

Review of Research on the Role of Irisin in Tumors

This article was published in the following Dove Press journal:
OncoTargets and Therapy

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Abstract: Irisin is a newly discovered exercise-induced cytokine, produced by the proteolytic hydrolysis of fibronectin type III domain-containing protein 5 (FNDC5). Irisin is widely distributed in the human body and is involved in the browning of white adipose tissue, improving insulin resistance, improving cognitive function, and regulating bone metabolism. Recent studies have shown that irisin concentration is elevated in a variety of tumor tissues as compared with that in normal tissues. However, irisin has different effects on the proliferation and apoptosis of tumor cells in breast cancer, lung cancer, and liver cancer through various mechanisms. Irisin plays an important role in the occurrence, development, and metastasis of different tumors, suggesting that irisin can be used as a potential target for tumor diagnosis and treatment. Therefore, studying the expression and function of irisin in tumors may be of great significance for the prevention and treatment of tumors. This article reviews the research progress on the role of irisin in tumors.

Keywords: irisin, cancer, diagnosis, treatment

Introduction

Irisin is an exercise-induced cytokine that promotes the conversion of white adipose tissue to brown adipose tissue. Brown adipose tissue contains a large concentration of uncoupling protein-1 (UCP-1), which can dissipate the energy generated by oxidization in the mitochondria as thermal energy and promote energy consumption, thus playing a role in regulating energy metabolism.¹ Recent studies have documented that irisin is involved in the occurrence and development of a variety of tumors. For example, researchers recently found that patients with bladder or prostate cancer had significantly lower serum irisin levels than the control subjects.^{2,3} The results indicate that irisin can be a potential target for tumor diagnosis and treatment. Studies have shown that exercise can reduce the risk of cancer and improve patient prognosis through direct or indirect anticancer mechanisms such as metabolism, epigenetics, and mental health.^{4,5} It is known that continuous exercise is related to the production of irisin, suggesting that irisin may be a part of the molecular mechanisms underlying the benefits of exercise. The present study reviews the structure and function of irisin and the research on the role of irisin in tumors (Table 1).

Structure and Biological Characteristics of Irisin

The precursor of irisin, FNDC5, is composed of 209 amino acids with a relative molecular weight of about 3.2×10^4 . The sequence from the N-terminus to the C-terminus comprises signal peptide (SP), fibronectin III domain (FND), hydrophobic domain (H), and c-terminal domain (C).^{1,6} FNDC5 is hydrolyzed by protease at amino

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Table 1 Expression of FNDC5/Irisin and Related Molecular Mechanism in Tumors

Tumor Type	Expression of FNDC5/Irisin in Tumor	Function and Potential Mechanism	Reference
Thyroid cancer	Protein increase	Irisin immunoreactivity can be used as a biomarker to distinguish oncocyctic variants of thyroid cancer from other types.	[29]
		Irisin has no in vitro effect on cell proliferation and malignant potential of thyroid cancer cell lines (SW579 and BHP7).	[30]
Esophageal cancer	Protein increase		[37]
		Irisin has no in vitro effect on cell proliferation and malignant potential of esophageal cancer cell lines (OE13 and OE33).	[30]
Lung cancer	Protein increase	Irisin may be a prognostic factor for survival in non-small cell lung cancer.	[31]
		Irisin inhibits epithelial-mesenchymal transition and reduces the invasion of lung cancer cells via the PI3K/AKT/Snail pathway.	[32]
Breast cancer	Serum decrease	Serum irisin may serve as a novel indicator for breast cancer detection and early diagnosis.	[33]
	Serum decrease(with spinal metastasis)	Serum irisin protects spine from breast cancer metastasis.	[34]
	Protein increase		[35]
		Irisin may offer therapeutic benefits for breast cancer prevention and treatment.	[36]
Gastric cancer	Protein increase		[37]
	Serum increase	Increased FNDC5 expression may have a cachectic effect in mice with induced cancer.	[38]
Hepatocellular carcinoma	Protein unaltered		[37]
	mRNA increase	FNDC5/Irisin may be a potential therapeutic strategy for the treatment of metabolic diseases and carcinogenesis.	[40]
	Serum unaltered	Irisin stimulates cell proliferation and invasion by targeting the PI3K/AKT pathway.	[41]
Pancreatic cancer	Protein increase		[37]
		Irisin inhibits pancreatic cancer cell growth via the AMPK-mTOR pathway.	[42]
		Irisin enhances doxorubicin-induced cell apoptosis in pancreatic cancer by inhibiting the PI3K/AKT/NF-kB pathway.	[43]
		Irisin inhibits malignant growth of human pancreatic cancer cells via downregulation of the PI3K/AKT pathway.	[44]
Colorectal cancer	Protein increase		[37]
	Serum decrease	Irisin may be used as potential serum diagnostic markers for colorectal cancer.	[45]
		Irisin has no in vitro effect on cell proliferation and malignant potential of colon cancer cell lines (HT29 and MCA38).	[30]
Renal cancer	Protein decrease or lost	Irisin immunoreactivity may be a useful test for differentiating benign lesions from renal cancer.	[46]
	Serum increase	FNDC5/Irisin may be used as a diagnostic biomarker for renal cancer.	[47]

(Continued)

Table 1 (Continued).

Tumor Type	Expression of FNDC5/Irisin in Tumor	Function and Potential Mechanism	Reference
Prostate cancer	Serum decrease	Irisin may be used as a biomarker for prostate cancer.	[3]
		The cytotoxic effects of irisin on prostate cancer cells are not dependent on androgen receptor mechanism.	[50]
Osteosarcoma		Irisin reversed IL-6-induced epithelial-mesenchymal transition of osteosarcoma cells through the STAT3/Snail pathway.	[51]

acid site 30 and site 142 to produce irisin under the action of peroxisome proliferator-activated receptor gamma coactivator 1- α (PGC1- α). Irisin is an *N*-glycosylated protein factor with a relative molecular weight of 2.2×10^4 , consisting of 112 amino acid residues. Irisin has two glycosylation sites, and the relative molecular weight after deglycosylation is about 1.5×10^4 .^{4,7} Irisin is highly conservative and its amino acid sequence is identical between humans and mice.¹

Irisin was first found in the cells of skeletal muscle. It has been proven that irisin is expressed in almost all tissues and organs of eukaryotic organisms.^{8,9} It was found that FNDC5 is highly expressed in skeletal muscles and muscle-rich tissues (such as pericardium and rectum), moderately expressed in the heart, and weakly expressed in the brain, kidney, liver, lung, and adipose tissue.¹⁰ In addition, FNDC5 is also expressed in the ovary, testis, and thyroid gland. Irisin can also be found in tissue and body fluids (such as plasma, cerebrospinal fluid, saliva, and milk).¹¹⁻¹³

Physiological Function of Irisin Inducing Browning of White Fat

Studies have shown that exercise can induce the expression of PGC1- α in skeletal muscle and promote the expression of FNDC5, thereby resulting in an increase in serum irisin levels and “browning” of white adipose tissue.^{14,15} White adipose tissue and brown adipose tissue are two different types of adipose tissues in the human body, which have different functions. White adipose tissue is mainly composed of triacylglycerol, which is the main constituent of fat stored in the body. It has important functions such as maintaining normal body temperature and protecting important organs. Promoting uncoupling of oxidative respiratory chain electron transfer, generating adenosine triphosphate (ATP), and promoting dissipation of energy in the form of thermal energy by using a large amount of UCP-1 in the mitochondria, thereby maintaining the energy balance in the body, are the main functions of brown adipose tissue.¹⁶

After intraperitoneal administration of 50 μ g of FNDC5 antibody to rats after 7 days of exercise, the up-regulation of UCP-1 expression in subcutaneous adipose tissue caused by exercise was suppressed, confirming that FNDC5 promotes the transformation of white adipocytes into brown adipocytes.¹ However, the mechanism underlying the browning of white fat is not clear. Studies have shown that irisin promotes the expression of related genes by activating the p38 MAPK/ERK pathway involved in the browning of white fat.⁷

Improving Insulin Resistance

Appropriate exercise causes skeletal muscle to secrete irisin, which increases glucose uptake and expression of glucose transporter 4, and to increase glucose utilization and sensitivity of skeletal muscle to insulin.¹⁷ Studies have shown that exogenous irisin significantly reduced insulin resistance in insulin-resistant rats in whom resistance was induced by a high-fat diet.¹ Type-2 diabetes mellitus (T2DM) is a heterogeneous disease characterized by insulin resistance, with decreased insulin secretion and increased glucose production. Choi et al¹⁸ found that as compared to subjects with normal glucose tolerance, T2DM patients showed significantly reduced serum irisin levels, suggesting that irisin plays an important role in the development of T2DM. Therefore, irisin plays an important regulatory role in reducing insulin resistance and may become a new target for diabetes treatment.

Improving Cognitive Function

The continuous formation of hippocampal neurons is necessary for the survival of humans and other vertebrates and for coping with the external environment. Brain-derived neurotrophic factor (BDNF) can promote the growth, differentiation, survival, and repair of neurons and maintain the structure and function of the nervous system, thereby improving cognitive ability.¹⁹ Studies have shown that FNDC5 protein injections

given into non-motile mice promoted the expression of the *BDNF* gene in mouse brains, thereby promoting neuronal growth; however, when the *FNDC5* gene was knocked out in mouse embryonic stem cells, neuronal differentiation was inhibited.^{20,21} In addition, irisin was found to promote the proliferation of mouse H19-7 cells in vitro at a pharmacological concentration and promote the STAT3 signal transduction pathway required for sensory neuron development.²² These studies suggest that irisin plays a potential role in the treatment of cognitive decline in the elderly, including neuropsychiatric diseases such as Alzheimer's disease. However, further exploratory research on neurological diseases and cognitive functions is needed.

Regulation of Bone Metabolism

Exercise is a good way to maintain bone formation and absorption balance and prevent diseases such as osteoporosis and bone metabolism disorders.²³ During human movement, some cytokines are secreted due to the interactions between the bone and skeletal muscles, affecting the physiological state.²⁴ Colaianni et al²⁵ conducted a study in animal models and found that irisin helped prevent and restore bone loss and hind-limb muscle atrophy in mice. Anastasilakis et al²⁶ found that proportion of fractures caused by osteoporosis in postmenopausal women was correlated to the level of irisin in the blood. Palermo et al²⁷ found a negative correlation between serum irisin levels and vertebral fractures and that irisin's protective effect on the bones was not achieved by increasing bone density. Colaianni et al²⁸ injected low doses of irisin into male mice and observed a significant increase in their cortical bone mass and strength. However, the specific mechanism of irisin-mediated bone metabolism is not clear, and further research is needed in this regard.

Irisin and Cancer

Thyroid Cancer

Ugur et al²⁹ carried out immunohistochemical studies to detect the expression of irisin in thyroid tumors. The results showed a significant increase in irisin synthesis in oncogenic variants of thyroid cancer as compared to that in other thyroid tumors. Therefore, irisin immunoreactivity can be used as a biomarker to distinguish oncogenic variants of thyroid cancer from other types. Moon et al³⁰ treated obesity-related cancer cell lines with irisin at physiological (5 to 10 nmol/L) and higher than physiological/pharmacological (50 to 100 nmol/L) concentrations. After 36 h of incubation, irisin had no in vitro effects on cell proliferation and malignant potential

of obesity-related cancer cell lines, namely endometrial (KLE and RL95-2), colon (HT29 and MCA38), thyroid (SW579 and BHP7), and esophageal (OE13 and OE33).

Lung Cancer

Katarzyna et al³¹ found that irisin was elevated in the cancer cells and tumor stromal fibroblasts of patients with non-small cell lung cancer (NSCLC). The expression levels of irisin in cancer cells vary between NSCLC subtypes, eg, the expression levels are higher in adenocarcinoma (AC) than in squamous-cell carcinoma (SCC). The expression of irisin in stromal fibroblasts may affect the proliferation of NSCLC cells, and this may be a prognostic factor for NSCLC patients. Shao et al³² treated human lung cancer cells with different concentrations (0, 10, 20, and 50 nM) of irisin for different time periods (0, 24, and 48 h), and the results showed that irisin significantly inhibited the proliferation, migration, and invasion of lung cancer cells in a time-dependent manner. With the increase in irisin concentration, the expression of E-cadherin increased, while the expression of N-cadherin, vimentin, and Snail decreased. At the same time, LY294002, an inhibitor of PI3K, could reverse the effect of irisin. The results showed that irisin could inhibit epithelial-mesenchymal transition (EMT) and the invasion of lung cancer cells through the PI3K/Akt/Snail pathway, suggesting that irisin can be a potential drug candidate for lung cancer metastasis.

Breast Cancer

Provatopoulou et al³³ studied 51 healthy women and 101 patients with invasive ductal breast cancer and found that serum irisin levels were significantly reduced in breast cancer patients. According to the experimental data, irisin level was closely related to the occurrence of breast cancer and was an independent predictor of breast cancer. It is estimated that for every one-unit increase in irisin levels, the risk of breast cancer decreases by nearly 90%. Irisin could effectively discriminate breast cancer patients at a cut-off point of 3.21 µg/mL, with 62.7% sensitivity and 91.1% specificity. Meanwhile, the serum level of irisin was positively correlated with tumor stage. These results suggest that irisin can be used in the early diagnosis, differential diagnosis, and prognosis of breast cancer.

Studies have shown that obesity increases the mortality risk of breast cancer patients by causing an increase in the concentration of estrogen and elevating the risk of inflammation and metabolic syndrome (MS). MS is a clinical syndrome characterized by disorders of metabolic factors

such as hypertension, obesity, and hyperglycemia. Zhang et al³⁴ studied 148 breast cancer patients, of whom, 53 (35.8%) had spinal metastases. The results showed that the serum level of irisin was higher in MS patients. Patients without spinal metastases had higher serum levels of irisin than the controls. Multivariate analysis showed that serum irisin had a protective effect against spinal metastases in breast cancer patients after adjusting for age and body mass index (BMI). In addition, there was a positive correlation between serum irisin levels and patient BMI. The results suggest that irisin can protect the spine from breast cancer metastasis. Kuloglu et al³⁵ studied the breast tissue by immunohistochemical staining and found that the expression level of irisin was significantly higher in invasive lobular carcinoma, intraductal papilloma, invasive ductal carcinoma, invasive papillary carcinoma, and mucinous carcinoma tissue than in normal breast tissue. Gannon et al³⁶ used different concentrations of irisin (0–625–20 nmol/L) to treat breast cancer cells and found that irisin could significantly reduce the cell number, migration, and viability and enhance the cytotoxic effect of doxorubicin (Dox) in malignant MDA-MB-231 cells, without affecting non-malignant MCF-10a cells. In addition, irisin enhanced the activity of caspase-3 and caspase-7, thus inducing apoptosis of MDA-MB-231 cells, and inhibited the activity of nuclear factor kappa B (NF- κ B), thus indicating its anti-inflammatory role.

Tumors of the Digestive System

Gastric Cancer

The immunohistochemical studies of Aydin et al³⁷ showed that irisin was expressed in normal gastric tissues, and there was no significant difference the expression of irisin and that of gastric neuroendocrine carcinoma tissues. However, the expression of irisin in gastric adenocarcinoma and signet ring cell carcinoma tissues was significantly higher than that in normal gastric tissues. Altay et al³⁸ induced gastric cancer in mice and detected the expression level of the *FNDC5* gene in stomach tissue, skeletal muscle, and fat. The results showed that as compared with the control group, the gastric cancer group showed no significant change in the expression of *FNDC5* in skeletal muscle but showed a significant increase in its expression in fat tissue. Increased *FNDC5* expression in white and brown adipose tissues may have a cachectic effect in mice with induced cancer.

Hepatocellular Carcinoma (HCC)

Previous studies have shown that in the liver, irisin is produced by hepatocytes, Kupffer cells, and sinusoidal endothelial cells, but its role in the liver is still unknown.³⁹ Gaggini et al⁴⁰ studied the liver tissue of 18 patients with HCC undergoing liver transplantation and of 18 deceased donors and found no significant difference in plasma irisin content between patients with HCC and deceased donors. At the same time, irisin, stearoyl COA dehydrogenase-1 (SCD-1), sterol regulatory element binding factor-1 (Srebf-1), and *Notch1* gene expression were detected in the liver tissue. In addition to Srebf-1, irisin, SCD-1, and *Notch1* levels were significantly higher in HCC livers than in deceased donors' livers. Gaggini et al speculate that during the development of liver cancer, irisin acts as a paracrine hormone to inhibit the production of lipids and limit the adipogenesis induced by cancer progression, thus exerting a protective effect on the liver. Aydin et al³⁷ found irisin in the hepatocytes of normal liver tissue, but there was no significant difference in irisin levels between HCC liver and normal liver tissue, which is not consistent with the results of Gaggini et al. There was a lack of consistency in the differences in irisin mRNA and protein expressions between HCC and normal liver tissues in both studies. These differences could be attributed to different tissue sample collection standards and detection methods and to the changes in mRNA transcription and post-translational modifications, such as metabolic degradation of proteins. Shi et al⁴¹ found that irisin significantly increased cell proliferation, invasion, and migration by activating the PI3K/AKT pathway and decreasing the cytotoxicity of Dox.

Pancreatic Cancer

Liu et al⁴² studied the effect of different concentrations (0, 5, 10, 50, and 100 nM) of irisin on pancreatic cancer cell lines (MIA PaCa-2 and Panc03.27) for different time periods (24, 48, and 72 h). The results showed that irisin inhibited the growth of pancreatic cancer cells via the AMPK-mTOR pathway and suppressed the migration and invasion of pancreatic cancer cells by inhibiting EMT. In addition, Liu et al⁴³ found that irisin increased the chemosensitivity of pancreatic cancer cells to Dox or gemcitabine by inactivating the PI3K/AKT/NF- κ B signaling pathway. Zhang et al⁴⁴ treated pancreatic cancer cell lines (PANC-1 and BxPC-3) with different concentrations (0, 10, 20 and 50 nM) of irisin for different time periods (24, 48, and 72 h). The results showed that irisin inhibited cell proliferation

and induced apoptosis of pancreatic cancer cells in a dose-dependent manner. In addition, irisin decreased the migration and invasion of pancreatic cancer cells. Finally, Western blot analysis revealed that irisin downregulated the PI3K/AKT signaling pathway. Therefore, irisin could be further developed as a novel potential therapeutic agent for the treatment of pancreatic cancer.

Colorectal Cancer (CRC)

Aydin et al³⁷ investigated the expression of irisin in colon cancers using immunocytochemistry. As compared with normal colon cells, colon adenocarcinoma and mucinous colon adenocarcinoma cells showed a significant increase in irisin immunoreactivity. Zhu et al⁴⁵ recruited 76 patients with CRC and 40 healthy controls and measured the serum levels of activating transcription factor 3 (ATF3) and irisin by enzyme-linked immunosorbent assay (ELISA). The results showed that the serum level of ATF3 in CRC patients increased by 37.2% and the irisin level decreased by 23.3% compared with the levels in the healthy control group. CRC was independently related to serum ATF3 and irisin levels. After adjusting for age, sex, BMI, and other biochemical parameters, individuals with high ATF3 levels were 22.3 times more likely to develop colorectal cancer than those with low ATF3 levels, while those with high irisin levels were 78.0% less likely to develop CRC than those with low irisin levels. The combination of ATF3 and irisin improves the accuracy of diagnosis, suggesting that ATF3 and irisin can be used as potential serum diagnostic markers for CRC.

Renal Cancer

Kuloglu et al⁴⁶ used immunohistochemical staining to analyze human renal cancers. Irisin immunoreactivity was absent in Fuhrman nuclear grade 1, 2, and 3 clear-cell renal-cell carcinoma (RCC) and papillary RCC samples and was low in chromophobe RCC samples. Irisin immunoreactivity may be a useful test for differential diagnosis of RCC. Altay et al⁴⁷ recruited 23 renal cancer patients and 25 healthy controls and collected their blood samples and measured the serum levels of FNDC5/irisin and carcinoembryonic antigen (CEA) by ELISA. The results showed that the serum levels of FNDC5/irisin and CEA in renal cancer patients were significantly higher than those in healthy controls. In addition, FNDC5/irisin levels are more sensitive and specific than CEA levels. The results suggested that serum FNDC5/irisin could be used as a biomarker for the diagnosis of renal cancer.

Prostate Cancer

Prostate cancer is a hormone-dependent tumor, and about 90% of prostate cancer cases are related to androgen stimulation, so blocking the action of androgen is an important step in treating prostate cancer.⁴⁸ However, prostate cancer has heterogeneity, and the effect of endocrine therapy on a few patients is not obvious.⁴⁹ Tekin et al⁵⁰ treated the androgen receptor-positive and negative human prostate cancer cells LNCaP and DU-145, respectively, with different concentrations (0, 0.1, 1, 10 and 100 nM) of irisin for 24 h. The results showed that irisin could inhibit the proliferation of prostate cancer cells in a dose-dependent manner. The results indicated that the toxic effect of irisin on prostate cancer cells does not depend on the androgen receptor, indicating the potential of this new approach in treating prostate cancer.

Osteosarcoma

Kong et al⁵¹ treated osteosarcoma cells U2OS and MG-63 with different concentrations (0, 25, 50, 100, and 200 ng/mL) of irisin for different time points (12, 24, and 48 h). The results showed that irisin inhibited the proliferation, migration, and invasion of U2OS and MG-63 osteosarcoma cells in a dose- and time-dependent manner. Meanwhile, irisin reversed the IL-6-induced action of EMT in osteosarcoma cells by regulating the expression of E-cadherin, vimentin, fibronectin, matrix metalloproteinases (MMP)-2, MMP-7, and MMP-9. In addition, irisin inhibited the phosphorylation of signal transducers and activators of transcription (STAT) 3 and the expression of Snail activated by IL-6 in osteosarcoma cells. Finally, the inhibition of STAT3 by WP1066 further enhanced the effect of irisin on the expression of EMT and Snail in osteosarcoma cells. The results suggest that irisin may be a potential drug for the treatment of osteosarcoma metastasis.

Conclusion

In summary, irisin plays an important role in the diagnosis, treatment, and prognosis of tumors. Considering the results of studies analyzed in this review, the protective effect of irisin has been demonstrated in several *in vitro* studies. However, there are still many contradictions in the research results of different experimental institutions, possibly due to differences in the (1) detection or experimental methods used, (2) detection reagents or antibodies used, (3) tissue or cell specificity, and (4) receptors or pathways. Therefore,

follow-up experiments are needed to improve experimental methods and reagents used in the study of irisin. At the same time, the receptors, pathways, and mechanisms involved in irisin action need to be further clarified.

The increased expression of irisin in different tumors suggests that it is closely related to the occurrence and development of tumors, making it an attracting new target for tumor prevention research. However, the mechanism of tumorigenesis and development is very complicated, and often, multiple influencing factors and signaling pathways are involved. At present, there are a few reports on the effects of irisin on tumors. Therefore, in-depth study of the role of irisin in tumorigenesis and development will help create a new approach for the prevention and treatment of tumors.

Acknowledgments

This work was supported by the Shandong Province Key Research and Development Project (#2018GSF118057), Qingdao Science and Technology Bureau Project (#19-6-2-58-cg), Qingdao Livelihood Science and Technology Project (#17-3-3-40-nsh), and Qingdao Outstanding Health Professional Development Fund.

Disclosure

The authors report no conflicts of interest in this work.

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