NEWPORT INTERNATIONAL JOURNAL OF SCIENTIFIC AND EXPERIMENTAL SCIENCES (NIJSES)

Volume 6 Issue 3 Page 143-150, 2025

©NIJSES PUBLICATIONS
Open Access

ONLINE ISSN:2992-5819
PRINT ISSN:2992-6149

https://doi.org/10.59298/NIJSES/2025/63.143150

Insulin/IGF Signaling Pathways as Shared Drivers in Obesity, Type 2 Diabetes, and Tumorigenesis

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ABSTRACT

The global rise in obesity and type 2 diabetes mellitus (T2DM) has paralleled a significant increase in the incidence of various cancers, suggesting the existence of shared pathogenic mechanisms. Among the most prominent is the dysregulation of insulin and insulin-like growth factor (IGF) signaling pathways. These pathways, critical for regulating glucose metabolism and cellular growth, are profoundly altered in obesity and T2DM due to chronic hyperinsulinemia, insulin resistance, and elevated IGF-1 levels. Such aberrations create a permissive environment for malignant transformation, proliferation, and survival. This review explores the intricate molecular crosstalk between insulin/IGF signaling and oncogenic pathways, focusing on how these mechanisms contribute to tumorigenesis in the context of metabolic dysfunction. We discuss the role of insulin/IGF in activating PI3K/Akt/mTOR and MAPK/ERK pathways, their influence on angiogenesis and apoptosis, and how metabolic inflammation further amplifies these effects. Moreover, we examine clinical and experimental evidence linking insulin/IGF axis dysregulation with cancer risk and progression, and assess current therapeutic strategies targeting these pathways in metabolic diseases and oncology. Understanding the convergence of metabolic and oncogenic signaling may pave the way for integrative interventions to combat both metabolic and malignant diseases.

Keywords: Insulin signaling, IGF-1 pathway, Obesity, Type 2 diabetes, Tumorigenesis

INTRODUCTION

Obesity and type 2 diabetes mellitus (T2DM) are increasingly viewed not just as metabolic conditions but as key players in the pathophysiology of numerous non-communicable diseases, particularly cancer[1–4]. The global upsurge in the prevalence of these conditions has paralleled a noticeable rise in the incidence of various cancer types, prompting extensive investigations into potential mechanistic links[2, 5, 6]. This growing body of research has revealed that the intersection between metabolic dysregulation and oncogenesis is neither coincidental nor indirect. Instead, it is underpinned by a constellation of cellular and molecular pathways that mediate the biological crosstalk between metabolic disorders and tumorigenesis[5–7].

Among these mechanisms, the insulin and insulin-like growth factor (IGF) signaling pathways have emerged as central mediators[8, 9]. These pathways, which evolved to regulate nutrient metabolism, growth, and cellular proliferation, are tightly regulated under normal physiological conditions. Insulin primarily governs glucose uptake and energy metabolism, while IGF-1, a hormone with structural similarity to insulin, plays a pivotal role in growth, development, and differentiation. Both hormones exert their effects via cognate receptors that initiate intracellular signaling cascades essential for maintaining cellular homeostasis[10–12].

However, in the pathological states of obesity and T2DM, this finely tuned signaling network becomes deranged. Chronic overnutrition, increased adiposity, and systemic insulin resistance result in compensatory hyperinsulinemia and elevated levels of circulating IGF-1[13, 14]. Simultaneously, a decrease in IGF-binding proteins (IGFBPs) enhances the bioavailability of free IGF-1. This aberrant hormonal milieu sets the stage for persistent activation of downstream signaling pathways such as PI3K/Akt/mTOR and MAPK/ERK, which are well-documented promoters of cell survival, proliferation, angiogenesis, and metastasis, hallmarks of cancer[14].

Moreover, adipose tissue in obesity acts as an active endocrine organ, secreting adipokines, pro-inflammatory cytokines (such as TNF-α, IL-6), and chemokines that drive chronic low-grade inflammation[11, 15, 16]. This

inflammatory state further exacerbates insulin resistance and amplifies oncogenic signaling by inducing oxidative stress, DNA damage, and alterations in the tumor microenvironment. Importantly, inflammation, in conjunction with elevated insulin/IGF signaling, promotes epithelial-to-mesenchymal transition (EMT), immune evasion, and other processes critical to cancer initiation and progression[17–19].

Epidemiological studies lend substantial support to these biological insights. Obese individuals and those with T2DM have been found to possess significantly elevated risks of developing cancers of the colon, pancreas, liver, breast (especially postmenopausal), endometrium, and kidney. In fact, it is estimated that 20–30% of common cancers may be attributable to obesity and diabetes-related metabolic disturbances[20]. Notably, cancer prognosis is often worse in patients with concurrent obesity and T2DM, likely due to delayed diagnosis, altered pharmacokinetics of chemotherapeutic agents, and an inherently pro-tumorigenic systemic environment[20, 21].

Understanding the pivotal role of the insulin/IGF signaling axis in mediating the relationship between metabolic disease and cancer has important clinical implications. It opens up avenues for targeted therapies that can modulate this axis, such as metformin—a widely used antidiabetic drug with reported antineoplastic properties. Furthermore, lifestyle interventions such as caloric restriction, weight loss, and physical activity that improve insulin sensitivity have shown promise in reducing cancer risk and improving outcomes in cancer patients. The convergence of obesity, T2DM, and cancer is increasingly recognized as a critical public health issue underpinned by shared molecular pathways. The insulin/IGF signaling network sits at the heart of this convergence, acting as a mechanistic bridge between metabolic dysfunction and oncogenic transformation. Future research aimed at dissecting the tissue-specific and context-dependent roles of this signaling axis will be crucial in devising effective preventive and therapeutic strategies.

2. Overview of Insulin and IGF Signaling Pathways

The insulin and insulin-like growth factor (IGF) signaling pathways are vital for regulating cellular metabolism, growth, and differentiation[22]. These signaling networks are evolutionarily conserved and rely on ligand-receptor interactions involving two structurally similar receptors: the insulin receptor (IR) and the IGF-1 receptor (IGF-1R). Despite their homology, these receptors initiate distinct and overlapping biological responses. Insulin predominantly controls glucose metabolism, while IGF-1 is mainly involved in growth and anabolic processes[23]. Both receptors are transmembrane receptor tyrosine kinases that, upon activation, initiate a cascade of intracellular events essential for maintaining metabolic and cellular homeostasis.

Upon ligand binding, IR and IGF-1R undergo autophosphorylation on specific tyrosine residues in their intracellular domains[24, 25]. This modification creates docking sites for adaptor proteins such as insulin receptor substrates (IRS-1 to IRS-4), Shc, and Gab1. These adaptor proteins subsequently activate two major signaling cascades: the phosphoinositide 3-kinase (PI3K)/Akt/mTOR pathway and the mitogen-activated protein kinase (MAPK)/ERK pathway. The PI3K/Akt/mTOR pathway is crucial for cell survival, growth, and metabolic regulation. Activation of PI3K leads to the generation of phosphatidylinositol-3,4,5-triphosphate (PIP3), which recruits Akt (also known as protein kinase B) to the cell membrane. Akt is then phosphorylated and activated by phosphoinositide-dependent kinase-1 (PDK1) and mTOR complex 2 (mTORC2)[26]. Activated Akt promotes protein synthesis via mTOR complex 1 (mTORC1), inhibits pro-apoptotic factors (e.g., BAD, FoxO), and enhances glucose uptake through GLUT4 translocation[26]. This pathway also stimulates lipid synthesis and cell proliferation, making it a key player in metabolic and oncogenic regulation.

The MAPK/ERK pathway, on the other hand, governs cell proliferation, differentiation, and gene expression[27]. This cascade is initiated by activation of the small GTPase Ras, which subsequently activates RAF kinases. RAF then phosphorylates MEK1/2, leading to the activation of ERK1/2. Activated ERK translocates to the nucleus, where it regulates transcription factors involved in cell cycle progression, proliferation, and differentiation. This pathway is particularly relevant in cancer biology, as persistent MAPK activation is associated with uncontrolled cell division and tumorigenesis[28].

Under normal physiological conditions, these pathways are tightly regulated to prevent excessive or inappropriate signaling. However, in states of obesity and T2DM, chronic nutrient overload, systemic insulin resistance, and compensatory hyperinsulinemia create a pathological environment characterized by either excessive stimulation or impaired desensitization of these pathways[29–31]. Adipose tissue dysfunction contributes to this imbalance by secreting pro-inflammatory cytokines and adipokines, further amplifying insulin resistance and perpetuating the hyperactivation of these signaling pathways.

Moreover, obesity and insulin resistance reduce the levels of insulin-like growth factor-binding proteins (IGFBPs), especially IGFBP-1 and IGFBP-2, thereby increasing the levels of free, bioactive IGF-1[32]. This enhances IGF-1R signaling, particularly in epithelial cells and pre-malignant lesions, where it promotes cellular proliferation, evasion of apoptosis, and angiogenesis—all key features of malignant transformation[32]. Interestingly, there is also cross-talk between IR and IGF-1R. These receptors can form hybrid receptors that respond to both insulin and IGF-1, although with varying affinities and signaling outcomes. The formation of such hybrid receptors is often upregulated in cancer cells and has been linked to enhanced mitogenic responses and resistance to targeted therapies[33].

In summarily, the insulin and IGF signaling pathways constitute a complex, highly integrated system essential for metabolic regulation and cellular homeostasis. In the context of metabolic disorders such as obesity and T2DM, these pathways become dysregulated, contributing not only to metabolic derangements but also to oncogenic processes[34]. Understanding the nuances of these signaling networks, their regulation, and their pathological activation offers critical insights into the mechanistic links between metabolism and cancer, thereby guiding the development of novel therapeutic and preventive strategies[34].

3. Dysregulation in Obesity and Type 2 Diabetes

The pathophysiological overlap between obesity and type 2 diabetes mellitus (T2DM) creates a metabolic environment that significantly alters the normal insulin and insulin-like growth factor (IGF) signaling cascade. Obesity, particularly visceral adiposity, is marked by a state of chronic insulin resistance[35]. This resistance compels pancreatic β-cells to produce and secrete higher levels of insulin to maintain euglycemia, a condition known as compensatory hyperinsulinemia. Simultaneously, elevated insulin levels suppress the hepatic synthesis of IGF-binding proteins, particularly IGFBP-1 and IGFBP-2. These proteins normally function to sequester IGF-1 in the circulation, thereby modulating its bioavailability. When their levels are reduced, the concentration of free IGF-1 increases, enhancing its interaction with the IGF-1 receptor (IGF-1R) on target cells[35].

This aberrant signaling is further compounded in T2DM, where persistent hyperglycemia, oxidative stress, and advanced glycation end products (AGEs) promote chronic inflammation. Pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and C-reactive protein (CRP) are upregulated in adipose tissue and systemically circulate throughout the body[36]. These cytokines activate intracellular stress pathways such as JNK and IKKβ/NF-κB, which impair insulin receptor signaling by serine phosphorylation of insulin receptor substrates (IRS-1 and IRS-2), exacerbating insulin resistance. Moreover, chronic inflammation and hyperglycemia fuel reactive oxygen species (ROS) production, leading to DNA damage and epigenetic modifications that promote malignant transformation[36]. Tissues that are particularly responsive to insulin and IGF-1, such as the liver, colon, endometrium, and breast, become more susceptible to these oncogenic insults. In these tissues, the persistent activation of insulin and IGF receptors promotes cellular proliferation and inhibits apoptosis, a hallmark of cancer progression[37].

The dysregulation also alters adipokine profiles. For instance, levels of adiponectin, an anti-inflammatory and insulin-sensitizing adipokine, are reduced in obesity and T2DM, while leptin levels increase. Leptin not only promotes inflammation but also exhibits mitogenic effects by activating pathways such as JAK/STAT and MAPK, thereby contributing to tumorigenesis[38]. In parallel, hyperlipidemia, commonly associated with metabolic syndrome, provides an abundant supply of lipids that fuel membrane biosynthesis and energy production in rapidly proliferating tumor cells[9, 38, 39]. Furthermore, chronic metabolic stress results in remodeling of the extracellular matrix and promotion of epithelial-mesenchymal transition (EMT), facilitating tumor invasion and metastasis[40–42]. Overall, the convergence of metabolic disturbances, chronic inflammation, hormonal imbalance, oxidative stress, and altered adipokine signalling creates a fertile ground for oncogenic processes in the context of obesity and T2DM.

4. Insulin/IGF Signaling in Tumorigenesis

The insulin and insulin-like growth factor (IGF) signaling axis plays a pivotal role in cellular processes that are frequently hijacked during tumor development and progression[25, 32]. Under normal physiological conditions, insulin and IGF-1 bind to their respective receptors insulin receptor (IR) and IGF-1 receptor (IGF-1R) to regulate metabolic homeostasis and growth. However, in cancerous conditions, especially in the presence of metabolic diseases like obesity and T2DM, this signaling axis becomes aberrantly activated, thereby contributing to tumorigenesis[22, 23]. One of the key oncogenic mechanisms of insulin/IGF signaling is the promotion of cell proliferation. Both IGF-1R and the A isoform of the insulin receptor (IR-A), which has a higher affinity for IGF-2, activate the Ras-Raf-MEK-ERK (MAPK) pathway upon ligand binding. This pathway promotes G1/S phase transition in the cell cycle by upregulating cyclins and downregulating cyclin-dependent kinase inhibitors, leading to uncontrolled cellular proliferation, a defining characteristic of cancer[43].

The signaling axis also promotes cell survival and resistance to apoptosis. Activation of the phosphoinositide 3-kinase (PI3K)/Akt pathway following receptor engagement inhibits apoptotic proteins such as Bad and enhances the activity of anti-apoptotic proteins like Bcl-2[44]. Additionally, Akt activates mTOR (mechanistic target of rapamycin), a central node in cellular metabolism and growth, leading to increased protein synthesis, ribosome biogenesis, and inhibition of autophagy all processes that support tumor growth and survival. Another critical aspect is the stimulation of angiogenesis, the formation of new blood vessels from pre-existing vasculature[45]. Insulin and IGF-1 upregulate the expression of vascular endothelial growth factor (VEGF), a potent angiogenic factor that ensures a consistent blood supply to growing tumors. This neovascularization is essential for sustaining tumor expansion and providing a conduit for metastasis[45].

Furthermore, insulin/IGF signaling contributes to metabolic reprogramming, a phenomenon wherein cancer cells shift their metabolic profile to meet the demands of rapid proliferation. This includes enhanced aerobic glycolysis (Warburg effect), increased glucose uptake via GLUT1 and GLUT4 transporters, and upregulated lipogenesis[46]. These changes are largely mediated through PI3K/Akt/mTOR signaling and are hallmarks

of metabolic plasticity in cancer. Cancers such as breast, prostate, colorectal, and hepatocellular carcinomas often exhibit upregulated expression of IGF-1R and IR-A, which sensitizes them to the mitogenic and anti-apoptotic effects of insulin and IGFs.[46] This overexpression correlates with poor prognosis and resistance to conventional therapies. Moreover, tumors can co-opt the local and systemic availability of insulin and IGFs, especially in obese and diabetic individuals, to sustain their growth and survival.

In sum, the insulin/IGF signaling axis orchestrates a suite of oncogenic processes—proliferation, survival, angiogenesis, and metabolic rewiring—that collectively drive tumor initiation and progression. The strong link between metabolic disorders and cancer underscores the therapeutic potential of targeting this pathway in metabolic disease-associated malignancies.

5. Interplay with Inflammatory and Adipokine Signaling

The pathological state of obesity is marked by chronic, low-grade inflammation and significant alterations in adipokine secretion, both of which profoundly influence insulin/IGF signaling pathways and contribute to tumorigenesis[47–49]. Adipose tissue, particularly visceral fat, functions as an active endocrine organ that secretes a wide array of bioactive molecules, including adipokines such as leptin, adiponectin, resistin, and pro-inflammatory cytokines like TNF-α, IL-6, and MCP-1. These mediators establish a pro-inflammatory microenvironment that synergizes with insulin and IGF signaling to support cancer development and progression[10, 11, 15].

Leptin, which is typically elevated in obese individuals, promotes cell proliferation, survival, angiogenesis, and metastasis by activating several oncogenic pathways, including JAK2/STAT3, PI3K/Akt, and MAPK[50–52]. It has also been shown to crosstalk with IGF-1 receptor (IGF-1R), amplifying mitogenic and anti-apoptotic signals in various cancer cell types, including breast and colorectal cancers. In contrast, adiponectin, often reduced in obesity, has tumor-suppressive properties. It activates AMP-activated protein kinase (AMPK), a critical energy sensor that inhibits the mTOR pathway, thereby reducing protein synthesis and cellular proliferation[50, 51, 53]. Lower adiponectin levels remove this inhibitory brake on tumor growth, allowing for unchecked cell division and metabolic activity.

Additionally, the chronic inflammatory state in obesity promotes insulin resistance, leading to compensatory hyperinsulinemia[11, 40, 54]. This state further enhances IGF signaling by decreasing the levels of IGF-binding proteins (IGFBPs), increasing the bioavailability of IGF-1. The combined action of adipokines and inflammatory cytokines creates a tumor-permissive environment that promotes oncogenic transformation, progression, and immune evasion[40, 55]. Thus, the interplay between inflammatory signaling, adipokines, and insulin/IGF pathways forms a vicious cycle that reinforces both metabolic dysfunction and cancer risk, making it a compelling target for preventive and therapeutic interventions.

6. Clinical and Experimental Evidence

A growing body of clinical and experimental evidence supports the link between dysregulated insulin/IGF signaling and cancer risk. Epidemiological studies have consistently demonstrated a higher incidence of several cancers—including breast, colorectal, pancreatic, and endometrial cancers—among individuals with obesity and type 2 diabetes mellitus (T2DM), particularly those with hyperinsulinemia[56]. Prospective cohort and case-control studies have shown that elevated fasting insulin or C-peptide levels are predictive of cancer risk and poorer prognosis, even after adjusting for confounding factors such as body mass index (BMI) and physical activity. Experimental models reinforce these findings. Mouse models with targeted deletion of the insulin receptor in specific tissues, or pharmacological inhibition of the IGF-1R, have exhibited reduced tumor growth, delayed cancer onset, and lower metastatic burden[56]. In vitro studies also show that insulin and IGF-1 stimulate proliferation and inhibit apoptosis in cancer cell lines through activation of PI3K/Akt and MAPK pathways.

From a clinical pharmacology standpoint, the type of anti-diabetic treatment appears to influence cancer risk. Patients using insulin analogs or sulfonylureas—which stimulate endogenous insulin secretion—often show a higher incidence of certain cancers[57]. In contrast, metformin users demonstrate a consistently lower cancer risk and improved outcomes across various malignancies. Metformin's dual effect—lowering insulin levels and activating AMPK—contributes to its anti-tumor properties, making it a subject of interest in cancer prevention trials[58–60].

These converging lines of evidence underscore a potentially causal relationship between hyperactive insulin/IGF signaling and malignancy. They also highlight the importance of considering metabolic status in cancer risk assessments and treatment strategies, especially in populations with a high prevalence of obesity and T2DM.

7. Therapeutic Implications and Future Directions

The pivotal role of insulin and IGF signaling in the pathogenesis of both metabolic disorders and cancer offers promising therapeutic avenues that could simultaneously address these co-morbid conditions. One of the most actively explored strategies involves the use of IGF-1 receptor (IGF-1R) antagonists, such as monoclonal antibodies (e.g., figitumumab) that block ligand binding and receptor activation. Similarly, small-molecule tyrosine kinase inhibitors (e.g., linsitinib) have been developed to inhibit downstream signaling cascades initiated by IGF-1R. These agents aim to disrupt the mitogenic and anti-apoptotic signals that drive tumor growth.

Another class of therapeutics targets the mTOR pathway, a central node downstream of insulin/IGF signaling. mTOR inhibitors like everolimus and temsirolimus have shown efficacy in various cancers and are already in clinical use, particularly for renal cell carcinoma and neuroendocrine tumors. Metabolic drugs like metformin, GLP-1 receptor agonists, and SGLT2 inhibitors offer dual benefits by improving insulin sensitivity and exerting anti-proliferative effects, making them attractive candidates for cancer prevention and therapy in diabetic or obese patients. However, the systemic nature of the insulin/IGF axis and its involvement in normal cellular processes necessitate precision in therapeutic targeting. Non-specific inhibition can lead to significant adverse effects, including growth abnormalities, insulin resistance, and metabolic dysregulation. Future research must prioritize patient stratification using molecular biomarkers to identify those who would derive the greatest benefit with minimal risk.

Combination therapies that integrate insulin/IGF pathway inhibitors with immunotherapy, chemotherapy, or targeted agents also hold promise. Moreover, integrating genomic and proteomic profiling into clinical workflows could allow for tailored interventions. Overall, a deeper understanding of the metabolic-oncogenic interface will be critical for developing safe and effective therapies targeting this shared signaling axis.

CONCLUSION

The insulin/IGF signaling pathways serve as a molecular bridge between obesity, type 2 diabetes, and cancer. Their dysregulation not only drives metabolic imbalance but also fuels tumorigenesis through overlapping mechanisms of proliferation, survival, and inflammation. As the burden of metabolic diseases continues to escalate globally, understanding these shared pathways offers a unique opportunity for integrated therapeutic approaches aimed at preventing and treating both metabolic and neoplastic diseases. Continued research into the insulin/IGF axis will be crucial for designing targeted interventions that can modify cancer risk in metabolically compromised individuals.

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CITE AS: Nagm Eldeen Mohamed Abbker Idreis (2025). Insulin/IGF Signaling Pathways as Shared Drivers in Obesity, Type 2 Diabetes, and Tumorigenesis. NEWPORT INTERNATIONAL JOURNAL OF SCIENTIFIC AND EXPERIMENTAL SCIENCES 6(3):143-150
https://doi.org/10.59298/NIJSES/2025/63.143150