anti-inflammatory, anti-apoptotic and anti-oxidative potential of irisin pertaining to various pathological conditions. Here, we explore multiple molecular pathways targeted by irisin therapy. Given the promising effects of irisin, many diseases with evident oxidative stress, inflammation and apoptosis can be targeted by irisin.

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1. Introduction

Irisin, named after the Greek messenger goddess "**Iris"**, is a 112 amino acid protein, proteolytically cleaved form of fibronectin type III domain-containing protein 5 (FNDC5) [1]. Peroxisome proliferator-activated receptor-γ co-activator 1α (PGC1α) is a transcription cofactor which stimulates the synthesis and secretion of FNDC5 protein initially consisting of 212 amino acids in humans [2] and 209 amino acids in mice [3] and rats [4], respectively. Since the remarkable discovery of irisin in 2012, more than 300 studies have been published highlighting its physiological role, regulation and potential therapeutic aspects.

Irisin is an exercise-induced metabolic hormone secreted primarily by skeletal and cardiac muscle cells. Small amounts of this myokine have been detected in adipose tissue, brain, subcutaneous glands, liver, stomach, spleen, and testis [5]. Numerous studies on animals and humans have demonstrated an increase in muscle-derived physiological secretion of irisin following exercise and exercise-induced ATP depletion [6–9]. However, a high intensity of heterogeneity exists in results possibly due to the variation in the protocols of exercises or time frame considered for evaluation of irisin levels [10]. Other factors like cold exposure, myostatin [11], leptin [12], pro-inflammatory cytokines [tumor necrosis factor – alpha (TNF-α) and interleukin – 1 beta (IL-1β)] [13], and content of glucose and lipid [14,15] may also regulate the secretion of irisin. Numerous studies have shown that exercise causes the release of irisin from skeletal muscles which in turn increases the expression of FNDC5 protein, thereby increasing irisin formation [16]. Once in circulation, this myokine transforms white adipose tissue (WAT) into brite/beige (brown in white) fat cells by upregulating the genes associated with browning (such as, UCP-1, PPARγ, and PRDM16) [17]. This effect is possibly mediated by pathways involving phosphorylation of p38 mitogen-activated protein kinase (p38 MAPK) and extracellular signal-related kinase (ERK) [18]. The resultant beige adipocytes are rich in mitochondrial UCP-1 and are specialized for heat production and energy expenditure [19]. Irisin up regulates lipolysis-related genes, such as HSL, ATGL, and FABP4, ultimately increasing glycerol release and reducing lipid accumulation in adipocytes [20]. Furthermore, it increases GLUT-4 expression in beige fat cells, thus boosting their insulin-mediated glucose uptake capacity [21]. These remarkable properties of irisin make this adipo-myokine a potential therapeutic candidate for obesity and other metabolic disorders. Researchers have observed a marked association between irisin levels and major chronic diseases like type-II diabetes, non-alcoholic fatty liver disease, chronic kidney disease, psoriasis, osteoporosis, hypertension, atherosclerosis and cancer [22–25]. Interestingly, plasma irisin levels appear to correlate with telomerase length – an established genetic marker of ageing [26]. In the current review, we discuss the anti-oxidative, anti-inflammatory and anti-apoptotic effects of irisin with respect to various diseases. We also review the major discrepancies in results between studies and propose direction for the future investigations (Tables 1 and 2).

Table 1
Changes in Irisin levels during various pathological conditions.

Pathological Conditions	Change in irisin Levels	Reference
Obesity	↑	[27]
Type 2 diabetes	↓	[27]
NAFLD	↑(early stage), ↓(late stage)	[28]
Breast cancer	↓	[29]
Gastrointestinal system cancers	↑	[30]
Osteoporosis	↓	[31]
Chronic kidney disease	↓	[32]
Psoriasis	↑	[25]
Polycystic ovary syndrome	↑	[33]
Chronic obstructive pulmonary disease	↓	[7]
Myocardial infarction	↓	[34]
Overt hypothyroidism	↑(short-term), ↓(long-lasting)	[35]
Metabolic syndrome	↑	[36]
Coronary artery disease	↑	[37]
Behçet's disease	↓	[38]

↑, Increase; ↓, Decrease.

2. Insights into structural-functional relationships of irisin

Irisin is an approximately 12 kDa hormone-like polypeptide which is produced by proteolytic cleavage of its precursor, FNDC5 [39]. FNDC5 is a glycosylated type I membrane protein that undergoes a proteolytic cleavage leading to release of N-terminal region of the protein containing 112 residues into the extracellular circulation [40]. The crystal structure of irisin (with resolution 2.28 Å) has been previously reported by Schumacher and colleagues [41]. This structure comprises of an N-terminal fibronectin III (FNIII)-like domain (residues 30–123) and a flexible C-terminal tail (residues 124–140). Despite low sequence homology between irisin and FNIII domains, they showed a highly conserved structure composed of seven β-strands, in which a four-stranded β-sheet packs against a three-stranded β-sheet by non-bonded connections resulting in an antiparallel β-sandwich fold (Fig. 1A). Intriguingly, in contrast to other FNIII domains, the β4 strand of irisin forms a tight interaction with β4 strand of another irisin monomer which results in a continuous antiparallel eight-stranded β-sheet, and eventually, creates an intersubunit β-sheet dimer (Fig. 1B). Calculation of irisin surface electrostatic potential revealed that β4 strand is a highly hydrophobic portion with small regions of positively- and negatively-charged residues implying the key role of hydrophobic interactions in formation of irisin dimer (Fig. 1C). A group of researchers also found that two regions of irisin including residues 55–58 and 106–108 have a considerable conformational fluctuation suggesting their possible role in interactions with other proteins (Fig. 1D) [41]. Further binding site predictions by bioinformatics tools uncovered that several regions of irisin may also be involved in