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Irisin as an exercise-stimulated hormone binding crosstalk between organs

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Abstract. – Irisin is a newly discovered 112 amino acid residues' glycosylated protein hormone that was firstly found up-regulated by exercise-induced peroxisome proliferator-activated receptor-gamma coactivator 1 alpha (PGC-1α) and then play an important role in circulation so as to target other organs. It conducts many downstream events including osteoblast differentiation, nerve cell and β-cell regeneration and so on. In clinical research, non-inflammation and inflammation related diseases correlated with basal level of irisin and they benefited from exercise-induced irisin endocrinology.

Key Words:
Irisin, Exercise, Metabolism, Endocrinology.

Introduction

In 1998 Spiegelman's group in Harvard University first discovered and reported the peroxisome proliferator-activated receptor-gamma coactivator 1 alpha (PGC-1α, a kind of auxiliary activator of transcription, which improve glucolipid transshipment and expenditure of energy, make skeletal muscle fiber a high degree of glucose tolerance, regulate the body's adaptive response after exercise[1,2] and become one of the important targets for the prevention and treatment of obesity[3], by increasing the production of mitochondria, angiogenesis, and insulin sensitivity. Most strikingly, the increase of PGC-1α expression can often benefit a lot of tissues besides muscle. However, the mechanism has not been clear, some scholars speculate that the expression of PGC-1α can stimulate the skeletal muscles release some special factors, which effect on other tissues[4]. Then in early 2012, Bostrom et al[1], also the group member of Spiegelman found and reported the new hormone Irisin which has effect reducing weight, it is named after the Greek goddess Iris. Studies find that exercise firstly induced skeletal muscle to express PGC-1α[5], which can promote pyrolysis of its downstream molecular FNDC5 (fibronectin type III domain-containing 5, FNDC5) to be cut into a new form in the body — Irisin. Huh et al[6] confirms that the excessive expression of PGC-1α, can stimulate muscle FNDC5 expression, which code a membrane protein, the latter by protease hydrolysis, generates a new hormone Irisin, released into the blood circulation. Although irisin was firstly discovered from skeletal muscles which may be at first released into circulation to regulate other organs, it ultimately expressed its wide range of powerful physiological characteristics in hippocampus[7-11], possibly because PGC-1α regulates Fndc5 gene expression in neurons in a positive feedback control manner, it's in brain that whole body benefits from exercise by irisin which could finally release into the blood circulation and regulate other organs and tissues by endocrine cycles.

Characterization of Irisin

Structural Characteristics

Irisin is a 112 amino acid residues' glycosylated protein hormone, the molecular weight of it is about 32 kDa, deglycosylation of its molecular weight is about 12 kDa[12]. FNDC5[13] is synthesized as a type I membrane protein which undergoes proteolytic cleavage and this results in release of N terminal part of protein into extracellular space. FNDC5 consists of three parts, a signal peptide, two fibronectin domains and hydrophobic domain with a C-terminal peptide. FNDC5 itself is a glycoprotein with glycosylated site 39Lys and 84Ala[14]. The X-ray crystallography structure[14] shows that irisin consists of an N-terminal fibronectin III (FNIII)-like domain which forms a continuous intersubunit β-sheet dimer and attaches to a flexible C-terminal tail. Biochemical data confirm that irisin is a dimer and that dimerization is unaffected by glycosylation. This finding suggests a possible mechanism for

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receptor activation by the irisin domain as a preformed myokine dimer ligand or as a paracrine or autocrine dimerization module on FNDC5-like receptors. Irisin is released from muscle in response to exercise. Irisin is the secretory portion of FNDC5 protein, being able to positively promote the beige of white adipose tissue and improve many metabolic diseases in both humans and mice[15].

Distribution Characteristics

Range of circulating irisin levels in humans[16,17] in both physiological and pathological circumstances showed abundant distribution of irisin. For example, irisin was associated with secretory organs such as adipose tissue, liver, the cardiovascular system, the brain, the bone, the pancreas, the kidney, the immune system, the ovary, the peripheral myelin sheath, the intestinal L cells and pancreatic islets. Aydin et al[16] discovered that the only part being stained was the perimysium which may clue the circulating of irisin secreted by other organs to play an important role. Strong immune-reactivity occurred in cardiac muscle than in skeletal muscle of young and old rats with or without exercise, notably in pericardial connective tissue.

Physiological Characteristics

Human exercise cohorts analyzed for FNDC5 mRNA expression in skeletal muscle after different modes of exercise[17] show that sprints or treadmill exercise or cycling at 70% VO_2 max for dozens of minutes and endurance or strength or resistance training for several weeks can induce circulating irisin levels directly after exercise. Although endured a lot of discussion and controversy for a while, exercise possibly and finally defeats controversy for its different time of inducing irisin after exercise, which in conclusion that exercises increase secretion of irisin.

Experiments on male 13-week-old C57/Bl6 wild-type mice with 30 days of voluntary free running-wheel exercise[8] indicate a high expression of irisin in cardiac muscles, brain, spinal cord and oxidative muscle, such as the soleus muscle. Whereas lung, liver, spleen, kidney, iBAT (interscapular brown adipose tissue) and ingWAT (inguinal white adipose tissue) indicate a relatively very low expression of irisin, which was showed in latter papers that dysfunction of these organs or tissues did not correlate with high expression of irisin[18,19]. Oxidative muscle which contains higher levels of PGC-1α than in glycolytic or mixed muscles, such as gastrocnemius or quadriceps muscle also contains higher levels of FNDC5 mRNA expression, which in conclusion that exercises increase secretion of irisin in way of up-regulation of PGC-1α, however, not only in that way. And, irisin is correlated with many pathophysiological processes.

Contracting skeletal muscles must be able to communicate to other organs via humoral factors, which are released into the circulation by different forms of exercise[20]. Such factors like irisin might directly or indirectly influence the function of other organs such as adipose tissue, liver, the cardiovascular system, the brain, the bone, the pancreas, the kidney, the immune system and so on (Figure 1). Clinical research showed that non-inflammation and inflammation related diseases correlated with basal level of irisin and they benefited from exercise-induced irisin endocrinology, which imply an interaction between physical activity of muscles and central nervous system.

Cell Signaling Map of Irisin

Exercise induced PGC-1α expression in muscle stimulates an increase in the expression of FNDC5 and secreted irisin and the latter acts on white adipose cells to stimulate UCP1expression, mediated via activation of p38 MAPK, and promotes the expression of β-trophin. On the other hand, lack of expression of PGC-1α is associated with age, which concurs with the fact that the aged population has lower levels of irisin and that adaptive β-cell regeneration declines with age in mammals[21]. The exercise factor (EF) could be produced locally in hippocampal neurons or reach the hippocampus from muscle via circulation. The latter would be detected by selective deletion of the FNDC5 gene in either muscle or hippocampus so as to test how exercise-induced irisin gene expression was firstly and secondly secreted. The circulating EF is likely distributed to various parts of the body. Irisin is able to activate PGC-1α gene expression in adipocytes. So, to investigate whether the circulating EF, a different FNDC5 cleavage product, stimulates hippocampal PGC-1α gene expression, which in turn induces irisin gene expression can then make it sense. In this way, the action of the circulating EF in hippocampus would be amplified[8,9]. Insulin-like growth factor binding protein 2 (IGFBP2) and wingless related MMTV integra-

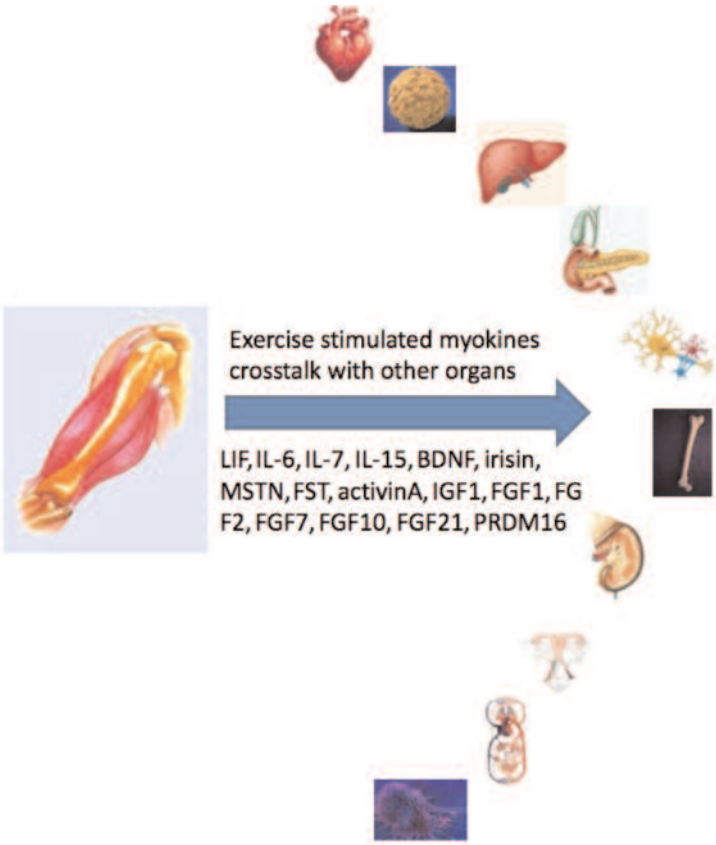

Figure 1. Exercise stimulated myokines crosstalk with other organs.

tion site 10b (WNT10b), gather considerable interest because they regulate both bone remodeling and energy metabolism from fat to bone mediated by muscle contraction[22].

The upstream regulation of irisin can be a lot of cytokines, such as CaM, PKA, PKB and so on and the downstream regulation of irisin can also be a lot of cytokines, such as LXRα, cAMP, SHC1, CTNNB1, SH2B, SHC4, DOK5, PLCG1 and so on. These cytokines inversely could conduct many upstream and downstream events (Figure 2). For example, irisin may correlate with Glut4, adiponectin receptor, leptin receptor, insulin receptor and α-adrenergic receptor. For its extensive relationship with so many cytokines and receptors associated with diseases, irisin, standing in the centre of the traffic jam and with its charming uniqueness, would explain for many pharmacological phenomenons that exercise couldn't explain before.

Clinical Research

Weight regain is associated with the promotion of insulin resistance which puzzled many simple and non-inflammatory dominated obese patients. Irisin that was proposed to be involved in the management of insulin sensitivity, could solve this problem. Circulating irisin predicts the insulin resistance onset in association with weight regain, the increased risk of insulin resistance during the follow-up period was related to high irisin levels at baseline[23]. Irisin is positively associated with carotid intima-media thickness (IMT) in humans, suggesting a compensatory increase in irisin to overcome an underlying irisin resistance[24].

However, other progressively inflammation related diseases such as Mets or previous osteoporotic fracture(s) or chronic kidney diseases or acute myocardial infarction (AMI) or preeclampsia were inversely related with basal level of irisin. For example, the basal level of circulating irisin was significantly reduced in metabolic syndrome (MetS) including type 2 diabetes patients especially in T2DM patients with macrovascular disease(MVD) and previous osteoporotic fracture(s) and heart failure[25-28]. Circulating irisin levels are lower in patients with both new-onset and long-term type 2 diabetes[29,30]. Women with gestational diabetes mellitus(GDM) had significantly lower mean serum irisin levels compared to control group[31]. Serum irisin levels

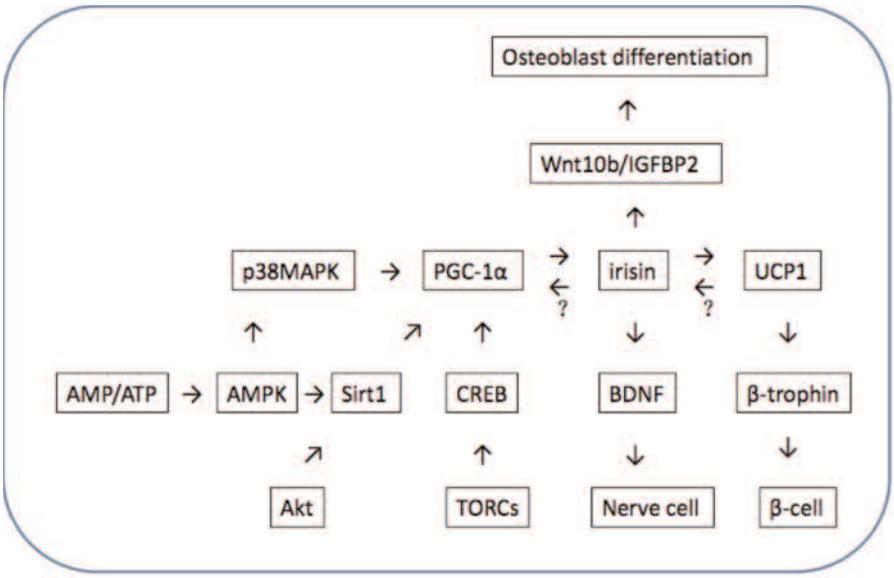

Figure 2. Cell signaling map of exercise induced irisin with other cytokines.

were reduced gradually with the increase of intrahepatic triglyceride (IHTG) contents and were independently associated with liver fat[32]. Wen et al[18] measured resting irisin levels in 38 patients with stage 5 chronic kidney disease and in 19 age- and sex-matched normal subjects. Plasma irisin levels were significantly decreased in chronic kidney disease patients. Saliva and serum irisin in AMI gradually decreased from up to 48 h, compared with the control group and after 12 h, saliva and serum irisin started to increase at 72 h[33]. Emanuele et al[34] demonstrate that healthy centenarians are characterized by increased serum irisin levels whereas levels of this molecule were found to be significantly lower in young patients with myocardial infarction. Serum irisin levels do not change throughout gestation in preeclamptic women, however, there were lower irisin levels during the third trimester when compared to the normal pregnant group[35].

Exercise, which can induce PGC-1α-dependent hormone irisin, maybe reverse such negative outcome of down-regulation of basal level of hormone or disease -induced chaos. For instance, circulating irisin levels at baseline were 111.0 ± 8.0 ng/ml and increased after the intervention by 12% in obese children[36]. whole body vibration increased the expression of PGC-1α and serum levels of irisin[19], which did not cause procedure-related adverse events and induced clinically significant benefits regarding exercise capacity and health-related quality of life for chronic obstructive pulmonary disease (COPD). Higher contractile activity in more aerobically fit heart failure (HF) patients promotes PGC-1α and FNDC5 expression and skeletal muscle abnormalities and functional decline among HF patients whose disease severity is at an advanced stage[25]. All these clue that age-related irisin expression may obscure a series of protective expression mechanisms with those non-inflammation and inflammation related diseases.

Moreover, stepwise multivariable linear regression analysis showed that fasting insulin, HbA1c, age, parathyroid hormone (PTH), creatinine and albumin/globulin ratio[26,27,37]. Plasma irisin was positively correlated with BMI, waist-hip ratio, leptin, fat mass, body cell mass, fat free mass, waist circumference, heredity, angiotensin2 in kids, TNF-α, follistatin and C-reactive protein (CRP)[38-40].

However, range of circulating irisin levels in healthy subjects varies many times from thousands to less than 1 ng/ml for the reason of not only the source of products[17]. It may puzzle many researchers that if the concentration of irisin varies in itself between subjects. At the same time, range of circulating irisin levels in unhealthy subjects also varies. This should be explored more systematically for the future.

Conclusions

With the discovery and explosion of irisin, more and more issues are found to be unresolved. The exact regulation diagram between physical

activities and diseases, not only the metabolic ones, should be researched thoroughly with all these hormones like irisin. Moreover, it's an opportunity to grasp and know more about the newly concept of secretory organs and crosstalk between these organs. Both advanced animal research and clinical research should be under well-planned experiment scheme with profound understanding of existing data. New hormones like irisin that regulate energy input and expenditure, and maintain energy homeostasis control the metabolic events. These hormones regulate the carbohydrates, lipids and proteins metabolism homeostasis. These hormones raise great hope for a series of pathological conditions that are characterized by different kinds of imbalance of energy demand and expenditure. Although irisin synthesized in several tissues, including the salivary gland, its major site of synthesis is within cardiac muscles, soleus, brain and spinal cord. It clues that circulating irisin levels increase secretion of itself in a positive-control manner in cardiac muscles, soleus, brain and spinal cord, which shows us a dazzling future in treating heart, amyotrophic and neurodegenerative diseases.

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Conflict of Interest

The Authors declare that they have no conflict of interests.

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