Irisin-precursor gene: molecular structure, expression regulation, biological functions, and its relationship with skeletal muscle fiber type transformation (Post-print)

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Abstract

Irisin is a newly discovered secretory myokine derived from a polypeptide fragment generated through the hydrolysis of fibronectin type III domain-containing protein 5. Current evidence has demonstrated that irisin and its precursor gene play important roles in the pathogenesis of glucose and lipid metabolic diseases and exercise therapy, and may be associated with skeletal muscle fiber type transformation. This paper summarizes the latest research advances in the molecular structural characteristics, expression regulation, and biological functions of irisin and its precursor gene, integrates these with the mechanisms of skeletal muscle fiber type transformation, and explores the potential molecular associations between the irisin-precursor gene pathway and skeletal muscle fiber type transformation, aiming to provide novel insights for the improvement of meat quality in livestock and poultry.

Full Text

Irisin and Its Precursor Gene: Molecular Structure, Expression Regulation, Biological Functions, and Associations with Skeletal Muscle Fiber Type Conversion

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Abstract: Irisin is a recently discovered secreted myokine derived from a proteolytic peptide fragment of fibronectin type III domain-containing protein 5 (FNDC5). Current evidence demonstrates that irisin and its precursor gene

play important roles in glucose and lipid metabolism, disease pathogenesis, and exercise therapy, potentially linking to skeletal muscle fiber type transformation. This review summarizes the latest research advances on the molecular structural characteristics, expression regulation, and biological functions of irisin and its precursor gene, and explores their potential molecular associations with skeletal muscle fiber type conversion mechanisms, aiming to provide novel insights for livestock meat quality improvement.

Keywords: irisin; precursor gene; peroxisome proliferator-activated receptor γ coactivator; meat quality traits

Skeletal muscle fiber type composition is a crucial factor influencing meat quality traits in livestock and poultry. Given the complex characteristics of muscle fiber types and the difficulty of measuring them in vivo, identifying effective genetic markers and nutritional regulation targets at the molecular level has become a research priority in this field. Various signaling pathways and factors—including thyroid hormones, insulin-like growth factors, calcium signaling pathways, Wnt signaling pathways, AMP-activated protein kinase (AMPK), peroxisome proliferator-activated receptors (PPARs), and peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α)—have been implicated in skeletal muscle fiber type transformation. However, most of these pathways and factors are widely distributed across multiple tissues and have broad functions, lacking specific association with skeletal muscle fiber type conversion. The recently discovered secreted myokine irisin participates in exercise therapy for metabolic diseases such as obesity and insulin resistance. Its expression is both PGC-1α-dependent and exercise-inducible, and serum irisin levels positively correlate with its physiological functions, offering new perspectives for research on genetic markers and nutritional regulation of skeletal muscle fiber types. This review synthesizes current findings on the irisin-FNDC5 pathway and its potential molecular links with skeletal muscle fiber type conversion.

1.1 Molecular Structural Characteristics

Irisin is a secreted glycoprotein discovered by Boström et al. in skeletal muscle, composed of 112 amino acids with a molecular weight of approximately 12 kDa. Irisin is derived from its precursor protein FNDC5, also known as fibronectin type III repeat-containing protein 2 or peroxisomal protein. As shown in Figure 1, the FNDC5 protein consists of three domains: a signal peptide (29 amino acids), a type III fibronectin domain (112 amino acids), and a C-terminal transmembrane domain (65 amino acids), with a total molecular weight of approximately 32 kDa. Following proteolytic cleavage, a secreted FNDC5 peptide fragment—irisin—is released into the circulatory system. This cleavage process shows remarkable similarity to the processing of epidermal growth factor (EGF) and transforming growth factor (TGF). Teufel et al. found that the FNDC5 gene is located on chromosome 4, spans approximately 5.1 kb, and contains six exons: the first exon contains the transcription initiation region; exons 1 and 2 jointly encode the signal peptide; exons 2 and 3 encode the type III fibronectin

domain; and exons 4 and 5 encode the transmembrane domain. FNDC5 protein and irisin exhibit high conservation across species—for instance, showing 100% similarity between humans and rodents, which is higher than the conservation observed for insulin (85%), glucagon (90%), and leptin (83%). This high degree of conservation provides a valuable reference basis for applying irisin-FNDC5 research to livestock meat quality regulation.

1.2 Expression and Regulation

FNDC5 gene expression and irisin secretion were first detected in human, rabbit, and mouse skeletal muscle and serum. Using quantitative PCR, Huh et al. found that FNDC5 mRNA is predominantly expressed in muscle-rich organs such as skeletal muscle, heart, tongue, and rectum, as well as in optic nerve and brain tissue, with lower expression in kidney, liver, and lung. Irisin has also been detected in human dermal and subcutaneous tissues. The degree of muscle tissue development directly affects blood irisin levels. Some studies have reported abundant expression of FNDC5 mRNA and irisin in adipose tissue of rodents and humans, leading to its characterization as an adipokine. Irisin has additionally been identified in human cerebrospinal fluid, breast milk, and saliva, expanding the scope for related research.

Irisin-FNDC5 gene expression is notably exercise-inducible and PGC-1α-dependent. Boström et al. demonstrated that specific knockout of the PGC-1α gene in mouse skeletal muscle reduced serum irisin content by 72%, while three weeks of voluntary wheel running increased it by 65%. As Hofmann et al. reported, both exercise type and individual differences significantly affect irisin-FNDC5 expression. In healthy individuals, FNDC5 gene expression is increased by endurance training only in elderly subjects, showing no response in young people or those undergoing intense or high-resistance training. In patients with cardiac contractile failure, FNDC5 mRNA expression can be induced by aerobic exercise. A one-year lifestyle intervention in obese children increased blood irisin levels by 12%. Aerobic exercise elevated serum irisin levels two-fold in non-obese diabetic men, with even greater increases observed in obese individuals, and similar elevations were confirmed in young mice. However, conflicting results exist: Lee et al. and Kurdiova et al. found that simulated exercise treatment in primary human skeletal muscle cells increased PGC-1α mRNA levels two-fold while decreasing FNDC5 mRNA by 18% and irisin concentration in culture medium by 20%. Other studies reported no change in serum irisin levels after 26 weeks of thrice-weekly exercise training. Hee et al. noted that serum irisin levels showed no significant correlation with dietary structure but were primarily influenced by exercise type. Exercise-induced irisin secretion in mammals likely evolved from shivering muscle contractions, similar to thermogenesis in brown adipose tissue, though the underlying regulatory mechanisms remain to be elucidated.

1.3 Biological Functions

The irisin-FNDC5 pathway participates in thermogenesis, fat conversion, and obesity development. Boström et al. administered full-length FNDC5 adenovirus to normal-diet and high-fat-induced obese mice, finding that in normal-diet mice, subcutaneous adipose tissue FNDC5 mRNA levels increased 15-fold, whole-blood irisin levels rose 3–4-fold, and uncoupling protein 1 (UCP1) mRNA levels increased 13-fold after 10 days, accompanied by significantly elevated cell death-inducing DFF45-like effector (Cidea) expression. Obese mice exhibited similar browning patterns in subcutaneous adipose tissue, with Cidea expression increasing three-fold, along with enhanced oxygen consumption, weight loss, improved glucose tolerance, and reduced fasting insulin levels. Cidea is primarily expressed in brown adipose tissue of adult mice and regulates lipid metabolism and obesity development. Boström et al. also found that 20 nmol/L FNDC5 protein increased UCP1 mRNA expression by 7–1,500-fold, leading to impaired ATP synthesis, increased heat production, and greater consumption of energy reserves (fat).

Serum irisin levels correlate with metabolic diseases such as obesity and diabetes. In obese patients, serum irisin levels positively correlate with body mass index and blood glucose, while negatively correlating with age, insulin, and cholesterol levels. Patients with type 2 diabetes exhibit lower serum irisin levels, which negatively correlate with disease incidence. Non-alcoholic fatty liver disease patients show relatively low serum irisin levels that gradually decrease with elevated intrahepatic triglyceride levels and negatively correlate with serum alanine aminotransferase and aspartate aminotransferase activities. Compared with normal pigs, hypercholesterolemic family pigs show significantly elevated irisin levels despite no difference in FNDC5 mRNA expression in muscle and adipose tissues. In intrauterine growth-restricted fetuses, umbilical cord blood irisin expression is reduced compared with normal fetuses, while large-for-gestational-age fetuses show no significant change; serum irisin levels positively correlate with birth weight and with insulin levels in normal and large-for-gestational-age groups. This may relate to metabolic disease risk later in life. Reduced irisin levels lead to less shivering thermogenesis in newborns and compensatory fat deposition, increasing metabolic disease risk, whereas elevated irisin levels enhance shivering thermogenesis, reduce fat deposition, and decrease metabolic disease susceptibility.

Irisin is also associated with oxidative stress, thyroid dysfunction, muscle injury, cardiovascular disease, and cancer. Exogenous irisin supplementation can reduce disease-related damage: recombinant irisin inhibits arginine methyltransferase-3 activity in non-alcoholic fatty liver cells, reducing oxidative stress and lipid synthesis; intraperitoneal irisin injection inhibits PKC-β/NADPH oxidase activity and NF- B/iNOS signaling pathways while reducing peroxynitrite formation, thereby improving vascular endothelial function in high-fat diet-induced type 2 diabetic mice. Additionally, FNDC5 protein injection in sedentary mice activates brain-derived neurotrophic factor

expression and promotes learning and memory neuron growth, demonstrating potential for treating neurodegenerative diseases such as age-related cognitive decline, Alzheimer' s disease, and Parkinson' s syndrome. Current evidence suggests irisin may function through p38 mitogen-activated protein kinase (MAPK), extracellular signal-regulated kinase (ERK)-MAPK, and PPARα signaling pathways. As irisin-FNDC5 expression and secretion are discovered in more tissues, additional biological functions and mechanisms will be elucidated.

2 Mechanism of Skeletal Muscle Fiber Type Conversion

Based on enzymatic histochemical properties (ATPase combined with succinate dehydrogenase) or myosin heavy chain (MyHC) subunit composition (types I, IIa, IIb, and IIx), animal skeletal muscle fibers are classified into different types, including fast oxidative, slow oxidative, intermediate, and fast glycolytic fibers in adult mammals. Different fiber types can interconvert through various intracellular and extracellular signaling pathways, such as the classic calcium (Ca^{2+}) signaling pathway. Under stimulation by extracellular signals including neural impulses and hormones, intracellular Ca^{2+} or calmodulin-dependent protein kinase (CaMK) concentrations increase, activating calcineurin (CaN) and causing dephosphorylation of nuclear factor of activated T cells (NFATs). Dephosphorylated NFATs translocate to the nucleus and interact with transcription factors such as myocyte enhancer factor 2 (MEF2), myogenic determination factor (MyoD), and PGC-1α, thereby participating in skeletal muscle fiber type conversion.

The NFAT family comprises five protein members including NFATc1, which selectively activates slow-twitch fiber-related gene expression while inhibiting MyoD-dependent fast-twitch fiber gene promoter activity by disrupting the binding between MyoD and the coactivator p300, consequently reducing fast-twitch fiber proportions. Dephosphorylated NFATs form complexes with activator protein 1 (AP1), MEF2, and transcription factors GATA2/4 to activate gene transcription, and are subsequently phosphorylated by glycogen synthase kinase-3β (GSK3-β), protein kinase A (PKA), p38-MAPK, and casein kinase before returning to the cytoplasm to terminate transcriptional activation. Insulin-like growth factor-1 (IGF-1) stimulates skeletal muscle hypertrophy and hyperplasia by enhancing NFATc1 and GATA2 activity, while tonic motor nerves promote slow oxidative fiber formation by increasing NFAT-MEF2 binding activity.

MEF2 is a transcription factor that activates specific genes containing A/T-rich cis-regulatory elements in muscle tissue and functions in muscle cell terminal differentiation mediated by p38MAPK and Ca^{2+}/CaMK/CaN pathways. Like NFATc1, MEF2 can bind to MyoD family members to form complexes that inhibit MyoD-dependent fast-twitch fiber gene expression. Forkhead box protein O1 (FoxO1) is a downstream target of the insulin/protein kinase B (Akt) signaling pathway; phosphorylation by Akt abolishes its ability to bind target genes. Transgenic mice overexpressing human FoxO1 exhibit reduced skeletal muscle mass, paler muscle color, and significantly decreased type I fiber expres-

sion without changes in type II fibers. FoxO1 expression is low in soleus muscle (predominantly type I fibers) but high in extensor digitorum longus muscle (predominantly type II fibers). RNAi-mediated FoxO1 knockdown in myoblasts upregulates fiber type-related genes including MEF2, CaMKII, NFATs, and MyoD. Thus, FoxO1 may reduce type I fiber content by inhibiting MEF2, CaMK, and NFAT pathways.

As illustrated in Figure 2, the PGC-1α gene promoter contains binding sites for MEF2, FoxO1, and cAMP response element (CRE), and its expression is regulated by multiple signaling pathways including insulin-Akt-FoxO1, cytokine/exercise-p38MAPK-MEF2/ATF2, exercise-CaN/CaMKIV-MEF2/CREB, cold stimulation-$ $3 - adrenergicreceptor(\ 3 - AR) - PKA - CREB, andglucagon - GLGNR - PKA - CREB.StudiesusingPGC - 1$ $ transgenic mice demonstrate that PGC-1α overexpression increases the proportion of type I and IIa fibers while elevating MyHC I and IIa mRNA expression and reducing MyHC IIb and IIx mRNA expression. PGC-1α knockout decreases oxidative respiration, mitochondrial content, endurance training capacity, and fatigue resistance in type I fibers. Clearly, PGC-1α serves as a key regulator of skeletal muscle fiber type conversion, particularly in oxidative fiber formation.

3 Potential Association Between Irisin-Precursor Gene and Skeletal Muscle Fiber Type Conversion

PGC-1α represents the primary molecular link between the irisin pathway and skeletal muscle fiber type conversion. PGC-1α exerts broad biological effects in skeletal muscle metabolism, including glycogen synthesis, fatty acid transport and oxidation, mitochondrial synthesis and repair, glucose uptake, lipid synthesis, autophagy, secretion of hyperplastic cytokines, muscle fiber type conversion, neuromuscular junction gene expression induction, myokine secretion, and proinflammatory cytokine secretion. Its main physiological functions include promoting angiogenesis, enhancing oxidative metabolism, improving exercise capacity, alleviating muscle atrophy and dystrophy, and regulating insulin sensitivity. PGC-1α can ameliorate age-related sarcopenia, mitochondrial dysfunction, and systemic inflammation, making it an important therapeutic target for metabolic diseases and a crucial foundation for understanding its role in linking skeletal muscle fiber types with the irisin-FNDC5 pathway.

As shown in Figure 3, aerobic exercise first stimulates PGC-1α expression through the AMPK pathway. PGC-1α then promotes FNDC5 gene expression and irisin secretion while simultaneously participating in metabolic regulation including muscle fiber type conversion. Exercise training also serves as an external factor altering muscle fiber type composition. Endurance training, stretching, and mechanical loading increase the proportion of non-glycolytic fibers while decreasing glycolytic fibers. Outdoor free-range rearing and cold environments increase oxidative fiber proportions in porcine muscle, likely related to shivering muscle contractions. Moreover, increased mitochondrial content is a hallmark

of oxidative fiber formation and a prominent outcome of irisin action. These findings suggest a potential association between the irisin-FNDC5 pathway and oxidative fiber formation, regulated by the common upstream gene PGC-1α, while irisin may also directly participate in establishing skeletal muscle fiber type characteristics—an area requiring further investigation.

4 Potential Role of Irisin-Precursor Gene in Livestock Meat Quality Regulation

Muscles with different fiber type compositions affect meat quality traits through variations in post-mortem glycogenolysis and phosphocreatine conversion (ATP-CP) capacity, which influence pH decline and pale, soft, exudative (PSE) meat formation; through differences in lipid oxidative metabolism affecting intramuscular fat deposition; and through cell cytoskeleton and matrix formation, antioxidant status, and mitochondrial ATP production. These mechanisms underscore the importance of fiber type composition in livestock meat quality regulation.

Given that irisin and its precursor gene regulate glucose and lipid metabolism and associate with skeletal muscle fiber type conversion, they will inevitably influence meat quality formation and regulation. First, they may serve as important molecular markers for skeletal muscle fiber type composition or meat quality traits, such as FNDC5 gene polymorphisms and serum irisin levels. Human studies indicate that FNDC5 gene polymorphisms correlate with blood pressure, lipid distribution, and glucose content in female diabetic patients, while serum irisin levels show ethnic differences. Second, they provide new evidence for meat quality nutritional regulation research. Although specific nutrients regulating the irisin-FNDC5 gene remain unreported, natural ligands of PGC-1α or mitochondrial nutrients may offer relevant references, given that FNDC5 participates in PGC-1α-regulated cardiac differentiation and mitochondrial formation. These applied research directions await confirmation of the irisin-FNDC5 gene' s role in skeletal muscle fiber type and meat quality formation.

5 Summary and Outlook

In summary, irisin, as a newly discovered myokine, demonstrates significant academic value in obesity resistance and diabetes treatment. However, the expression regulation and mechanisms of irisin-FNDC5 remain unclear, including the cell signaling pathways regulating irisin-FNDC5 expression and secretion, the target sites and functional effects of FNDC5 protein and irisin, and factors influencing irisin proteolytic secretion. These knowledge gaps limit further applications. Current irisin research is confined to experimental animals and human medicine, with scarce reports in livestock meat quality formation and improvement. In-depth investigation of the irisin-FNDC5 pathway' s regulatory role in skeletal muscle fiber type differentiation and metabolic characteristic formation will undoubtedly provide new scientific foundations for future livestock meat quality improvement.

References

[1] BOSTRÖM P, WU J, JEDRYCHOWSKI M P, et al. A PGC1-α-dependent myokine that drives brown-fat-like development of white fat and thermogenesis[J]. Nature, 2012, 481(7382): 463–468.

[2] FERRER-MARTÍNEZ A, RUIZ-LOZANO P, CHIEN K R. Mouse PeP: a novel peroxisomal protein linked to myoblast differentiation and development[J]. Developmental Dynamics, 2002, 224(2): 154–167.

[3] TEUFEL A, MALIK N, MUKHOPADHYAY M, et al. Frcp1 and Frcp2, two novel fibronectin type III repeat containing genes[J]. Gene, 2002, 297(1/2): 79–83.

[4] ZHOU Wei, CHEN Jun. Research progress on exercise and PGC-1α-dependent myokine irisin[J]. Chinese Journal of Sports Medicine, 2014, 33(7): 746–752.

[5] ERICKSON H P. Irisin and FNDC5 in retrospect: an exercise hormone or a transmembrane receptor?[J]. Adipocyte, 2013, 2(4): 289–293.

[6] HUH J Y, PANAGIOTOU G, MOUGIOS V, et al. FNDC5 and irisin in humans: I. Predictors of circulating concentrations in serum and plasma and II. mRNA expression and circulating concentrations in response to weight loss and exercise[J]. Metabolism, 2012, 61(12): 1725–1738.

[7] HOFMANN T, ELBELT U, STENGEL A. Irisin as a muscle-derived hormone stimulating thermogenesis-A critical update[J]. Peptides, 2014, 54: 89–100.

[8] KULOGLU T, AYDIN S, EREN M N, et al. Irisin: a potentially candidate marker for myocardial infarction[J]. Peptides, 2014, 55: 85–91.

[9] ROCA-RIVADA A, CASTELAO C, SENIN L L, et al. FNDC5/irisin is not only a myokine but also an adipokine[J]. PLoS One, 2013, 8(4): e60563.

[10] MORENO-NAVARRETE J M, ORTEGA F, SERRANO M, et al. Irisin is expressed and produced by human muscle and adipose tissue in association with obesity and insulin resistance[J]. Journal of Clinical Endocrinology and Metabolism, 2013, 98(4): E769–E778.

[11] PIYA M K, HARTE A L, SIVAKUMAR K, et al. The identification of irisin in human cerebrospinal fluid: influence of adiposity, metabolic markers, and gestational diabetes[J]. American Journal of Physiology Endocrinology and Metabolism, 2014, 306(5): E512–E518.

[12] AYDIN S, KULOGLU T, AYDIN S. Copeptin, adropin and irisin concentrations in breast milk and plasma of healthy women and those with gestational diabetes mellitus[J]. Peptides, 2013, 47: 66–70.

[13] AYDIN S, AYDIN S, KULOGLU T, et al. Alterations of irisin concentrations in saliva and serum of obese and normal-weight subjects, before and after

45 min of a Turkish bath or running[J]. Peptides, 2013, 50: 13–18.

[14] TIMMONS J A, BAAR K, DAVIDSEN P K. Is irisin a human exercise gene?[J]. Nature, 2012, 488(7413): E9-E10.

[15] LECKER S H, ZAVIN A, CAO P R, et al. Expression of the irisin precursor FNDC5 in skeletal muscle correlates with aerobic exercise performance in patients with heart failure[J]. Circulation: Heart Failure, 2012, 5: 812–818.

[16] LAWSON E A, ACKERMAN K E, SLATTERY M, et al. Oxytocin secretion is related to measures of energy homeostasis in young amenorrheic athletes[J]. Journal of Clinical Endocrinology and Metabolism, 2014, 99(5): E881-E885.

[17] BESSE-PATIN A, MONTASTIER E, VINEL C, et al. Effect of endurance training on skeletal muscle myokine expression in obese men: identification of apelin as a novel myokine[J]. International Journal of Obesity, 2014, 38(5): 707–713.

[18] AYDIN S, KULOGLU T, AYDIN S, et al. Cardiac, skeletal muscle and serum irisin responses to with or without water exercise in young and old male rats: cardiac muscle produces more irisin than skeletal muscle[J]. Peptides, 2013, 52: 68–73.

[19] LEE P, LINDERMAN J D, SMITH S, et al. Irisin and FGF21 are cold-induced endocrine activators of brown fat function in humans[J]. Cell Metabolism, 2014, 19(2): 302–309.

[20] KURDIOVA T, BALAZ M, MAYER A, et al. Exercise-mimicking treatment fails to increase Fndc5 mRNA & irisin secretion in primary human myotubes[J]. Peptides, 2014, 56: 1–7.

[21] HEE P H, ZAICHENKO L, PETER P, et al. Diet quality is associated with circulating C-reactive protein but not irisin levels in humans[J]. Metabolism Clinical and Experimental, 2014, 63(2): 233–241.

[22] ITO M, NAGASAWA M, OMAE N, et al. Differential regulation of CIDEA and CIDEC expression by insulin via Akt1/2- and JNK2-dependent pathways in human adipocytes[J]. Journal of Lipid Research, 2011, 52: 1450–1462.

[23] CHOI Y K, KIM M K, BAE K H, et al. Serum irisin levels in new-onset type 2 diabetes[J]. Diabetes Research and Clinic Practice, 2013, 100(1): 96–101.

[24] LIU J J, WONG M D S, TOY W C, et al. Lower circulating irisin is associated with type 2 diabetes mellitus[J]. Journal of Diabetes and Its Complications, 2013, 27(4): 365–369.

[25] ZHANG H J, ZHANG X F, MA Z M, et al. Irisin is inversely associated with intrahepatic triglyceride contents in obese adults[J]. Journal of Hepatology, 2013, 59(3): 557–562.

[26] FAIN J N, COMPANY J M, BOOTH F W, et al. Exercise training does not increase muscle FNDC5 protein or mRNA expression in pigs[J]. Metabolism

Clinical and Experimental, 2013, 62(10): 1503-1511.

[27] BAKA S, MALAMITSI-PUCHNER A, BOUTSIKOU T, et al. Cord blood irisin at the extremes of fetal growth[J]. Metabolism Clinical and Experimental, 2015, 64(11): 1515-1520.

[28] JOUNG K E, PARK K H, FILIPPAIOS A, et al. Cord blood irisin levels are positively correlated with birth weight in newborn infants[J]. Metabolism Clinical and Experimental, 2015, 64(11): 1507-1515.

[29] HUH J Y, MANTZOROS C S. Irisin physiology, oxidative stress, and thyroid dysfunction: what next?[J]. Metabolism Clinical and Experimental, 2015, 64(7): 765-767.

[30] PARK M J, KIMA D I, CHOI J H, et al. New role of irisin in hepatocytes: the protective effect of hepatic steatosis in vitro[J]. Cellular Signalling, 2015, 27(9): 1831-1839.

[31] ZHU D, WANG H C, ZHANG J L, et al. Irisin improves endothelial function in type 2 diabetes through reducing oxidative/nitrative stresses[J]. Journal of Molecular and Cellular Cardiology, 2015, 87: 138-147.

[32] WRANN C D, WHITE J P, SALOGIANNNIS J, et al. Exercise induces hippocampal BDNF through a PGC-1α/FNDC5 pathway[J]. Cell Metabolism, 2013, 18(5): 649-659.

[33] HIUKKA A, MARANGHI M, MATIKAINEN N, et al. PPARα: an emerging therapeutic target in diabetic microvascular damage[J]. Nature Reviews Endocrinology, 2010, 6(8): 454-463.

[34] ZHANG Y, LI R, MENG Y, et al. Irisin stimulates browning of white adipocytes through mitogen-activated protein kinase p38 MAP kinase and ERK MAP kinase signaling[J]. Diabetes, 2014, 63(2): 514-525.

[35] LEFAUCHEUR L, HOFFMAN R K, GERRARD D E, et al. Evidence for three adult fast myosin heavy chain isoforms in type II skeletal muscle fibers in pigs[J]. Journal of Animal Science, 1998, 76(6): 1584-1593.

[36] SCHULZ R A, YUTZEY K E. Calcineurin signaling and NFAT activation in cardiovascular and skeletal muscle development[J]. Developmental Biology, 2004, 266(1): 1-16.

[37] HOGAN P G, CHEN L, NARDONE J, et al. Transcriptional regulation by calcium, calcineurin, and NFAT[J]. Genes & Development, 2003, 17(18): 2205-2232.

[38] FRAYSSE B, DESAPHY J F, PIERNO S, et al. Decrease in resting calcium and calcium entry associated with slow-to-fast transition in unloaded rat soleus muscle[J]. The FASEB Journal, 2003, 17(13): 1916-1918.

[39] EHLERS M L, CELONA B, BLACK B L. NFATc1 controls skeletal muscle fiber type and is a negative regulator of MyoD activity[J]. Cell Reports, 2014,

8(6): 1639-1648.

[40] HORSLEY V, JANSEN K M, MILLS S T, et al. IL-4 acts as a myoblast recruitment factor during mammalian muscle growth[J]. Cell, 2003, 113(4): 483-494.

[41] NAYA F J, OLSON E. MEF2: a transcriptional target for signaling pathways controlling skeletal muscle growth and differentiation[J]. Current Opinion in Cell Biology, 1999, 11(6): 683-691.

[42] WU H, ROTHERMEL B, KANATOUS S, et al. Activation of MEF2 by muscle activity is mediated through a calcineurin-dependent pathway[J]. The EMBO Journal, 2001, 20(22): 6414-6422.

[43] NISSIM H. Biochimica et biophysica acta (BBA)-molecular[J]. Cell Research, 2011(1813): 1965-1970.

[44] KAMEI Y, MIURA S, SUZUKI M, et al. Skeletal muscle FOXO1 (FKHR)-transgenic mice have less skeletal muscle mass, down-regulated type I (slow twitch/red muscle) fiber genes, and impaired glycemic control[J]. Journal of Biological Chemistry, 2004, 279(39): 41114-41123.

[45] YANG Yanjun, PANG Weijun, BAI Liang, et al. Expression of FoxO1 gene in muscle tissue of Bamei pigs, Landrace pigs and Landrace × Bamei hybrid pigs[J]. Hereditas, 2008, 30(2): 185-189.

[46] PANG Weijun. Cloning of porcine FoxO1 gene cDNA and its regulatory role in the differentiation of preadipocytes and myoblasts[D]. PhD Thesis. Yangling: Northwest A&F University, 2007.

[47] FERNANDEZ-MARCOS P J, AUWERX J. Regulation of PGC-1α, a nodal regulator of mitochondrial biogenesis[J]. American Society for Nutrition, 2011, 93(4): 884S-890S.

[48] HANDSCHIN C, CHIN S, LI P, et al. BM. Skeletal muscle fiber-type switching, exercise intolerance, and myopathy in PGC-1α muscle-specific knock-out animals[J]. Journal of Biological Chemistry, 2007, 282(41): 30014-30021.

[49] MORTENSEN O H, FRANDSEN L, SCHJERLING P, et al. PGC-1α and PGC-1β have both similar and distinct effects on myofiber switching toward an oxidative phenotype[J]. American Journal of Physiology Endocrinology and Metabolism, 2006, 291(4): E807-E816.

[50] LEONE T C, LEHMAN J J, FINCK B N, et al. PGC-1α deficiency causes multi-system energy metabolic derangements: muscle dysfunction, abnormal weight control and hepatic steatosis[J]. PLoS Biology, 2005, 3(4): 672-687.

[51] SVENSSON K, HANDSCHIN C. Modulation of PGC-1α activity as a treatment for metabolic and muscle-related diseases[J]. Drug Discovery Today, 2014, 19(7): 1024-1029.

[52] HUH J Y, DINCER F, MESFUM E, et al. Irisin stimulates muscle growth-related genes and regulates adipocyte differentiation and metabolism in humans[J]. International Journal of Obese, 2014, 38(12): 1538–1544.

[53] STARON R S, KARAPONDO D L, KRAEMER W J, et al. Skeletal muscle adaptations during early phase of heavy-resistance training in men and women[J]. Journal of Applied Physiology, 1994, 76(3): 1247–1255.

[54] CAIOZZO V J, HADDAD F, BAKER M J, et al. Microgravity-induced transformations of myosin isoforms and contractile properties of skeletal muscle[J]. Journal of Applied Physiology, 1996, 81(1): 123–132.

[55] BEE G. Effect of early-gestation feeding, birth weight, and gender of progeny on muscle fiber characteristics of pigs at slaughter[J]. Journal of Animal Science, 2004, 82(3): 826–836.

[56] XU Ziwei, MEN Xiaoming, QI Keke. Discussion on the relationship and mechanism between porcine muscle fiber types and their metabolic characteristics and meat quality formation[C]//Advances in Animal Nutrition Research (2012 Edition). Beijing: China Agricultural Science and Technology Press, 2012: 85–96.

[57] BRONDANI L A, BOELTER G, ASSMANN T S, et al. Irisin-encoding gene (FNDC5) variant is associated with changes in blood pressure and lipid profile in type 2 diabetic women but not in men[J]. Metabolism Clinical and Experimental, 2015, 64(9): 952–957.

[58] TANISAWA K, TANIGUCHI H, SUN X M, et al. Common single nucleotide polymorphisms in the FNDC5 gene are associated with glucose metabolism but do not affect serum irisin levels in Japanese men with low fitness levels[J]. Metabolism Clinical and Experimental, 2014, 63(4): 574–583.

[59] ZADEGAN F G, GHAEDI K, KALANTAR S M, et al. Cardiac differentiation of mouse embryonic stem cells is influenced by a PPAR γ/PGC-1α-FNDC5 pathway during the stage of cardiac precursor cell formation[J]. European Journal of Cell Biology, 2015, 94(6): 257–266.

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