NEWPORT INTERNATIONAL JOURNAL OF SCIENTIFIC AND EXPERIMENTAL SCIENCES (NIJSES)

Volume 6 Issue 3 Page 212-220, 2025

©NIJSES PUBLICATIONS
Open Access

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

https://doi.org/10.59298/NIJSES/2025/63.212220

Metabolic Reprogramming in Obesity-Linked Cancers: Interplay with Diabetic Pathophysiology

Kato Jumba K.

Faculty of Science and Technology Kampala International University Uganda

ABSTRACT

The global escalation of obesity and type 2 diabetes mellitus (T2DM) has unveiled a troubling nexus with cancer development and progression. Obesity-linked cancers, including those of the breast, colon, pancreas, liver, and endometrium, share metabolic hallmarks driven by the intricate reprogramming of cellular energy pathways. This metabolic reprogramming facilitates cancer cell survival, proliferation, and immune evasion under the altered systemic conditions created by obesity and diabetes. Central to this pathological triad is insulin resistance, hyperinsulinemia, and chronic inflammation, which together disrupt adipokine signaling, stimulate oncogenic insulin/IGF pathways, and foster a pro-tumorigenic microenvironment. Additionally, excess lipid availability and mitochondrial dysfunction in obese-diabetic states fuel aberrant glycolysis, lipogenesis, and glutamine metabolism, hallmarks of cancer cell metabolic flexibility. This review critically examines the intersection of obesity-induced metabolic alterations and diabetic pathophysiology in driving cancer progression, emphasizing key regulatory molecules such as HIF-1α, mTOR, AMPK, and SREBP-1. We also discuss emerging therapeutic interventions targeting metabolic pathways, such as metformin, PPAR agonists, and lipid metabolism inhibitors, offering promising directions for managing obesity-associated malignancies. Understanding the metabolic crosstalk between obesity, diabetes, and cancer may yield novel biomarkers and intervention strategies with potential for precision oncology.

Keywords: Obesity, Type 2 Diabetes Mellitus, Cancer Metabolism, Metabolic Reprogramming, Insulin Resistance

INTRODUCTION

Obesity and type 2 diabetes mellitus (T2DM) are two of the most pressing public health challenges worldwide, both of which are intricately linked and share several overlapping pathophysiological mechanisms[1–4]. Obesity is defined by the excessive accumulation of adipose tissue and is often accompanied by chronic low-grade inflammation, dysregulated lipid metabolism, and hormonal imbalances[5, 6]. T2DM, on the other hand, is characterized by persistent hyperglycemia due to insulin resistance and impaired insulin secretion. These metabolic disorders are not only risk factors for cardiovascular and renal diseases but also have profound implications for cancer development and progression[7–9].

A growing body of evidence suggests that the metabolic disturbances inherent in obesity and T2DM create a pro-tumorigenic microenvironment. Both conditions disrupt normal insulin and insulin-like growth factor (IGF) signaling, which are critical regulators of cellular growth, metabolism, and survival[10, 11]. Hyperinsulinemia and increased IGF-1 bioavailability can stimulate mitogenic and anti-apoptotic pathways in cells, promoting unchecked proliferation and resistance to cell death—hallmarks of cancer. Additionally, adipose tissue in obese individuals functions as an active endocrine organ, secreting a wide range of adipokines and inflammatory cytokines that influence cancer biology[4, 12]. For instance, leptin levels are typically elevated, while adiponectin levels are decreased in obesity, contributing to tumorigenesis via modulation of cell proliferation, angiogenesis, and immune responses. Chronic inflammation, driven by cytokines such as IL-6 and TNF-α, also plays a critical role in DNA damage, epigenetic alterations, and the promotion of tumor-supportive immune phenotypes[8, 13–16].

One of the most significant adaptations in cancer cells within the metabolic landscape of obesity and T2DM is metabolic reprogramming. Cancer cells exhibit a preference for aerobic glycolysis, known as the Warburg effect, even in the presence of oxygen. This shift allows for rapid ATP generation and the accumulation of metabolic intermediates needed for biosynthetic processes[17–20]. Furthermore, these cells often show increased lipid synthesis, mitochondrial remodeling, and altered amino acid metabolism to support their high proliferative and survival needs. In this review, we look into the mechanisms by which metabolic abnormalities in obesity and T2DM contribute to oncogenesis. Special emphasis is placed on shared molecular pathways—such as insulin/IGF signaling, adipokine dysregulation, and inflammation—and how they reprogram cancer cell metabolism. By understanding these interconnected pathways, we can better appreciate the complex link between metabolic disease and cancer and identify novel therapeutic targets. Ultimately, this review aims to shed light on the metabolic crosstalk that bridges obesity, diabetes, and cancer, highlighting potential interventions that may disrupt this pathological triad.

2. Obesity and Cancer: Metabolic and Hormonal Links

Obesity significantly increases the risk of developing various cancers, including breast, colorectal, pancreatic, and endometrial cancers[21–23]. This increased risk stems from a cascade of metabolic and hormonal disturbances that favor tumor initiation, progression, and metastasis. One of the central mechanisms involves the dysregulation of adipose tissue, which serves not only as an energy reservoir but also as an active endocrine organ. In obese individuals, adipose tissue undergoes hypertrophy and hyperplasia, leading to hypoxia, immune cell infiltration, and the production of pro-inflammatory mediators[21].

These enlarged fat depots release a variety of bioactive molecules, including pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and C-reactive protein (CRP). These molecules contribute to chronic low-grade systemic inflammation—a known driver of carcinogenesis[24, 25]. They activate nuclear factor-kappa B (NF-κB) and signal transducer and activator of transcription 3 (STAT3), which promote the transcription of genes involved in cell proliferation, survival, and angiogenesis[24]. Adipokines, particularly leptin and adiponectin, also play key roles in mediating the cancer-promoting effects of obesity. Leptin, usually elevated in obese individuals, enhances cancer cell growth through activation of several oncogenic pathways, including JAK/STAT, MAPK/ERK, and PI3K/Akt. It also promotes angiogenesis by upregulating vascular endothelial growth factor (VEGF) and supports metastatic potential by influencing epithelial-to-mesenchymal transition (EMT)[26–28]. In contrast, adiponectin exerts anti-inflammatory, anti-proliferative, and insulin-sensitizing effects, and its reduced levels in obesity remove an important check against tumorigenesis[5, 29–31].

Obesity is also associated with elevated circulating levels of insulin and insulin-like growth factors due to insulin resistance[8, 32, 33]. This hormonal imbalance fuels cancer progression by enhancing cellular proliferation and inhibiting apoptosis through activation of IR and IGF-1R. Additionally, excess free fatty acids (FFAs) released from hypertrophic adipocytes contribute to lipotoxicity, mitochondrial dysfunction, and oxidative stress, all of which can result in DNA damage and genomic instability key steps in tumorigenesis. Another critical aspect is the increased aromatase activity within adipose tissue in obese individuals, particularly in postmenopausal women. Aromatase converts androgens into estrogens, leading to elevated estrogen levels that can stimulate the growth of hormone-sensitive tumors, such as breast and endometrial cancers[34, 35]. These hormones act through estrogen receptors to promote cell cycle progression and suppress apoptosis. The metabolic and hormonal disturbances in obesity create a favorable environment for cancer development and progression[36]. These changes not only alter local tissue homeostasis but also have systemic effects that promote a pro-oncogenic phenotype. Understanding the molecular basis of these associations opens avenues for targeted interventions aimed at mitigating cancer risk in obese individuals.

3. Diabetic Pathophysiology and Tumorigenesis

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder that significantly elevates the risk of developing several types of cancer, including liver, pancreatic, colorectal, and breast cancers[37]. The link between T2DM and cancer is mediated by a constellation of interrelated pathophysiological changes—most notably chronic hyperglycemia, hyperinsulinemia, and insulin resistance. These metabolic disturbances interact with and amplify the tumor-promoting effects of obesity, creating a permissive environment for oncogenesis[37].

One of the hallmark features of T2DM is insulin resistance, in which peripheral tissues become less responsive to insulin, prompting pancreatic β-cells to produce more insulin in a compensatory manner[38]. The resulting hyperinsulinemia is not merely a biomarker of disease progression but also an active driver of cancer. Insulin can directly stimulate cell growth by binding to the insulin receptor (IR), and it also promotes the bioavailability of insulin-like growth factor 1 (IGF-1) by suppressing IGF-binding proteins (IGFBPs), particularly IGFBP-1 and IGFBP-2. IGF-1 acts on its receptor (IGF-1R) to activate mitogenic signaling cascades such as Ras/Raf/MEK/ERK and PI3K/Akt/mTOR, which enhance proliferation, inhibit apoptosis, and promote metastasis[39].

Chronic hyperglycemia in T2DM serves as a metabolic fuel for cancer cells, providing ample glucose to support glycolysis and biosynthetic processes. Cancer cells preferentially utilize aerobic glycolysis (Warburg effect), and the high glucose availability in diabetes further supports this reprogramming[40]. Hyperglycemia also contributes to the formation of advanced glycation end products (AGEs), which interact with their receptors (RAGE) to generate reactive oxygen species (ROS), induce DNA damage, and activate pro-inflammatory signaling pathways—all of which are conducive to cancer initiation and progression[41, 42]. Additionally, T2DM is associated with dyslipidemia and increased circulating levels of amino acids, lipids, and ketone bodies, which can be hijacked by tumor cells to meet their energetic and biosynthetic demands[41]. Insulin resistance alters substrate metabolism, increasing the systemic availability of nutrients such as glucose, glutamine, and fatty acids—key building blocks for rapidly proliferating tumor cells.

The inflammatory milieu of T2DM also plays a critical role in tumorigenesis. Pro-inflammatory cytokines like IL-6, TNF-α, and MCP-1 are elevated and can activate signaling pathways such as NF-κB and STAT3, leading to a tumor-supportive microenvironment[43]. These cytokines also contribute to insulin resistance, creating a vicious cycle that sustains both metabolic dysfunction and carcinogenesis. The complex metabolic and signaling perturbations in T2DM significantly contribute to cancer development and progression[43]. The synergy between hyperinsulinemia, hyperglycemia, and inflammation not only drives the initiation of malignancies but also promotes resistance to therapy [44]. Elucidating these mechanisms is crucial for developing integrated strategies that address both metabolic control and cancer prevention in diabetic patients.

4. Metabolic Reprogramming in Obesity-Linked Cancers

Cancer cells are metabolically plastic, adapting to the nutrient-rich but dysregulated environment of obese-diabetic individuals. Hallmark alterations include:

4.1. Enhanced Glycolysis and Glucose Uptake: In obese-diabetic patients, tumors frequently demonstrate enhanced glucose uptake and glycolytic activity, a phenomenon known as the Warburg effect. This metabolic reprogramming is facilitated by the overexpression of glucose transporters, particularly GLUT1, which enables cancer cells to absorb large quantities of glucose from the microenvironment[45]. This uptake fuels glycolysis, even under normoxic conditions, producing ATP and metabolic intermediates necessary for cell proliferation. The transcription factor hypoxia-inducible factor 1-alpha (HIF-1α) plays a central role in this shift[46]. HIF-1α is commonly stabilized in the hypoxic and inflamed milieu of obese adipose tissue and tumors, promoting the transcription of glycolytic enzymes such as hexokinase 2 (HK2) and lactate dehydrogenase A (LDHA)[47–50]. These enzymes facilitate anaerobic glycolysis and lactate production, supporting tumor survival and growth even in oxygen-deprived environments. Additionally, the chronic low-grade inflammation associated with obesity and type 2 diabetes mellitus (T2DM) further amplifies HIF-1α activity through cytokines like TNF-α and IL-6[50]. The increased glycolytic flux provides biosynthetic precursors for macromolecule synthesis and enhances acidification of the tumor microenvironment, facilitating invasion and immune evasion. This metabolic adaptation contributes significantly to tumor aggressiveness and therapy resistance in obese-diabetic cancer patients.

4.2. Lipid Metabolism and De Novo Lipogenesis: Obesity is characterized by an oversupply of circulating lipids, including free fatty acids and triglycerides, which tumors exploit for various metabolic needs[6]. In the context of cancer, lipid metabolism is reprogrammed to support rapid proliferation, membrane biosynthesis, and energy production. Tumor cells activate key lipogenic regulators such as sterol regulatory element-binding protein 1 (SREBP-1) and fatty acid synthase (FASN), promoting de novo lipogenesis even in the presence of exogenous lipids[51]. This endogenous lipid production ensures a steady supply of phospholipids for membrane formation and lipid signaling molecules that regulate oncogenic pathways. Elevated FASN expression is frequently observed in aggressive tumors and is associated with poor prognosis, particularly in prostate, breast, and liver cancers. Moreover, de novo lipogenesis is tightly linked with other metabolic pathways, including acetyl-CoA generation and NADPH production, which support cell survival under metabolic stress. The inflammatory and insulin-resistant environment in obesity and T2DM further enhances lipogenesis by upregulating insulin and mTOR signaling pathways, which in turn stimulate SREBP-1 activity[17, 52, 53]. Thus, aberrant lipid metabolism not only fuels cancer cell growth but also contributes to metastasis and chemoresistance, making it a promising target for metabolic therapies in obesity-associated malignancies.

4.3. Mitochondrial Dysfunction and Oxidative Stress: In obese-diabetic individuals, persistent metabolic stress results in mitochondrial dysfunction across various tissues, including those susceptible to tumorigenesis[54]. This dysfunction is marked by impaired oxidative phosphorylation (OXPHOS) and a compensatory reliance on glycolysis. Defective mitochondria in this context produce excessive reactive oxygen species (ROS), including superoxide and hydrogen peroxide, which can overwhelm cellular antioxidant defenses[54]. Elevated ROS levels induce oxidative damage to DNA, proteins, and lipids, contributing to genomic instability, mutagenesis, and oncogenic transformation. Furthermore, ROS act as signaling molecules that activate pathways such as NF-κB and MAPK, which promote inflammation, proliferation, and survival of pre-malignant and malignant cells[55]. In tumors arising in the metabolic environment of obesity and T2DM, this redox imbalance supports aggressive behavior, angiogenesis, and resistance to apoptosis. The accumulation

of ROS is also linked to the stabilization of HIF-1α and activation of pro-survival genes, further enhancing tumor adaptability under hypoxic conditions[56]. Additionally, dysfunctional mitochondria alter metabolic fluxes, disrupting the balance of key metabolites like succinate and fumarate, which can function as oncometabolites. These mitochondrial alterations not only initiate cancer development but also sustain tumor progression, positioning mitochondrial health as a key factor in obesity-related carcinogenesis.

4.4. Glutamine and Amino Acid Metabolism: In the altered metabolic landscape of cancer, glutamine becomes a critical nutrient, particularly in tumors arising in obese-diabetic individuals. Glutamine serves as a carbon and nitrogen source essential for nucleotide, amino acid, and lipid biosynthesis[56]. Cancer cells upregulate glutamine transporters (e.g., SLC1A5) and enzymes like glutaminase (GLS), which converts glutamine to glutamate. Glutamate then fuels the tricarboxylic acid (TCA) cycle through conversion to α-ketoglutarate, supporting ATP production and anaplerosis[57]. This is particularly vital when glucose metabolism is diverted to biosynthetic pathways, leaving the TCA cycle dependent on alternative substrates. In addition to energy production, glutamine metabolism supports redox homeostasis by supplying glutathione precursors, helping cells manage oxidative stress. The insulin resistance and inflammatory signals prevalent in obesity and T2DM can enhance oncogenic signaling pathways like mTORC1, which increases demand for amino acids and promotes glutaminolysis. Moreover, branched-chain amino acids (BCAAs) and serine/glycine metabolism are also dysregulated in cancer, with increased uptake and utilization observed in many tumors[58]. The reprogramming of amino acid metabolism provides metabolic plasticity that allows cancer cells to adapt to fluctuating nutrient availability, sustain proliferation, and resist stress, particularly within the metabolically altered microenvironment of obese-diabetic individuals.

5. Key Molecular Regulators

Key Signaling Molecules and Metabolic Regulators in Obesity, Diabetes, and Cancer Metabolism

HIF-1α (Hypoxia-Inducible Factor 1-alpha) plays a central role in adapting cells to hypoxic and inflammatory microenvironments, conditions often present in obese and diabetic individuals[59]. In tumors, hypoxia stabilizes HIF-1α, allowing it to translocate to the nucleus and activate transcription of genes involved in glycolysis, such as GLUT1 and hexokinase. This enhances glucose uptake and anaerobic glycolysis (Warburg effect), even in the presence of oxygen, enabling sustained ATP production and survival of rapidly dividing cancer cells[59]. Moreover, HIF-1α promotes angiogenesis by upregulating VEGF, ensuring nutrient delivery and expansion of the tumor mass.

AMP-activated protein kinase (AMPK) functions as an energy sensor that maintains cellular metabolic balance by inhibiting anabolic processes during energy stress. In obesity and type 2 diabetes, AMPK activity is frequently suppressed due to chronic nutrient excess and inflammation[60]. This downregulation impairs fatty acid oxidation and glucose uptake, thereby contributing to insulin resistance and metabolic dysfunction. In the context of cancer, AMPK suppression removes its inhibitory effect on biosynthetic pathways, facilitating tumor growth. Interestingly, pharmacological activation of AMPK (e.g., by metformin) has shown potential in restoring metabolic control and inhibiting tumor progression[60].

mTOR (mechanistic Target of Rapamycin) integrates signals from insulin, IGF-1, nutrients, and cellular energy levels to regulate cell growth, proliferation, and metabolism. In obesity and diabetes, hyperinsulinemia and increased IGF-1 activate mTOR, driving protein synthesis, lipogenesis, and glycolysis[61]. This persistent activation of mTOR in cancer cells promotes tumor development and survival. mTOR forms two complexes: mTORC1 and mTORC2, both implicated in oncogenic processes. Therapeutically, mTOR inhibitors such as everolimus and rapamycin derivatives have shown efficacy in several cancer types, particularly those associated with metabolic dysregulation[61].

SREBP-1 (Sterol Regulatory Element-Binding Protein 1) is a transcription factor that governs genes involved in de novo lipogenesis, including fatty acid synthase (FASN) and acetyl-CoA carboxylase[62]. In obesity and diabetes, elevated insulin and nutrient levels enhance SREBP-1 activity, fueling lipid accumulation in both adipose and tumor tissues. Tumor cells exploit this lipogenic reprogramming to generate membrane lipids, signaling molecules, and energy for rapid proliferation[62]. SREBP-1 also interacts with mTOR signaling, forming a feed-forward loop that sustains cancer cell metabolism. Inhibiting SREBP-1 or its downstream effectors has emerged as a potential anticancer strategy.

PPAR-γ (Peroxisome Proliferator-Activated Receptor Gamma) is a nuclear receptor involved in adipocyte differentiation, lipid storage, and insulin sensitization. While PPAR-γ agonists such as thiazolidinediones improve insulin sensitivity in diabetes, their role in cancer is complex[63]. In some contexts, PPAR-γ activation suppresses inflammation and inhibits cell proliferation[63]. However, its dysregulation, particularly in adipose-rich environments, may support tumor growth by modulating lipid metabolism and enhancing energy availability. Therefore, the therapeutic utility of targeting PPAR-γ in cancer requires careful consideration of tissue-specific and disease-specific contexts. The interplay of these signaling molecules illustrates the intricate link between metabolic disorders and cancer. Chronic inflammation, nutrient overload, and hormonal imbalances seen in obesity and T2DM drive the dysregulation of these key regulators, creating a pro-tumorigenic environment[8, 14, 22]. Targeting these molecules offers promising avenues for therapeutic intervention,

particularly in patients with obesity-associated malignancies. Understanding the crosstalk among HIF-1α, AMPK, mTOR, SREBP-1, and PPAR-γ is crucial for developing metabolism-based therapies that can disrupt cancer progression while restoring metabolic balance. Continued research into the context-dependent roles of these regulators is essential for precision oncology.

6. Therapeutic Implications

The metabolic vulnerabilities of obesity-linked cancers offer novel opportunities for therapeutic intervention. Metformin, a frontline antidiabetic drug, is a well-studied example. It lowers systemic insulin levels, reduces hepatic glucose production, and activates AMPK, thereby inhibiting mTOR signaling[64, 65]. These mechanisms not only improve glycemic control but also impair cancer cell growth and survival. Epidemiological studies and clinical trials have shown that metformin use is associated with reduced cancer incidence and improved outcomes in patients with breast, colorectal, and prostate cancers, particularly those with coexisting T2DM or insulin resistance.

PPAR agonists, such as pioglitazone, modulate glucose and lipid metabolism through PPAR-γ activation. By enhancing insulin sensitivity and suppressing pro-inflammatory pathways, these agents potentially reduce the oncogenic drive associated with obesity and T2DM[66]. Preclinical studies suggest that PPAR-γ activation can inhibit tumor cell proliferation and induce differentiation. However, concerns over long-term safety and tumor-promoting effects in certain contexts have limited the widespread use of thiazolidinediones in cancer therapy[66]. Thus, selective modulators and tissue-specific targeting strategies are under investigation to maximize their therapeutic benefit while minimizing adverse outcomes.

Inhibitors of lipogenesis-related enzymes, such as FASN and SREBP-1, are gaining attention for their ability to restrict lipid availability in tumor cells. Targeting SREBP-1, in particular, may attenuate tumor growth by reducing membrane biosynthesis and lipid-mediated signaling[67]. Meanwhile, mTOR inhibitors like everolimus and temsirolimus have shown clinical success in certain cancers, especially renal cell carcinoma and hormone receptor-positive breast cancer. These drugs interrupt oncogenic signaling downstream of insulin/IGF pathways, making them particularly relevant for tumors arising in hyperinsulinemic and metabolically altered states[67].

Beyond pharmacological approaches, lifestyle interventions such as dietary modification, regular physical activity, and weight loss have shown significant promise in reducing cancer risk and improving outcomes in metabolically compromised individuals[68, 69]. Caloric restriction and exercise enhance insulin sensitivity, decrease systemic inflammation, and modulate key metabolic pathways, including AMPK and mTOR. These changes can suppress tumor-promoting signals and restore metabolic homeostasis. Furthermore, combining lifestyle interventions with targeted therapies may synergistically improve therapeutic efficacy and patient survival[68].

The advent of personalized medicine offers a pathway to tailor treatments based on individual metabolic profiles and tumor characteristics. By using biomarkers of metabolic dysregulation such as insulin levels, adipokine profiles, or gene expression patterns of key regulators, clinicians can stratify patients and choose optimal therapeutic combinations. For example, patients with high mTOR activity might benefit from metformin or mTOR inhibitors, while those with lipid-rich tumors could respond to FASN or SREBP-1 inhibitors. Integrating metabolic profiling into oncology care will be instrumental in improving outcomes for patients with obesity-linked malignancies. As our understanding of cancer metabolism deepens, the therapeutic landscape continues to evolve. Targeting metabolic derangements common in obesity and diabetes not only offers a novel approach to cancer treatment but also bridges the gap between metabolic and oncologic care. Ongoing clinical trials and translational research are critical to validating these strategies and optimizing their use in diverse patient populations. Ultimately, a comprehensive approach that combines pharmacological, lifestyle, and personalized interventions holds the greatest promise in mitigating the cancer burden in the context of metabolic disease.

7. Conclusion and Future Perspectives

The interplay between obesity, T2DM, and cancer is underpinned by complex metabolic reprogramming that favors oncogenesis. Understanding the molecular undercurrents of this triad provides insights into novel preventive and therapeutic strategies. Further research is required to elucidate tissue-specific mechanisms and identify predictive biomarkers of metabolic reprogramming in cancer. Integrating metabolic profiling into oncology practice holds promise for improving outcomes in patients with obesity-associated cancers.

REFERENCES

1. Allocca, S., Monda, A., Messina, A., Casillo, M., Sapuppo, W., Monda, V., Polito, R., Di Maio, G., Monda, M., La Marra, M.: Endocrine and Metabolic Mechanisms Linking Obesity to Type 2 Diabetes: Implications for Targeted Therapy. Healthcare. 13, 1437 (2025). https://doi.org/10.3390/healthcare13121437
2. Chandrasekaran, P., Weiskirchen, R.: The Role of Obesity in Type 2 Diabetes Mellitus—An Overview. International Journal of Molecular Sciences. 25, 1882 (2024). https://doi.org/10.3390/ijms25031882

3. Fernandez, C.J., George, A.S., Subrahmanyan, N.A., Pappachan, J.M.: Epidemiological link between obesity, type 2 diabetes mellitus and cancer. World Journal of Methodology. 11, 23–45 (2021). https://doi.org/10.5662/wjm.v11.i3.23
4. Janssen, J.A.M.J.L.: Hyperinsulinemia and Its Pivotal Role in Aging, Obesity, Type 2 Diabetes, Cardiovascular Disease and Cancer. Int J Mol Sci. 22, 7797 (2021). https://doi.org/10.3390/ijms22157797
5. Umoru, G.U., Atangwho, I.J., David-Oku, E., Uti, D.E., Agwupuye, E.I., Obeten, U.N., Maitra, S., Subramaniyan, V., Wong, L.S., Aljarba, N.H., Kumarasamy, V.: Tetracarpidium conophorum nuts (African walnuts) up-regulated adiponectin and PPAR-γ expressions with reciprocal suppression of TNF-α gene in obesity. J Cell Mol Med. 28, e70086 (2024). https://doi.org/10.1111/jcmm.70086
6. Umoru, G.U., Atangwho, I.J., David-Oku, E., Uti, D.E., De Campos, O.C., Udeozor, P.A., Nfona, S.O., Lawal, B., Alum, E.U.: Modulation of Lipogenesis by Tetracarpidium conophorum Nuts via SREBP-1/ACCA-1/FASN Inhibition in Monosodium-Glutamate-Induced Obesity in Rats. Natural Product Communications. 20, 1934578X251344035 (2025). https://doi.org/10.1177/1934578X251344035
7. Alum, E.U.: Optimizing patient education for sustainable self-management in type 2 diabetes. Discov Public Health. 22, 44 (2025). https://doi.org/10.1186/s12982-025-00445-5
8. Zatterale, F., Longo, M., Naderi, J., Raciti, G.A., Desiderio, A., Miele, C., Beguinot, F.: Chronic Adipose Tissue Inflammation Linking Obesity to Insulin Resistance and Type 2 Diabetes. Front Physiol. 10, 1607 (2020). https://doi.org/10.3389/fphys.2019.01607
9. Ejemot-Nwadiaro, R.I., Betiang, P.A., Basajja, M., Uti, D.E.: Obesity and Climate Change: A Two-way Street with Global Health Implications. Obesity Medicine. 56, 100623 (2025). https://doi.org/10.1016/j.obmed.2025.100623
10. Kim, D.-S., Scherer, P.E.: Obesity, Diabetes, and Increased Cancer Progression. Diabetes Metab J. 45, 799–812 (2021). https://doi.org/10.4093/dmj.2021.0077
11. Behrooz, A.B., Cordani, M., Fiore, A., Donadelli, M., Gordon, J.W., Klionsky, D.J., Ghavami, S.: The obesity-autophagy-cancer axis: Mechanistic insights and therapeutic perspectives. Seminars in Cancer Biology. 99, 24–44 (2024). https://doi.org/10.1016/j.semcancer.2024.01.003
12. Martinez, D.: Hyperinsulinemia does not reduce plasma sex hormone-binding globulin levels in obesity. In: Endocrine Abstracts. Bioscientifica (2020)
13. Gkrinia, E.M.M., Belančić, A.: The Mechanisms of Chronic Inflammation in Obesity and Potential Therapeutic Strategies: A Narrative Review. Current Issues in Molecular Biology. 47, 357 (2025). https://doi.org/10.3390/cimb47050357
14. Tripathi, S., Sharma, Y., Kumar, D.: Unveiling the link between chronic inflammation and cancer. Metabolism Open. 25, 100347 (2025). https://doi.org/10.1016/j.metop.2025.100347
15. Mann, V., Sundaresan, A., Shishodia, S.: Overnutrition and Lipotoxicity: Impaired Efferocytosis and Chronic Inflammation as Precursors to Multifaceted Disease Pathogenesis. Biology. 13, 241 (2024). https://doi.org/10.3390/biology13040241
16. Uti, D.E., Atangwho, I.J., Omang, W.A., Alum, E.U., Obeten, U.N., Udeozor, P.A., Agada, S.A., Bawa, I., Ogbu, C.O.: Cytokines as key players in obesity low grade inflammation and related complications. Obesity Medicine. 54, 100585 (2025). https://doi.org/10.1016/j.obmed.2025.100585
17. Badoiu, S.C., Greabu, M., Miricescu, D., Stanescu-Spinu, I.-I., Ilinca, R., Balan, D.G., Balcangiu-Stroescu, A.-E., Mihai, D.-A., Vacaroiu, I.A., Stefani, C., Jinga, V.: PI3K/AKT/mTOR Dysregulation and Reprogramming Metabolic Pathways in Renal Cancer: Crosstalk with the VHL/HIF Axis. International Journal of Molecular Sciences. 24, 8391 (2023). https://doi.org/10.3390/ijms24098391
18. Hua, W., ten Dijke, P., Kostidis, S., Giera, M., Hornsveld, M.: TGFβ-induced metabolic reprogramming during epithelial-to-mesenchymal transition in cancer. Cell. Mol. Life Sci. 77, 2103–2123 (2020). https://doi.org/10.1007/s00018-019-03398-6
19. Jiang, C., Tang, M., Su, Y., Xie, J., Shang, Q., Guo, M., An, X., Lin, L., Wang, R., Huang, Q., Zhang, G., Li, H., Wang, F.: Nanomedicine-driven tumor glucose metabolic reprogramming for enhanced cancer immunotherapy. Acta Pharmaceutica Sinica B. 15, 2845–2866 (2025). https://doi.org/10.1016/j.apsb.2025.04.002
20. Navarro, C., Ortega, Á., Santeliz, R., Garrido, B., Chacín, M., Galban, N., Vera, I., De Sanctis, J.B., Bermúdez, V.: Metabolic Reprogramming in Cancer Cells: Emerging Molecular Mechanisms and Novel Therapeutic Approaches. Pharmaceutics. 14, 1303 (2022). https://doi.org/10.3390/pharmaceutics14061303
21. Andò, S., Gelsomino, L., Panza, S., Giordano, C., Bonofiglio, D., Barone, I., Catalano, S.: Obesity, Leptin and Breast Cancer: Epidemiological Evidence and Proposed Mechanisms. Cancers (Basel). 11, 62 (2019). https://doi.org/10.3390/cancers11010062

22. Divella, R., De Luca, R., Abbate, I., Naglieri, E., Daniele, A.: Obesity and cancer: the role of adipose tissue and adipo-cytokines-induced chronic inflammation. J Cancer. 7, 2346–2359 (2016). https://doi.org/10.7150/jca.16884
23. Alum, E.U.: Metabolic memory in obesity: Can early-life interventions reverse lifelong risks? Obesity Medicine. 55, 100610 (2025). https://doi.org/10.1016/j.obmed.2025.100610
24. You, K., Gu, H., Yuan, Z., Xu, X.: Tumor Necrosis Factor Alpha Signaling and Organogenesis. Front. Cell Dev. Biol. 9, (2021). https://doi.org/10.3389/fcell.2021.727075
25. Obasi, D.C., Abba, J.N., Aniokete, U.C., Okoroh, P.N., Akwari, A.Ak.: Evolving Paradigms in Nutrition Therapy for Diabetes: From Carbohydrate Counting to Precision Diets. Obesity Medicine. 100622 (2025). https://doi.org/10.1016/j.obmed.2025.100622
26. Al-Amrani, S., Al-Zadjali, F., Jeelani, Y., Al-Jabri, Z., Al-Bulushi, M., AlRawahi, M., Al Zaabi, A., AlShekaili, J., Al-Huneini, M., Al-Khabori, M.: Expression of JAK/STAT Signaling Proteins at Diagnosis and Remission in Patients with Acute Myeloid Leukemia. Oman Med J. 39, e633 (2024). https://doi.org/10.5001/omj.2024.80
27. Hu, X., Li, J., Fu, M., Zhao, X., Wang, W.: The JAK/STAT signaling pathway: from bench to clinic. Sig Transduct Target Ther. 6, 402 (2021). https://doi.org/10.1038/s41392-021-00791-1
28. Liang, D., Wang, Q., Zhang, W., Tang, H., Song, C., Yan, Z., Liang, Y., Wang, H.: JAK/STAT in leukemia: a clinical update. Mol Cancer. 23, 25 (2024). https://doi.org/10.1186/s12943-023-01929-1
29. Bocian-Jastrzębska, A., Malczewska-Herman, A., Kos-Kudła, B.: Role of Leptin and Adiponectin in Carcinogenesis. Cancers (Basel). 15, 4250 (2023). https://doi.org/10.3390/cancers15174250
30. Li, S., Han, X., Song, J., Dong, M., Xie, T.: Mechanism of Action and Risk Prediction of Adiponectin in Cardiovascular Diseases. FBL. 29, 286 (2024). https://doi.org/10.31083/j.fbl2908286
31. Naimo, G.D., Gelsomino, L., Catalano, S., Mauro, L., Andò, S.: Interfering Role of ERα on Adiponectin Action in Breast Cancer. Front. Endocrinol. 11, (2020). https://doi.org/10.3389/fendo.2020.00066
32. Al-Mansoori, L., Al-Jaber, H., Prince, M.S., Elrayess, M.A.: Role of Inflammatory Cytokines, Growth Factors and Adipokines in Adipogenesis and Insulin Resistance. Inflammation. 45, 31–44 (2022). https://doi.org/10.1007/s10753-021-01559-z
33. Barber, T.M., Kyrou, I., Randeva, H.S., Weickert, M.O.: Mechanisms of Insulin Resistance at the Crossroad of Obesity with Associated Metabolic Abnormalities and Cognitive Dysfunction. Int J Mol Sci. 22, 546 (2021). https://doi.org/10.3390/ijms22020546
34. Kuryłowicz, A.: Estrogens in Adipose Tissue Physiology and Obesity-Related Dysfunction. Biomedicines. 11, 690 (2023). https://doi.org/10.3390/biomedicines11030690
35. Bartkowiak-Wieczorek, J., Jaros, A., Gajdzińska, A., Wojtyła-Buciora, P., Szymański, I., Szymaniak, J., Janusz, W., Walczak, I., Jonaszka, G., Bienert, A.: The Dual Faces of Oestrogen: The Impact of Exogenous Oestrogen on the Physiological and Pathophysiological Functions of Tissues and Organs. International Journal of Molecular Sciences. 25, 8167 (2024). https://doi.org/10.3390/ijms25158167
36. Chimento, A., De Luca, A., Avena, P., De Amicis, F., Casaburi, I., Sirianni, R., Pezzi, V.: Estrogen Receptors-Mediated Apoptosis in Hormone-Dependent Cancers. Int J Mol Sci. 23, 1242 (2022). https://doi.org/10.3390/ijms23031242
37. Zhang, Y.-Y., Li, Y.-J., Xue, C.-D., Li, S., Gao, Z.-N., Qin, K.-R.: Effects of T2DM on cancer progression: pivotal precipitating factors and underlying mechanisms. Front Endocrinol (Lausanne). 15, 1396022 (2024). https://doi.org/10.3389/fendo.2024.1396022
38. Ugwu, O.P.-C., Alum, E.U., Okon, M.B., Aja, P.M., Obeagu, E.I., Onyeneke, E.C.: Ethanol root extract and fractions of Sphenocentrum jollyanum abrogate hyperglycaemia and low body weight in streptozotocin-induced diabetic Wistar albino rats. RPS Pharmacy and Pharmacology Reports. 2, rqad010 (2023). https://doi.org/10.1093/rpsppr/rqad010
39. Singh, S., Kriti, M., K.s., A., Sarma, D.K., Verma, V., Nagpal, R., Mohania, D., Tiwari, R., Kumar, M.: Deciphering the complex interplay of risk factors in type 2 diabetes mellitus: A comprehensive review. Metabolism Open. 22, 100287 (2024). https://doi.org/10.1016/j.metop.2024.100287
40. DeBerardinis, R.J., Chandel, N.S.: We need to talk about the Warburg effect. Nat Metab. 2, 127–129 (2020). https://doi.org/10.1038/s42255-020-0172-2
41. Chen, Y., Meng, Z., Li, Y., Liu, S., Hu, P., Luo, E.: Advanced glycation end products and reactive oxygen species: uncovering the potential role of ferroptosis in diabetic complications. Mol Med. 30, 141 (2024). https://doi.org/10.1186/s10020-024-00905-9
42. Ikpozu, E.N., Offor, C.E., Igwenyi, I.O., Obaroh, I.O., Ibiam, U.A., Ukaidi, C.U.A.: RNA-based diagnostic innovations: A new frontier in diabetes diagnosis and management. Diabetes & Vascular Disease Research. 22, 14791641251334726 (2025). https://doi.org/10.1177/14791641251334726
43. Zhao, L., Hu, H., Zhang, L., Liu, Z., Huang, Y., Liu, Q., Jin, L., Zhu, M., Zhang, L.: Inflammation in diabetes complications: molecular mechanisms and therapeutic interventions. MedComm (2020). 5, e516 (2024). https://doi.org/10.1002/mco2.516

44. Umoru, G.U., Uti, D.E., Aja, P.M., Ugwu, O.P., Orji, O.U., Nwali, B.U., Ezeani, N.N., Edwin, N., Orinya, F.O.: Hepato-Protective Effect of Ethanol Leaf Extract of *Datura stramonium* in Alloxan-Induced Diabetic Albino Rats. Journal of Chemical Society of Nigeria. 47, (2022). https://doi.org/10.46602/jcsn.v47i5.819
45. Akter, R., Awais, M., Boopathi, V., Ahn, J.C., Yang, D.C., Kang, S.C., Yang, D.U., Jung, S.-K.: Inversion of the Warburg Effect: Unraveling the Metabolic Nexus between Obesity and Cancer. ACS Pharmacology & Translational Science. 7, 560 (2024). https://doi.org/10.1021/acsptsci.3c00301
46. Acuña-Pilarte, K., Koh, M.Y.: The HIF axes in cancer: angiogenesis, metabolism, and immune-modulation. Trends in Biochemical Sciences. (2025). https://doi.org/10.1016/j.tibs.2025.06.005
47. Basheeruddin, M., Qausain, S.: Hypoxia-Inducible Factor 1-Alpha (HIF-1α) and Cancer: Mechanisms of Tumor Hypoxia and Therapeutic Targeting. Cureus. 16, e70700. https://doi.org/10.7759/cureus.70700
48. Li, H.-S., Zhou, Y.-N., Li, L., Li, S.-F., Long, D., Chen, X.-L., Zhang, J.-B., Feng, L., Li, Y.-P.: HIF-1α protects against oxidative stress by directly targeting mitochondria. Redox Biol. 25, 101109 (2019). https://doi.org/10.1016/j.redox.2019.101109
49. Magar, A.G., Morya, V.K., Kwak, M.K., Oh, J.U., Noh, K.C.: A Molecular Perspective on HIF-1α and Angiogenic Stimulator Networks and Their Role in Solid Tumors: An Update. Int J Mol Sci. 25, 3313 (2024). https://doi.org/10.3390/ijms25063313
50. Ruan, H., Zhang, Q., Zhang, Y., Li, S., Ran, X.: Unraveling the role of HIF-1α in sepsis: from pathophysiology to potential therapeutics—a narrative review. Critical Care. 28, 100 (2024). https://doi.org/10.1186/s13054-024-04885-4
51. Cheng, C., Geng, F., Cheng, X., Guo, D.: Lipid metabolism reprogramming and its potential targets in cancer. Cancer Commun (Lond). 38, 27 (2018). https://doi.org/10.1186/s40880-018-0301-4
52. Barzegar Behrooz, A., Talaie, Z., Jusheghani, F., Łos, M.J., Klonisch, T., Ghavami, S.: Wnt and PI3K/Akt/mTOR Survival Pathways as Therapeutic Targets in Glioblastoma. Int J Mol Sci. 23, 1353 (2022). https://doi.org/10.3390/ijms23031353
53. Eichhorn, P.J.A., Gili, M., Scaltriti, M., Serra, V., Guzman, M., Nijkamp, W., Beijersbergen, R.L., Valero, V., Seoane, J., Bernards, R., Baselga, J.: PI3K Hyperactivation Results in Lapatinib Resistance that is Reversed by the mTOR/PI3K Inhibitor NVP-BEZ235. Cancer Res. 68, 9221–9230 (2008). https://doi.org/10.1158/0008-5472.CAN-08-1740
54. Gonzalez-Franquesa, A., Gama-Perez, P., Kulis, M., Szczepanowska, K., Dahdah, N., Moreno-Gomez, S., Latorre-Pellicer, A., Fernández-Ruiz, R., Aguilar-Mogas, A., Hoffman, A., Monelli, E., Samino, S., Miró-Blanch, J., Oemer, G., Duran, X., Sanchez-Rebordelo, E., Schneeberger, M., Obach, M., Montane, J., Castellano, G., Chapaprieta, V., Sun, W., Navarro, L., Prieto, I., Castaño, C., Novials, A., Gomis, R., Monsalve, M., Claret, M., Graupera, M., Soria, G., Wolfrum, C., Vendrell, J., Fernández-Veledo, S., Enríquez, J.A., Carracedo, A., Perales, J.C., Nogueiras, R., Herrero, L., Trifunovic, A., Keller, M.A., Yanes, O., Sales-Pardo, M., Guimerà, R., Blüher, M., Martín-Subero, J.I., Garcia-Roves, P.M.: Remission of obesity and insulin resistance is not sufficient to restore mitochondrial homeostasis in visceral adipose tissue. Redox Biology. 54, 102353 (2022). https://doi.org/10.1016/j.redox.2022.102353
55. Rigotto, G., Basso, E.: Mitochondrial Dysfunctions: A Thread Sewing Together Alzheimer's Disease, Diabetes, and Obesity. Oxidative Medicine and Cellular Longevity. 2019, 7210892 (2019). https://doi.org/10.1155/2019/7210892
56. Zhang, Z., Huang, Q., Zhao, D., Lian, F., Li, X., Qi, W.: The impact of oxidative stress-induced mitochondrial dysfunction on diabetic microvascular complications. Front. Endocrinol. 14, (2023). https://doi.org/10.3389/fendo.2023.1112363
57. Kumar, M.A., Baba, S.K., Khan, I.R., Khan, M.S., Husain, F.M., Ahmad, S., Haris, M., Singh, M., Akil, A.S.A.-S., Macha, M.A., Bhat, A.A.: Glutamine Metabolism: Molecular Regulation, Biological Functions, and Diseases. MedComm. 6, e70120 (2025). https://doi.org/10.1002/mco2.70120
58. Wei, Z., Liu, X., Cheng, C., Yu, W., Yi, P.: Metabolism of Amino Acids in Cancer. Frontiers in Cell and Developmental Biology. 8, 603837 (2021). https://doi.org/10.3389/fcell.2020.603837
59. Zhang, J., Gao, P., Chang, W.-R., Song, J.-Y., An, F.-Y., Wang, Y.-J., Xiao, Z.-P., Jin, H., Zhang, X.-H., Yan, C.-L.: The role of HIF-1α in hypoxic metabolic reprogramming in osteoarthritis. Pharmacological Research. 213, 107649 (2025). https://doi.org/10.1016/j.phrs.2025.107649
60. Cui, Y., Chen, J., Zhang, Z., Shi, H., Sun, W., Yi, Q.: The role of AMPK in macrophage metabolism, function and polarisation. Journal of Translational Medicine. 21, 892 (2023). https://doi.org/10.1186/s12967-023-04772-6
61. Kennedy, B.K., Lamming, D.W.: The mechanistic Target of Rapamycin: The grand conducTOR of metabolism and aging. Cell Metab. 23, 990–1003 (2016). https://doi.org/10.1016/j.cmet.2016.05.009
62. Zhao, Q., Lin, X., Wang, G.: Targeting SREBP-1-Mediated Lipogenesis as Potential Strategies for Cancer. Frontiers in Oncology. 12, 952371 (2022). https://doi.org/10.3389/fonc.2022.952371

63. Tyagi, S., Gupta, P., Saini, A.S., Kaushal, C., Sharma, S.: The peroxisome proliferator-activated receptor: A family of nuclear receptors role in various diseases. J Adv Pharm Technol Res. 2, 236–240 (2011). https://doi.org/10.4103/2231-4040.90879
64. Basheer, H.A., Salman, N.M., Abdullah, R.M., Elsalem, L., Afarinkia, K.: Metformin and glioma: Targeting metabolic dysregulation for enhanced therapeutic outcomes. Translational Oncology. 53, 102323 (2025). https://doi.org/10.1016/j.tranon.2025.102323
65. Gu, C., Loube, J., Lee, R., Bevans-Fonti, S., Wu, T.D., Barmine, J.H., Jun, J.C., McCormack, M.C., Hansel, N.N., Mitzner, W., Polotsky, V.Y.: Metformin Alleviates Airway Hyperresponsiveness in a Mouse Model of Diet-Induced Obesity. Front. Physiol. 13, (2022). https://doi.org/10.3389/fphys.2022.883275
66. Misal, S., Patil, V.M., Ramaa, C.S., Lavecchia, A.: Peroxisome proliferator-activated receptor antagonists as emerging therapeutics in cancer treatment. Bioorganic Chemistry. 163, 108693 (2025). https://doi.org/10.1016/j.bioorg.2025.108693
67. Hajirahimkhan, A., Brown, K.A., Clare, S.E., Khan, S.A.: SREBP1-Dependent Metabolism as a Potential Target for Breast Cancer Risk Reduction. Cancers. 17, 1664 (2025). https://doi.org/10.3390/cancers17101664
68. Motevalli, M., Stanford, F.C.: Personalized Lifestyle Interventions for Prevention and Treatment of Obesity-Related Cancers: A Call to Action. Cancers. 17, 1255 (2025). https://doi.org/10.3390/cancers17081255
69. Alum, E.U.: AI-driven biomarker discovery: enhancing precision in cancer diagnosis and prognosis. Discov Onc. 16, 313 (2025). https://doi.org/10.1007/s12672-025-02064-7

CITE AS: Kato Jumba K. (2025). Metabolic Reprogramming in Obesity-Linked Cancers: Interplay with Diabetic Pathophysiology. NEWPORT INTERNATIONAL JOURNAL OF SCIENTIFIC AND EXPERIMENTAL SCIENCES 6(3):212-220 https://doi.org/10.59298/NIJSES/2025/63.212220