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The role of Irisin in modulating hypoxia-related disorders: New insights and implications for cancer therapy

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ABSTRACT

Regular physical activity is well-known for its health benefits, including reducing the risk of chronic diseases like cancer. Irisin, a myokine released by skeletal muscles during exercise, has emerged as a key regulator in hypoxia-related disorders.Hypoxia, defined by reduced oxygen availability, is a hallmark of various pathological conditions, especially cancer, where it drives tumor growth, metastasis, and resistance to therapy. Recent studies suggest that irisin can modulate hypoxia-induced pathways, impacting processes such as angiogenesis, inflammation, and metabolic adaptation. By targeting these mechanisms, irisin may enhance the efficacy of cancer treatments, reduce tumor aggressiveness, and potentially overcome therapy resistance. Additionally, irisin's influence on the tumor microenvironment highlights its potential as a therapeutic agent to counteract hypoxia-driven cancer progression. This review summarizes current findings on irisin's role in hypoxia-related disorders, focusing on its molecular mechanisms and potential applications in oncology. Despite promising preclinical studies, further research is necessary to fully understand irisin's therapeutic potential, optimize delivery methods, and validate its safety and efficacy in clinical settings. Exploiting exercise-derived molecules such as irisin may enable novel strategies for cancer treatment and other hypoxia-related diseases.

1. Introduction

Cancer is the second leading cause of death in the United States overall, and it is the primary cause of death among individuals under 85 years old. In 2024, the United States is expected to see 2,001,140 new cancer cases and 611,720 cancer-related deaths (Siegel et al., 2024). Muscle tissue, especially skeletal muscle, shows significant resistance to both primary and metastatic cancers (Seely, 1980). The most prevalent tumors arising in muscle are sarcomas, which are malignant tumors that develop in muscles, connective tissues, and bones. Common types of sarcomas include rhabdomyosarcoma, leiomyosarcoma, and undifferentiated pleomorphic sarcoma. Rhabdomyosarcoma, a cancer that originates from immature skeletal muscle cells, is the most common soft tissue sarcoma in children and adolescents. It accounts for approximately 3–4% of all pediatric cancers, with about 350 new cases diagnosed annually in the United States (Agamanolis et al., 1986; Skapek et al., 2019; McEvoy et al., 2023). Leiomyosarcoma is an aggressive tumor originating from smooth muscle and is among the most prevalent subtypes of sarcoma. Its incidence rises with age, peaking in individuals in their 60s. However, uterine leiomyosarcoma predominantly affects perimenopausal women. Uterine leiomyosarcoma is an uncommon smooth muscle tumor, with an annual occurrence rate of just 0.35 to 0.64 cases per 100,000 women in the United States (Wang et al., 2020a).

Irisin, a recently discovered myokine, is released into the bloodstream by skeletal muscles and the heart during exercise. It originates from the extracellular portion of the type I membrane protein Known as fibronectin type III domain-containing protein 5 (FNDC5), a protein containing a fibronectin type III domain, this myokine is widespread throughout the human body and is involved in transforming white fat tissue into brown, regulating bone metabolism, enhancing cognitive function, and enhancing insulin sensitivity. Notably, irisin's impact on tumor cell proliferation and apoptosis varies across different cancer types (Zhang et al., 2020a).

Exposure to high-altitude environments causes hypoxia and skeletal muscle atrophy. Irisin aids in muscle regeneration and helps reduce skeletal muscle atrophy (Liu et al., 2022a). Hypoxia is a condition where cells receive insufficient oxygen, deviating from their normal physiological state. This can happen in various situations, both physiological

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and pathological, such as high altitudes, intense physical activity, cardiovascular diseases, and cancer. In solid tumors, hypoxia is a frequent occurrence, often resulting in poor prognosis and reduced effectiveness of therapies. It significantly influences several serious features of cancer, including angiogenesis, metabolic reprogramming, genomic instability, extracellular matrix remodeling, immune evasion, stem cell maintenance, and resistance to radiation and chemotherapy (McKeown, 2014; Lee et al., 2019; Bai et al., 2022).

Recent advancements in cancer research have increasingly highlighted the role of the tumor microenvironment, particularly the effects of hypoxia, in driving cancer progression and therapy resistance (Roy et al., 2020). Hypoxia-induced changes in the tumor microenvironment create conditions that promote angiogenesis, immune evasion, and metabolic reprogramming, all of which contribute to tumor aggressiveness and poor treatment outcomes (Li et al., 2021). Exercise-induced myokines, such as irisin, represent a novel area of investigation in this context, as they may counteract these hypoxia-driven mechanisms (Gonzalez-Gil and Elizondo-Montemayor, 2020). By modulating key signaling pathways, irisin has shown the potential to influence cancer cell metabolism, reduce tumor proliferation, and enhance the efficacy of existing therapies (Tsiani et al., 2021). This growing body of evidence underscores the importance of understanding the interaction between irisin and hypoxia, as it may provide critical insights into developing innovative, exercise-inspired therapeutic strategies for cancer management. This review summarized the available in-vitro, in-vivo, and human studies that explore the relationship between irisin and hypoxia in the context of cancer. The aim is to elucidate and understand the potential role of irisin in mitigating hypoxia as a protective factor against cancer.

2. Irisin

Irisin, a recently discovered muscle-derived factor, is released from muscle tissue immediately after exercise. It is secreted by FNDC5, a protein made up of 209 amino acids with a molecular weight of roughly 32,000 Da. The irisin peptide is fully conserved in humans, mice, rats, and cattle, with only three conservative substitutions in chickens (Komolka et al., 2014). Through the action of Peroxisome proliferator-activated receptor-gamma coactivator-1alpha (PGC1-α), a coactivator of the peroxisome proliferator-activated receptor gamma (PPARγ), FNDC5 is cleaved by proteases at amino acid positions 30 and 142 to produce irisin. Irisin is a glycosylated protein with a molecular weight of 22,000 Da, consisting of 112 amino acid residues (Boström et al., 2012). It contains two glycosylation sites, and its molecular weight decreases after deglycosylation is approximately 15,000 Da (Thomas et al., 2017). Notably, irisin is highly conserved, with an identical amino acid sequence in both humans and mice. The X-ray crystallography and biochemical studies on irisin have revealed that its folding pattern resembles that of fibronectin type III (FNIII) domain-containing proteins. However, unlike typical FNIII domains, which inhibit dimerization, irisin forms a continuous inter-subunit β-sheet dimer. The crystal structure shows that two irisin subunits associate tightly, primarily through antiparallel β-strand interactions, forming an extended eight-strand β-sheet across the dimer interface. This association is further stabilized by van der Waals forces and hydrophobic interactions, burying an interface area of approximately 1400 $Å^2$, indicative of a high-affinity interaction. Additionally, irisin exhibits strong binding affinity for activated integrin receptors, which are heterodimeric membrane proteins composed of non-covalently associated α and β subunits. These integrins interact with extracellular matrix proteins such as fibronectin, suggesting a potential mechanism for irisin's biological effects (Maak et al., 2021). (Mu et al., 2023; Schumacher et al., 2013). Irisin's unique ability to interact with integrin receptors and influence various cellular pathways positions it as a molecule of significant interest in oncology and hypoxia-related research (Park et al., 2020). By binding to activated integrins, irisin can modulate cellular signaling pathways associated with survival, proliferation, and apoptosis, and these processes are critically altered in the tumor microenvironment, particularly under hypoxic conditions where integrin signaling contributes to cancer progression and therapy resistance (Liu et al., 2022b). Furthermore, irisin's widespread expression in tissues and its presence in body fluids make it a promising candidate for systemic therapeutic interventions, and the exploration of irisin's molecular interactions and mechanisms provides a foundation for understanding its potential role in mitigating the effects of hypoxia, particularly in cancer biology (Zhang et al., 2023). Irisin was initially discovered in skeletal muscle cells. Subsequent research has demonstrated that Irisin is expressed in nearly all tissues and organs. (Thomas et al., 2017; Aydin et al., 2014). FNDC5, the precursor to irisin exhibits high expression in skeletal muscles. Also, it shows moderate expression in the heart and lower expression levels in the kidneys, brain, adipose tissue, liver, and lungs (Huh et al., 2012). FNDC5 is also found in the testis, thyroid gland, and ovary. Additionally, irisin can be detected in various tissues and body fluids, including milk, cerebrospinal fluid, plasma, and saliva (Zhang et al., 2020b; Aydin et al., 2013a, 2013b).

Although irisin has been widely studied as an exercise-induced myokine, its existence and physiological relevance in humans remain a topic of debate. Albrecht et al. argued that irisin might be a myth, questioning the reliability of antibody-based detection methods such as ELISA (Albrecht et al., 2015). FNDC5 and irisin have primarily been identified using three antibody-dependent methods: Western blot, enzyme-linked immunosorbent assays, and protein liquid chip assays. Additionally, various mass spectrometry (MS) methods have been used for the identification or quantification of irisin (Maak et al., 2021). A major challenge in accurately measuring circulating irisin levels is the reliability and specificity of commercially available enzyme-linked immunosorbent assays (ELISAs). Recent studies have questioned the presence of irisin in human circulation, highlighting concerns related to the non-canonical ATA start codon of the FNDC5 gene and the lack of specificity in antibodies used in ELISA-based detection. However, a recent study utilizing MS, with stable isotope-labeled peptides as internal standards, successfully identified and quantified irisin in human blood. This advanced technique confirmed that irisin is translated from its non-canonical start codon and circulates at approximately 3.6 ng/ml in sedentary individuals, increasing to around 4.3 ng/ml after aerobic interval training. These findings provide strong evidence that irisin exists in human circulation and is modulated by exercise (Jedrychowski et al., 2015).

2.1. Role of Irisin in physiological condition

Irisin plays a crucial role in various organs, including regulation of fat browning, metabolism of glucose, promoting the growth and differentiation of neurons, and maintaining musculoskeletal homeostasis (Fig. 1) (Liu et al., 2022c). Aerobic exercise and exposure to cold temperatures cause a rise in irisin levels in the bloodstream. This increase promotes the "browning" of white adipose tissue by enhancing the expression of thermogenic genes such as uncoupling protein 1 (UCP1), Prdm16, CIDEA, PGC-1α, Cox-7a, and Dio2 (Boström et al., 2012; Liu et al., 2022c; Sammons and Price, 2014). White adipose tissue primarily consists of triacylglycerol, the main component of body fat, and plays crucial roles in regulating body temperature and safeguarding essential organs. Brown adipose tissue, on the other hand, is primarily involved in energy balance. It does this by promoting producing ATP, and dissipating energy as heat through the extensive use of UCP-1 in mitochondria (Sammons and Price, 2014). Research shows that irisin activates the browning of white adipose tissue by triggering the addition of phosphate groups to activate thep38 MAPK and ERK signaling pathways. (Zhang et al., 2014; Panati et al., 2016). In vitro studies have shown that irisin exposure induces an increase in peroxisome proliferator-activated receptor alpha (PPARα) in white adipocytes, leading to elevated UCP1 mRNA levels. However, the interpretation of this effect is challenging, as

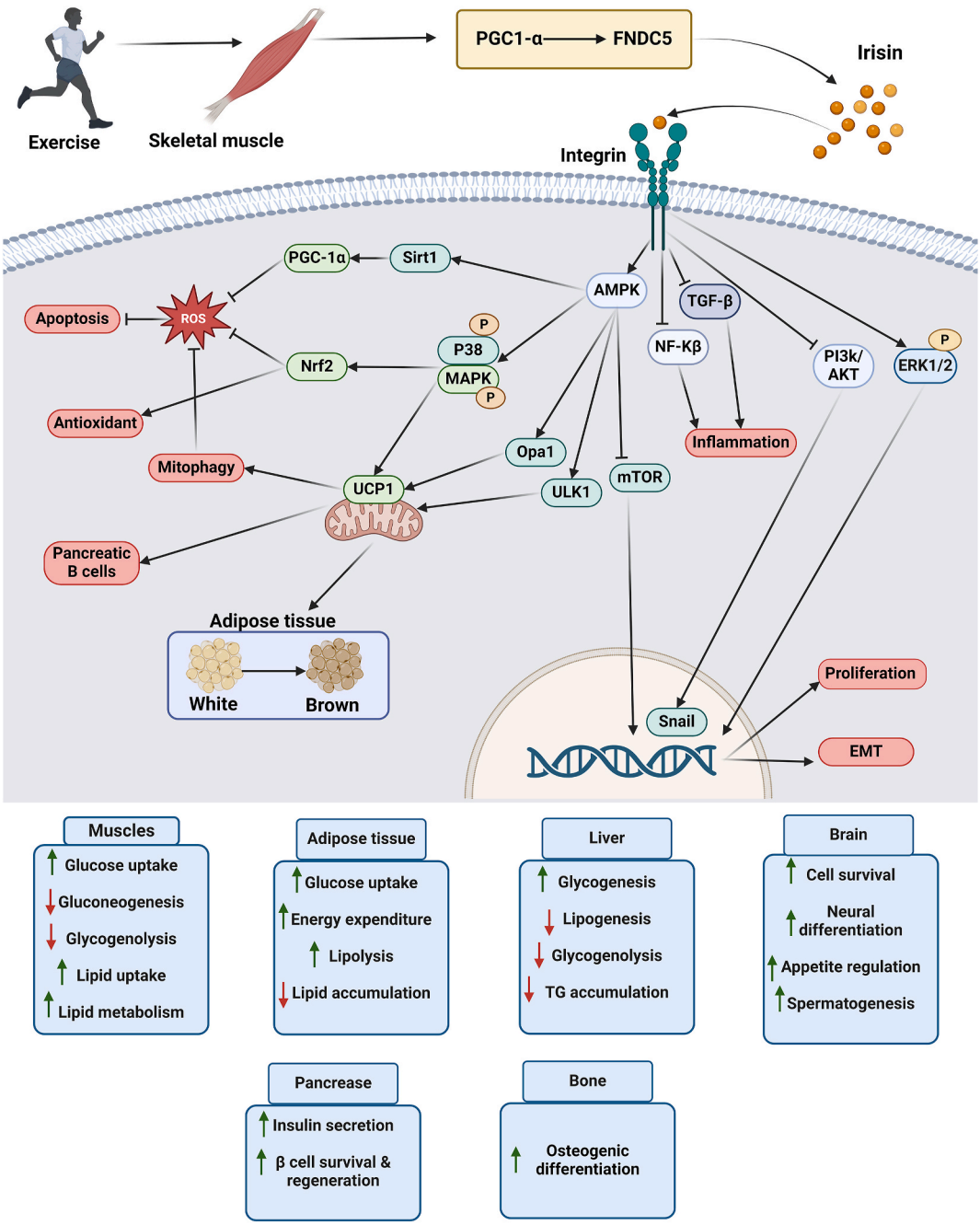

Fig. 1. Schematic representation of the roles of Irisin in various signaling pathways and molecular processes involved in cancer progression, including proliferation, angiogenesis, apoptosis, metabolic changes, epithelial-mesenchymal transition (EMT), and migration of cancer cells. The figure highlights the main physiological activities mediated by Irisin through MAP-kinase signaling pathways. Additionally, it illustrates the diverse physiological activities of Irisin across different organs, including muscles, adipose tissue, liver, brain, pancreas, and bone (Illustration created with BioRender.com).

white adipocytes in culture typically do not express UCP1 mRNA, and the receptor mediating irisin's action remains unidentified (Boström et al., 2012; Petrovic et al., 2010).

Exercise induces the secretion of irisin from skeletal muscles, which enhances glucose uptake through the overexpression of Glut4. Additionally, Irisin enhances how skeletal muscle utilizes glucose and its insulin sensitivity, thereby reducing insulin resistance (Liu, 2015). This reduction in insulin resistance is achieved by activating PI3K/Akt/-FOXO1 pathway, which mediates G6Pase and PEPCK. Furthermore, Irisin stimulates liver glycogenesis through the PI3K/Akt/GSK3 signaling pathway. Consequently, irisin plays a crucial regulatory role in diminishing insulin resistance and holds potential as a novel target for diabetes treatment (Liu et al., 2015). A study using a diabetic mouse model demonstrated that irisin enhances glucose metabolism and lipid regulation. It improved glucose tolerance and uptake, as shown by increased 18F-FDG accumulation and GLUT4 translocation in diabetic skeletal muscle. Similarly, irisin stimulated glucose uptake in myocytes exposed to high glucose and fatty acid conditions (Xin et al., 2016).

The liver is the primary site for gluconeogenesis and glycogenesis, essential processes for maintaining energy metabolism. Research indicates that irisin reduces the expression of G6Pase and PEPCK, thereby inhibiting gluconeogenesis in the liver. This effect is diminished when AMPK is suppressed using siRNA, suggesting that irisin prevents gluconeogenesis by activating the AMPK pathway (Xin et al., 2016).

Similarly, studies have shown that irisin mitigates glucosamine or palmitate-induced insulin resistance in primary hepatocytes by activating the PI3K/Akt/FOXO1 pathway, which also mediates PEPCK and G6Pase. Additionally, irisin enhances liver glycogen synthesis via the PI3K/Akt/GSK3 signaling pathway (Liu et al., 2015). Xin et al. demonstrated that irisin suppresses PEPCK and G6Pase, key gluconeogenesis enzymes in the liver, leading to reduced hepatic glucose production. It also decreased fat mass, total cholesterol, and triglyceride levels while increasing acetyl-CoA carboxylase-β phosphorylation in muscle and UCP1 expression in fat tissue, thereby promoting lipid metabolism. Moreover, irisin enhanced fatty acid oxidation in myocytes through AMP-activated protein kinase (AMPK). AMPK knockdown or inhibition significantly diminished irisin's effects on glucose uptake, lipid oxidation, and gluconeogenic enzyme expression, underscoring its role as a key mediator of irisin's metabolic actions (Xin et al., 2016).

FNDC5/irisin is emerging as a novel therapeutic factor that can enhance memory, learning, and cognition. Studies have shown that FNDC5/irisin expression is decreased in the cerebrospinal fluid and hippocampi of models of Alzheimer's disease. Inhibiting FNDC5 in the brain disrupts the memory function in animal models and cancels out the brain-protective benefits of physical activity on memory while increasing irisin levels in mice improves memory (Lourenco et al., 2019). Studies have demonstrated that injecting FNDC5 protein into immobile mice stimulated the expression of the brain-derived neurotrophic factor (BDNF) gene in their brains. This gene plays a key role in promoting the differentiation, growth, survival, and repair of neurons, as well as maintaining the organization and operation of the nervous system, which promotes the growth of neurons. In contrast, deleting the FNDC5 gene in mouse embryonic stem cells hindered neuronal differentiation (Bekinschtein et al., 2014; Wrann et al., 2013). Physical activity offers significant clinical benefits in Parkinson's disease (PD), partly due to irisin, an exercise-induced polypeptide secreted by skeletal muscle that crosses the blood-brain barrier. Research has shown that irisin protects against α-synuclein (α-syn)-induced neurodegeneration in a preformed fibril (PFF) mouse model of sporadic PD. Intravenous delivery of irisin via viral vectors after intrastriatal α-syn PFF injection reduced pathological α-syn accumulation, preserved dopamine neurons, and prevented striatal dopamine loss. Behavioral tests, including the pole and grip strength assessments, demonstrated improved motor function. In primary cortical neurons, recombinant irisin treatment reduced α-syn toxicity by limiting phosphorylated serine 129 α-syn formation and preventing neuronal cell death. Mass spectrometry and biochemical analyses further revealed that irisin promotes endolysosomal degradation of pathological α-syn. These findings highlight irisin's potential as a therapeutic target for slowing PD progression (Kam et al., 2022).

Exercise is an effective method for maintaining the balance between bone formation and absorption, thereby preventing conditions like osteoporosis and other disorders affecting bone metabolism. Research conducted on animal models has demonstrated that irisin helps prevent and reverse bone loss as well as hind-limb muscle atrophy in mice (Colaianni et al., 2017). Additional evidence has shown that there is an inverse relationship between serum irisin levels and vertebral fractures, indicating that irisin's protective effect on bones is not due to an increase in bone density (Palermo et al., 2015). The levels of FNDC5/irisin are significantly associated with cortical bone mineral density and overall bone health. The results of a study revealed that low serum concentrations of irisin are linked to an increased risk of hip fractures and osteoporosis in postmenopausal women (Kawao et al., 2021). Kan et al. demonstrated that irisin promotes fracture healing by enhancing osteogenesis and angiogenesis. In an irisin-treated group, the expression of CD31, BMP2, and VEGF in callus tissue was significantly increased. In mouse bone mesenchymal stem cells, irisin stimulated ALP expression, mineralization, and the upregulation of key osteogenic genes, including Runx2, BMP2, OSX, ALP, OPG, and OCN. Additionally, irisin facilitated HUVEC migration and tube formation while increasing the expression of angiogenic genes such as ANGPT1, ANGPT2, CD31, VEGFb, FGF2, and PDGFRB in vein endothelial cells (HUVECs). These findings suggest that irisin plays a crucial role in bone regeneration by simultaneously promoting bone formation and vascularization (Kan et al., 2022).

Beyond its roles in metabolic and musculoskeletal health, irisin also contributes to systemic homeostasis by modulating inflammation and oxidative stress, factors that play a pivotal role in chronic diseases, including cancer (Zhang et al., 2023). Research indicates that irisin can reduce inflammatory cytokines such as TNF-α, IL-6, and IL-1β, while enhancing the production of anti-inflammatory cytokines like IL-10 (Pinkas and Brzozowski, 2024). These immunomodulatory effects help maintain a balanced immune response, protecting against chronic inflammation—a known driver of tumorigenesis (Pinkas and Brzozowski, 2024). Furthermore, irisin has been shown to enhance antioxidant defenses by upregulating enzymes such as superoxide dismutase (SOD) and glutathione peroxidase (GPx), which mitigate oxidative damage to cells (Mazur-Bialy and Pochec, 2021; Wang et al., 2020b). These findings suggest that irisin's influence extends beyond isolated physiological processes, potentially intersecting with mechanisms critical to preventing cancer initiation and progression under hypoxic and stress-related conditions.

2.2. *The role of Irisin in cancer prevention*

Regular physical exercise, which elevates irisin levels, has been shown in some studies to influence the occurrence and prevention of various types of cancer through the role of FNDC5/irisin. Irisin mitigates cancer progression by affecting several signaling pathways and molecular processes, including angiogenesis, proliferation, apoptosis, hypoxia, the epithelial-mesenchymal transition (EMT), metabolic changes, and migration of cancer cells (Table .1) (Pinkowska et al., 2021a).

2.2.1. *Pre-clinical evidence*

Shao et al. found that irisin prevents the proliferation, invasion, and migration of lung cancer cells. Additionally, irisin plays a new function in regulating the PI3K/AKT pathway within these cells. By reversing EMT activity and inhibiting Snail expression through the PI3K/AKT pathway, irisin effectively reduces the invasion of lung cancer cells. These findings demonstrate that irisin inhibits EMT and diminishes lung cancer cell invasion via the PI3K/AKT/Snail pathway (Shao et al., 2017). In vitro studies conducted by Kong et al. reported that irisin has an inhibitory effect on EMT. They demonstrated that Irisin was found to hinder the movement of osteosarcoma cells, thus decreasing their ability to metastasize. The study revealed that irisin counteracted IL-6-induced effects by upregulating E-cadherin and suppressing vimentin, E-cadherin, and MMP proteins, which are typically promoted by IL-6. Additionally, irisin inhibited the STAT3 signaling pathway and Snail, a transcription factor critical for EMT in osteosarcoma cells. While both IL-6 and irisin can activate similar signaling pathways, their effects are highly context-dependent. IL-6 exhibits both pro- and anti-inflammatory properties depending on its mode of signaling (classical vs. *trans*--signaling) and cell type. Similarly, irisin has been shown to promote cell proliferation in some contexts (e.g., muscle regeneration) while suppressing tumor progression in others. In osteosarcoma, irisin appears to modulate STAT3 activity in a manner that opposes IL-6-driven EMT, suggesting a complex interplay rather than a strictly antagonistic relationship. Further studies are needed to elucidate the precise molecular mechanisms governing this interaction. (Kong et al., 2017). Liu et al. revealed that irisin suppressed the growth of pancreatic cancer cells by activating AMPK, which in turn downregulated the mTOR pathway and inhibited the EMT of these cells. As a result, irisin decreased the ability of pancreatic cancer cells to migrate and spread to other parts of the body (Liu et al., 2018). Another study found that irisin/FNDC5 was overexpressed in ovarian cancer tissues, suggesting it may regulate the EMT through the PI3K/Akt signaling pathway, thereby inhibiting the proliferation, invasion, and migration of epithelial ovarian cancer cells

Table 1
Summary of preclinical and clinical research on Irisin's role in various cancer types.

Types of cancer	Results	Ref
Pre-clinical Evidence		
Lung cancer	Irisin regulates the PI3K/AKT pathway, reversing EMT and inhibiting Snail expression, thereby reducing lung cancer cell invasion.	Shao et al. (2017)
Osteosarcoma	Irisin inhibits osteosarcoma cell migration and reduces metastatic potential by upregulating E-cadherin while suppressing vimentin, and MMP proteins.	Kong et al. (2017)
Pancreatic cancer	Irisin inhibited pancreatic cancer cell growth by activating AMPK, which downregulated the mTOR pathway and suppressed EMT.	Liu et al. (2018)
Ovarian cancer	Irisin is overexpressed in ovarian and inhibits epithelial cell proliferation, invasion, and migration.	Zhu et al. (2022)
Pancreatic cancer	Irisin reduced cell movement and invasion while inhibiting the PI3K/AKT signaling pathway.	Zhang et al. (2019a)
Breast cancer	Irisin inhibits breast cancer cell proliferation and migration while enhancing Doxorubicin efficacy.	Gannon et al. (2015)
Lung cancer	Combining irisin with paclitaxel may offer potential benefits in treating lung cancer.	Fan et al. (2020a)
Breast cancer	Irisin significantly reduced breast cancer cell malignancy by decreasing colony and sphere formation, inhibiting invasion and migration.	Lee et al. (2024)
Clinical Evidence		
Breast cancer	Lower levels of irisin in breast cancer suggest its potential as a diagnostic biomarker for the disease.	Provatopoulou et al. (2015)
Bladder cancer	Higher irisin levels were associated with significantly better overall survival rates, suggesting that irisin may serve as a prognostic biomarker.	Esawy and Abdel-Samd (2020)
Hepatocellular Carcinoma	Preoperative low serum irisin levels were strongly associated with higher CCI scores after hepatectomy.	Pazgan-Simon et al. (2020b)
Non-small cell lung cancer	Irisin levels decline with increasing tumor size and malignancy grade.	Nowinska et al. (2019)
colorectal cancer	Irisin protein levels in the blood and mRNA expression in adipose tissue were significantly lower in colorectal cancer (CRC) patients compared to healthy individuals.	Zhu et al. (2018a)

(Zhu et al., 2022). Zhang et al. conducted an in-vitro study on pancreatic cancer cells. The findings indicated that irisin suppressed the growth of pancreatic cancer cells by causing cell death at varying doses. Moreover, irisin also decreased the movement and penetration capabilities of these cells. Western blot analysis additionally demonstrated that irisin decreased the activity of the PI3K/AKT signaling pathway (Zhang et al., 2019a). An in vitro and in vitro model demonstrated that irisin inhibits the proliferation and migration of breast cancer cells. Furthermore, the study revealed that irisin enhances the efficacy of Doxorubicin by reducing its toxic effects on healthy cells, thereby decreasing the complications associated with cancer therapy (Gannon et al., 2015). They propose that irisin might offer therapeutic advantages in preventing and treating breast cancer by reducing inflammation, inducing apoptosis, and increasing tumor sensitivity to antineoplastic agents like Doxorubicin. Their study showed that irisin exposure significantly decreased the viability and migration of MDA-MB-231 breast cancer cells, partly by stimulating caspase activity, which leads to apoptosis. Additionally, irisin suppresses NFκB activation, contrasting with other myokines like TNF-α(57). Fan et al. concluded that combining irisin with paclitaxel could be advantageous in treating lung cancer. Their findings indicated that silencing FNDC5 reduced lung cancer cells' sensitivity to paclitaxel. However, patients who received irisin before treatment exhibited increased sensitivity to the drug, with increased activity of proteins that promote cell death (such as p53 and Bax) and reduced levels of proteins that inhibit cell death (like Bcl-2). Additionally, irisin may help reduce the common issue of rising resistance to paclitaxel (Fan et al., 2020a). A recent study found that regular exercise influences the secretion of myokines, with irisin specifically playing a role in suppressing metastasis by reducing the expression of proteins that regulate self-renewal and invasion in breast cancer. In vitro studies demonstrated that irisin significantly decreased the number of colonies and sphere formations, inhibited invasion and cell migration, and reduced breast cancer cell malignancy by lowering the expression of MMP-2, MMP-9, vimentin, and HIF-1, while increasing the expression of TIMP-1 and TIMP-2(59).

2.2.2. *Clinical evidence*

Several clinical studies have indicated that serum irisin levels are lower in cancer patients compared to healthy individuals, suggesting its potential as a preventive factor in cancer progression, as well as its utility as a cancer marker. Provatopoulou et al. specifically implicate irisin in breast cancer, proposing its use as a new diagnostic indicator for the disease. Their findings show serum irisin levels are considerably lower in breast cancer patients than in controls (Provatopoulou et al., 2015). Esawy and Abdel-Samd assessed serum irisin levels in patients with bladder cancer, discovering that these patients had lower irisin levels than the control group. With a cutoff level of irisin set at $\leq$ 1.2 μg/mL, the specificity was 99.7% and the sensitivity was 74.7%. Additionally, patients with higher irisin levels had significantly better overall survival rates compared to those with lower levels. The authors concluded that irisin could serve as a valuable marker for diagnosing BC and act as a prognostic factor for patient survival (Esawy and Abdel-Samd, 2020). Another study analyzed kidney cancer tissues using IHC, revealing significantly decreased irisin levels in renal cell carcinoma samples. No differences in irisin expression were observed between benign oncocytoma and healthy tissues. This suggests that assessing irisin expression levels may serve as an effective tool for distinguishing benign lesions from renal cancer (Kuloğlu et al., 2019). Pazgan-Simon et al. assessed irisin levels in patients with hepatocellular carcinoma. They suggested that Irisin might offer a protective benefit, and reduced levels of it could hasten tumor growth and fibrosis. They discovered that irisin levels were decreased in hepatocellular carcinoma patients, while no significant differences were observed between cirrhosis patients and the control group. Additionally, irisin levels were considerably reduced in the later stages. of hepatocellular carcinoma (Pazgan-Simon et al., 2020a). Zhang et al. conducted studies showing reduced FNDC5 expression in tissues from hepatocellular carcinoma (HCC) patients and lower serum irisin levels in these patients before hepatectomy. Low levels of serum irisin before surgery were strongly linked to higher comprehensive complication index (CCI) scores following hepatectomy. Additionally, analysis of the TCGA dataset revealed that FNDC5/irisin levels were reduced in HCC tissues (Zhang et al., 2019b). Nowinska et al. discovered a link between irisin levels expressed in tumor cells and different clinicopathological factors. The study found that irisin expression in stromal cells could serve as an independent prognostic factor. In tumor cells, irisin levels decreased with higher malignancy grades and larger tumor sizes. Changes in the expression of irisin were also observed about lymph node metastases. Tumors that had metastasized to mediastinal lymph nodes showed elevated levels of irisin compared to tumors without lymph node metastasis, as well as those with metastases limited to hilar and mediastinal lymph nodes. Additionally, Patients who had distant metastases showed elevated levels of irisin expression compared to patients without metastasis (Nowinska et al., 2019). Zhu et al. identified irisin as a potential diagnostic biomarker for colorectal cancer (CRC). In their study, they assessed the levels of FNDC5/irisin protein in the blood and mRNA levels in adipose tissue from 76 patients with CRC and 40 individuals

who were healthy. Using ELISA kits for serum irisin levels and RT-qPCR for mRNA expression, They discovered that irisin levels in the blood of CRC patients were markedly lower compared to those in healthy individuals (Zhu et al., 2018a).

The emerging clinical evidence underscores the potential of irisin as a diagnostic and prognostic biomarker across various cancer types where its consistent association with reduced serum levels in cancer patients compared to healthy individuals suggests a protective role in cancer biology (Provatopoulou et al., 2015; Pinkowska et al., 2021b). Lower irisin levels are often correlated with advanced disease stages, larger tumor sizes, and poor prognosis (Tsiani et al., 2021), as seen in hepatocellular carcinoma (Pazgan-Simon et al., 2020a), colorectal cancer (Wozniak et al., 2022), and breast cancer (Provatopoulou et al., 2015). This highlights irisin's potential utility in early cancer detection and monitoring disease progression. Additionally, the observation of altered irisin expression in tumor tissues, as well as its association with clinicopathological factors like lymph node metastases and distant spread, further supports its relevance in assessing tumor behavior (Cebulski et al., 2023). The clinical implications of these findings are significant, as they suggest that irisin could not only serve as a biomarker but also as a therapeutic target. However, the variability in irisin levels across different cancers and patient populations calls for further investigation to standardize its application and elucidate its underlying mechanisms in cancer pathophysiology.

3. The role of hypoxia on cancer development

Hypoxia refers to a condition where cells receive less oxygen than normal, typically around 10 mm Hg, compared to the usual 60 mm Hg in healthy tissues. Hypoxemia, a reduction in blood oxygen levels, can lead to pathological conditions in various organs such as the heart, lungs, liver, and kidneys (McKeown, 2014). Hypoxia is commonly seen in solid

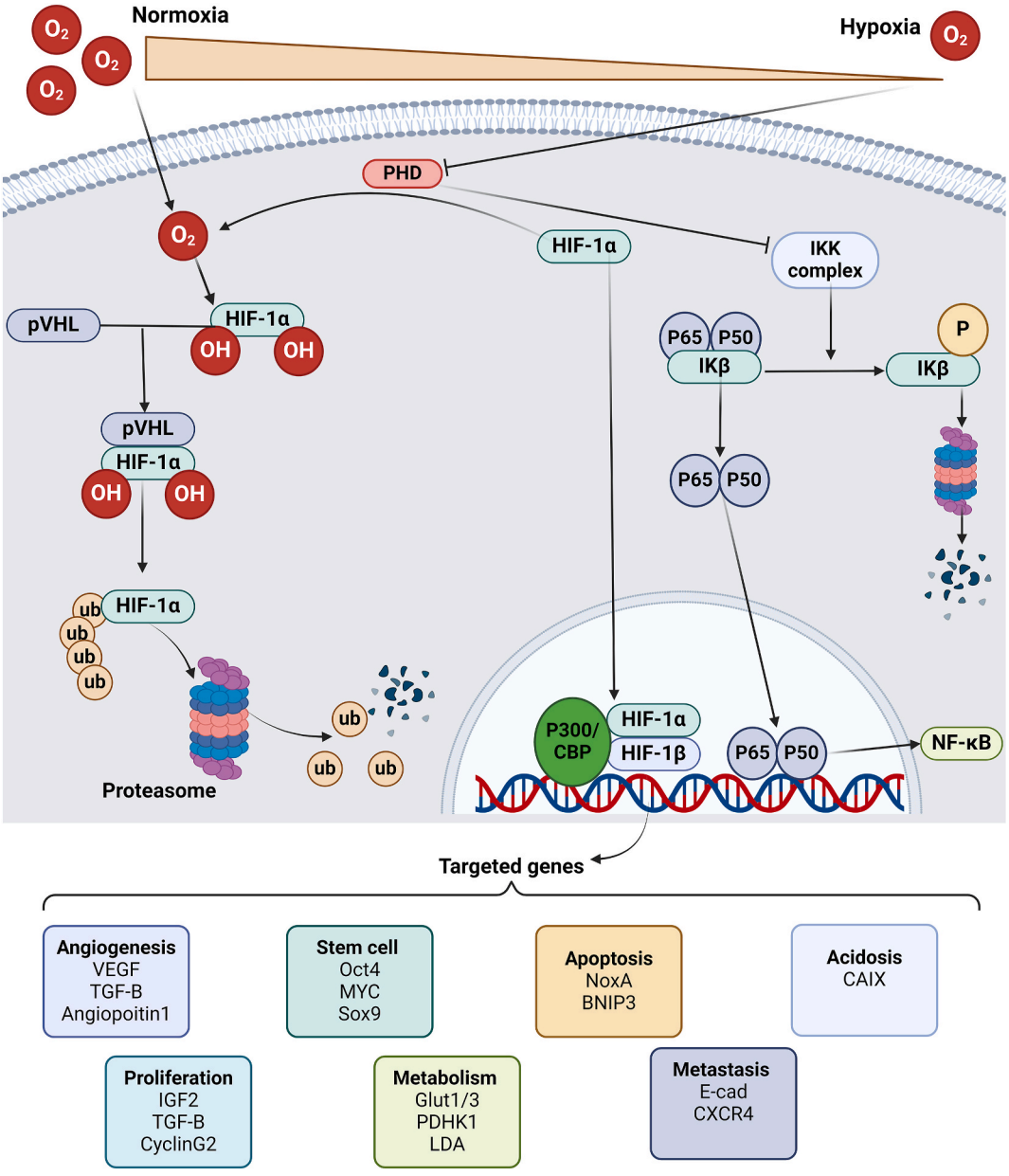

Fig. 2. Schematic representation of HIF regulation under different oxygen conditions. In oxygenated conditions, HIF is hydroxylated on proline residues by prolyl-4-hydroxylases (PHDs) and polyubiquitinated by the von Hippel–Lindau protein (pVHL), leading to its degradation by the proteasome system. In hypoxic conditions, HIF is stabilized and translocated into the nucleus, where it binds to its dimerization partner HIF1B, enhancing the transcription of target genes related to angiogenesis, cell growth, stem cell maintenance, metabolism, invasion, and metastasis (Illustration created with BioRender.com).

tumors and correlates with a negative outlook and decreased therapy efficacy. It significantly influences several critical aspects of cancer, including the formation of new blood vessels (angiogenesis), changes in cellular metabolism, genomic instability, remodeling of the extracellular matrix, evasion of the immune system, maintenance of cancer stem cells, and resistance to both radiation and chemotherapy (Bai et al., 2022). Under normal oxygen levels (normoxia), proline residues on HIF-α subunits are modified by PHDs, enzymes that require oxygen to catalyze prolyl hydroxylation. Following this, the Von Hippel–Lindau protein (pVHL), an E3 ubiquitin ligase, attaches to these hydroxylated HIF-α subunits, marking them for degradation in the proteasome. Additionally, asparagine residues on HIF-α undergo hydroxylation by factors inhibiting HIFs (FIHs), which prevents HIF from binding to coactivators such as p300/CREB-binding protein. In conditions of low oxygen (hypoxia), PHDs and FIHs become inactive, which allows HIF-α subunits to migrate to the nucleus and form complexes with HIF-1β. These HIF-α/β complexes then bind to hypoxia-responsive elements (HREs) found in specific genes, resulting in increased transcription of these genes (Lee et al., 2019; Marxsen et al., 2004). Furthermore, hypoxia triggers the activation of signaling pathways such as the nuclear factor-κB (NF-κB) pathway independent of HIF. Initial research indicated that hypoxia induces phosphorylation of IκBα, causing its degradation and subsequent activation of NF-κB (Fig. 2) (Koong et al., 1994). Hypoxia plays a critical role in driving tumor progression by activating complex molecular pathways, including HIF-1α and HIF-2α signaling, which regulate key processes such as EMT, angiogenesis, and metabolic adaptation (Muz et al., 2015). Preclinical studies have demonstrated that hypoxia-induced overexpression of HIF-1α promotes tumor invasion, metastasis, and resistance to therapies across multiple cancer types (Bui et al., 2022). Mechanistically, hypoxia stabilizes HIF-α subunits, enabling their interaction with co-factors like p300 and subsequent activation of hypoxia-responsive genes and these pathways not only facilitate tumor survival under low oxygen conditions but also enhance cancer stem cell maintenance and genomic instability (Lu and Kang, 2010). Clinical evidence corroborates these findings, linking elevated hypoxia biomarkers such as HIF-1α and CAIX with poor prognosis, treatment resistance, and increased metastatic potential in cancers like pancreatic (Sadozai et al., 2024), breast (Dales et al., 2005), and colon cancer (Chen et al., 2014). These insights highlight hypoxia as a central target for therapeutic intervention, with emerging approaches like HIF-α inhibitors and hypoxia biomarkers offering promising strategies for improving cancer management and patient outcomes.

3.1. Pre-clinical evidence

Several studies have shown that heightened HIF-1α expression caused by hypoxia can promote the spread of cancer by activating genes crucial to the process of metastasis, such as MMP1, uPAR, CXCR4, OPN, IL-8, and VEGF (Shyu et al., 2007; Dong et al., 2019; Zhu et al., 2018b; Colla et al., 2007; Wei et al., 2022). Young et al. found that under conditions of low oxygen levels, DNA over-replication occurs and enhances the metastatic ability of tumor cells in mice. Using flow cytometric analysis, they confirmed that hypoxia followed by reoxygenation disrupts the cell cycle and induces DNA overreplication in these tumor cells (Young et al., 1988). In a research project involving different types of tumors like fibrosarcoma (KHT-C2-LP1), squamous cell carcinoma (SC-CVII), and melanoma (B16F10-A1) in mouse models, scientists extracted cells from the hypoxic zones of implanted murine tumors. These cells were evaluated to determine their responsiveness to anticancer medications and their capacity to initiate secondary growths elsewhere in the body. The findings of the study indicated that gene amplification resulting from excessive DNA replication plays a crucial role in enhancing the tumors' ability to spread to other locations (Young and Hill, 1990). Cairns et al. discovered that acute hypoxia can enhance certain effects in cervical carcinoma. Their findings indicate that fluctuating oxygen levels in these tumors might slow tumor growth but may also increase the likelihood of tumor cells metastasizing to local lymph nodes, as human cervical carcinoma was observed to develop in a mouse as an orthotopic model (Cairns and Hill, 2004). In a study, Arylsulfonamide 64B was employed to block the increased expression of CXCR4 and c-Met induced by hypoxia, which are crucial for tumor invasion and metastasis in melanoma. Mice implanted with melanoma cells in their uvea were treated with 64B. This therapy interrupted the HIF-1 complex by stopping HIF-1α from attaching to p300/CBP co-factors, leading to decreased p300 recruitment to the MET and CXCR4 gene promoters. Furthermore, 64B could enhance the stability of p300, suggesting that 64B binds directly to p300 (Dong et al., 2019). In hepatocellular carcinoma (HCC) cells, CCR1 mediates osteopontin (OPN)-promoted metastasis. CCR1 and CXCR6 are the most upregulated chemokine receptors due to OPN. Blocking the OPN-CCR1 axis significantly reduces OPN's promotion of HCC progression and metastasis by inhibiting HIF-1α. OPN increases CCR1 expression by activating the PI3K/AKT pathway and HIF-1α in HCC cells (Zhu et al., 2018b). A study found that HPIP interacts with SRP14, a part of the signal recognition particle, and enhances MMP9 production under low oxygen conditions. In normal oxygen conditions, HPIP stabilizes HIF-1α, facilitating the Warburg effect to support cell proliferation. Moreover, a mutual feedback loop between HIF-1α and HPIP controls phenotypic plasticity in breast cancer cells (Khumukcham et al., 2022). Ding et al. found that CTHRC1 is highly expressed in tumor tissues and linked to poor prognosis in gastric cancer, according to data from GEO and TCGA databases. Functional studies showed that overexpression of CTHRC1 significantly enhanced cell migration and invasion in gastric cancer. However, these effects were eliminated when CXCR4 was silenced. Additionally, CTHRC1 increased CXCR4 expression by upregulating HIF-1α, and inhibiting HIF-1α reduced CXCR4 levels and suppressed cell migration and invasion (Ding et al., 2020). Research has shown that RAB11B-AS1 boosts the expression of angiogenic factors like ANGPTL4 and VEGFA in hypoxic breast cancer cells by promoting the recruitment of RNA polymerase II (Zuo et al., 2016). The researchers examined HIF-1α expression under hypoxia in two breast cancer cell lines using Western blot. They observed that HIF-1α expression increased in the MDA-MB-231 cell line, impacting the expression of EMT markers such as vimentin, E-cadherin, snail, and MMP9 (Maroufi et al., 2020). Syu JP et al. confirmed that Nrf2 plays a pivotal role in promoting resistance to chemotherapy under hypoxic conditions by orchestrating the ROS-Nrf2-GCLC-GSH pathway in MCF7 cells (Syu et al., 2016).

3.2. Clinical evidence

Yang et al. demonstrated that in pancreatic cancer, HIF-2α stimulates EMT by controlling Twist2's interaction with the E-cadherin promoter. Their study involved examining HIF-2α and E-cadherin expression in 70 pancreatic cancer patients using immunohistochemistry (IHC) and Western blotting. These findings suggest that targeting HIF-2α and its associated pathway could be a promising therapeutic strategy for combating pancreatic cancer, given their role in promoting EMT (Yang et al., 2016). The study investigated the expression of HIF-1α and ANXA3 in human colon carcinoma, colon cells, and an animal model. Both HIF-1α and ANXA3 showed higher expression in colon cancer tissues under hypoxic conditions than in normal colon tissues. When HIF-1α was knocked down, the expression of both ANXA3 and HIF-1α decreased, resulting in the suppression of colon cancer cell proliferation and growth. In a nude mouse model, silencing HIF-1α resulted in reduced xenograft tumor volume and decreased ANXA3 expression (Du et al., 2020). Lui et al. discovered that HIF-1α directly activates the Long Intergenic Non-Coding RNA (lncRNA) GAPLINC in gastric cancer. They observed elevated levels of GAPLINC in gastric cancer tissues, which correlated with increased tumor migration and invasiveness. High expression of GAPLINC also indicated a poorer prognosis among gastric cancer patients. The researchers propose GAPLINC as a promising target for new therapies aimed at overcoming chemoradioresistance and

improving patient survival (Liu et al., 2016). In a different study, researchers propose that the interaction between MTA2TR and HIF-1α could significantly influence the regulation of pancreatic cancer development, suggesting new potential approaches for treating the disease. They demonstrated that increased MTA2TR expression correlates with elevated levels of MTA2 and poorer overall survival rates among pancreatic cancer patients (Zeng et al., 2019). Zuo et al. demonstrated that in laryngeal cancer cells, hypoxia induces the expression of Glut1, N-cadherin, and vimentin via EMT. This molecular process is associated with increased metastasis and poorer overall survival among patients with laryngeal cancer (Zuo et al., 2016). Nicolay et al. conducted a clinical trial involving 49 patients with locally advanced head-and-neck cancer (HNSCC) undergoing chemoradiation. They found that elevated levels of the tissue-based hypoxia biomarkers HIF1α and CAIX were linked to unfavorable hypoxia patterns observed through PET imaging during treatment. Specifically, higher CAIX levels correlated with greater rates of loco-regional recurrence. These findings suggest that hypoxia biomarkers could be valuable predictors for understanding hypoxia dynamics and identifying patients at risk of radiation resistance due to hypoxia (Nicolay et al., 2020). The clinical trial (NCT02974738) evaluating belzutifan's inhibition of HIF-2α in renal cell carcinoma showed that patients tolerated belzutifan well. The findings suggest that inhibiting HIF-2α could be a promising treatment approach for clear cell renal cell carcinoma (Choueiri et al., 2021). In a clinical study, blood biomarkers associated with hypoxia (osteopontin, OPN, and carbonic anhydrase IX, CA-IX) were evaluated to predict prognosis in non-small cell lung cancer. OPN notably enhanced the predictive accuracy of a clinical model that already included gender (Carvalho et al., 2016). Zhang et al. identified three hypoxia-related genes (TES, LDHA, and ANXA2) that correlate with patient survival. These genes were chosen to create a prognostic signature (Zhang et al., 2022). A separate investigation found that HIF-1α, specifically, serves as a valuable prognostic indicator in patients diagnosed with astrocytic tumors that exhibit necrosis on MRI scans. HIF-2α did not demonstrate similar prognostic significance in this context (Mashiko et al., 2011).

4. Irisin ameliorate hypoxia

Evidence suggests that muscle tissue undergoes adaptations in response to hypoxia, and Irisin may emerges as a potential factor in this context (Hoppeler and Vogt, 2001; Chaillou, 2018). This section examines research on the role of irisin in the response to hypoxia, exploring various studies to understand this relationship better. The goal is to gain insights into how irisin influences hypoxic conditions across different diseases (Table .2).

Evidence revealed that irisin plays a role in enhancing muscle regeneration and alleviating hypoxia-induced skeletal muscle atrophy. Circulating irisin levels are considered a novel biomarker for muscle weakness and atrophy, offering potential treatment opportunities for hypoxia-induced muscle conditions. Sliwicka et al. found a positive correlation between serum irisin and hypoxia, discovering that irisin levels decreased in humans after two weeks of climbing in the Alps (Śliwicka et al., 2017). A study found that hypoxic treatment raised HIF-1a levels while reducing irisin and its precursor FNDC5 in the bloodstream and skeletal muscle. The reduction in myotube size and diameter due to hypoxia was reversed by using YC-1 to inhibit HIF-1a (Liu et al., 2022a). In a study using a mouse model, researchers found that palmitic acid caused muscle atrophy. Their results indicated that irisin helps prevent skeletal muscle atrophy in chronic kidney disease by inhibiting fatty acid oxidation and pyroptosis (Zhou et al., 2023). Moscoso et al. demonstrated that hypoxia reduces FNDC5/irisin expression in H9C2 cardiomyocytes. However, they found that increasing irisin levels can mitigate lipotoxic-induced apoptosis in these hypoxic cells by triggering the Akt signaling pathway, indicating irisin's potential as a therapeutic agent for ischemic heart disease (Moscoso et al., 2019). Fan et al. studied how irisin affects cardiomyocyte death triggered by hypoxia-reoxygenation under high glucose conditions. They created an in vitro hypoxia-reoxygenation model with high glucose treatment and found that this injury increased cardiomyocyte apoptosis. However, irisin was able to counteract this effect by improving mitochondrial function. This research suggests a new role for irisin in protecting cardiomyocytes under these conditions (Fan et al., 2020b). Yue et al. discovered that pre-treating mouse cardiomyocytes with irisin can mitigate ischemia-reperfusion damage. In their study, cardiomyocytes subjected to hypoxia and reoxygenation showed increased survival rates and reduced apoptosis and caspase 3 activity when pre-treated with irisin. Additionally, irisin pre-treatment significantly lowered the release of cytochrome *c* from mitochondria and lactate dehydrogenase (LDH) into the extracellular space, suggesting a protective effect of irisin on cardiomyocytes (Yue et al., 2022). A study found that irisin has protective effects on cardiomyocytes under hypoxia/reoxygenation conditions, preventing cell death, increasing cell survival, and reducing apoptosis. Researchers examined cells overexpressing HDAC4, an important heart enzyme, and wild-type H9c2 cells exposed to 24 h of hypoxia followed by 1 h of reoxygenation, both with and without irisin. They discovered that HDAC4 overexpression heightened cardiomyocyte vulnerability to hypoxia/reoxygenation, but irisin treatment mitigated

Table 2
Summary of the effects of irisin on hypoxia-associated disorders.

Condition	Results	Ref
Low oxygen at high altitudes	Irisin levels in humans decreased after two weeks of climbing in the Alps.	Śliwicka et al. (2017)
Muscle atrophy	High HIF-1a levels reduced the circulation of irisin.	Liu et al. (2022a)
Muscle atrophy	Irisin protects against skeletal muscle atrophy in chronic kidney disease by suppressing fatty acid oxidation and preventing pyroptosis	Zhou et al. (2023)
Hypoxic cardiomyoblasts	Irisin protected hypoxic cardiomyoblasts from lipotoxic-induced apoptosis by activating the Akt signaling pathway.	Moscoso et al. (2019)
Hypoxia-reoxygenation cardiomyocyte model	Irisin was able to counteract this effect by improving mitochondrial function.	Fan et al. (2020b)
Ischemia-reperfusion damage	Pre-treatment with irisin enhanced cardiomyocyte survival and reduced apoptosis and caspase-3 activity under hypoxia-reoxygenation conditions.	Yue et al. (2022)
hypoxia/reoxygenation conditions	Irisin improved mitochondrial function and reduced apoptosis, protecting cardiomyocytes.	Zhao et al. (2016)
Hypoxic cardiomyoblasts	Elevated irisin expression enhanced cell survival, inhibited ferroptosis, and mitigated hypoxia-induced mitochondrial damage	Cao et al. (2022)
hypoxia/reoxygenation conditions	Irisin preserved mitochondrial function by preventing permeability transition pore opening and reducing mitochondrial swelling.	Wang et al. (2017)
ovarian cancer	Irisin notably downregulated HIF-1α, c-Myc, and LDHA gene expression in SKOV3 and Caov4 cells.	Alizadeh et al. (2023)
obesity	Hypoxic training modulates serum irisin levels and activates the PGC-1α-FNDC5-UCP1 signaling pathway in skeletal muscles.	Li et al. (2018)
Hypoxic-ischemic encephalopathy	Irisin enhanced neurobehavioral function while reducing brain damage, cerebral infarction, and edema.	Xu et al. (2023)
Hypoxia/reoxygenation stress	Irisin inhibits apoptosis and downregulates pro-inflammatory cytokine expression.	Yu et al. (2022)
Hypoxic-ischemic brain damage	Irisin reduced hypoxic-ischemic brain damage in neonatal rats.	Xu et al. (2020)
Type 1 diabetes	Irisin alleviated hypoxic-ischemic brain damage in neonatal rats.	Żebrowska et al. (2020)

these effects. Irisin promoted HDAC4 sumoylation and time-dependent degradation. Overall, irisin improved mitochondrial function and reduced apoptosis, protecting cardiomyocytes from HDAC4 overexpression's harmful impacts during hypoxia/reoxygenation. (Zhao et al., 2016). In another study, it was found that low oxygen levels (hypoxia) led to cell death, increased a specific type of cell death called ferroptosis, and disrupted mitochondrial function in heart muscle cells (cardiomyocytes). Interestingly, boosting the expression of FNDC5 or administering its derivative irisin improved cell survival, reduced ferroptosis, and reversed the damage to mitochondria caused by hypoxia. The mechanism behind this protective effect involves FNDC5/irisin activating the Nrf2/HO-1 pathway, which reduces ferroptosis and reinstates mitochondrial function in cardiomyocytes during hypoxia. This research highlights the potential of FNDC5/irisin as a therapeutic strategy to counteract ferroptosis and mitochondrial dysfunction in hypoxia-induced heart cell damage (Cao et al., 2022). Wang et al. demonstrated through both laboratory and animal studies that irisin treatment effectively reduced damage caused by hypoxia/reoxygenation in heart muscle cells (cardiomyoblasts). This was evidenced by lower levels of lactate dehydrogenase leakage and fewer apoptotic cardiomyocytes. Additionally, irisin treatment inhibited the opening of the mitochondrial permeability transition pore, reduced mitochondrial swelling, and preserved mitochondrial function. These findings suggest that irisin could be a promising new strategy for protecting the heart, particularly by improving mitochondrial health (Wang et al., 2017).

Researchers investigated how the exercise-triggered myokine irisin affects the proliferation and aggressiveness of ovarian cancer cells through the HIF-1α signaling pathway. They utilized real-time PCR to gauge the expression of aerobic metabolism-related genes in these cancer cells, both with and without irisin. The findings indicated that irisin notably decreased the expression levels of HIF-1α, LDHA, and c-Myc genes in Caov4 and SKOV3 cells compared to the control group (Alizadeh et al., 2023).

Li et al. investigated the impact of different oxygen levels during hypoxic training on serum irisin levels and the PGC-1α-FNDC5-UCP1 signaling pathway in the skeletal muscles of obese rats. Their results showed that exposure to hypoxia and hypoxic training at varying concentrations notably increased the expression of PGC-1α and FNDC5 genes in skeletal muscle. Moreover, the levels of PGC-1α and FNDC5 proteins were significantly higher in the hypoxia, endurance exercise, and hypoxic training groups compared to the control group. Training under oxygen levels of 13.3% and 11.3% notably raised serum irisin levels, and 11.3% hypoxic training specifically enhanced the PGC-1α-Irisin-UCP1 signaling pathway in skeletal muscle (Li et al., 2018).

Xu et al. found that administering irisin to rats with Hypoxic-ischemic encephalopathy lowered IL-6 levels without affecting TNF-α or IL-1β. Irisin effectively mitigates brain damage by diminishing oxidative stress and safeguarding the integrity of the blood-brain barrier. Administering 25 μg/kg of irisin directly into the lateral ventricle enhanced neurobehavioral performance and markedly reduced brain damage, cerebral infarction, and cerebral edema in young male rats with hypoxic-ischemic brain damage (Xu et al., 2023). Research findings demonstrate that Irisin provides robust neuroprotection and anti-inflammatory benefits to cerebral neurons under hypoxia/reoxygenation stress. It was observed that Irisin treatment effectively reduced apoptosis in rat cerebral neurons exposed to such conditions. Moreover, Irisin was found to inhibit the activation of the MAPK signaling pathway and suppress the expression of pro-inflammatory cytokines in these neurons. Importantly, the study also revealed that Irisin's effects were similar to those achieved by using three different MAPK signaling inhibitors, highlighting its potential therapeutic value in combating neuronal injury and inflammation (Yu et al., 2022). In a rat model of hypoxic-ischemic brain damage induced by right common carotid artery ligation and subsequent hypoxic treatment, different groups received irisin interventions. The study used TUNEL, TTC, and hematoxylin-eosin staining to examine brain histopathological changes and employed Western blot analysis to measure levels of apoptosis-related proteins BCL-2, caspase-3, and BAX. Results showed that irisin dose-dependently alleviated hypoxic-ischemic brain damage in neonatal rats, with a notable reduction in cell apoptosis observed in the cerebral cortex and hippocampus (Xu et al., 2020). In a study involving 14 patients with type 1 diabetes, researchers investigated the impact of normoxia and hypoxia on various biological factors. They found that moderate-intensity continuous exercise has positive effects on levels of brain-derived neurotrophic factor (BDNF) and insulin-like growth factor 1 (IGF-1). Specifically, exercising in hypoxic conditions appeared to enhance the availability of IGF-1 more effectively. The changes observed in irisin levels after exercise, along with alterations in the IGF-1 system, may contribute to improved glycemic control in individuals with type 1 diabetes (Żebrowska et al., 2020).

5. Conclusion

Regular physical activity is well-established as a cornerstone of overall health, reducing the risk of numerous diseases, including cancer. However, the underlying molecular mechanisms that drive these benefits are not yet fully understood. Irisin, a myokine secreted by skeletal muscles during exercise, has emerged as a promising candidate linking physical activity to improved health outcomes, particularly in hypoxia-related conditions such as cancer. Irisin's ability to modulate critical pathways involved in cancer progression, including angiogenesis, EMT, and inflammation, positions it as a potential therapeutic agent. In hypoxic tumor environments, irisin has shown the ability to counteract mechanisms that promote tumor growth and therapy resistance by targeting pathways such as PI3K/AKT, AMPK/mTOR, and HIF signaling. Preclinical studies provide compelling evidence that irisin can inhibit cancer cell proliferation, invasion, and migration while enhancing the effectiveness of conventional therapies like chemotherapy. Furthermore, its immunomodulatory and antioxidant effects add to its potential as a multifaceted agent in cancer prevention and treatment. Despite these promising findings, the translation of irisin into clinical applications remains in its infancy. Variability in irisin levels among individuals, as well as differences in its effects across cancer types, underscores the need for comprehensive studies. Future research should focus on elucidating irisin's molecular mechanisms using robust animal models and large-scale clinical trials to validate its therapeutic potential. Understanding the interplay between exercise, irisin, and cancer biology could pave the way for innovative therapeutic strategies that harness the natural benefits of exercise and myokines. As a biomarker and therapeutic target, irisin holds significant promise for advancing personalized medicine and improving cancer outcomes. Continued research in this area could revolutionize the role of lifestyle interventions and exercise-based therapies in oncology.

CRediT authorship contribution statement

Ghazaleh Khalili-Tanha: Writing – original draft, Visualization, Data curation, Conceptualization. **Alireza Shoari:** Writing – review & editing, Conceptualization. **Elham Nazari:** Writing – review & editing, Validation, Supervision.

Ethics approval and consent to participate

Not applicable.

Consent for publication

The author consents to publishing this article.

Availability of data and materials

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The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

Agamanolis, D.P., Dasu, S., Krill, Jr CE., 1986. Tumors of skeletal muscle. Hum. Pathol. 17 (8), 778–795.
Albrecht, E., Norheim, F., Thiede, B., Holen, T., Ohashi, T., Schering, L., et al., 2015. Irisin–a myth rather than an exercise-inducible myokine. Sci. Rep. 5 (1), 8889.
Alizadeh, Zarei M., Seyed Hosseini, E., Haddad Kashani, H., Ahmad, E., Nikzad, H., 2023. Effects of the exercise-inducible myokine irisin on proliferation and malignant properties of ovarian cancer cells through the HIF-1 α signaling pathway. Sci. Rep. 13 (1), 170.
Aydin, S., Kuloglu, T., Aydin, S., 2013a. Copeptin, adropin and irisin concentrations in breast milk and plasma of healthy women and those with gestational diabetes mellitus. Peptides 47, 66–70.
Aydin, S., Aydin, S., Kuloglu, T., Yilmaz, M., Kalayci, M., Sahin, İ., et al., 2013b. 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. Peptides 50, 13–18.
Aydin, S., Kuloglu, T., Aydin, S., Kalayci, M., Yilmaz, M., Cakmak, T., et al., 2014. A comprehensive immunohistochemical examination of the distribution of the fat-burning protein irisin in biological tissues. Peptides 61, 130–136.
Bai, R., Li, Y., Jian, L., Yang, Y., Zhao, L., Wei, M., 2022. The hypoxia-driven crosstalk between tumor and tumor-associated macrophages: mechanisms and clinical treatment strategies. Mol. Cancer 21 (1), 177.
Bekinschtein, P., Cammarota, M., Medina, J.H., 2014. BDNF and memory processing. Neuropharmacology 76, 677–683.
Boström, P., Wu, J., Jedrychowski, M.P., Korde, A., Ye, L., Lo, J.C., et al., 2012. A PGC1-α-dependent myokine that drives brown-fat-like development of white fat and thermogenesis. Nature 481 (7382), 463–468.
Bui, B.P., Nguyen, P.L., Lee, K., Cho, J., 2022. Hypoxia-Inducible factor-1: a novel therapeutic target for the management of cancer, drug resistance, and cancer-related pain. Cancers 14 (24).
Cairns, R.A., Hill, R.P., 2004. Acute hypoxia enhances spontaneous lymph node metastasis in an orthotopic murine model of human cervical carcinoma. Cancer Res. 64 (6), 2054–2061.
Cao, G., Yang, C., Jin, Z., Wei, H., Xin, C., Zheng, C., et al., 2022. FNDC5/irisin reduces ferroptosis and improves mitochondrial dysfunction in hypoxic cardiomyocytes by Nrf2/HO-1 axis. Cell Biol. Int. 46 (5), 723–736.
Carvalho, S., Troost, E.G., Bons, J., Menheere, P., Lambin, P., Oberije, C., 2016. Prognostic value of blood-biomarkers related to hypoxia, inflammation, immune response and tumour load in non-small cell lung cancer–A survival model with external validation. Radiother. Oncol. 119 (3), 487–494.
Cebulski, K., Piotrowska, A., Kmiecik, A., Haczkiewicz-Lesniak, K., Ciesielska, U., Grzegrzolka, J., et al., 2023. The role of irisin/FNDC5 expression and its serum level in breast cancer. Int. J. Mol. Sci. 24 (10).
Chaillou, T., 2018. Skeletal muscle fiber type in hypoxia: adaptation to high-altitude exposure and under conditions of pathological hypoxia. Front. Physiol. 9, 1450.
Chen, J., Ding, Z., Peng, Y., Pan, F., Li, J., Zou, L., et al., 2014. HIF-1alpha inhibition reverses multidrug resistance in colon cancer cells via downregulation of MDR1/P-glycoprotein. PLoS One 9 (6), e98882.
Choueiri, T.K., Bauer, T.M., Papadopoulos, K.P., Plimack, E.R., Merchan, J.R., McDermott, D.F., et al., 2021. Inhibition of hypoxia-inducible factor-2α in renal cell carcinoma with belzutifan: a phase 1 trial and biomarker analysis. Nat. Med. 27 (5), 802–805.
Colaianni, G., Mongelli, T., Cuscito, C., Pignataro, P., Lippo, L., Spiro, G., et al., 2017. Irisin prevents and restores bone loss and muscle atrophy in hind-limb suspended mice. Sci. Rep. 7 (1), 2811.
Colla, S., Tagliaferri, S., Morandi, F., Lunghi, P., Donofrio, G., Martorana, D., et al., 2007. The new tumor-suppressor gene inhibitor of growth family member 4 (ING4) regulates the production of proangiogenic molecules by myeloma cells and suppresses hypoxia-inducible factor-1 α (HIF-1α) activity: involvement in myeloma-induced angiogenesis. Blood, The Journal of the American Society of Hematology 110 (13), 4464–4475.
Dales, J.P., Garcia, S., Meunier-Carpentier, S., Andrac-Meyer, L., Haddad, O., Lavaut, M. N., et al., 2005. Overexpression of hypoxia-inducible factor HIF-1alpha predicts early relapse in breast cancer: retrospective study in a series of 745 patients. Int. J. Cancer 116 (5), 734–739.
Ding, X., Huang, R., Zhong, Y., Cui, N., Wang, Y., Weng, J., et al., 2020. CTHRC1 promotes gastric cancer metastasis via HIF-1α/CXCR4 signaling pathway. Biomed. Pharmacother. 123, 109742.
Dong, L., You, S., Zhang, Q., Osuka, S., Devi, N.S., Kaluz, S., et al., 2019. Arylsulfonamide 64B inhibits hypoxia/HIF-induced expression of c-Met and CXCR4 and reduces primary tumor growth and metastasis of uveal melanoma. Clin. Cancer Res. 25 (7), 2206–2218.
Du, K., Ren, J., Fu, Z., Wu, X., Zheng, J., Li, X., 2020. ANXA3 is upregulated by hypoxia-inducible factor 1-alpha and promotes colon cancer growth. Transl. Cancer Res. 9 (12), 7440.
Esawy, M.M., Abdel-Samd, K.M., 2020. The diagnostic and prognostic roles of serum irisin in bladder cancer. Curr. Probl. Cancer 44 (4), 100529.
Fan, G.-H., Zhu, T.-Y., Huang, J., 2020a. FNDC5 promotes paclitaxel sensitivity of non-small cell lung cancers via inhibiting MDR1. Cell. Signal. 72, 109665.
Fan, J., Zhu, Q., Wu, Z., Ding, J., Qin, S., Liu, H., et al., 2020b. Protective effects of irisin on hypoxia-reoxygenation injury in hyperglycemia-treated cardiomyocytes: role of AMPK pathway and mitochondrial protection. J. Cell. Physiol. 235 (2), 1165–1174.
Gannon, N.P., Vaughan, R.A., Garcia-Smith, R., Bisoffi, M., Trujillo, K.A., 2015. Effects of the exercise-inducible myokine irisin on malignant and non-malignant breast epithelial cell behavior in vitro. Int. J. Cancer 136 (4), E197–E202.
Gonzalez-Gil, A.M., Elizondo-Montemayor, L., 2020. The role of exercise in the interplay between myokines, hepatokines, osteokines, adipokines, and modulation of inflammation for energy substrate redistribution and fat mass loss: a review. Nutrients 12 (6).
Hoppeler, H., Vogt, M., 2001. Muscle tissue adaptations to hypoxia. J. Exp. Biol. 204 (18), 3133–3139.
Huh, J.Y., Panagiotou, G., Mougios, V., Brinkoetter, M., Vamvini, M.T., Schneider, B.E., et al., 2012. 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. Metabolism 61 (12), 1725–1738.
Jedrychowski, M.P., Wrann, C.D., Paulo, J.A., Gerber, K.K., Szpyt, J., Robinson, M.M., et al., 2015. Detection and quantitation of circulating human irisin by tandem mass spectrometry. Cell Metab. 22 (4), 734–740.
Kam, T.-I., Park, H., Chou, S.-C., Van Vranken, J.G., Mittenbühler, M.J., Kim, H., et al., 2022. Amelioration of pathologic α-synuclein-induced Parkinson's disease by irisin. Proc. Natl. Acad. Sci. USA 119 (36), e2204835119.
Kan, T., He, Z., Du, J., Xu, M., Cui, J., Han, X., et al., 2022. Irisin promotes fracture healing by improving osteogenesis and angiogenesis. Journal of orthopaedic translation 37, 37–45.
Kawao, N., Iemura, S., Kawaguchi, M., Mizukami, Y., Takafuji, Y., Kaji, H., 2021. Role of irisin in effects of chronic exercise on muscle and bone in ovariectomized mice. J. Bone Miner. Metabol. 39, 547–557.
Khumukcham, S.S., Penugurti, V., Soni, A., Uppala, V., Hari, K., Jolly, M.K., et al., 2022. A reciprocal feedback loop between HIF-1α and HPIP controls phenotypic plasticity in breast cancer cells. Cancer Lett. 526, 12–28.
Komolka, K., Albrecht, E., Schering, L., Brenmoehl, J., Hoeflich, A., Maak, S., 2014. Locus characterization and gene expression of bovine FNDC5: is the myokine irisin relevant in cattle? PLoS One 9 (1), e88060.
Kong, G., Jiang, Y., Sun, X., Cao, Z., Zhang, G., Zhao, Z., et al., 2017. Irisin reverses the IL-6 induced epithelial-mesenchymal transition in osteosarcoma cell migration and invasion through the STAT3/Snail signaling pathway. Oncol. Rep. 38 (5), 2647–2656.
Koong, A.C., Chen, E.Y., Giaccia, A.J., 1994. Hypoxia causes the activation of nuclear factor κB through the phosphorylation of IκBα on tyrosine residues. Cancer Res. 54 (6), 1425–1430.
Kuloğlu, T., Artaş, G., Yardim, M., Aydin, Y., Beyoğlu, N., Özercan, İ., et al., 2019. Immunostaining characteristics of irisin in benign and malignant renal cancers. Biotech. Histochem. 94 (6), 435–441.
Lee, J.W., Ko, J., Ju, C., Eltzschig, H.K., 2019. Hypoxia signaling in human diseases and therapeutic targets. Exp. Mol. Med. 51 (6), 1–13.
Lee, Y., Park, S., Park, S., Kwon, H.J., Lee, S.-H., Kim, Y., et al., 2024. Exercise affects high-fat diet-stimulated breast cancer metastasis through irisin secretion by altering cancer stem cell properties. Biochemistry and Biophysics Reports 38, 101684.
Li, Z., Weng, X., Song, X., Zhao, F., Chen, H., Lin, W., 2018. Hypoxic training increases the concentration of serum irisin and reduces weight in diet-induced obese rats. bioRxiv, 500603.
Li, Y., Zhao, L., Li, X.F., 2021. Hypoxia and the tumor microenvironment. Technol. Cancer Res. Treat. 20, 15330338211036304.
Liu, J., 2015. Irisin as an exercise-stimulated hormone binding crosstalk between organs. Eur. Rev. Med. Pharmacol. Sci. 19 (2).
Liu, T.-Y., Shi, C.-X., Gao, R., Sun, H.-J., Xiong, X.-Q., Ding, L., et al., 2015. Irisin inhibits hepatic gluconeogenesis and increases glycogen synthesis via the PI3K/Akt pathway in type 2 diabetic mice and hepatocytes. Clin. Sci. 129 (10), 839–850.
Liu, L., Zhao, X., Zou, H., Bai, R., Yang, K., Tian, Z., 2016. Hypoxia promotes gastric cancer malignancy partly through the HIF-1α dependent transcriptional activation of the long non-coding RNA GAPLINC. Front. Physiol. 7, 420.
Liu, J., Song, N., Huang, Y., Chen, Y., 2018. Irisin inhibits pancreatic cancer cell growth via the AMPK-mTOR pathway. Sci. Rep. 8 (1), 15247.
Liu, S., Fu, P., Ning, K., Wang, R., Yang, B., Chen, J., et al., 2022a. HIF-1α negatively regulates irisin expression which involves in muscle atrophy induced by hypoxia. Int. J. Mol. Sci. 23 (2), 887.
Liu, S., Cui, F., Ning, K., Wang, Z., Fu, P., Wang, D., et al., 2022b. Role of irisin in physiology and pathology. Front. Endocrinol. 13, 962968.
Liu, S., Cui, F., Ning, K., Wang, Z., Fu, P., Wang, D., et al., 2022c. Role of irisin in physiology and pathology. Front. Endocrinol. 13, 962968.
Lourenco, M.V., Frozza, R.L., de Freitas, G.B., Zhang, H., Kincheski, G.C., Ribeiro, F.C., et al., 2019. Exercise-linked FNDC5/irisin rescues synaptic plasticity and memory defects in Alzheimer's models. Nat. Med. 25 (1), 165–175.
Lu, X., Kang, Y., 2010. Hypoxia and hypoxia-inducible factors: master regulators of metastasis. Clin. Cancer Res. 16 (24), 5928–5935.
Maak, S., Norheim, F., Drevon, C.A., Erickson, H.P., 2021. Progress and challenges in the biology of FNDC5 and irisin. Endocr. Rev. 42 (4), 436–456.

Maroufi, N.F., Amiri, M., Dizaji, B.F., Vahedian, V., Akbarzadeh, M., Roshanravan, N., et al., 2020. Inhibitory effect of melatonin on hypoxia-induced vasculogenic mimicry via suppressing epithelial-mesenchymal transition (EMT) in breast cancer stem cells. Eur. J. Pharmacol. 881, 173282.
Marxsen, J.H., Stengel, P., Doege, K., Heikkinen, P., Jokilehto, T., Wagner, T., et al., 2004. Hypoxia-inducible factor-1 (HIF-1) promotes its degradation by induction of HIF-α-prolyl-4-hydroxylases. Biochem. J. 381 (3), 761–767.
Mashiko, R., Takano, S., Ishikawa, E., Yamamoto, T., Nakai, K., Matsumura, A., 2011. Hypoxia-inducible factor 1α expression is a prognostic biomarker in patients with astrocytic tumors associated with necrosis on MR image. Journal of neuro-oncology 102, 43–50.
Mazur-Bialy, A.I., Pochec, E., 2021. The time-course of antioxidant irisin activity: role of the Nrf2/HO-1/HMGB1 Axis. Antioxidants 10 (1).
McEvoy, M.T., Siegel, D.A., Dai, S., Okcu, M.F., Zobeck, M., Venkatramani, R., et al., 2023. Pediatric rhabdomyosarcoma incidence and survival in the United States: an assessment of 5656 cases, 2001–2017. Cancer Med. 12 (3), 3644–3656.
McKeown, S., 2014. Defining normoxia, physoxia and hypoxia in tumours—implications for treatment response. Br. J. Radiol. 87 (1035), 20130676.
Moscoso, I., Cebro-Márquez, M., Rodríguez-Mañero, M., González-Juanatey, J.R., Lage, R., 2019. FNDC5/Irisin counteracts lipotoxic-induced apoptosis in hypoxic H9c2 cells. J. Mol. Endocrinol. 63 (2), 151–159.
Mu, A., Wales, T.E., Zhou, H., Draga-Coletă, S.-V., Gorgulla, C., Blackmore, K.A., et al., 2023. Irisin acts through its integrin receptor in a two-step process involving extracellular Hsp90α. Mol. Cell 83 (11), 1903, 20. e12.
Muz, B., de la Puente, P., Azab, F., Azab, A.K., 2015. The role of hypoxia in cancer progression, angiogenesis, metastasis, and resistance to therapy. Hypoxia 3, 83–92.
Nicolay, N.H., Wiedenmann, N., Mix, M., Weber, W.A., Werner, M., Grosu, A.L., et al., 2020. Correlative analyses between tissue-based hypoxia biomarkers and hypoxia PET imaging in head and neck cancer patients during radiochemotherapy—results from a prospective trial. Eur. J. Nucl. Med. Mol. Imag. 47, 1046–1055.
Nowinska, K., Jablonska, K., Pawelczyk, K., Piotrowska, A., Partynska, A., Gomulkiewicz, A., et al., 2019. Expression of Irisin/FNDC5 in cancer cells and stromal fibroblasts of non-small cell lung cancer. Cancers 11 (10), 1538.
Palermo, A., Strollo, R., Maddaloni, E., Tuccinardi, D., D'Onofrio, L., Briganti, S.I., et al., 2015. Irisin is associated with osteoporotic fractures independently of bone mineral density, body composition or daily physical activity. Clin. Endocrinol. 82 (4), 615–619.
Panati, K., Suneetha, Y., Narala, V., 2016. Irisin/FNDC5-An updated review. Eur. Rev. Med. Pharmacol. Sci. 20 (4).
Park, E.J., Myint, P.K., Ito, A., Appiah, M.G., Darkwah, S., Kawamoto, E., et al., 2020. Integrin-ligand interactions in inflammation, cancer, and metabolic disease: insights into the multifaceted roles of an emerging ligand irisin. Front. Cell Dev. Biol. 8, 588066.
Pazgan-Simon, M., Zuwala-Jagiello, J., Menzyk, T., Bator, M., Derra, A., Lekstan, A., et al., 2020a. Serum betatrophin and irisin levels in hepatocellular carcinoma. J. Physiol. Pharmacol. 71 (1).
Pazgan-Simon, M., Zuwala-Jagiello, J., Menzyk, T., Bator, M., Derra, A., Lekstan, A., et al., 2020b. Serum betatrophin and irisin levels in hepatocellular carcinoma. J. Physiol. Pharmacol. 71 (1), 113–123.
Petrovic, N., Walden, T.B., Shabalina, I.G., Timmons, J.A., Cannon, B., Nedergaard, J., 2010. Chronic peroxisome proliferator-activated receptor γ (PPARγ) activation of epididymally derived white adipocyte cultures reveals a population of thermogenically competent, UCP1-containing adipocytes molecularly distinct from classic brown adipocytes. J. Biol. Chem. 285 (10), 7153–7164.
Pinkas, M., Brzozowski, T., 2024. The role of the myokine irisin in the protection and carcinogenesis of the gastrointestinal tract. Antioxidants 13 (4).
Pinkowska, A., Podhorska-Okołów, M., Dzięgiel, P., Nowińska, K., 2021a. The role of irisin in cancer disease. Cells 10 (6), 1479.
Pinkowska, A., Podhorska-Okolow, M., Dziegiel, P., Nowinska, K., 2021b. The role of irisin in cancer disease. Cells 10 (6).
Provatopoulou, X., Georgiou, G.P., Kalogera, E., Kalles, V., Matiatou, M.A., Papapanagiotou, I., et al., 2015. Serum irisin levels are lower in patients with breast cancer: association with disease diagnosis and tumor characteristics. BMC Cancer 15, 1–9.
Roy, S., Kumaravel, S., Sharma, A., Duran, C.L., Bayless, K.J., Chakraborty, S., 2020. Hypoxic tumor microenvironment: implications for cancer therapy. Exp Biol Med (Maywood) 245 (13), 1073–1086.
Sadozai, H., Acharjee, A., Kayani, H.Z., Gruber, T., Gorczynski, R.M., Burke, B., 2024. High hypoxia status in pancreatic cancer is associated with multiple hallmarks of an immunosuppressive tumor microenvironment. Front. Immunol. 15, 1360629.
Sammons, M.F., Price, D.A., 2014. Modulation of adipose tissue thermogenesis as a method for increasing energy expenditure. Bioorg. Med. Chem. Lett 24 (2), 425–429.
Schumacher, M.A., Chinnam, N., Ohashi, T., Shah, R.S., Erickson, H.P., 2013. The structure of irisin reveals a novel intersubunit β-sheet fibronectin type III (FNIII) dimer: implications for receptor activation. J. Biol. Chem. 288 (47), 33738–33744.
Seely, S., 1980. Possible reasons for the high resistance of muscle to cancer. Med. Hypotheses 6 (2), 133–137.
Shao, L., Li, H., Chen, J., Song, H., Zhang, Y., Wu, F., et al., 2017. Irisin suppresses the migration, proliferation, and invasion of lung cancer cells via inhibition of epithelial-to-mesenchymal transition. Biochem. Biophys. Res. Commun. 485 (3), 598–605.
Shyu, K.-G., Hsu, F.-L., Wang, M.J., Wang, B.-W., Lin, S., 2007. Hypoxia-inducible factor 1α regulates lung adenocarcinoma cell invasion. Exp. Cell Res. 313 (6), 1181–1191.
Siegel, R.L., Giaquinto, A.N., Jemal, A., 2024. Cancer statistics, 2024. CA: a cancer journal for clinicians 74 (1), 12–49.
Skapek, S.X., Ferrari, A., Gupta, A.A., Lupo, P.J., Butler, E., Shipley, J., et al., 2019. Rhabdomyosarcoma. Nat. Rev. Dis. Primers 5 (1), 1.
Śliwicka, E., Cisoń, T., Kasprzak, Z., Nowak, A., Pilaczyńska-Szcześniak, Ł., 2017. Serum irisin and myostatin levels after 2 weeks of high-altitude climbing. PLoS One 12 (7), e0181259.
Syu, J.-P., Chi, J.-T., Kung, H.-N., 2016. Nrf2 is the key to chemotherapy resistance in MCF7 breast cancer cells under hypoxia. Oncotarget 7 (12), 14659.
Thomas, R.J., Kenfield, S.A., Jimenez, A., 2017. Exercise-induced biochemical changes and their potential influence on cancer: a scientific review. Br. J. Sports Med. 51 (8), 640–644.
Tsiani, E., Tsakiridis, N., Kouvelioti, R., Jaglanian, A., Klentrou, P., 2021. Current evidence of the role of the myokine irisin in cancer. Cancers 13 (11).
Wang, H., Zhao, Y.T., Zhang, S., Dubielecka, P.M., Du, J., Yano, N., et al., 2017. Irisin plays a pivotal role to protect the heart against ischemia and reperfusion injury. J. Cell. Physiol. 232 (12), 3775–3785.
Wang, L., Li, S., Zhang, Z., Jia, J., Shan, B., 2020a. Prevalence and occult rates of uterine leiomyosarcoma. Medicine 99 (33), e21766.
Wang, Y.J., Chen, Y., Zhang, X.Y., Lu, Y.P., Chen, H.X., 2020b. New insights in intestinal oxidative stress damage and the health intervention effects of nutrients: a review. J. Funct.Foods 75.
Wei, H., Xu, Z., Chen, L., Wei, Q., Huang, Z., Liu, G., et al., 2022. Long non-coding RNA PAARH promotes hepatocellular carcinoma progression and angiogenesis via upregulating HOTTIP and activating HIF-1α/VEGF signaling. Cell Death Dis. 13 (2), 102.
Wozniak, S., Nowinska, K., Chabowski, M., Dziegiel, P., 2022. Significance of irisin (FNDC5) expression in colorectal cancer. In Vivo 36 (1), 180–188.
Wrann, C.D., White, J.P., Salogiannnis, J., Laznik-Bogoslavski, D., Wu, J., Ma, D., et al., 2013. Exercise induces hippocampal BDNF through a PGC-1α/FNDC5 pathway. Cell Metab. 18 (5), 649–659.
Xin, C., Liu, J., Zhang, J., Zhu, D., Wang, H., Xiong, L., et al., 2016. Irisin improves fatty acid oxidation and glucose utilization in type 2 diabetes by regulating the AMPK signaling pathway. Int. J. Obes. 40 (3), 443–451.
Xu, X.-P., Huang, L.-Y., Zhao, F.-Y., Ying, J.-J., Li, S.-P., Yue, Y., et al., 2020. Effect of irisin on hypoxic-ischemic brain damage in neonatal rats. Zhongguo Dang dai er ke za zhi= Chinese Journal of Contemporary Pediatrics 22 (1), 58–64.
Xu, X., Zhou, R., Ying, J., Li, X., Lu, R., Qu, Y., et al., 2023. Irisin prevents hypoxic-ischemic brain damage in rats by inhibiting oxidative stress and protecting the blood-brain barrier. Peptides 161, 170945.
Yang, J., Zhang, X., Zhang, Y., Zhu, D., Zhang, L., Li, Y., et al., 2016. HIF-2α promotes epithelial-mesenchymal transition through regulating Twist2 binding to the promoter of E-cadherin in pancreatic cancer. J. Exp. Clin. Cancer Res. 35, 1–10.
Young, S., Hill, R., 1990. Effects of reoxygenation on cells from hypoxic regions of solid tumors: anticancer drug sensitivity and metastatic potential. JNCI: J. Natl. Cancer Inst. 82 (5), 371–380.
Young, S., Marshall, R., Hill, R., 1988. Hypoxia induces DNA overreplication and enhances metastatic potential of murine tumor cells. Proc. Natl. Acad. Sci. USA 85 (24), 9533–9537.
Yu, Q., Li, G., Li, J., Sun, L., Yang, Y., Tao, L., 2022. Irisin protects cerebral neurons from hypoxia/reoxygenation via suppression of apoptosis and expression of pro-inflammatory cytokines. Neuroimmunomodulation 29 (4), 425–432.
Yue, R., Lv, M., Lan, M., Zheng, Z., Tan, X., Zhao, X., et al., 2022. Irisin protects cardiomyocytes against hypoxia/reoxygenation injury via attenuating AMPK mediated endoplasmic reticulum stress. Sci. Rep. 12 (1), 7415.
Żebrowska, A., Sikora, M., Konarska, A., Zwierzchowska, A., Kamiński, T., Robins, A., et al., 2020. Moderate intensity exercise in hypoxia increases IGF-1 bioavailability and serum irisin in individuals with type 1 diabetes. Therapeutic Advances in Endocrinology and Metabolism 11, 2042018820925326.
Zeng, Z., Xu, F-y, Zheng, H., Cheng, P., Chen, Q-y, Ye, Z., et al., 2019. LncRNA-MTA2TR functions as a promoter in pancreatic cancer via driving deacetylation-dependent accumulation of HIF-1α. Theranostics 9 (18), 5298.
Zhang, Y., Li, R., Meng, Y., Li, S., Donelan, W., Zhao, Y., et al., 2014. Irisin stimulates browning of white adipocytes through mitogen-activated protein kinase p38 MAP kinase and ERK MAP kinase signaling. Diabetes 63 (2), 514–525.
Zhang, D., Zhang, P., Li, L., Tang, N., Huang, F., Kong, X., et al., 2019a. Irisin functions to inhibit malignant growth of human pancreatic cancer cells via downregulation of the PI3K/AKT signaling pathway. OncoTargets Ther. 7243–7249.
Zhang, J., Ke, M., Ren, Y., Bi, J., Du, Z., Zhang, M., et al., 2019b. Serum irisin predicts posthepatectomy complications in patients with hepatocellular carcinoma. Dis. Markers 2019 (1), 9850191.
Zhang, D., Tan, X., Tang, N., Huang, F., Chen, Z., Shi, G., 2020a. Review of research on the role of irisin in tumors. OncoTargets Ther. (13), 4423–4430, 2020.
Zhang, D., Tan, X., Tang, N., Huang, F., Chen, Z., Shi, G., 2020b. Review of research on the role of irisin in tumors. OncoTargets Ther. 4423–4430.
Zhang, J-j, Shao, C., Yin, Y-x, Sun, Q., Li, Y-n, Zha, Y-w, et al., 2022. Hypoxia-related signature is a prognostic biomarker of pancreatic cancer. Dis. Markers 2022 (1), 6449997.
Zhang, Y., Wang, L., Kang, H., Lin, C.Y., Fan, Y., 2023. Unlocking the therapeutic potential of irisin: harnessing its function in degenerative disorders and tissue regeneration. Int. J. Mol. Sci. 24 (7).
Zhao, Y.T., Wang, H., Zhang, S., Du, J., Zhuang, S., Zhao, T.C., 2016. Irisin ameliorates hypoxia/reoxygenation-induced injury through modulation of histone deacetylase 4. PLoS One 11 (11), e0166182.
Zhou, T., Wang, S., Pan, Y., Dong, X., Wu, L., Meng, J., et al., 2023. Irisin ameliorated skeletal muscle atrophy by inhibiting fatty acid oxidation and pyroptosis induced by palmitic acid in chronic kidney disease. Kidney Blood Press. Res. 48 (1), 628–641.
Zhu, H., Liu, M., Zhang, N., Pan, H., Lin, G., Li, N., et al., 2018a. Serum and adipose tissue mRNA levels of ATF3 and FNDC5/irisin in colorectal cancer patients with or without obesity. Front. Physiol. 9, 1125.

Zhu, Y., Gao, X.M., Yang, J., Xu, D., Zhang, Y., Lu, M., et al., 2018b. C-C chemokine receptor type 1 mediates osteopontin-promoted metastasis in hepatocellular carcinoma. Cancer Sci. 109 (3), 710–723.

Zhu, T., Zhang, W., Zhang, Y., Lu, E., Liu, H., Liu, X., et al., 2022. Irisin/FNDC5 inhibits the epithelial–mesenchymal transition of epithelial ovarian cancer cells via the PI3K/Akt pathway. Arch. Gynecol. Obstet. 306 (3), 841–850.

Zuo, J., Wen, J., Lei, M., Wen, M., Li, S., Lv, X., et al., 2016. Hypoxia promotes the invasion and metastasis of laryngeal cancer cells via EMT. Med. Oncol. 33, 1–9.