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Metabolic Reprogramming in Obese Cancer Patients: Natural Product Interventions Targeting AMPK/mTOR Pathways

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ABSTRACT

Obesity-induced metabolic reprogramming fosters a tumor-promoting environment by altering key signaling pathways involved in energy homeostasis, including AMP-activated protein kinase (AMPK) and mammalian target of rapamycin (mTOR). These pathways are intricately involved in cellular energy balance, proliferation, autophagy, and survival, making them crucial targets in the treatment of obesity-associated cancers. Dysregulation of AMPK/mTOR signaling in obese individuals facilitates oncogenic metabolic adaptation, thereby increasing cancer risk, progression, and resistance to therapy. Natural products, including polyphenols, alkaloids, terpenoids, and flavonoids, have emerged as potent modulators of AMPK/mTOR signaling, offering a promising chemopreventive and therapeutic approach. This review explores the underlying mechanisms of metabolic reprogramming in obese cancer patients, emphasizing the role of the AMPK/mTOR axis. It also highlights recent findings on natural compounds that modulate these pathways to suppress tumor growth, restore metabolic balance, and enhance sensitivity to anticancer therapies. Understanding the molecular interplay between obesity, metabolic signaling, and natural product interventions may lead to more personalized and effective cancer treatments.

Keywords: Obesity, Metabolic Reprogramming, AMPK, mTOR, Natural Products

INTRODUCTION

The global surge in obesity has precipitated an alarming increase in the incidence and mortality of obesity-associated malignancies, notably breast, colon, liver, pancreatic, kidney, and endometrial cancers[1–3]. With more than 650 million adults classified as obese worldwide, obesity has emerged not only as a public health crisis but also as a critical oncogenic risk factor[4–6]. Epidemiological studies consistently link excess adiposity with elevated cancer risk, aggressive tumor behavior, and poorer prognosis, particularly in hormone-sensitive and metabolically active tissues[7, 8]. The interplay between obesity and cancer is complex and multifactorial, involving systemic metabolic disturbances, hormonal dysregulation, chronic inflammation, immune modulation, and alterations in adipokine signaling[9–11].

Among the various mechanistic pathways connecting obesity and cancer, metabolic reprogramming has garnered increasing attention[5, 12]. Cancer cells in obese individuals undergo profound alterations in energy metabolism to support their heightened demands for proliferation, survival, invasion, and resistance to therapy. This phenomenon, often referred to as the "Warburg effect," is characterized by increased glucose uptake and aerobic glycolysis, even in the presence of oxygen[13, 14]. However, beyond glycolysis, tumor cells also exploit lipid metabolism, amino acid utilization, and mitochondrial dynamics in a highly orchestrated manner. In obese individuals, the nutrient-rich and pro-inflammatory microenvironment further exacerbates this reprogramming, tipping the metabolic balance in favor of tumorigenesis[15–17].

Central to this process are two key regulators of cellular energy homeostasis: AMP-activated protein kinase (AMPK) and the mammalian target of rapamycin (mTOR)[18–20]. AMPK serves as a cellular energy sensor that is activated under conditions of energy stress, such as glucose deprivation or increased AMP/ATP ratio. Once activated, AMPK inhibits anabolic processes and promotes catabolic pathways to restore energy balance.

In contrast, mTOR is a master regulator of cell growth, proliferation, and protein synthesis, and is frequently hyperactivated in both obesity and cancer[21–23]. Under normal conditions, AMPK negatively regulates mTOR activity through phosphorylation of upstream effectors like TSC2 and Raptor. However, in obesity, persistent hyperinsulinemia, elevated levels of insulin-like growth factor 1 (IGF-1), and increased nutrient availability lead to chronic mTOR activation and diminished AMPK signaling, creating a pro-tumorigenic environment[18, 19].

Moreover, obesity-driven chronic inflammation significantly contributes to the dysregulation of the AMPK/mTOR axis[24]. Adipose tissue in obese individuals becomes infiltrated with immune cells, particularly pro-inflammatory macrophages, which secrete cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and monocyte chemoattractant protein-1 (MCP-1). These cytokines not only impair insulin signaling and promote insulin resistance but also activate oncogenic pathways, including PI3K/Akt/mTOR, while suppressing AMPK activity[25–27]. This metabolic and inflammatory crosstalk creates a feedforward loop that sustains tumor growth and resistance to apoptosis.

In recent years, natural products have emerged as promising candidates for targeting dysregulated metabolic pathways in obesity-associated cancers[28, 29]. Derived from plants, marine organisms, and microorganisms, these bioactive compounds possess a wide range of pharmacological activities, including anti-inflammatory, antioxidant, anti-proliferative, and pro-apoptotic effects. Importantly, many natural compounds have been shown to modulate the AMPK/mTOR axis[30, 31]. For example, resveratrol, a polyphenol found in grapes and berries, activates AMPK and downregulates mTOR signaling, thereby inhibiting tumor growth and enhancing autophagy[32, 33]. Similarly, curcumin, derived from turmeric, exerts anti-cancer effects through multiple mechanisms, including the activation of AMPK and suppression of the Akt/mTOR pathway[34–36]. Other natural agents such as berberine, epigallocatechin gallate (EGCG), quercetin, and ginsenosides have also demonstrated significant regulatory effects on AMPK/mTOR signaling in preclinical models of obesity and cancer[37–39]. These compounds not only suppress tumor proliferation and induce apoptosis but also improve insulin sensitivity and lipid metabolism, highlighting their dual benefits in metabolic disease and oncologic contexts. Furthermore, emerging evidence suggests that combining natural products with conventional therapies may enhance treatment efficacy and overcome resistance, particularly in metabolically reprogrammed tumors.

Despite the promising preclinical data, challenges remain in translating these findings into clinical success. Issues such as bioavailability, pharmacokinetics, dosage optimization, and potential toxicity must be addressed through rigorous pharmacological and clinical evaluations. Nevertheless, the integration of natural product-based strategies targeting metabolic vulnerabilities offers a novel and potentially effective approach in the prevention and treatment of obesity-related cancers.

This review provides a comprehensive overview of the AMPK/mTOR signaling network in the context of obesity-driven carcinogenesis and highlights the therapeutic potential of natural product interventions. By focusing on the mechanisms through which these compounds restore metabolic balance and inhibit tumor progression, we aim to underscore the importance of metabolism-based strategies in modern oncology and metabolic disease management.

2. Obesity and Cancer: A Metabolic Nexus

Obesity is increasingly recognized not only as a major public health crisis but also as a complex, systemic condition with significant implications for cancer development and progression[40–42]. Epidemiological data robustly link obesity to an increased risk of various malignancies, including breast, colorectal, endometrial, pancreatic, liver, kidney, and esophageal cancers[43]. At the heart of this association lies a confluence of metabolic, hormonal, and inflammatory alterations that create a fertile ground for tumorigenesis[43].

One of the central features of obesity is the persistent state of hyperinsulinemia and insulin resistance[44, 45]. In an attempt to compensate for reduced insulin sensitivity, pancreatic β-cells secrete more insulin[44]. Chronically elevated insulin levels not only regulate glucose homeostasis but also activate insulin and insulin-like growth factor-1 (IGF-1) signaling pathways. These pathways promote cell proliferation and survival by stimulating downstream effectors such as PI3K/Akt and mTOR, which are frequently dysregulated in cancer. Thus, insulin resistance in obese individuals acts as a mitogenic signal that fuels malignant transformation and tumor growth[44].

Another hallmark of obesity is chronic low-grade inflammation, also known as "meta-inflammation[10]." This arises from the infiltration of adipose tissue by immune cells, particularly M1 macrophages, which secrete pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and C-reactive protein (CRP). These inflammatory mediators not only interfere with insulin signaling but also activate transcription factors like NF-κB and STAT3, which promote tumor cell survival, proliferation, angiogenesis, and metastasis. Inflammation further exacerbates oxidative stress and DNA damage, setting the stage for carcinogenesis[22, 25, 44].

Leptin, an adipokine whose levels are elevated in obese individuals, also plays a critical role in linking obesity to cancer[3, 46, 47]. Leptin stimulates cell proliferation, angiogenesis, and migration while inhibiting apoptosis

through activation of JAK/STAT, MAPK, and PI3K/Akt signaling pathways. Its counterpart, adiponectin, which exerts anti-inflammatory and anti-proliferative effects, is paradoxically decreased in obesity, further tilting the balance toward tumor promotion[48, 49]. The altered adipokine milieu in obesity thus fosters a tumor-supportive environment. Another crucial metabolic alteration in obesity is the elevation of circulating free fatty acids (FFAs) and ectopic lipid deposition in non-adipose tissues. Excess FFAs can be taken up by cancer cells and used for membrane biosynthesis, β-oxidation, and as signaling molecules. FFAs activate peroxisome proliferator-activated receptors (PPARs) and other transcription factors that regulate cell proliferation and survival. Lipid overload also induces endoplasmic reticulum (ER) stress, which cancer cells exploit to adapt and survive under adverse conditions[50].

At the cellular level, obesity-induced metabolic stress promotes metabolic reprogramming—a hallmark of cancer[51]. This includes the shift from oxidative phosphorylation to aerobic glycolysis (the Warburg effect), enhanced glutaminolysis, and increased de novo lipogenesis. These metabolic pathways provide rapidly proliferating cancer cells with ATP, biosynthetic precursors, and reducing equivalents needed for growth and survival[51]. Obesity essentially equips cancer cells with the tools they need to thrive in a nutrient-rich, growth-permissive environment.

The AMPK/mTOR signaling axis is a key regulator of cellular metabolism and energy homeostasis that is dysregulated in obesity[24]. AMPK (AMP-activated protein kinase) functions as an energy sensor that activates catabolic pathways to restore ATP levels, while mTOR (mechanistic target of rapamycin) promotes anabolic processes including protein synthesis, nucleotide production, and lipid biosynthesis. In obese states, AMPK activity is often diminished due to nutrient surplus and inflammation, whereas mTOR activity is enhanced, leading to unchecked cellular growth and proliferation[24]. This imbalance not only accelerates tumor progression but also confers resistance to anti-cancer therapies.

Hence, obesity and cancer are metabolically intertwined. The hormonal imbalances, inflammatory signals, and metabolic shifts associated with obesity create a microenvironment that is conducive to cancer initiation and progression. Understanding this metabolic nexus offers a valuable framework for developing targeted interventions that can disrupt the obesity-cancer link, potentially leading to improved therapeutic outcomes and preventive strategies.

3. The AMPK/mTOR Signaling Axis in Cancer Metabolism

The AMPK/mTOR signaling axis serves as a central metabolic hub that governs cellular growth, proliferation, survival, and autophagy in response to nutrient and energy availability[52]. Its dysregulation is a hallmark of cancer metabolism and is often exacerbated in the context of obesity[52]. Understanding this signaling axis provides critical insights into the metabolic vulnerabilities of cancer cells and reveals potential therapeutic targets.

AMPK (AMP-activated protein kinase) acts as a cellular energy sensor[52]. When intracellular ATP levels decline and AMP or ADP levels rise—as occurs during energy stress or hypoxia—AMPK is activated through phosphorylation by upstream kinases like LKB1. Once activated, AMPK promotes energy-generating catabolic pathways (e.g., glycolysis and fatty acid oxidation) and inhibits energy-consuming anabolic processes (e.g., lipid and protein synthesis)[53]. This response helps restore cellular energy balance and maintain metabolic homeostasis.

On the other hand, mTOR (mechanistic target of rapamycin), particularly mTOR complex 1 (mTORC1), is a master regulator of anabolic metabolism. mTORC1 is activated by growth factors, amino acids, and insulin, and it promotes protein synthesis, lipogenesis, and nucleotide biosynthesis—processes essential for cell growth and proliferation[54, 55]. In cancer, mTORC1 is often hyperactivated due to mutations in upstream regulators such as PI3K, PTEN, or Akt, as well as external cues like insulin and IGF-1, which are elevated in obesity. This hyperactivation drives tumor progression by supporting biosynthetic needs and inhibiting autophagy[54].

AMPK and mTORC1 are functionally antagonistic. AMPK activation inhibits mTORC1 through multiple mechanisms. Firstly, it phosphorylates TSC2 (tuberous sclerosis complex 2), enhancing its GTPase activity that inhibits Rheb, an activator of mTORC1[56]. Secondly, AMPK directly phosphorylates raptor, a component of mTORC1, suppressing its function. Through these mechanisms, AMPK acts as a metabolic brake on cell growth when energy is scarce, whereas mTORC1 functions as the metabolic accelerator when nutrients and growth signals are abundant[56].

Beyond its role in inhibiting mTOR, AMPK orchestrates a broader anti-cancer metabolic program. It inhibits acetyl-CoA carboxylase (ACC), suppressing fatty acid synthesis, and downregulates SREBP-1c, a transcription factor involved in lipogenesis[57]. These actions reduce lipid availability for membrane biosynthesis, which is critical for proliferating cells. AMPK also promotes autophagy, a process by which cells degrade and recycle damaged organelles and proteins, providing substrates for energy production and mitigating stress. In cancer cells, this can either inhibit tumorigenesis or enable survival under nutrient-limited conditions, depending on context. In contrast, mTORC1 promotes the synthesis of proteins and lipids necessary for rapid cell division[57]. It phosphorylates S6K1 and 4E-BP1, leading to increased translation of mRNAs that encode for ribosomal proteins and other growth-related proteins. mTOR also enhances glycolysis by activating HIF-1α, a

transcription factor that upregulates glycolytic enzymes and glucose transporters, thereby sustaining the Warburg effect—a common metabolic feature of cancer cells.

In obesity, the balance between AMPK and mTORC1 is disrupted. Excess nutrients and hyperinsulinemia suppress AMPK and activate mTORC1, pushing cells into a pro-growth state. This imbalance not only promotes tumorigenesis but also contributes to therapy resistance by enhancing DNA repair, reducing apoptosis, and limiting autophagy[18]. Thus, restoring AMPK activity or inhibiting mTORC1 offers a strategic avenue for intervention.

Therapeutically, targeting the AMPK/mTOR axis has garnered significant attention. Metformin, an AMPK activator, has shown promise in reducing cancer incidence and improving outcomes, particularly in obese or diabetic patients[58]. mTOR inhibitors like rapamycin and its analogs (rapalogs) have been developed, although their efficacy is limited by feedback activation of upstream pathways and toxicity. Combining AMPK activators with mTOR inhibitors may offer synergistic benefits, simultaneously restraining anabolic metabolism and enhancing energy stress[58].

The AMPK/mTOR signaling axis serves as a critical metabolic switch that determines the fate of cancer cells. Its dysregulation in cancer, exacerbated by obesity, underscores its importance as a therapeutic target. Manipulating this axis offers a compelling approach to disrupt cancer cell metabolism, suppress tumor growth, and potentially overcome obesity-related oncogenic signaling.

4. Natural Products Modulating AMPK/mTOR Pathways

Natural compounds represent a promising frontier in the fight against cancer, particularly in the context of obesity-driven malignancies[59–61]. These bioactive agents, often derived from plants and dietary sources, offer a wide array of mechanisms to restore metabolic homeostasis and suppress oncogenic pathways. Unlike conventional chemotherapeutics, many of these compounds exhibit minimal toxicity and have demonstrated the ability to selectively target metabolic and signaling pathways central to cancer progression[28]. Their ability to modulate critical cellular processes such as autophagy, apoptosis, insulin sensitivity, and lipid metabolism makes them particularly valuable in addressing the unique metabolic challenges faced by obese cancer patients. Moreover, these natural compounds frequently act through the AMP-activated protein kinase (AMPK) and mammalian target of rapamycin (mTOR) pathways—key regulators of cellular energy and growth—thereby offering therapeutic leverage against metabolically reprogrammed tumor cells[62, 63].

Resveratrol, a well-studied polyphenol found in grapes and red wine, exemplifies the therapeutic promise of natural bioactives. It has been shown to activate AMPK and inhibit mTOR signaling, which together enhance autophagic flux and suppress tumor growth [64]. In both breast and colon cancer models, resveratrol mitigates inflammatory cytokine levels, downregulates lipogenic enzymes, and inhibits insulin-like growth factor signaling—factors often elevated in obesity-associated cancers[65–67]. Similarly, berberine, an isoquinoline alkaloid extracted from plants of the *Berberis* genus, enhances AMPK activity and significantly reduces de novo lipogenesis. Its capacity to improve insulin sensitivity and attenuate hepatic steatosis further positions it as a potent adjunct for treating metabolic disorders that fuel oncogenesis. In combination, these compounds not only arrest tumor cell proliferation but also target the metabolic dysfunctions that exacerbate cancer risk in obese individuals, offering a holistic and multitargeted therapeutic approach[68].

Curcumin, the principal curcuminoid derived from turmeric (*Curcuma longa*), also demonstrates dual regulation of AMPK and mTORC1 signaling. It has been widely investigated for its anti-inflammatory, antioxidant, and anticancer properties. In various cancer models, including pancreatic, prostate, and breast cancers, curcumin suppresses tumorigenesis by promoting apoptosis and inhibiting cell cycle progression[34, 69]. Notably, it sensitizes tumor cells to chemotherapeutic agents and reduces the expression of hypoxia-inducible factors and angiogenic markers. Epigallocatechin gallate (EGCG), the predominant catechin in green tea, mirrors many of curcumin's actions[70]. EGCG activates AMPK and suppresses mTOR activity, reducing the viability and invasiveness of several cancer cell lines. Additionally, EGCG modulates lipid and glucose metabolism, decreasing the pro-oncogenic effects of metabolic dysregulation often seen in obesity[71, 72]. These features make both curcumin and EGCG attractive candidates for combination therapy, offering metabolic correction alongside direct anticancer effects.

Quercetin, a naturally occurring flavonoid found in apples, onions, and other fruits and vegetables, further enriches the portfolio of promising metabolic regulators[73, 74]. It activates AMPK, inhibits mTOR signaling, and interferes with several oncogenic transcription factors such as NF-κB and STAT3. These actions result in reduced inflammation, decreased oxidative stress, and inhibition of tumor cell proliferation and migration. Quercetin has also been shown to enhance the efficacy of chemotherapy and radiation, making it a valuable adjunct in integrated cancer care. Importantly, all these compounds exhibit low toxicity and often display synergistic effects when combined with conventional therapies[74, 75]. This makes them particularly advantageous for use in obese cancer patients, where toxicity and comorbidities complicate treatment regimens. As such, the integration of these natural compounds into mainstream oncologic care holds great promise for improving outcomes through metabolic modulation and cancer suppression.

5. Clinical Implications and Future Directions

Despite compelling preclinical evidence supporting the efficacy of natural products in modulating cancer metabolism, their clinical translation faces significant obstacles. A major limitation is the poor bioavailability of many phytochemicals, such as curcumin, resveratrol, and berberine, which undergo rapid metabolism and clearance, resulting in subtherapeutic concentrations at tumor sites. Additionally, inconsistencies in extract purity and composition across batches of natural product formulations further challenge reproducibility and safety assessment in clinical trials. Furthermore, there is a lack of standardized dosing regimens, making it difficult to determine optimal therapeutic windows for efficacy and minimizing adverse effects.

To address these challenges, several innovative strategies are being pursued. Nanoparticle-based delivery systems, including liposomes, solid lipid nanoparticles, and polymeric micelles, can enhance the solubility, stability, and targeted delivery of natural compounds [76]. Prodrug development is also gaining traction, allowing inactive precursors to be metabolized into active agents within the tumor microenvironment, thus improving pharmacokinetics. Moreover, combinatorial approaches that integrate natural compounds with existing chemotherapies or metabolic inhibitors may produce synergistic effects, lower required doses, and reduce drug resistance.

Importantly, patient stratification based on metabolic phenotypes such as insulin resistance, lipid profiles, and inflammatory markers could significantly enhance therapeutic outcomes. This personalized approach allows for selecting patients who are more likely to benefit from AMPK/mTOR-targeted natural interventions. Future clinical trials should incorporate metabolic biomarkers and molecular profiling to evaluate patient responsiveness and treatment efficacy.

Ultimately, integrating natural product research with precision oncology and systems biology holds promise for optimizing cancer therapy in obese populations. Interdisciplinary collaboration across pharmacology, oncology, and bioengineering is critical to overcoming existing translational hurdles and unlocking the full therapeutic potential of nature-derived compounds in metabolic cancer treatment.

CONCLUSION

The intricate relationship between obesity and cancer is increasingly understood through the lens of metabolic reprogramming, with the AMPK/mTOR axis serving as a pivotal regulatory pathway. Obesity-induced metabolic disturbances, such as chronic nutrient surplus, insulin resistance, and altered adipokine signaling, result in aberrant activation of growth-promoting pathways and suppression of energy-sensing regulators like AMPK. This imbalance facilitates unchecked cellular proliferation, angiogenesis, and resistance to apoptosis, all hallmarks of cancer progression. Natural products have emerged as promising therapeutic agents capable of restoring this disrupted metabolic homeostasis. Compounds such as resveratrol, berberine, quercetin, and EGCG have demonstrated the ability to activate AMPK, inhibit mTOR signaling, and suppress downstream effectors involved in tumorigenesis. Their ability to target multiple molecular nodes makes them particularly attractive in the context of complex diseases like obesity-associated cancers. Moreover, their generally low toxicity profile supports their long-term use in prevention or adjunctive therapy. In obese cancer patients, these compounds not only inhibit tumor growth but may also improve systemic metabolic health, reduce inflammation, and restore insulin sensitivity, creating a more hostile environment for cancer cells. Furthermore, by enhancing the efficacy of standard treatments like chemotherapy and radiotherapy, these agents offer a dual benefit. However, to fully harness their potential, further research is essential. Investigations into the molecular targets, pharmacodynamics, and interactions of natural products with host metabolism will inform rational drug design and clinical application. Additionally, robust clinical trials involving obese patient cohorts, metabolic profiling, and biomarker-driven endpoints are necessary to confirm their therapeutic efficacy. In conclusion, targeting AMPK/mTOR signaling using natural compounds represents a novel and integrative approach to combat obesity-driven cancers. With continued investment in translational research and precision medicine, these nature-derived interventions may soon find a central place in metabolic oncology.

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