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REVIEW

Irisin's Dual Role in Malignant Tumors and Its Potential as a Biomarker and Therapeutic Target

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Abstract: Irisin, a myokine secreted by skeletal muscle, has garnered significant attention for its multifaceted physiological roles and emerging potential as both a biomarker and therapeutic target in oncology. This review consolidates current understanding of irisin's impact across various malignancies, focusing on its complex regulation of tumorigenesis through interactions with key signaling pathways including PI3K/AKT, AMPK-mTOR, and STAT3/Snail. Critically, irisin exhibits a paradoxical dual role: it suppresses proliferation, migration, and invasion in cancers such as lung, breast, and pancreatic carcinoma, yet paradoxically promotes the progression of hepatocellular carcinoma. This tissue-specific dichotomy presents a significant therapeutic challenge. Furthermore, inconsistent findings regarding irisin expression levels even within the same tumor type highlight the urgent need for further mechanistic investigation. Future research must prioritize elucidating the context-dependent mechanisms of irisin within the tumor microenvironment and rigorously evaluating its clinical utility as a biomarker through large-scale trials. Resolving these contradictions is essential for developing a unified understanding of irisin's role in cancer biology. Such insights hold promise for paving the way toward novel therapeutic strategies, potentially enhancing the efficacy of personalized cancer therapy.

Keywords: irisin, malignant tumors, biomarkers, therapeutic target, signaling pathways, epithelial-mesenchymal transition

Introduction

Cancer continues to rank as a leading cause of global mortality, and its intricate nature and heterogeneity significantly complicate early diagnosis and effective treatment.[1] As research delves deeper into the tumor microenvironment's role in cancer progression, there is an intensified search for novel therapeutic targets and biomarkers.[2]

Irisin, a myokine secreted by skeletal muscle in response to exercise, has recently gained attention for its complex and context-dependent effects on cancer biology.[3] While irisin is well-known for its physiological roles in promoting energy expenditure, maintaining metabolic health, and modulating inflammation, emerging evidence reveals its dual effects in oncology.[4] Specifically, irisin has been shown to suppress cancer progression in lung, breast, and pancreatic cancers, yet it paradoxically promotes the development of hepatocellular carcinoma.[5–9] This review aims to comprehensively analyze irisin's dichotomous impacts across these cancer types, with a particular focus on its interactions with key oncogenic pathways, including PI3K/AKT (which regulates cell survival and metabolism), AMPK-mTOR (which orchestrates energy sensing and anabolic processes), and STAT3/Snail (which drives epithelial-mesenchymal transition and metastasis).[7,10,11]

Despite promising results from preclinical studies, several critical knowledge gaps remain. Irisin's effects across different tumor stages and molecular subtypes have not been consistently elucidated.[12,13] Additionally, confounding factors such as obesity and metabolic comorbidities may potentially obscure irisin's utility as a biomarker.[14] This review evaluates irisin's potential as both a diagnostic/prognostic biomarker and a therapeutic target while addressing these uncertainties. Through

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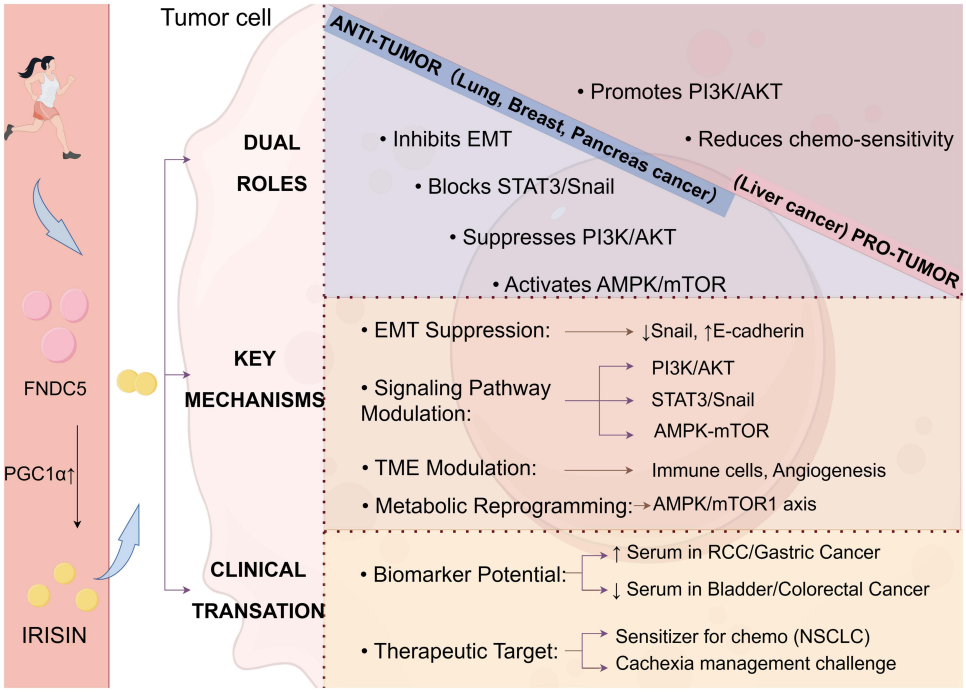
Graphical Abstract



dissecting its complex signaling crosstalk and modulation of the tumor microenvironment,[6,15] this review seeks to provide insights that can inform strategies for personalized cancer interventions and ultimately enhance patient outcomes.

Physiological Roles of Irisin

Irisin is a polypeptide hormone produced by proteolytic cleavage of fibronectin type III domain-containing protein 5 (FNDC5) precursor protein. The FNDC5 gene is located on human chromosome 1p31.3, and its encoded precursor protein consists of 209 amino acid residues, including an N-terminal signal sequence (28 amino acids), a fibronectin III domain (93 amino acids), a linker (30 amino acids), a transmembrane region (19 amino acids), and a C-terminal part (39 amino acids).[16] Under physiological conditions, the FNDC5 protein is translated under the guidance of the N-terminal signal sequence and then undergoes glycosylation modification in the endoplasmic reticulum. Eventually, it is cleaved by proteases to generate irisin and released into the circulatory system.[3,17] Irisin is a 112-amino acid fragment produced by proteolytic cleavage of the extracellular part of the FNDC5 protein, which includes the fibronectin III domain and 19 amino acids of the linker (including amino acids 29 to 140). It mainly exists in the form of a homodimer and its structure is stabilized by hydrogen bonds and interactions between the side chains of adjacent subunits.[18,19] In addition, the FNDC5 protein of irisin undergoes N-glycosylation during post-translational modification, with glycosylation sites concentrated at Asn-59 and Asn-103. Different sugar chain structures cause the molecular weight of the FNDC5 protein to fluctuate between 20 and 32 kDa.[20] The irisin peptide is 100% conserved in humans, mice, rats, and cattle, while only three conserved substitutions are present in chickens. The peptide shows greater differences in fish, and the FNDC5 gene is completely absent in amphibians.[3,21] As a potential therapeutic target, the function and mechanism of irisin have been deeply studied in various physiological and pathological processes, including muscle-fat communication, insulin sensitivity regulation, neuroprotection, etc. It improves metabolic balance by enhancing mitochondrial function and reducing oxidative stress.[22]

Irisin is a myokine secreted by skeletal muscle, initially recognized as a hormone induced by exercise. During contraction, skeletal muscle releases a variety of myokines into circulation, including the peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1-α), and the membrane protein FNDC5, which is cleaved by

enzymes to generate irisin upon activation by PGC1-α.[4] The FNDC5 gene is widely expressed in different tissues throughout the body,[23,24] and irisin has also been found in human breast milk and saliva.[25–27] The secretion of irisin varies among different tissues and even within the same tissue at different sites,for example, subcutaneous adipose tissue secretes more irisin than visceral adipose tissue.[28] Irisin has a molecular weight of approximately 12 kDa and exhibits a highly conserved amino acid sequence and functionality across most mammalian species[3] (Figure 1).

Irisin primarily functions by upregulating the expression of the mitochondrial uncoupling protein 1 (UCP 1), mediating the browning of white adipose tissue into beige adipose tissue, which aids in increasing energy expenditure and thermoregulation.[29] Additionally, irisin exhibits neuroprotective effects by inducing the expression of brain-derived neurotrophic factor (BDNF) in the hippocampus, combating the onset and progression of neurodegenerative diseases.[20] Irisin can also significantly reduce IL-6 levels.IL-6 is an upstream activator of the extracellular signal-regulated kinase (ERK) and signal transducer and activator of transcription 3 (STAT3) signaling pathways. By inhibiting IL-6/ERK signaling, irisin decreases STAT3 signaling, thereby enhancing the activity/levels of neprilysin (NEP), playing an anti-inflammatory role.[30] Irisin can increase the production of anti-inflammatory cytokines, reduce the migration and proliferation of macrophages by affecting their activation state, and also inhibit the activation of TLR4, MyD88, NRF2, and AMPK, subsequently suppressing the activation of the pro-inflammatory transcription factor NF-κB. It may also exert regulatory effects during inflammatory processes by aiding in the prevention of inflammasome formation and the inhibition of increased vascular permeability.[31] Numerous studies have shown that irisin plays a role in promoting energy expenditure, improving metabolic health, modulating inflammatory responses, enhancing neuroprotection, and various physiological processes related to exercise and aging, and is closely associated with the progression of malignant tumors.[4,32]

The Role of Irisin in Tumors

Irisin influences the biological behavior of tumor cells by activating or inhibiting specific signaling pathways that play a crucial role in the occurrence and development of cancer. Primarily, irisin suppresses the epithelial-mesenchymal transition (EMT) by modulating signaling pathways, acting on transcription factors, and affecting the expression of EMT markers, thereby inhibiting the proliferation, migration, and invasion of tumor cells. EMT refers to the biological process by which epithelial cells undergo a specific program to transform into cells with a mesenchymal phenotype, an important biological process for epithelial-derived malignant tumor cells to acquire the ability to migrate and invade, mainly occurring during embryonic development, wound healing, and tumor metastasis.[33–37] Additionally, irisin can affect the development process of tumors by regulating the tumor microenvironment.

Irisin and the PI3K/AKT Pathway

The PI3K/AKT pathway is a crucial intracellular signaling pathway in mammalian cells that regulates a variety of biological processes, playing a key role in cell survival, proliferation, metabolism, and angiogenesis.[38,39] In cancer cells, the abnormal

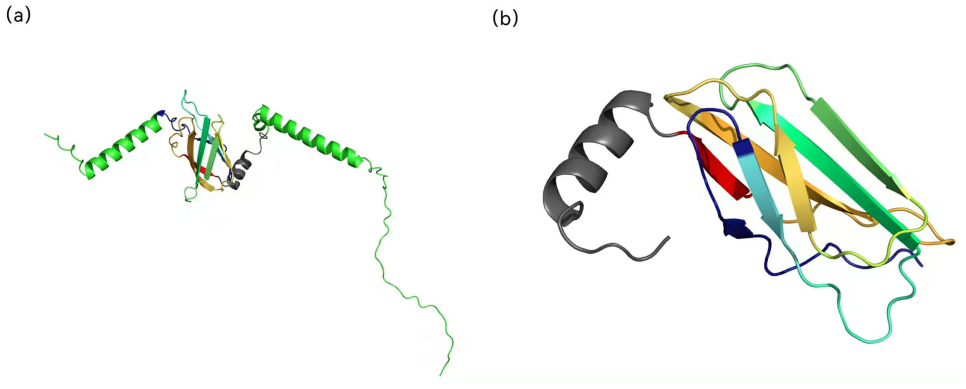


Figure 1 Protein Structures of FNDC5 and Irisin. Panel (**a**) shows the protein structure encoded by the FNDC5 gene, with the excised irisin structure highlighted in different colors, and the monomer structure of irisin is separately presented in Panel **(b)**. The FNIII domains are colored, and the linker between the FNIII domain and the transmembrane helix is shown as a non-structured coil. Panels (**a**) and (**b**) were constructed in PyMOL (PyMOL Molecular Graphics System, Version 3.0).

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activation of the PI3K/AKT pathway can promote glucose uptake and glycolysis, providing the necessary energy and biosynthetic precursors for tumor cells, thus facilitating the growth and spread of tumors. Furthermore, the activation of AKT is also associated with the metabolic reprogramming of tumor cells, promoting the synthesis of acetyl-CoA, which in turn affects the acetylation state of histones, playing a key role in the proliferation and survival of tumor cells.[40]

Irisin suppresses PI3K/AKT pathway phosphorylation through tissue-specific receptor activation patterns and oxidative stress-dependent signaling remodeling, downregulating downstream cell cycle proteins such as Cyclin D1 to block tumor cell transition from G1 to S phase. This is exemplified in cervical cancer HeLa cells where irisin treatment paradoxically increases p-AKT and Cyclin D1 expression, promoting proliferation; however, AKT inhibitor co-treatment reverses this effect by elevating G1-phase cell proportion, reducing S-phase percentage, and suppressing proliferation. This functional dichotomy stems from irisin's context-dependent duality: in normal tissues (eg, skeletal muscle, pancreatic β-cells), it activates PI3K/AKT via integrin αV/β5 binding to enhance metabolic adaptation and cell survival,[41] whereas in high-oxidative-stress tumor microenvironments (eg, triple-negative breast cancer), irisin induces NOX4/ROS complex formation to inhibit PI3K/AKT phosphorylation through: 1) TXNIP-mediated PP2A phosphatase activation, wherein ROS bursts trigger thioredoxin-interacting protein (TXNIP) dissociation to activate PP2A for direct dephosphorylation of AKT at Ser473;[42,43] 2) IRS-1/JNK signaling axis dysregulation, where inflammatory factors (eg, TNF-α) enable irisin to potentiate JNK-mediated IRS-1 phosphorylation at Ser307, blocking PI3K-IRS-1 interaction;[44] and 3) disruption of the E2F4-PI3K feedback loop, observed in pancreatic cancer where irisin-induced CRL4 ubiquitin ligase degrades E2F4 to relieve transcriptional repression of PI3K catalytic subunit p110δ (a mechanism that fails in E2F4-deficient tumors, permitting sustained pathway activation).[45] Thus, irisin exhibits bidirectional regulation: activating PI3K/AKT to promote metabolism physiologically while exerting dominant inhibitory effects in tumors, with this functional switch critically dependent on tissue-specific variations in oxidative stress gradients, inflammatory profiles, and epigenetic modifications within the microenvironment.

Irisin and the AMPK-mTOR Pathway

The AMPK/mTOR pathway is extensively involved in processes such as cell proliferation and migration and is associated with the occurrence and development of various tumors.[46] Studies have indicated that irisin can suppress epithelial-mesenchymal transition (EMT) and the migration and invasion of pancreatic cancer cells by activating the AMPK-mTOR pathway. Activation of the AMPK (AMP-activated protein kinase) pathway by irisin can enhance the control of tumor cell metabolism, and the inhibition of mTOR (mammalian target of rapamycin) signaling may restrict the abilities of tumor cells to proliferate, migrate, and invade. Liu J et al confirmed that irisin also reverses EMT activity by upregulating the expression of E-cadherin and downregulating the expression of vimentin, thereby inhibiting the migration and invasion of pancreatic cancer cells.[47]

Irisin, an exercise-induced myokine, activates AMPK via binding to the transmembrane receptor integrin αV/β5, initiating LKB1-dependent phosphorylation of AMPK at Thr172.[48–50] This process involves the LKB1-STRAD-MO25 complex that directly catalyzes AMPKα subunit phosphorylation, whereas under calcium-signaling conditions, irisin alternatively induces Thr172 phosphorylation through a CaMKKβ-dependent pathway.[51–53]

Activated AMPK orchestrates metabolic reprogramming by sensing elevated AMP/ATP ratios to suppress anabolic pathways (eg, glycolysis and lipogenesis) while stimulating catabolic processes such as fatty acid β-oxidation.[54,55] Concomitantly, AMPK phosphorylates and inhibits Acetyl-CoA Carboxylase (ACC) to repress de novo fatty acid synthesis, while its suppression of mTORC1 signaling attenuates glycolytic flux and protein translation, thereby disrupting bioenergetic supply essential for tumor progression.[56–58]

The AMPK-mTORC1 axis is bidirectionally regulated through dual inhibitory mechanisms: AMPK suppresses mTORC1 activity both by phosphorylating TSC2 to enhance its GTPase-activating protein (GAP) function toward Rheb, thereby preventing mTORC1 lysosomal translocation,[59,60] and by directly modifying the Raptor subunit via phosphorylation-induced conformational changes that impair mTORC1 kinase activity.[61] These coordinated actions trigger profound biological consequences—concomitantly activating autophagy through relieving mTORC1-mediated suppression of the ULK1 complex to initiate autophagosome formation (facilitating clearance of damaged organelles and maintenance of redox homeostasis),[62]

while suppressing anabolic processes via translational repression of key transcription factors including SREBP1 for lipogenesis and HIF-1α for glycolytic flux, ultimately attenuating tumor biosynthetic demands.[63–65]

Irisin and the STAT3/Snail Pathway

STAT3 is a transcription factor that responds to signals from various cytokines and growth factors, thereby regulating the expression of downstream genes. The persistent abnormal activation of STAT3 is associated with the progression, metastasis, and immune evasion of various tumors. Particularly in the tumor microenvironment, the activation of STAT3 can promote the proliferation, survival, and angiogenesis of tumor cells.[66] Snail is a transcriptional repressor that promotes the occurrence of EMT by suppressing the expression of epithelial markers such as E-cadherin. The upregulation of Snail expression is a hallmark of EMT and is closely related to the invasiveness and metastatic potential of tumor cells.[67] Persistent activation of STAT3 serves as a pivotal driver of epithelial-mesenchymal transition (EMT) in malignancies. Inflammatory cytokines such as IL-6 induce tyrosine phosphorylation of STAT3 at Tyr705, facilitating its dimerization, nuclear translocation, and binding to the γ-activated sequence (GAS) element within the Snail promoter.[68,69] This direct transcriptional upregulation of Snail, a zinc-finger transcriptional repressor, orchestrates EMT by suppressing E-cadherin expression and inducing mesenchymal markers (eg, Vimentin, N-cadherin).[70,71] Clinically, metastatic breast cancer patients exhibit a positive correlation between STAT3 and Snail co-expression, EMT phenotypes, and circulating tumor cells (CTCs).[72,73]

Furthermore, STAT3 synergistically amplifies EMT through crosstalk with the TGF-β/Smad3 pathway. Phosphorylated STAT3 (pTyr705) enhances the kinase activity of TGF-β receptor type I (TβRI), promoting carboxyl-terminal phosphorylation of Smad3 (pSmad3C). The resultant STAT3/pSmad3C transcriptional complex co-occupies the Snail promoter, elevating its transcriptional efficiency by 3.5-fold compared to either pathway alone.[74] In lung cancer models, combined IL-6 and TGF-β1 treatment induces markedly stronger EMT than either cytokine individually, an effect dependent on STAT3-Smad3 physical interaction.[75–77]

Irisin can indirectly inhibit excessive STAT3 activation by activating upstream regulators. Evidence suggests that irisin boosts PPARδ/SIRT1 pathway expression, suppressing STAT3 phosphorylation and transcriptional activity. For instance, in high-fat-induced skeletal muscle cells, irisin analogs like IL-38 leverage the PPARδ/SIRT1 axis to reduce STAT3 phosphorylation. This, in turn, mitigates STAT3-mediated inflammatory responses and oxidative stress, improving insulin resistance.[78,79] In addition, in astrocytes, irisin downregulates the ERK-STAT3 cascade, curbing amyloid-β (Aβ) accumulation and underscoring its direct negative regulation of STAT3 signaling.[11,80,81]

STAT3, acting as a transcription factor, directly binds to the promoter region of the Snail gene and activates its expression, thereby promoting the EMT process. Irisin, however, inhibits the nuclear translocation and DNA-binding ability of STAT3, thus blocking its transcriptional regulation of Snail.[11] In esophageal squamous cell carcinoma (ESCC) studies, both gene silencing and pharmacological inhibition of STAT3 markedly cut Snail expression, thus curbing EMT and tumor metastasis.[82] Irisin may interfere with the STAT3/Snail axis via a similar mechanism, yet specific experimental evidence remains to be further explored.

Irisin also activates pathways such as AMPK/PI3K-AKT to antagonize STAT3. In vascular smooth muscle cells (VSMCs), irisin inhibits PDGF-BB-induced phenotypic switching via a STAT3-dependent mechanism, thereby blocking the transition to a synthetic, proliferative, and migratory phenotype. This involves dynamically balancing STAT3 activity, not just simple inhibition. Irisin's activation of AMPK/PI3K-AKT pathways further antagonizes STAT3.[83] This indicates that irisin's impact on STAT3 is context - dependent. In pathologically overactivated states like cancer or metabolic disorders, irisin inhibits STAT3. But during physiological repair, it may transiently enhance STAT3 activation (Figure 2).

Irisin and the ERK/MAPK Signaling Pathway

In oral squamous cell carcinoma induced by TNF-α, the activation of the MAPK signaling pathway is associated with reduced expression of EMT markers E-cadherin and Claudin-1. The use of inhibitors targeting the MAPK signaling pathway can increase the expression of these markers and decrease the invasive and metastatic capabilities of cancer cells.[84] Irisin modulates the proliferation and apoptosis of tumor cells by affecting the ERK/MAPK signaling pathway. The specific

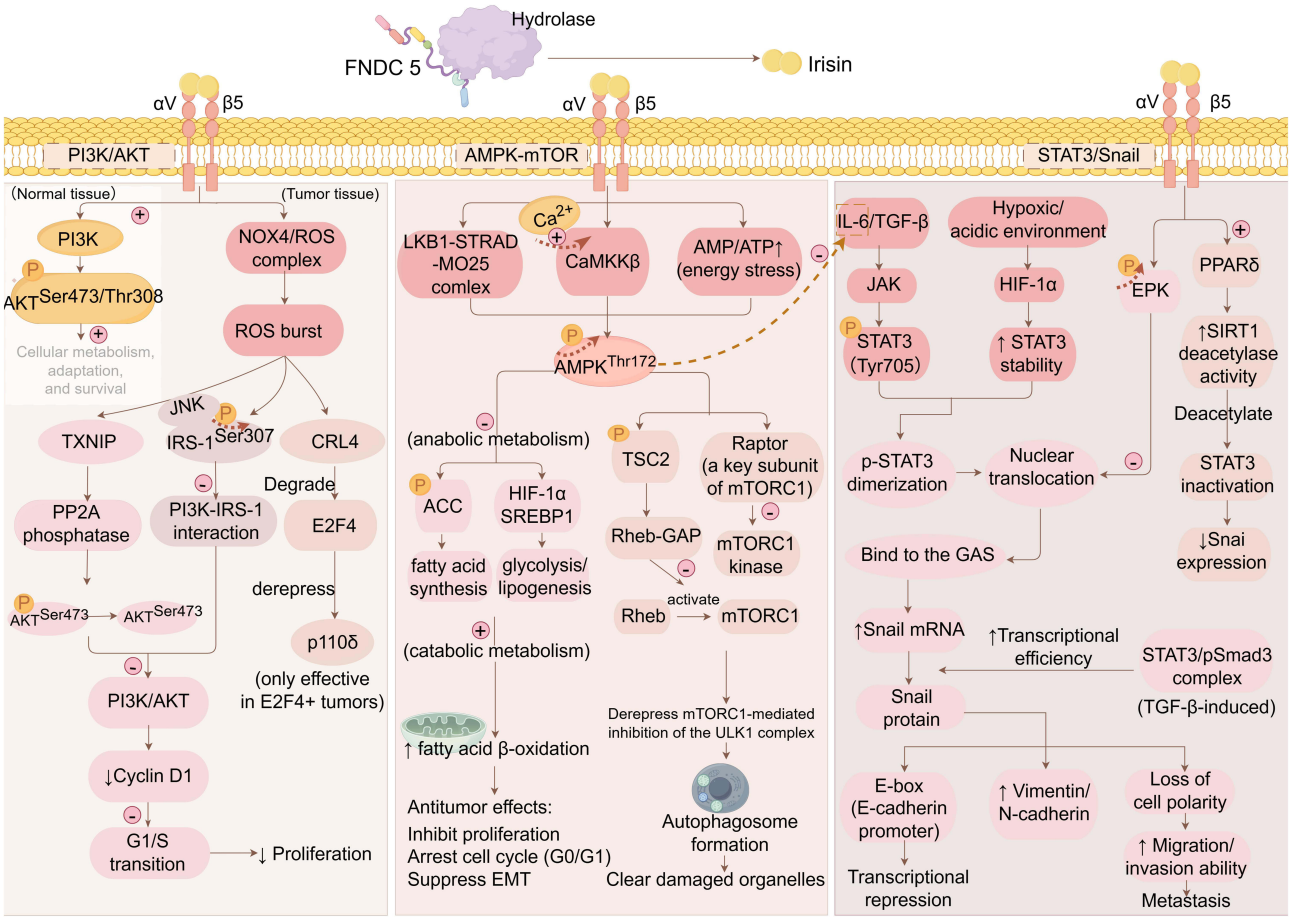

Figure 2 Dual Regulatory Effects of Irisin on Tumor Progression. Irisin modulates tumor progression via distinct signaling cascades: (1) PI3K/AKT: Integrin αVβ5 binding activates PI3K/AKT in normal tissues. Under tumor oxidative stress, irisin triggers NOX4/ROS→TXNIP→PP2A→IRS-1/JNK signaling to inhibit AKT-Ser473 phosphorylation, suppressing Cyclin D1 and G1/S transition; aberrant PI3K/AKT activation promotes proliferation/migration in hepatocellular carcinoma. (2) AMPK-mTOR: During energy stress, irisin activates AMPK (via LKB1-STRAD-MO25/CaMKKβ), phosphorylating TSC2/Raptor to inhibit mTORC1. This suppresses anabolic metabolism (glycolysis, lipogenesis), enhances catabolism (β-oxidation), and induces ULK1-mediated autophagy/G0-G1 arrest (eg, pancreatic cancer). (3) STAT3/Snail: Irisin upregulates PPARδ/SIRT1, suppressing STAT3-Tyr705 phosphorylation to inhibit dimerization, nuclear translocation, Snail promoter binding, and STAT3/pSmad3 complex formation. This downregulates Snail, inhibiting EMT (↑E-cadherin; ↓N-cadherin, vimentin), migration, and metastasis (eg, lung cancer, osteosarcoma). Pathway outcomes are dictated by tumor microenvironment and tissue specificity. ↑ indicates upregulation/increase; ↓ indicates downregulation/decrease. By FigDraw.

mechanisms involve activation or inhibition of various components within the ERK/MAPK signaling pathway, such as Raf, MEK, and ERK, thereby influencing the biological behavior of tumor cells. Irisin not only directly affects tumor cells but may also indirectly influence tumor development by modulating other cells and molecules in the tumor microenvironment, such as immune cells and cytokines. The regulatory role of the MAPK/ERK signaling pathway in the tumor microenvironment may be related to these indirect effects of irisin. Irisin holds promise as a potential target for cancer therapy. Modulating the levels of irisin or its signaling pathways may contribute to the inhibition of tumor occurrence and development.[13]

Irisin and Other Signaling Pathways

Beyond the pathways detailed above, irisin modulates additional oncogenic cascades. Its inhibitory impact on tumor progression is prominently mediated by suppression of the Wnt/β-catenin signaling pathway. As demonstrated in colorectal cancer models, irisin downregulates critical downstream oncogenic targets of this pathway, including c-Myc and cyclin D1, leading to suppressed tumor cell proliferation and induction of apoptosis.[85] Furthermore, irisin modulates Wnt/β-catenin-dependent malignant behaviors, specifically inducing G0/G1 phase cell cycle arrest to prevent S-phase entry and inhibit proliferation, while also attenuating cancer stem cell properties.[86] Concurrently, irisin effectively attenuates NF-κB signaling pathway activation. This suppression reduces the production of pro-inflammatory cytokines (eg, IL-6, TNF-α) and chemokines that

facilitate tumor growth and metastasis.In breast cancer models, this NF-κB inhibition mitigates tumor-associated inflammation, enhances tumor cell apoptosis, and reduces apoptotic resistance, contributing to irisin's overall antitumor efficacy.[87,88]

Irisin and the Tumor Microenvironment (TME)

The tumor microenvironment (TME) is composed of various cell types, including immune cells, tumor-associated fibroblasts (CAFs), and endothelial cells, which influence tumor development through intercellular communication. Tumor cells adapt to the nutrient-deprived conditions in the TME through metabolic reprogramming, such as increasing glycolysis and fatty acid oxidation to meet their energy demands. Angiogenesis within the TME supplies the tumor with essential oxygen and nutrients and also promotes tumor invasion and metastasis.[89,90]

The impact of irisin on immune cells, particularly regulatory T cells (Treg) and dendritic cells, within the TME is an important mechanism for regulating the tumor immune response. Treg cells exert an inhibitory effect within the TME by expressing immunosuppressive molecules such as CTLA-4 and PD-1, affecting the immune surveillance and the efficacy of immunotherapy.[91,92] Dendritic cells, especially mature dendritic cells (mregDC), may interact with Treg cells to promote their activation and immunosuppressive functions, potentially mediated by specific chemokines and receptors such as CCL22/17-CCR4.[93] Irisin may alter the spatial distribution of these cells within the TME by modulating the expression and functional state of these cell surface molecules, thereby affecting tumor immune evasion and progression.

Irisin can reduce the infiltration of inflammatory cells in the alveoli and the secretion of pro-inflammatory factors, such as inhibiting the production of IL-1β, IL-18, and tumor necrosis factor-α induced by lipopolysaccharide (LPS).[94] Furthermore, irisin may also affect the inflammatory cytokine network within the TME, such as IL-1, IL-6, IL-12, IL-17, TNF-α, and TGF-β. These factors not only recruit inflammatory cells to the tumor site and amplify inflammatory effects but also promote tumor cell growth, metastasis, and the formation of blood and lymphatic vessels.[32] These actions of irisin may give it potential positive effects in tumor immunotherapy, enhancing the efficacy of immunotherapy by modulating immune cells and inflammatory factors within the TME.[32]

Tumor angiogenesis is a key step in tumor growth and metastasis, and irisin, as a potential regulatory factor, may regulate the vascular supply of tumors by affecting the function of vascular endothelial cells.[4] Angiogenesis involves the complex process of generating new blood vessels from existing ones, promoted by various growth factors and cytokines such as VEGF and FGF, and regulated by enzymatic substances like matrix metalloproteinases. The TME plays a crucial role in this process, where hypoxia, acidic environments, and the presence of immune cells can all affect the secretion of angiogenic factors and the function of vascular endothelial cells.[95,96]

Despite recent advances, the precise molecular mechanisms by which irisin modulates immune cell interactions (eg, Treg and dendritic cells) and metabolic crosstalk within the TME remain poorly understood. Further investigations are needed to elucidate how irisin influences chemokine signaling (eg, CCL22/CCL17) and metabolic pathways (eg, AMPK/mTOR) to reshape the immunosuppressive or pro-tumorigenic niche (Figure 3).

Irisin and Tumors

In the extensive research of oncology, the discovery of biomarkers is of significant importance for the early diagnosis of cancer, monitoring of treatment responses, and assessment of prognosis. The latest research has revealed the potential role of irisin in tumor development. Specifically, the association between the changes in serum levels of irisin and tumors offers a new direction for clinical oncological research. In vitro tumor cell studies have shown varying effects of irisin on different types of tumor cells. Irisin induces the proliferation, migration, and invasion of liver cancer cells, while it exhibits inhibitory effects on lung cancer, pancreatic cancer, glioblastoma, breast cancer, prostate cancer, and osteosarcoma tumor cells (Table 1).

Irisin and Liver Cancer

Irisin exhibits opposite effects on liver cancer cells compared to other tumor cells, characterized by its ability to induce the proliferation, migration, and invasion of liver cancer cells. In HepG2 and SMCC7721 liver cancer cells, the expression of irisin is significantly upregulated, and it increases cancer cell proliferation, metastasis, and invasion by activating the PI3K/AKT pathway; moreover, irisin reduces the cytotoxicity of doxorubicin (DOX) to HepG2 cells, thereby decreasing the sensitivity to chemotherapy.[9]

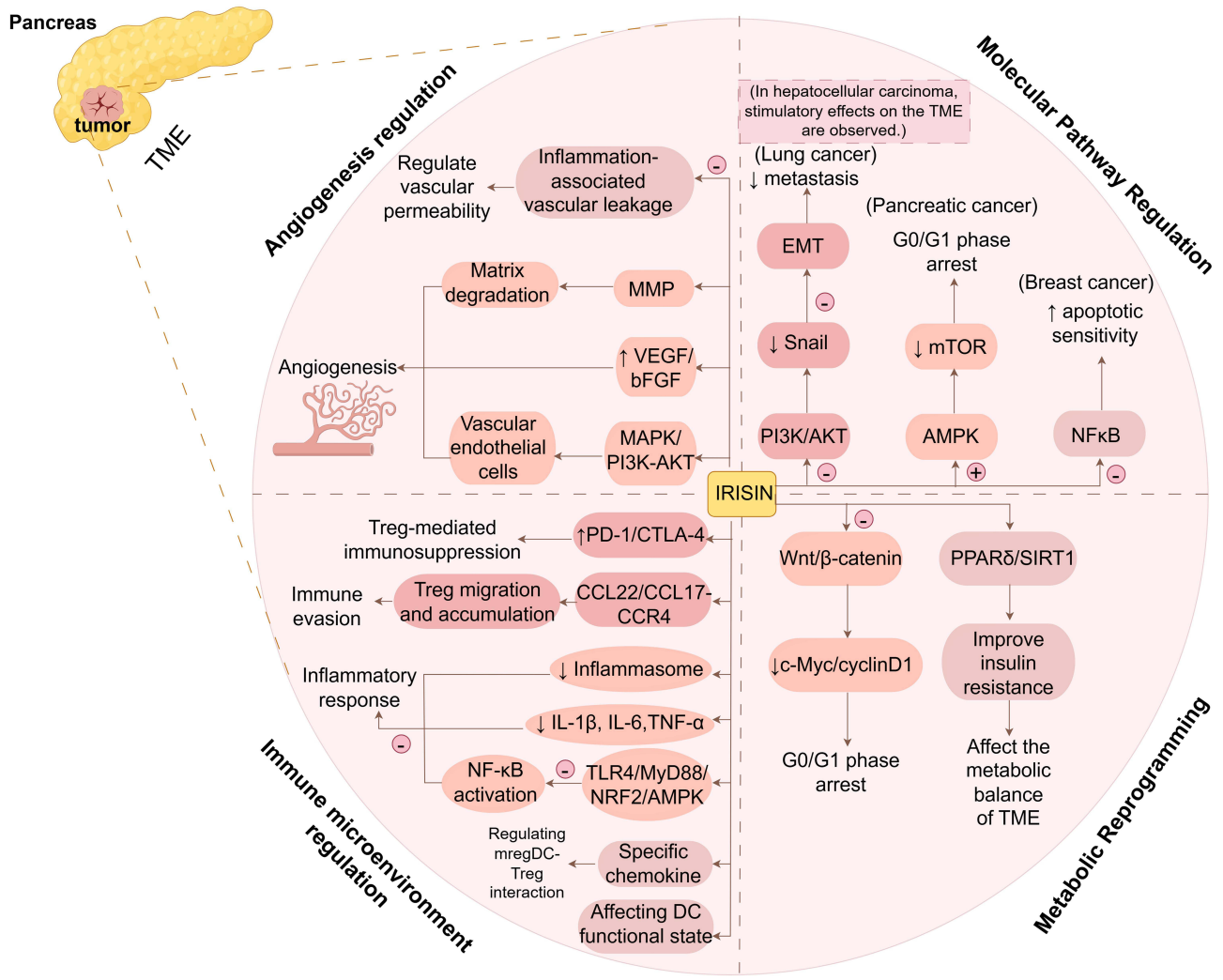

Figure 3 Schematic depicting irisin-mediated regulation of the tumor microenvironment (TME). Key mechanisms include: (1) Immunomodulation promoting Treg recruitment/function (CCR4 axis, PD-1/CTLA-4) and suppressing inflammation (reduced IL-1β/IL-6/TNF-α, inhibited NF-κB/AMPK pathways); (2) Angiogenesis activation via MAPK/PI3K-AKT signaling, enhancing matrix degradation (MMP) and VEGF/bFGF expression while regulating vascular permeability; (3) Metabolic reprogramming inducing cell cycle arrest (Wnt/β-catenin inhibition) and altering TME metabolism (PPARδ/SIRT1 activation). Cancer-specific effects involve G0/G1 arrest in pancreatic cancer (AMPK-mTOR), suppressed metastasis in lung cancer (PI3K/AKT/Snail inhibition), and enhanced apoptosis in breast cancer (NF-κB inhibition), collectively reshaping the immunosuppressive TME. ↑ indicates increase/upregulation; ↓ indicates decrease/downregulation. By FigDraw.

Serum levels of irisin in patients with hepatocellular carcinoma (HCC) are significantly lower than in healthy individuals, and the decline in irisin concentration in the serum of patients with advanced HCC is even more pronounced, showing a negative correlation with the severity of liver dysfunction.[97]

There is no difference in irisin serum levels between liver transplant patients with HCC and healthy donors, but the expression of irisin in liver cells of HCC patients is significantly higher than that in liver cells from healthy donors.[99] Additionally, the expression level of irisin mRNA is strongly transcriptionally associated with genes such as SREBF-1/SCD-1, TNF-α/IL-6, and NOTCH1, which are markers of lipid formation, inflammation, and tumor formation, suggesting that irisin may play a role in these harmful processes.[113] During the progression of liver cancer, the liver's abnormal lipid production increases, and irisin is compensatorily secreted to limit the abnormal lipid production induced by cancer progression.[99] Irisin may have a protective effect against liver damage.

There is still no consensus on the expression level of irisin in hepatocellular carcinoma (HCC). Research by Shi et al indicates that irisin levels are significantly elevated in liver cancer tissues in HepG2 and SMCC7721 liver cancer cells, but serum irisin levels are unaffected.[9] S Aydin's study shows no significant difference in irisin between HCC and normal liver

Table 1 Irisin Expression in Tumor Cells, Tissues, and Serum and Its Mechanism in Tumorogenesis

Tumor Type	Cell/Tissue	Serum	Effect	Mechanism of Action
Liver Cancer	↑/↓/-[9,97,98]	↓ [97] /- [99]	+	Activation of PI3K/AKT pathway; reduction of DOX-induced cytotoxicity in HepG2 cells[9]
Lung Cancer	↑[5,100]	NA	-	Inhibition of PI3K/AKT/Snail pathway; ↓ N-cadherin/vimentin; ↑ E-cadherin[38,100]
Breast Cancer	↑[98,101]	↓ (metastasis risk)[47] / ↑ (diagnostic)[102]	-	Caspase activation; NF-κB inhibition; ↑doxorubicin sensitivity[87]
Prostate Cancer	NA	↓[103] / - (Gleason grade)[104]	-	Androgen receptor-independent cytotoxicity[103]
Pancreatic Cancer	NA	NA	-	AMPK-mTOR activation (G0/G1 arrest); PI3K/AKT suppression[47,105]
Bladder Cancer	NA	↓ (NMIBC/MIBC)[106]	-	Potential integrin αV/β5 modulation[17]
Renal Cell Carcinoma	↓[107]	↑[108]	-	Diagnostic cutoff >105 pg/mL [108]
Osteosarcoma	↓[109]	↓[109]	-	STAT3/Snail inhibition; suppression of IL-6-induced EMT[11]
Glioblastoma Multiforme	NA	NA	-	G2/M arrest; ↑ p21 and TFPI-2[110]
Gastrointestinal Cancer	↑[98,111]	↓(Colorectal cancer);[47] ↑ (Gastric cancer)[111]	-	ATP synthesis inhibition; thermogenesis[98]
Thyroid Cancer	↑[98,112]	NA	-	Mitochondrial-rich cell-specific effects[98,112]

Notes: In the mechanism of action, "NA" is utilized to denote instances where a specific mechanism has not been elucidated or where corresponding research has not been identified. However, this does not preclude the existence of a general mechanism by which irisin may influence tumor biology. "↑" indicates increase/upregulation; "↓" indicates decrease/downregulation; "-" indicates no difference.

tissues.[98] In contrast, Zhang's research suggests that irisin expression is downregulated in liver cancer tissues compared to healthy tissues.[97] Currently, there is no reasonable explanation for these divergent conclusions. One explanation for why irisin levels do not increase in liver cancer may be that irisin inhibits gluconeogenesis,[114] the liver being an organ that produces glucose, which provides energy for cancer cells (Warburg effect).[98] If irisin levels were elevated in liver cancer, the energy reserve would decrease, which may be the reason why irisin levels do not increase in liver cancer.[113]

Irisin and Lung Cancer

Non-small cell lung cancer (NSCLC) represents 80% of all lung cancers and is among the malignancies with the most adverse prognosis. Adenocarcinoma (AC) and squamous cell carcinoma (SCC) are the two most significant subtypes of NSCLC.[115] There is a disparity in the distribution of irisin within the lungs; it is expressed in pulmonary macrophages, while normal lung parenchymal epithelial cells lack irisin expression. The expression levels of irisin vary among NSCLC subtypes, with higher expression in AC tumor cells compared to SCC tumor cells, and lower expression in the stromal cells of AC tumors compared to SCC stromal cells.[5] Studies utilizing laser capture microdissection to isolate cancer and stromal cells from NSCLC patients, followed by tissue microarray and immunohistochemical analysis to assess irisin expression, have observed for the first time an elevated expression of irisin in both cancer cells and stromal fibroblasts within the tumor tissue of NSCLC patients. This increase may foster the proliferation of cancer cells and could serve as an independent prognostic factor for NSCLC patients.[5]

Irisin is highly expressed in tumor stromal cells with extensive invasion and high malignancy; conversely, its expression is lower in tumor cells with higher malignancy and later pathological staging.[11] In tumor stromal cells, irisin may promote the formation and proliferation of lung cancer, while in cancer cells, it may inhibit cancer progression.[5,100] L. Shao et al have discovered that irisin inhibits the epithelial-mesenchymal transition (EMT) by suppressing the PI3K/AKT/Snail pathway, thereby reducing the invasiveness of lung cancer cells.[100]

Experiments have indicated that irisin can also decrease the expression of mesenchymal markers such as N-cadherin and vimentin in lung cancer cells and increase the expression of the epithelial marker E-cadherin in a concentration-dependent manner. The administration of a PI3K inhibitor has reversed the irisin-induced expression of E-cadherin and the suppression of N-cadherin and vimentin in lung cancer cells.[38]

Irisin and Breast Cancer

Irisin significantly reduces the number, metastasis, and viability of breast cancer cells without affecting normal mammary cells. The mechanism may involve irisin activating caspases to induce apoptosis in cancer cells. Additionally, irisin may improve the therapeutic effect of breast cancer treatment by enhancing the tumor's sensitivity to anticancer drugs, such as doxorubicin, through its anti-inflammatory response, inhibition of NF-κB activation, suppression of inflammatory factors, and induction of apoptotic cell death.[87]

In women who exercise regularly, serum irisin levels are significantly increased, reducing the risk of breast cancer by 30–40%. Moreover, for each unit increase in irisin, the incidence rate of breast cancer decreases by nearly 90%.[116,117] Irisin may exert a protective effect on patients with breast cancer through its antitumor cell proliferation, pro-apoptotic, antiestrogenic, and anti-inflammatory properties.[118–120] Serum irisin levels are also correlated with tumor metastasis; patients with higher serum irisin levels have a nearly 20% reduced likelihood of spinal metastasis.[47] Irisin can inhibit the differentiation of osteoclasts, promote the differentiation of osteoblasts, prevent bone loss, and thereby decrease the incidence of breast cancer metastasis.[121–123]

In various types of breast cancer tumor tissues, such as infiltrating lobular carcinoma, intraductal papilloma carcinoma, infiltrating ductal carcinoma, infiltrating papillary carcinoma, and mucinous carcinoma, the expression of irisin is significantly higher than in healthy individuals.[98] Compared with patients with normal BMI, obese breast cancer patients have increased expression of irisin in tumor tissues, which may be related to irisin's inhibition of ATP synthesis and promotion of heat production, thereby limiting cancer cell division and promoting cancer cell death.[101] Grigorios et al assessed the levels of omentin-1 and irisin in women with benign and/or malignant breast tumors and found that serum irisin levels were increased in both benign and malignant breast tumors compared to the healthy control group, suggesting that irisin may serve as a potential diagnostic and prognostic marker for malignant breast tumors.[102]

Irisin and Prostate Cancer

To assess the impact of irisin on the viability of human prostate cancer cells, Suat Tekin et al treated androgen receptor-positive (LNCaP) and androgen receptor-negative (DU-145, PC3) human prostate cancer cells with 0.1, 1, 10, and 100 nM concentrations of irisin. It was found that physiological (10 nM) and pharmacological (100 nM) concentrations of irisin significantly reduced the cell viability of both androgen receptor-positive (LNCaP) and negative (DU-145, PC3) prostate cancer cell lines in a dose-dependent manner.[103] The cytotoxic effect of irisin on prostate cancer cells may be mediated through a mechanism that is independent of the androgen receptor.

Serum irisin levels in patients with prostate cancer are significantly lower than those in healthy individuals. However, when using the Gleason grading system, there is no significant difference in serum irisin levels between the healthy group and the disease group.[104] Prostate-specific antigen (PSA), both free and total, is significantly higher in patients with prostate cancer compared to healthy individuals and is the most commonly used serum biomarker for the detection of prostate cancer. The overall sensitivity of PSA is 21%, with a specificity ranging from 51% to 91% when the PSA threshold is greater than 4 ng/mL.[124,125] Irisin shows a sensitivity and specificity of 80.5% and 90.0%, respectively, for the diagnosis of prostate cancer, suggesting its potential as an auxiliary biomarker for diagnosing prostate cancer.

Irisin and Pancreatic Cancer

Irisin receptors are present on the surface of pancreatic cancer cells. Irisin induces cell cycle arrest at the G0/G1 Phase In pancreatic cancer cells by activating the AMPK-mTOR signaling pathway and induces G1 phase arrest in a dose-dependent manner, inhibiting the growth of pancreatic cancer cells.[47] It also suppresses multiple cellular processes such as proliferation, differentiation, and survival of pancreatic cancer cells by downregulating the activity of the PI3K/AKT

signaling pathway,[105] and an upregulation of the expression and activity of PI3K and AKT in pancreatic cancer cells is associated with poor prognosis.[126,127]

Irisin inhibits the proliferation, migration, and invasion of pancreatic cancer PANC-1 cells and BxPC-3 cells, and induces apoptosis in BxPC-3 cells in a dose-dependent manner.[7] The effect of irisin on the growth of pancreatic cancer cells also depends on the type of pancreatic cancer cell. The inhibitory effect of irisin on Panc03.27 cells is more pronounced than on MIA PaCa-2 cells, which may be related to differences in gene expression, protein levels, and cellular molecular mechanisms between MIA PaCa-2 and Panc03.27 cells.[128]

Irisin and Bladder Cancer

Research has found that, compared to the healthy control group, the average serum levels of irisin in patients with bladder cancer are significantly reduced (4.53 ± 2.55 vs 16.5 ± 5.67, $p < 0.001$). Furthermore, the serum levels of irisin in patients with muscle-invasive bladder cancer (MIBC) are also lower than those in patients with non-muscle-invasive bladder cancer (NMIBC) (3.19 ± 1.47 vs 5.18 ± 2.73, $p < 0.001$). Serum irisin demonstrates a sensitivity of 86.2% and a specificity of 89.7% in distinguishing patients with bladder cancer from healthy individuals, with an area under the curve (AUC) of 0.859; in differentiating NMIBC from MIBC, the sensitivity is 75%, the specificity is 73.7%, and the AUC is 0.732. This suggests that serum irisin levels have the potential to serve as a biomarker for the diagnosis of bladder cancer and may help to distinguish different grades and stages of the tumor.[106] Although there are no direct research results indicating the specific application of irisin in the treatment of bladder cancer, the mechanisms of action of irisin in other cancer types have been explored. For example, irisin may have a similar regulatory effect in bladder cancer by affecting the biological behavior of tumor cells through its receptor integrin $\alpha V/\beta 5$.[17] Currently, there are no studies investigating the expression levels of irisin in vitro in bladder cancer cells.

Irisin and Renal Cancer

Studies have indicated that the serum levels of FNDC5/Irisin in patients with renal cell carcinoma are significantly higher than those in the healthy control group ($p=0.0001$), suggesting a marked increase of FNDC5/Irisin in the serum of patients with renal cell carcinoma. Measured by the enzyme-linked immunosorbent assay (ELISA) method, the average value of FNDC5/Irisin in patients with renal cancer was 208 pg/mL, compared to 110 pg/mL in the control group. The study also found that the optimal diagnostic cutoff for FNDC5/Irisin is >105 pg/mL, while for CEA it is >2.67 ng/mL, indicating that it has high sensitivity and specificity in the diagnosis of renal cancer and can serve as a diagnostic biomarker.[108]

The expression of irisin in renal cancer varies. In healthy tissues, irisin is expressed in the proximal and distal tubules, with no expression observed in the glomeruli. Irisin expression is absent in Fuhrman grades 1, 2, and 3 clear cell renal cell carcinoma (RCC) and papillary RCC, and is expressed in only 2% of Fuhrman grade 4 renal cell carcinomas. Benign renal tumors such as oncocytomas express irisin. The expression of irisin may be utilized to differentiate renal cancer from benign renal conditions.[107]

Irisin and Glioblastoma Multiforme, Osteosarcoma

Glioblastoma multiforme (GBM) is the most common aggressive glial tumor with a poor prognosis. Chiun-Wei Huang and et al have found that irisin effectively inhibits the proliferation, invasion, and growth of GBM cells. It arrests GBM cells in the G2/M phase and elevates the levels of p21, a negative regulator of the cell cycle, thereby inhibiting cell proliferation. Additionally, irisin upregulates TFPI-2, a serine protease inhibitor that suppresses tumor metastasis, thereby inhibiting the invasion of GBM. Irisin can also decelerate the growth of GBM, and radiolabeled irisin has specific tumor-targeting capabilities in vivo, accumulating only in adipocytes near the tumor, especially around the invasive areas. This suggests the potential of irisin to develop into a molecular imaging and therapeutic anticancer drug.[110] For glioblastoma, although there are currently no specific data on the expression levels of irisin, given the research findings of irisin in other cancer types, it may also play a role in GBM. Future studies may reveal the specific role of irisin in the development of GBM and its potential as a therapeutic target or biomarker.

Irisin plays an important role in bone metabolism, specifically in promoting bone formation, protecting bone cells from induced apoptosis, preventing the loss of bone and muscle mass, and accelerating fracture healing. To explore the

impact and mechanism of irisin on the migration and invasion of osteosarcoma cells, Kong and et al discovered that irisin inhibits the proliferation, migration, and invasion of osteosarcoma cells. Further research suggests that irisin may suppress the EMT induced by IL-6 in osteosarcoma cells through the inhibition of the STAT3/Snail signaling pathway, thereby playing a significant antitumor role.[11] In patient serum, irisin levels are decreased. Compared to normal tissue, osteosarcoma cell tissue also exhibits a reduction in irisin levels.[109]

Irisin and Other Cancers

Serum irisin levels in patients with colorectal cancer are significantly lower than those in healthy individuals, and serum irisin levels are negatively correlated with the condition of colorectal cancer, suggesting that irisin may be an important protective factor against colorectal cancer.[47] However, in patients with gastric cancer, serum irisin levels are significantly higher than those in healthy individuals.[111] Except for liver cancer, gastrointestinal system tumor tissues highly express irisin,[98] possibly because: (1) the increase of irisin in cancer tissues may inhibit the synthesis of ATP, thereby controlling cell division; (2) the increase of irisin reduces the production of ATP but generates more heat, which may help kill cancer cells.

Irisin is present in the follicular cells of normal thyroid tissue, and the content of irisin varies in different thyroid tumor tissues.[129] Irisin is not detected in medullary thyroid carcinoma (MTC) tissues; papillary thyroid carcinoma and follicular thyroid carcinoma tissues express irisin, and the content of irisin significantly increases in oncocytic variant papillary thyroid carcinoma tissues and follicular thyroid carcinoma tissues. More than 75% of oncocytic cells show a structure similar to mitochondria-rich Hurthle cells, which can synthesize more ATP.[112,113,130] In oncocytic variant cancer tissues of the thyroid, the expression of irisin increases, inhibits ATP synthesis, promotes heat production, and restricts the growth of cancer cells; papillary and follicular thyroid cancer tissues have less mitochondrial content and less expression of irisin, resulting in less local heat production, and papillary and follicular thyroid cancers are more aggressive tumors.[98,112,130] However, some studies have reported opposite results, suggesting that oncocytic variant papillary and follicular thyroid cancers have a stronger invasiveness than thyroid cancers without oncocytic changes.[131] Currently, there are no studies on the expression levels of irisin in vitro in thyroid tissues or cells.

Irisin at physiological and pharmacological concentrations does not affect the proliferation of endometrial (KLE and RL95-2), colon (HT29 and MCA38), thyroid (SW579 and BHP7), and esophageal (OE13 and OE33) cells, and does not regulate cell adhesion and/or colony formation in a dose-dependent manner, according to Moon HS et al.[132] These findings highlight the diverse in vitro effects of irisin on different cancer cells, indicating that its potential antitumor properties require further in-depth research.

However, The inherent flaws of the widely used enzyme-linked immunosorbent assay (ELISA) and cell-based detection methods, as systematically reviewed by Steffen Maak et al, have been brought to light. These antibody-dependent techniques are prone to cross-reactivity and interference from endogenous antibodies in samples, resulting in reduced sensitivity, compromised specificity, and irreproducible results. Such technical variabilities not only mask the pathophysiological significance of irisin but also introduce confounding biases in studies exploring its association with disease progression or treatment responses.[16,42] Therefore, before investigating the effects of irisin on tumors, it is essential to establish unified and standardized detection methods for irisin to ensure the reliability and reproducibility of research findings and to accurately elucidate its genuine role within the tumor microenvironment.

The Potential of Irisin as an Anti-Tumor Agent

Expression of irisin is reduced in non-small cell lung cancer (NSCLC) cell lines, and further downregulated in paclitaxel-resistant cells.[133] Irisin increases the sensitivity of paclitaxel-resistant NSCLC cell lines to paclitaxel by downregulating the multidrug resistance protein 1 (MDR1). Further research has found that irisin improves the sensitivity of NSCLC cells to paclitaxel by inhibiting the NF-κB/MDR1 signaling pathway, which may present a new target for the treatment of NSCLC. Similarly, irisin enhances the sensitivity of breast cancer cells to doxorubicin.[87] The addition of irisin to breast cancer MDA-MB-231 cells enhances the cytotoxic effects of doxorubicin, while the same result is not observed in non-malignant MCF-10a cells. However, the effect of irisin on the sensitivity of human liver cancer cells (HepG2) to doxorubicin is different; Irisin reduces the cytotoxicity of Dox to HepG2 cells through the PI3K/AKT pathway, thereby

reducing the sensitivity to chemotherapy.[9] Irisin can regulate multiple pathways related to the process of tumorigenesis and holds promise as a novel therapeutic agent for the treatment of cancer.

The Dual Nature of Irisin in Anti-Cancer Processes

Cachexia is a secondary systemic metabolic disorder triggered primarily by cytokines released by tumor cells and the host. It is estimated that 50% to 80% of cancer patients will experience cancer cachexia, characterized by irreversible weight loss. Recent studies have indicated that changes in the gene expression of mitochondrial membrane uncoupling proteins in cancer cells are one of the significant causes of the markedly increased basal metabolic rate in cancer patients.[134] Concurrently, Lipolysis-Stimulated Lipoprotein, Lipolysis-Stimulated Lipokine (LSL), and Zinc-alpha-2-glycoprotein have also been found to directly promote the breakdown and destruction of adipose tissue, thereby exacerbating the symptoms of cachexia.[135,136]

It is noteworthy that gastrointestinal system tumor tissues commonly overexpress irisin, a finding that has attracted extensive attention from researchers and has been closely linked to the high incidence of cachexia in upper digestive tract tumors. Irisin, as a molecule with unique functions, can reduce the production of ATP necessary for the survival and proliferation of cancer cells while converting it into a large amount of heat. This mechanism has a dual effect in biology: on the one hand, it may induce or exacerbate the symptoms of cachexia because the energy supply of cancer cells is limited, leading to an overall metabolic imbalance in the body; on the other hand, due to the intolerance of cancer cells to high-temperature environments, this characteristic of irisin provides certain potential for its application in the field of anti-cancer.[98]

In light of the potential link between cachexia and the fat-destructive effects of irisin, researchers have begun to explore the possibility of using irisin antagonists to prevent cachexia. However, this strategy is not without risks. Since irisin has certain advantages in controlling the division of cancer cells, the use of antagonists may weaken this anti-cancer effect, posing a therapeutic dilemma. How to maintain the anti-cancer activity of irisin while effectively combating cachexia has become a key issue that needs to be resolved. It requires the development of new therapeutic strategies that can balance its anti-cancer effects and potential side effects based on a deeper exploration of the mechanism of action of irisin. This necessitates not only a more in-depth understanding of the biological functions of irisin but also extensive exploration and research in drug design and clinical trials.[137]

The dual role of irisin reflects the complexity of tumor-host interactions. Its clinical application must transcend the traditional binary thinking and move toward precise spatiotemporal regulation and multidimensional intervention strategies. Only through interdisciplinary collaboration (eg, metabolomics, pharmaceutical engineering, and clinical oncology) can a win-win outcome of enhanced anti-cancer efficacy and improved quality of life be achieved, thereby providing cancer patients with more sustainable treatment options.

Clinical Applications and Technological Challenges

Anti-Tumor Strategies with Derivatives

Irisin and its derivatives offer promising new anti-tumor strategies. For example, Irisquinone (Irisin quinone) targets and inhibits thioredoxin reductase (TrxR), inducing ROS-mediated apoptosis and pyroptosis, thereby enhancing radiotherapy sensitivity in lung and esophageal cancers.[138] Additionally, Erianin analogs suppress melanoma metastasis by inhibiting the VEGF-α/PI3K/AKT pathway, with mechanisms overlapping with those of irisin.[139] Development of these derivatives expands irisin's cancer treatment applications and provides new approaches to overcome tumor drug resistance.

Diagnostic Applications

Irisin's varying expression levels across multiple tumors indicate its potential as a biomarker. Currently, serum ELISA (eg, for cervical and breast cancers) and tissue mRNA detection (eg, for lung cancer) are primary detection methods. Developing novel, highly specific and sensitive detection technologies like mass spectrometry-based absolute quantification can improve irisin detection accuracy. However, significant differences in irisin expression patterns among tumor types (eg, low in breast cancer vs high in cervical cancer) pose challenges for diagnostic reagent development.[5,15,87,117,140] Future research should focus on optimizing detection methods, improving specificity and sensitivity, and establishing unified standards to ensure reliable clinical applications.

Therapeutic Target Translation

Irisin has shown potential as an anti-tumor therapeutic target by inhibiting tumor cell proliferation and invasion through modulating multiple signaling pathways, such as PI3K/AKT, AMPK-mTOR, and STAT3/Snail.[141] Developing irisin pathway modulators for different cancers (eg, activators for lung cancer and inhibitors for cervical cancer) is a crucial future direction.[141,142] Moreover, combination therapy of irisin with immune checkpoint inhibitors (eg, PD-1) also holds great promise. By modulating the tumor microenvironment, irisin may enhance the efficacy of immune checkpoint inhibitors and improve treatment outcomes.

Lack of Standardization

Mass Spectrometry Detection Method: Mass spectrometry is a gold standard for irisin detection, offering high specificity and accuracy. For example, Mark P. Jedrychowski et al employed it to identify and quantify irisin in human blood, reporting concentrations of approximately 3.6 ng/mL at rest, which increased to approximately 4.3 ng/mL following aerobic interval training. By selecting specific peptides as standards and using stable-isotope-enriched heavy-labeled peptides as internal standards, this method improves the accuracy and sensitivity of detection.[18]

ELISA Detection Method: Even with antibody specificity issues, ELISA is still the most commonly used method for irisin detection. The ELISA kits from Phoenix Pharmaceuticals (eg, EK-067-29) were the early widely used tools for irisin detection. However, the first-generation kits had antibody specificity problems, resulting in a high coefficient of variation (CV) in test results (13–15%) and significant discrepancies with the true values measured by mass spectrometry. The subsequent second-generation kits improved biotinylated peptide specificity, making detection results closer to the mass spectrometry "true values", but still had high intra - and inter-assay variations (CV of about 11–15%).[18,143]

The high-sensitivity ELISA kits from Aviscera (eg, SK00170 - 06), verified by Western blot, use two monoclonal antibodies that can specifically recognize glycosylated irisin recombinant proteins (from HEK293 cells). They showed good specificity in both Western blot and ELISA. For example, in their 2023 study, Kim et al used the Aviscera kit to detect irisin levels and confirmed its ability to identify glycosylated irisin through Western blot. The results showed that the kit could accurately detect exogenously added irisin.[80] When using such kits, it is recommended to prioritize validated ones and avoid comparing kits from different companies within the same study to minimize result bias.

Western Blot Detection Method: Western Blot can confirm the presence and specificity of irisin. For instance, when detecting irisin expression in non-small-cell lung cancer (NSCLC), using specific antibodies (eg, the NBP2-14024 antibody from Novus Biologicals) for immunohistochemical reactions provides detailed information on irisin protein size and expression levels, which helps verify results from other detection methods.[5]

Regardless of the detection method used, sample processing and pretreatment are crucial for obtaining accurate results. For example, when detecting irisin expression in breast cancer, materials are preserved with RNAlater. RNA is extracted using the RNeasy Mini Kit, cDNA is synthesized with the High-Capacity cDNA Reverse Transcription Kit, and real - time PCR is performed.[144] Standardized sample processing reduces experimental errors and enhances result comparability across different laboratories.

Currently, irisin detection methods are varied, each with its pros and cons. Mass spectrometry is precise but complex and expensive to operate. ELISA is convenient but has limited specificity. Western Blot provides detailed information but has low throughput. Differences in results between methods and across laboratories pose challenges for irisin research and clinical applications. Future studies should consider the advantages and limitations of these methods, and establish unified irisin detection standards, including sample processing, detection platforms, and quality control systems, to ensure data reliability and result reproducibility.

Dynamic Monitoring Bottlenecks

The dynamic monitoring of irisin during cancer therapy is critical. Current detection methods cannot track real-time irisin changes. Developing new liquid- biopsy-based detection technologies like circulating tumor DNA (ctDNA) and exosome detection enables real-time monitoring of irisin levels, better guiding personalized treatment.[145]

Discussion

Most in vitro models have confirmed that irisin has an inhibitory effect on the proliferation, metastasis, and invasiveness of cancer cells, with cancer cell metastasis potentially being primarily due to irisin's suppression of epithelial-mesenchymal transition. The levels of irisin in the serum of patients with different cancers vary, with decreases observed in bladder and colorectal cancers, increases in renal, liver, and gastric cancers, and either increases or decreases in breast cancer. The observed differences may stem from the fact that irisin is released by different tissues, and not all irisin released into tissues necessarily enters the bloodstream. The levels of irisin in different cancer tissues are also not entirely consistent, with reasons involving the limitations of the studies, including insufficient sample size and a lack of correlation between study results and clinical pathological factors.

The inconsistent findings regarding irisin expression levels within the same tumor type highlight significant limitations in current research frameworks. These limitations include insufficient sample sizes, weak associations with clinical parameters, and, most critically, the heterogeneity of detection methods. Despite the extensive exploration of irisin's multiple biological functions in disease models, the absence of standardized and widely validated detection protocols has severely hindered its translational potential as a reliable biomarker or therapeutic target.To address the observational inconsistencies in current research, the field of irisin studies urgently requires the establishment of standardized detection protocols.

The research findings on irisin's ability to enhance or diminish the sensitivity to chemotherapy drugs indicate that irisin should be used cautiously and individualized when used in conjunction with drugs and chemotherapy for anti-tumor purposes. Furthermore, irisin fights cancer cells on one hand and induces cachexia on the other. Balancing the anti-tumor and cachexia-inducing effects of irisin will also be a significant challenge in future medication use.

Despite the tremendous potential demonstrated by irisin in the field of oncology, its clinical application still requires a deeper exploration of its molecular mechanisms. Future research should focus on the role of irisin in the tumor microenvironment and its impact on the sensitivity to chemotherapy, while also addressing the double-edged sword effect of irisin in anti-tumor and cachexia promotion. Large-scale clinical trials are essential for verifying the reliability of irisin as a biomarker and for guiding its application in clinical decision-making.

Future Research Directions

Firstly, there is an urgent need to standardize irisin detection procedures, including precise sample processing, unified detection platforms, and strict quality control systems, to ensure data reliability and experimental reproducibility. Currently, significant differences exist in the use of ELISA and Western blot methods across studies, and the establishment of unified standards is imperative. Secondly, further investigation into irisin's role in the tumor microenvironment is required. Existing research has confirmed the important role of cancer-associated fibroblasts (CAFs) in tumor progression, yet the regulatory effects of irisin on CAFs remain unclear. Additionally, the impact of irisin on immune cells, such as T cells and macrophages, and its role in tumor immune evasion warrant deeper study. Thirdly, large-scale clinical trials are needed to systematically evaluate the practical application value of irisin as a biomarker and therapeutic target. Most current studies are in the preclinical stage, and high-level clinical evidence supporting its clinical translation is lacking. Fourthly, it is crucial to precisely balance irisin's anti-tumor activity with the risk of cachexia. On one hand, irisin effectively inhibits tumor cell proliferation and invasion by suppressing signaling pathways such as PI3K/AKT. On the other hand, overexpression of irisin may exacerbate cachexia symptoms. Therefore, in-depth studies are needed on its roles in different tumor types and disease stages. The development of smart drug delivery systems to achieve precise regulation of irisin is essential to enhance anti-tumor efficacy and improve patients' quality of life.

Reasons for Heterogeneity

Methodological Heterogeneity

Differences in sample sources may be one reason for the inconsistencies in irisin expression levels and functions in the same tumor type. For instance, in hepatocellular carcinoma research, irisin is highly expressed in cancerous parenchyma but serum levels are reduced, reflecting a local tissue retention effect. Serum testing alone cannot fully reflect the bioactive concentrations in the tumor microenvironment (TME). Currently, irisin detection techniques are relatively

limited. Most studies rely on ELISA and immunohistochemistry. However, variations exist across studies in terms of antibody specificity, sample preparation methods (eg, serum or tissue lysate preparation), and standardization protocols. Glycosylation modifications of the FNDC5 protein can cause fluctuations in molecular weight (20–32 kDa), potentially affecting antibody binding efficiency and leading to quantification deviations.

Tumor Biological Heterogeneity

Molecular subtypes may lead to differences in irisin expression. For example, in breast cancer, the effects of irisin on hormone receptor-positive and triple-negative subtypes may differ due to variations in integrin receptor (αV/β5) expression. Similarly, in hepatocellular carcinoma, different driver gene mutations (eg, TP53 vs CTNNB1) may alter PI3K/AKT pathway activity, mediating irisin's dual pro-tumor and anti-tumor effects. Gradients of inflammatory factors in the TME (eg, IL-6/TGF-β) can regulate STAT3/Snail pathway activity. Irisin's inhibitory efficacy against this pathway may fluctuate with the inflammatory state of the microenvironment, resulting in divergent outcomes across different stages of the same tumor type (eg, opposing effects in lung cancer stromal cells and cancer cells).

Interference From Metabolic and Treatment Backgrounds

In obese patients, increased irisin secretion from adipose tissue and a positive correlation between tumor irisin expression and BMI may obscure expression patterns in gastric and colorectal cancers. Treatment-induced adaptations may also be influencing factors. Chemotherapy drugs like paclitaxel can downregulate irisin expression and induce resistance. Retrospective studies that do not control for treatment history may mask the true association between baseline expression levels and prognosis.

Limitations of Experimental Design

The lack of representativeness in cell models may be an important reason for irisin expression differences. In vitro studies often use single cell lines (eg, HepG2 liver cancer cells). However, genetic backgrounds of different cell lines (eg, MIA PaCa-2 and Panc03.27 pancreatic cancer cells show varying sensitivity to irisin) and culture microenvironments (hypoxic/normoxic) can significantly alter pathway responses. Clinical sample bias can also lead to irisin expression differences. Small-sample studies (eg, analyses of different thyroid cancer subtypes) fail to capture intratumoral heterogeneity. The absence of multicenter validation cohorts limits the generalizability of conclusions.

Detailed Discussion of Clinical Trial Data

Although irisin has shown unique potential in oncology, its clinical translation is still in its infancy. Most current clinical trials related to irisin focus on metabolic diseases, with few trials in oncology, and data often originate from retrospective cohort studies. In terms of diagnostic value, serum irisin levels in bladder cancer patients are significantly lower than in healthy controls (4.53 ± 2.55 vs 16.5 ± 5.67 ng/mL, $p < 0.001$), with diagnostic sensitivity of 86.2% and specificity of 89.7% (AUC=0.859), and it can distinguish muscle-invasive subtypes (AUC=0.732). In prostate cancer, irisin demonstrates diagnostic sensitivity of 80.5% and specificity of 90.0%, surpassing traditional PSA indicators. In renal cell carcinoma, serum FNDC5/Irisin levels are significantly elevated (208 vs 110 pg/mL, p=0.0001), with a cutoff value of>105 pg/mL. Regarding prognostic associations, high irisin expression in the tumor stroma of NSCLC patients is independently associated with adverse prognosis (HR=1.82, 95% CI: 1.24–2.68). In breast cancer patients, each 1-unit increase in serum irisin reduces the risk of bone metastasis by nearly 20%. In terms of predicting treatment responses, preclinical studies suggest that irisin can reverse paclitaxel resistance, but no human pharmacodynamic trial data are available yet.

Translation Strategies

To advance irisin from mechanistic research to clinical application, the following translation strategies can be adopted. In diagnostic reagent development, the short-term goal is to establish tumor type-specific serum irisin cut-off values based on multicenter cohorts (>1000 cases), replacing ELISA with mass spectrometry to address antibody cross-reactivity issues. The mid-term goal is to develop diagnostic models combining irisin with traditional biomarkers, such as PSA +IRISIN for prostate cancer, to enhance early detection rates. In terms of therapeutic application pathways, for local delivery systems, considering irisin's tissue-specific effects, tumor-targeted nanocarriers can be designed, such as

liposomes encapsulating irisin for intratumoral injection to avoid systemic side effects. For combination therapy regimens, in irisin-sensitizing cancers (eg, NSCLC, breast cancer), phase I/II trials can be conducted to evaluate the safety and synergistic effects of "paclitaxel + recombinant irisin." When combined with immune checkpoint inhibitors, based on irisin's regulatory role on Treg/DC, its potential to reverse the immunosuppressive tumor microenvironment can be explored. For cachexia risk management, bifunctional molecules of irisin/antagonists can be developed to release active irisin locally in tumors while systemically administering antagonists to block lipolysis. A cachexia early warning model can be established to dynamically monitor the serum irisin/adiponectin ratio and intervene early in metabolic imbalances. Additionally, a three-tier interdisciplinary validation platform integrating "organoid-PDX models-clinical trials" can be established. Patient-derived organoids can first be used to screen irisin-sensitive subtypes, followed by evaluating targeted delivery efficiency in PDX models, and finally designing umbrella clinical trials stratified by biomarkers.

Overall, a comprehensive understanding of irisin will provide an important foundation for the development of new cancer treatment strategies, with the hope of achieving personalized medicine and improving the effectiveness of cancer treatment.

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