Obesity and Cancer Mechanisms: Cancer Metabolism

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ABSTRACT

Obesity is a risk factor for cancer development and is associated with poor prognosis in multiple tumor types. The positive energy balance linked with obesity induces a variety of systemic changes including altered levels of insulin, insulin-like growth factor-1, leptin, adiponectin, steroid hormones, and cytokines. Each of these factors alters the nutritional milieu and has the potential to create an environment that favors tumor initiation and progression. Although the complete ramifications of obesity as it relates to cancer are still unclear, there is convincing evidence that reducing the magnitude of the systemic hormonal and inflammatory changes has significant clinical benefits. This review will examine the changes that occur in the obese state and review the biologic mechanisms that connect these changes to increased cancer risk. Understanding the metabolic changes that occur in obese individuals may also help to elucidate more effective treatment options for these patients when they develop cancer. Moving forward, targeted clinical trials examining the effects of behavioral modifications such as reduced carbohydrate intake, caloric restriction, structured exercise, and/or pharmacologic interventions such as the use of metformin, in obese populations may help to reduce their cancer risk.

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INTRODUCTION

Cancer is a set of diseases in which normal cells undergo neoplastic transformation through a series of incremental steps that occur under selective pressure. Any change can be critical to tipping the scales toward the progression to malignancy.¹ The growth and proliferation of cells in a multicellular organism must be coordinated with the presence of sufficient nutrients that support macromolecule synthesis. Therefore, intracellular and systemic signaling networks that control growth are closely entwined with those that communicate nutrient status. Obesity, as a state of nutrient excess, chronically activates cellular growth factor signaling pathways and increases the risk for neoplastic transformation (Fig 1).

In the United States, obesity is an epidemic, with one in three adults classified as obese.²⁻⁴ Obesity is a risk factor for several tumor types including breast, endometrial, prostate, pancreatic, and colon cancer^{5,6} and obese patients with cancer have a higher risk of death.⁷ Although body mass index (BMI) is the reference standard for measuring adiposity, this metric ignores the composition of a unit of weight, which is quite variable in patients with cancer.⁸ Recently developed image-processing software can measure

adipose and skeletal muscle content from routine computed tomography (CT) images. Using this software, large clinical studies that acquire CT images to track tumor progression in patients with cancer can also obtain accurate measures of adiposity and skeletal muscle mass instead of relying on BMI as a surrogate marker. These measurements have highlighted the importance of sarcopenia to medication toxicity and mortality.^{8,9}

Adipose tissue is an integral part of the signaling network that maintains energy balance, so the enlargement of adipose depots in obesity has systemic signaling effects. Nutrient availability is communicated to cells and tissues via a systemic hormonal (endocrine) system. Within this system, specialized tissues coordinate nutrient homeostasis. For example, glucose homeostasis is a complex interplay among metabolic organs such as the pancreas, liver, kidney, adipose tissue, and skeletal muscle that regulate the storage, release, and utilization of glucose for all cells in the body. In regard to glucose metabolism, insulin is the most important hormone at the cellular level. Insulin binds to the insulin receptor (IR) at the cell surface and initiates signaling through multiple cascades that affect key cellular processes. These responses include the trafficking of glucose transporters to the cell membrane to increase the uptake of glucose, the production of biosynthetic

Fig 1. The signaling of obesity. (A) Changes in the size of adipose depots affect systemic homeostasis and lead to increases in insulin (INS), insulin-like growth factor (IGF), leptin, inflammatory cytokines, and result in decreased levels of adiponectin. IL-6, interleukin 6. (B) These signaling molecules activate cell surface receptors and drive signaling through the Janus kinase (JAK)/signal transducers and activators of transcription (STAT), mitogen-activated protein kinase (MAPK), and phosphatidylinositol 3-kinase (PI3K) signaling pathways, all of which are frequently altered in cancer. By chronically activating metabolic signaling cascades, the obese state lowers the barrier for oncogenic transformation by driving cell growth and proliferation, and resisting apoptosis. It is these functions that make components of these signaling pathways some of the most frequently altered in human cancers. Glut4, glucose transporter type 4; GP130, glycoprotein 130; IGFR, insulin-like growth factor receptor; INSR, insulin receptor; ObR, leptin receptor.

macromolecules, the activation of protein synthesis, and cell cycle progression.¹⁰

The endocrine system tightly controls cellular growth and proliferation; however, this link is abolished in cancer. In cancer, oncogenic mutations arise that alter cellular metabolism to support the biomass and energy demands of a hyperproliferative state. As first described by Otto Warburg, tumors have a propensity to shift away from oxidative phosphorylation for ATP production in favor of glycolysis.¹¹ Although this shift is in some ways paradoxical because it means that the cells generate far less ATP per molecule of glucose, it has been proposed that this change in metabolism provides the excess metabolites necessary for sustained proliferation.¹² This Warburg effect can be partially explained by a molecular switch in glycolysis that enhances expression of specific isoforms of the glycolytic enzymes such as pyruvate kinase and lactate dehydrogenase.

Obesity develops as a result of chronic caloric excess. The excess energy is stored as lipid in adipose tissue and may accumulate in other metabolic organs (such as the liver) and skeletal muscle. An increased amount of lipid significantly alters the normal metabolic milieu and creates an environment that chronically transmits a signal of nutrient excess to the cell. As a result, signaling cascades that drive glucose uptake, cell growth, cell proliferation, and angiogenesis are activated and lower the barrier for oncogenic transformation. For example, hyperinsulinemic rodents and humans are predisposed to developing multiple types of cancer.¹³⁻¹⁷ In addition to the extracellular signals driving cells to grow, the specific mutations present in the tumors are likely to play a role in the tumor response to the obese state. For example, tumors with

alterations in the phosphatidylinositol 3-kinase (PI3K) pathway have been shown to be more resistant to caloric restriction, whereas those without alterations in this pathway maintain sensitivity.¹⁸

Obesity may also fuel cancer cell growth by providing excess substrate for ATP production and lipid membrane generation. Despite the dependence of most cancer cells on glycolysis, there are examples of cells that can hijack the energy production power of beta oxidation.¹⁹⁻²² In the body, fatty acids produced from local adipose depots may feed nearby cancer cells, as has been described in models of ovarian cancer.²³ Therefore, large visceral lipid stores found in obesity may support tumor progression and uncontrolled cellular growth.²⁴ In cancer types that can use beta oxidation, direct targeting of fatty acid entry into the mitochondria with etomoxir may be a promising adjuvant therapy, as has been shown in cellular models of prostate and lung cancer.^{20,22}

ADIPOKINES

Adipokines are a set of cytokines secreted by adipose tissue that have pleiotropic effects on satiety, metabolism, cellular and systemic signaling, and inflammatory pathways.⁵ The increases in adipose tissue associated with obesity correlate with increases in leptin levels and with reductions in adiponectin levels. Leptin regulates appetite and energy balance through activation of a negative feedback loop between the adipose tissue and the CNS.²⁵ In culture, leptin has been shown to activate cell proliferation and survival in cancer cell lines including those of the prostate, breast, endometrium, and colon.²⁶⁻²⁸ Leptin activates multiple signaling

cascades including the PI3K, mitogen-activated protein kinase (MAPK), and Janus kinase/signal transducers and activators of transcription (JAK/STAT) pathways.^{29,30} Leptin can also induce interleukin-6 production, suggesting that changes in leptin levels may contribute to the systemic inflammation that is seen in the obese state.³¹

Adiponectin balances many of the protumorigenic effects of leptin. It inhibits cell growth in models of breast, endometrial, prostate, and colon cancers. In some instances, increasing adiponectin levels has been shown to increase rates of apoptosis, suggesting that it has a protective role in cancer.³²⁻³⁵ Adiponectin activates adenosine monophosphate-activated protein kinase, which has a variety of cellular effects including induction of cell cycle arrest and inhibition of mammalian target of rapamycin (mTOR) activity. Thus, the decrease in adiponectin levels seen in the obese state have the potential to promote tumor cell growth and alter tumor signaling and metabolism. Because leptin and adiponectin have opposing effects in cells, it has been proposed that the change in the ratio of the two adipokines is a critical change that links obesity and cancer.^{36,37}

STEROID HORMONES

Estrogens, androgens, progestogens, and adrenal steroids have also been demonstrated to connect obesity and cancer. For example, obesity has been established as a risk factor for breast and endometrial cancer in postmenopausal women.^{38,39} Estrogens are predominantly produced by the ovary through the aromatization of testosterone and androstenedione by aromatase. Adipose tissue also produces aromatase; therefore, in men and postmenopausal women, the conversion of androgens to estrogens is dependent upon adipose tissue. Estrogen signaling has multiple effects that are thought to promote tumor growth: It can stimulate cellular proliferation, inhibit apoptosis, and induce angiogenesis.^{40,41} Additionally, obesity is associated with lower levels of sex hormone-binding globulin, which increases the free estradiol that is associated with a greater cancer risk.⁴²

The connection between other steroid hormones and obesity is less clear. The androgen receptor can be activated by interleukin-6 and insulin-like growth factor-1 (IGF-1), which are both elevated in the obese state and can lead to prostate cancer cell survival and proliferation.^{43,44} Glucocorticoids are thought to be anti-inflammatory and capable of inducing p27, thereby acting in an antitumorigenic role by negatively regulating the cell cycle.^{45,46} The levels of bioactive androgens and glucocorticoids, however, are not clearly altered in mild (BMI, 30 to 35 kg/m²) and moderate (BMI, 36 to 40 kg/m²) obesity.^{47,48}

INSULIN/IGF SIGNALING

Insulin/IGF signaling is highly evolutionarily conserved.⁴⁹ In humans, insulin is produced in pancreatic beta cells, which secrete insulin in response to a variety of physiologic cues, most notably high blood glucose levels. Once secreted, insulin enters the blood stream and circulates throughout the body, where it can bind to IR on the cell surface. This extracellular interaction activates the tyrosine kinase domain of IR, allowing it to catalyze the

phosphorylation of the IR substrate proteins 1 and 2, which propagate the signal to multiple signaling pathways within cells including both the PI3K and MAPK signaling pathways.⁵⁰⁻⁵⁴ IR has been shown to be elevated in breast cancer, which may explain this tumor's sensitivity to hyperinsulinemia.⁵⁵⁻⁵⁷ There are two splice variants of IR, A (IR-A) and B (IR-B), of which the former is believed to play more of a mitogenic role whereas the latter has been linked to metabolism.⁵⁸ IR-A expression is dominant in many cancer types including breast, endometrial, lung, colon, hepatocellular, and renal.⁵⁹⁻⁶¹

Distinct from insulin, IGF-1 is secreted by the liver in response to growth hormone. The levels of active IGF-1 in the blood are regulated by IGF binding proteins (IGFBPs), which bind free IGF-1 and inhibit binding to the IGF-1 receptor (IGF1R). In this manner, the ratio of IGF-1 to IGFBPs is critical to determining the bioactive levels of IGF-1 in circulation. Serum IGF-1 levels are associated with an elevated risk of cancer including prostate and breast.⁶²⁻⁶⁴ Its mechanism of action is similar to that of insulin except that IGF-1 binds to IGF1R instead of IR. The downstream signaling cascades are also similar to those of insulin. Despite these similarities, there is evidence that IR and not IGF1R plays a critical role in tumor progression and metastasis in mouse models of breast cancer.⁶⁵ In other cancer types, IGF1R is upregulated. For example, IGF1R expression is more than five-fold higher in endometrial adenocarcinoma compared with normal endometrium.⁵⁹ Also, non-small-cell lung cancer prominently expresses IGF1R, and trials using targeted therapies are underway.⁶⁶

Insulin-like growth factor-2 (IGF-2) is a small peptide, produced mainly by the liver, that circulates at a concentration three-fold higher than IGF-1.⁶⁷ IGF-2 concentrations correlate with BMI and are elevated in patients with type 2 diabetes, an insulin-resistant state.⁶⁸ IGF-2 can act through IGF1R or IR-A to promote tumorigenesis.^{69,70} Increased expression of IGF-2 is found in tumors such as Wilms' tumor where specific epigenetic control is lost (eg, loss of imprinting).⁷¹ Loss of imprinting of the *IGF-2* gene is most commonly found in mesenchymal tumors; however, imprinting changes can also be detected in colon cancer.^{72,73} Expression in mesenchymal tumors can be so high that IGF-2 can induce refractory hypoglycemia.⁷⁴

After insulin or IGF have activated their receptors, the signaling induces a variety of cellular responses that are unique depending on the tissue of origin. The liver, for example, responds to insulin to maintain glucose homeostasis by controlling the synthesis and storage of glucose and other nutrients.^{75,76} Hepatocytes release glucose in times of low nutrient abundance, and this gluconeogenic process is inhibited in the presence of insulin. Skeletal muscle is the major site of glucose disposal in response to insulin, which stimulates glucose uptake and glycogen synthesis. In adipose tissue, however, the main role of insulin is controlling the storage of lipid and inhibition of lipolysis. When glucose and insulin levels are high for prolonged periods as a result of overeating and lack of exercise, insulin can stimulate storage of lipid in nonadipose tissue such as skeletal muscle. This inappropriate accumulation of intramuscular fatty acids is the most well-accepted mechanism of how obesity alters insulin signaling.^{76a} The exact signaling mechanism leading to insulin resistance is unclear, but probably has to do with fatty acid metabolites, such as diacylglycerol and fatty acyl-CoA, disrupting the ability of insulin receptor substrate 1 to associate with PI3K.

Most other nonendocrine tissues respond to insulin/IGF by increasing glucose uptake and activating anabolic pathways that are mediated, in part, through transcription factors such as hypoxia inducible factor and c-Myc. In this manner, insulin/IGF signaling stimulates cell growth and cell proliferation.^{10,77} Thus on the level of the human organism, insulin signaling is a critical component of metabolic homeostasis, balancing the storage and production of available nutrients.

In the context of neoplastic cells, increased glucose uptake in the setting of hyperinsulinemia can be used to meet the increased metabolic demand for both energy and biomass that is created by the hyperproliferative state.¹² Insulin increases hepatic production of IGF-1 and downregulates production of IGFBP-1, which are changes that result in increased bioavailable IGF-1.⁷⁸ Whether a cell responds to insulin, IGF-1, or both depends on which receptors and IGFs are expressed. For example, myocytes, adipocytes, and hepatocytes have high levels of IR, whereas other tissues express IGF1R or both IGF1R and IR.

By signaling through both the PI3K and MAPK pathways, insulin/IGF balance cell growth (PI3K) with proliferation (MAPK), and the crosstalk between these signaling cascades is critically important for normal development.⁷⁹ As a result of the entwined nature of these signaling networks, changes in activity of one of these cascades (which frequently occurs in cancer) can result in altered signaling through the other. These roles of insulin and IGF-1 underpin our understanding of why insulin resistance and hyperinsulinemia, two common comorbidities of the obese state, increase the risk of myriad cancer types including endometrial, breast, kidney, colorectal, and pancreatic.^{45,80} These epidemiologic findings have been supported by multiple studies in mouse models of breast cancer, which have demonstrated that hyperinsulinemia promotes breast cancer proliferation and metastasis, and profoundly affects the response of tumors to PI3K inhibitors.^{13,81}

Minimizing the Impact of Obesity

Obesity activates numerous oncogenic signaling pathways that promote tumor cell survival, proliferation, and metabolism. Therefore, it is critically important to minimize the impact of obesity in the care of the patient with cancer. The most obvious intervention to minimize the effects of obesity is weight loss. Epidemiologic studies show that intentional weight loss could reduce cancer incidence.⁸² The most effective way to induce weight loss is via a hypocaloric diet.⁸³ Although the macronutrient content of the diet does not play a significant role in the degree of weight loss over time,^{84,85} choosing a low-carbohydrate option may be beneficial in regard to tumor growth. Low-carbohydrate (ketogenic) diets lower blood glucose and insulin levels, and improve insulin sensitivity in humans⁸⁶ and in murine models.^{87,88} Ketogenic diets have proven safe and feasible in children with tuberous sclerosis⁸⁹ and adults with advanced cancer.⁹⁰ In patients with glioblastoma multiforme, the ketogenic diet is effective in lowering serum glucose, even in the setting of high-dose glucocorticoids.^{91,92}

These effects are expected to be beneficial to patients whose tumors evolved in the presence of the signaling imbalance of the obese state. Therefore, it seems plausible, and even probable, that a ketogenic diet could slow the progression of some types of cancer. However, the available evidence is only preliminary.⁹³

Another logical way to decrease serum insulin is by using drugs that suppress blood glucose levels. The widely used antidiabetic drug metformin increases insulin sensitivity in the liver and thereby reduces blood glucose and insulin levels. Metformin activates adenosine monophosphate-activated protein kinase, which suppresses multiple pathways involved in cell growth and reverses some of the proliferative signaling changes that occur as a result of the obese state. The impact of metformin on cancer cells may be the result of a direct effect on tumors or the more systemic improvement in insulin sensitivity.^{10,94-96}

Unlike the liver, which expresses high levels of organic cation transporters (OCT) that facilitate metformin uptake, the levels of OCT in tumors are variable.^{94,97,98} Direct tumor uptake is dependent upon OCT expression, and many tumors will probably not express sufficiently high levels of these transporters for efficient metformin entry. Therefore, the systemic effect of metformin to suppress insulin levels is more likely to account for the observed reduction in cancer risk seen in epidemiologic studies.^{99,100}

In regard to the treatment of cancer with metformin, the data are strongest for gynecologic cancer.¹⁰¹ In breast cancer, neoadjuvant metformin was shown to be safe and resulted in cellular changes consistent with anticancer effects, such as a dose-dependent reduction in the tumor proliferation marker Ki67¹⁰²⁻¹⁰⁵ and increased tumor apoptosis as measured by terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling staining.¹⁰³ This effect may be limited to patients with insulin resistance¹⁰⁶ and mediated by reduced Akt and extracellular regulated kinase 1/2 phosphorylation together with decreased insulin and IR levels.^{97,105,107} Additional information is expected to be gained from larger randomized, placebo-controlled, adjuvant trials such as the National Cancer Institute of Canada Clinical Trials Group MA.32.¹⁰⁸ Similarly, in endometrial cancer, metformin reduced tumor Ki67 staining¹⁰⁹⁻¹¹¹ and decreased markers of PI3K/Akt/mTOR signaling including reduced tumor Akt, S6, and 4E-BP1 phosphorylation.^{110,111} Results from studies in nongynecologic tumor types such as metastatic pancreatic cancer,¹¹²⁻¹¹⁴ non-small-cell lung cancer,¹¹⁵ esophageal dysplasia,¹¹⁶ and colorectal cancer^{100,117} have been either underpowered, from a poorly designed trial, or disappointing.

Other antidiabetic drugs may also be beneficial in limiting the effects of obesity on cancer development. For example, inhibitors of sodium-glucose cotransporters in the kidney lower blood glucose by blocking reabsorption of glucose from the kidney, which indirectly lowers insulin levels and induces weight loss;¹¹⁸ however, such interventions would still require investigation in clinical trials.

Because tumors frequently alter components of metabolic signaling pathways (eg, *KRAS* and *PIK3CA* mutations), these pathways have increasingly become the focus of targeted therapeutic development. Because these therapies are used in clinical trials and enter clinical practice, it will be critical to recognize the relationships that exist between the oncogenes being targeted and their role in metabolic signaling. Trials using these types of agents need to account for the systemic effects of the inhibitors (eg, the hyperglycemia and hyperinsulinemia caused by IR/IGF1R or PI3K inhibitors) as well as the effect of the patient's metabolic state (eg, obesity) on treatment efficacy.

Augmenting the therapies to limit the detrimental effects that these factors have on systemic signaling may be a critical component for the identification of effective therapeutic regimens. This

may be particularly important in the context of inhibitors that effect insulin signaling in endocrine tissues (such as PI3K, IGF1R/IR, and AKT inhibitors), which causes reflex hyperglycemia and hyperinsulinemia¹¹⁹⁻¹²¹ and has led to increased interest in pre-clinical approaches that combine targeted cancer therapies with metformin or other metabolic interventions to maximize therapeutic efficacy.^{94,122}

In contrast to most cancer drugs, agents such as metformin that suppress insulin levels are well tolerated.¹²³ Ketogenic diets are also well tolerated and can even be beneficial in reducing obesity, which could help to rebalance systemic metabolic signaling.⁸⁵ Less severe diets, which eliminate sugars and other rapidly released carbohydrates but still allow consumption of complex carbohydrates that are slowly released into the blood, can also be effective in reducing serum glucose and insulin levels. These approaches may have profound effects on cancer prevention as well as enhance the efficacy of small-molecule inhibitors that target insulin signaling.

Another limitation with metabolically focused agents, such as PI3K inhibitors, is the multiple intracellular feedback mechanisms that tightly control cellular metabolism and growth. Inhibition of PI3K induces upregulation of MAPK signaling, which allows tumors to escape the beneficial effects of the drug on inhibiting growth.¹²⁴ Trials that combine PI3K and MEK inhibitors are an obvious solution. Unfortunately, this approach targets critical survival pathways in all tissues and results in combined toxicities that limit the achievable therapeutic dose and clinical efficacy.¹²⁵ One potential therapeutic strategy, which may overcome systemic toxicity, is to coordinate dosing of targeted inhibitors correctly with peaks of intracellular feedback. For example, one could imagine a trial design where a PI3K inhibitor is administered on day 1, followed by a MEK inhibitor on day 3. These types of trials would require more detailed information on tumor signaling over time, which is best done in the preclinical setting.

Clinical trials are needed to evaluate the efficacy of approaches that target metabolic alterations in the obese state with combination therapies (such as PI3K and/or MEK inhibitors with chemotherapies). These trials should carefully quantify adiposity

via readily available CT techniques and assess markers of insulin resistance such as fasting glucose and insulin levels. A multidisciplinary team should be established during trial design and include members from oncology, cancer biology, endocrinology, and nutrition. The effectiveness of any targeted intervention on tumor signaling/metabolism should be evaluated using immunologic markers of MAPK/extracellular regulated kinase and PI3K/Akt/mTOR pathway activity, as is already being done in the neo-adjuvant setting with gynecologic tumors.^{97,109-111}

There are legitimate concerns that ketogenic diets, low-sugar diets, or sodium-glucose cotransporter inhibitors that lower serum glucose and insulin could lead to weight loss and exacerbate cachexia, which increases susceptibility to chemotherapeutic toxicity, reduces quality-of-life scores, decreases response to chemotherapy, and increases mortality.^{9,126,127} However, in light of the overwhelming evidence that obesity is a significant risk factor for cancer development, cancer progression, and a patient's response to therapy, it is critical to identify new clinical regimens that reduce the negative effects of this all-too-common metabolic state.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

AUTHOR CONTRIBUTIONS

Conception and design: All authors

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Collection and assembly of data: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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