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REVIEW ARTICLE

Energy Balance, Host-Related Factors, and Cancer Progression

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ABSTRACT

Obesity is associated with an increased risk and worsened prognosis for many types of cancer, but the mechanisms underlying the obesity–cancer progression link are poorly understood. Several energy balance–related host factors are known to influence tumor progression and/or treatment responsiveness after cancer develops, and these have been implicated as key contributors to the complex effects of obesity on cancer outcome. These host factors include leptin, adiponectin, steroid hormones, reactive oxygen species associated with inflammation, insulin, insulin-like growth factor–1, and sirtuins. Each of these host factors is considered in this article in the context of energy balance and cancer progression. In addition, future research directions in this field are discussed, including the importance of study designs addressing energy balance across the life course, the development and application of highly relevant animal models, potential roles of cancer stem cells in the response to energy balance modulation, and emerging pharmacologic approaches that target energy balance–related pathways.

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INTRODUCTION

Obesity is an established epidemiologic risk factor for a broad spectrum of cancers; it also negatively affects prognosis for many but not all types of cancer.[1-4] Although the prevalence of obesity has risen steadily for the past several decades in the United States and many other countries,[5,6] the mechanisms underlying the poorer outcomes in many obese patients with cancer and cancer survivors are complex and may include obesity-mediated effects on cancer-related processes such as tumor progression; problems associated with adjusting dose of cancer therapeutics in obese patients; and/or other comorbid conditions associated with obesity such as diabetes, cardiovascular disease, and thromboembolic conditions. Significant evidence suggests that although these factors may influence survival, several energy balance–related host factors clearly affect tumor progression and/or treatment responsiveness after cancer develops.

Hormones and other host factors regulate many energy balance–related physiologic processes, including appetite, energy expenditure, body temperature control, and nutrient and energy metabolism.[7] Recent findings, particularly from animal models of cancer progression in which specific pathways have been altered, provide evidence that key host factors associated with metabolic syndrome link energy balance to cancer progression and/or responsiveness to therapy.[7] This mechanistic review focuses on these host factors, including leptin, adiponectin, steroid hormones, reactive oxygen species associated with inflammatory processes, insulin, insulin-like growth factor–1 (IGF-1), and sirtuins. Articles in this review were identified using a MEDLINE database search (from September 1, 1969, to September 1, 2009) for the keywords cancer OR carcinogenesis AND progression OR prognosis AND obesity OR energy balance.

LEPTIN

The peptide hormone leptin is secreted from adipocytes and involved in appetite control and energy metabolism through its effects on the hypothalamus.[8] High circulating levels of leptin are characteristic of an obese state. Leptin resistance explains the inability of exogenous leptin administration to prevent weight gain.[9] Epidemiologic studies suggest an association between circulating leptin levels and cancer progression, with the strongest links shown in colon, prostate, and breast cancers.[10-12] As demonstrated in in vitro studies, leptin stimulates preneoplastic and neoplastic colon cell proliferation without inducing normal cell proliferation.[13] Leptin

also promotes proliferation in some (but certainly not all) mammary and other cancer cell lines in vitro and promotes tumor invasion and angiogenesis in some (but not all) animal models.[14,15]

Although not well studied, and with some inconsistency across model systems, leptin remains positioned as an important component in the association between energy balance and cancer. It communicates the size of fat stores to the CNS, because levels of leptin and adipose tissue strongly correlate in animals and humans.[8] The Janus kinase 2/signal transducer and activator of transcription 3 pathway transduces the signal of leptin from its receptor.[16,17] There is emerging evidence of crosstalk between the Janus kinase/signal transducer and activator of transcription family of transcription factors, the insulin/IGF-1/Akt pathway, and adenosine monophosphate–activated protein kinase (AMPK).[18] In addition, leptin production and hepatic IGF-1 synthesis may be coregulated at the level of the hypothalamus/pituitary/adrenal axis.[16] Leptin also functions as an adipocytokine and can influence inflammatory responses, possibly by triggering release of interleukin (IL) -6 and other obesity-related cytokines.[16,17]

ADIPONECTIN

The peptide hormone adiponectin is produced by adipocytes and involved in the regulation of carbohydrate and lipid metabolism and insulin sensitivity.[19] Plasma levels of adiponectin, in contrast with other adipokines, are decreased in response to several metabolic impairments, including type 2 diabetes, dyslipidemia, and extreme obesity.[19] Lower levels of adiponectin are consistently related to increased risk of multiple malignancies, including uterine,[20] postmenopausal breast,[21] colorectal,[22] and higher-grade prostate tumors.[23] This association may be explained by the observation that adiponectin downregulates several growth-promoting pathways,[19,24,25] and decreased adiponectin may have a permissive effect on tumor growth. The obesity-related decrease in adiponectin can be partially reversed by weight loss, although these changes are relatively small unless there are drastic weight changes, such as those occurring after moderate to severe caloric restriction (CR) or surgical intervention.[19] Recent findings suggest leptin and adiponectin interact antagonistically to influence carcinogenesis,[26] although this interaction has not been clearly established in terms of cancer progression in vivo.

STEROID HORMONES

Estrogens, androgens, progesterone, and adrenal steroids are also involved in the relationship between energy balance and certain types of cancer. Estrogen synthesis in men and postmenopausal or otherwise ovarian hormone–deficient women occurs primarily in adipose tissue via aromatase-catalyzed conversion of gonadal and adrenal androgens to estrogens.[27] In addition, increased adiposity results in increased insulin and bioactive IGF-1 levels, leading to decreased levels of sex hormone binding globulin and thus increased bioavailable estradiol.[27] The risk of postmenopausal breast, endometrial, and colon cancers is associated with increased bioavailability of estradiol.[27] Adrenal glucocorticoid hormones may also play a role in the anticancer effects of CR, especially at restriction levels above 30%, which markedly increase corticosterone levels in rodents.[28,29] Glucocorticoid hormones have long been known to inhibit tumor promotion.[28,30] In addition to its anti-inflammatory effects, corticosterone can induce p27 and thus influence cell-cycle machinery.[29] Birt et al[28] have shown that the CR induction of corticosterone can inhibit protein kinase C and mitogen-activated protein kinase signaling, including reduced extracellular signal-regulated kinase–1 and –2 signaling and activator protein–1: DNA binding.

INFLAMMATION

The links between obesity and inflammation and between chronic inflammation and cancer have been well described.[31] Chronic, low-grade systemic inflammation typically accompanying obesity is associated with two- to three-fold increases in the circulating levels of the cytokines tumor necrosis factor (TNF) –α, soluble TNF receptor, IL-1β, IL-6, IL-1 receptor antagonist, and C-reactive protein.[32] The source of these elevated cytokines may be adipocytes or immune cells such as macrophages.[32] Activated macrophages exhibit either a classic proinflammatory M1 phenotype or an immunosuppressive M2 phenotype depending on the cytokine and chemokine environments.[33,34] In obesity, the M1 macrophage phenotype in adipose tissue typically predominates,[35] although the ability of CR, exercise, or other energy balance–related interventions to shift the proinflammatory M1 phenotype toward an anti-inflammatory M2 phenotype has not been well studied.

OXIDATIVE STRESS

Increased oxidative stress, commonly associated with obesity as a result of metabolic and inflammatory changes,[25,36] is characterized by an increased abundance of reactive oxygen species (ROS).[37] These highly reactive free radicals created by incomplete reduction of oxygen result in molecules of singlet oxygen and superoxide. Unless these free radicals are neutralized by antioxidant cell protective mechanisms, they can cause damage to lipids, proteins, and nucleic acids.[36-38] ROS have also been shown to contribute to activation of the P13K/Akt pathway by some of the obesity-associated cytokines and growth factors[39] and mutagenic changes,[40,41] potentially leading to progressive genetic instability, tumor progression, and metastasis.

INSULIN AND IGF-1

Insulin resistance or hyperinsulinemia increases the risk for and progression of several types of cancer, particularly colorectal, pancreatic, postmenopausal breast, and endometrial cancers.[42-45] Insulin exerts its tumor-enhancing effects directly via the insulin receptor (IR) or hybrid IR/IGF-1 receptors (IGF-1Rs) on preneoplastic and neoplastic cells or indirectly via IGF-1, estrogens, or other hormones. From a mechanistic viewpoint, the binding of insulin (or IGF-1, which exerts similar effects) to cell-surface receptors on tumors or precancerous cells activates the P13K/Akt pathway, leading to downstream activation of the mammalian target of rapamycin (mTOR) complex, which serves as a central regulator of cell growth and mitogenesis.[46] In addition, high circulating levels of insulin increase the biologic activity of IGF-1 by upregulating hepatic synthesis of IGF-1 and downregulating IGF binding protein (BP) –1 production.[46,47] Both insulin and IGF-1

are mitogens that promote cancer-cell proliferation in vitro and suppress apoptosis.[47] Intra-abdominal obesity promotes insulin resistance, a state of reduced responsiveness of tissues to the physiologic actions of insulin.[48] Clinical and epidemiologic evidence suggests that type 2 diabetes, which is usually characterized by chronic hyperinsulinemia and insulin resistance, is associated with poor prognosis in endometrial, pancreatic, kidney, colon, and pre- and postmenopausal breast cancers.[1-4,46-48]

IGF-1 is a major endocrine and paracrine regulator of tissue growth and metabolism. Supplementation of culture media with IGF-1 enhances in vitro proliferation and inhibits apoptosis in a variety of cancer-cell lines.[49] Epidemiologic studies suggest that elevated circulating IGF-1 is associated with increased risk and/or poorer prognosis of several types of human cancers, most notably prostate, postmenopausal breast, and colon cancers.[50-56] IGF-1 also appears to mediate many of the antiproliferative and anticancer effects of CR; restoration of IGF-1 levels in mice undergoing CR has been shown to abolish the antitumor effects of CR in multiple preclinical models.[49,57,58] Conversely, we have shown that diet-induced obesity can lead to insulin resistance, with increased IGF-1 and decreased IGFBP-1, which can result in enhanced IGF-1 signaling.[59,60]

IGF-1 acts either directly on cells via its receptor, IGF-1R (or hybrid IR/IGF-1Rs), or indirectly through interaction with other cancer-related molecules such as the p53 tumor suppressor.[61] Levels of circulating IGF-1 are determined primarily by growth hormone–regulated hepatic synthesis, which is influenced by dietary intake of energy and protein.[57] To a lesser extent, IGF-1 synthesis can also occur in extrahepatic tissues, but this entails a complex integration of signals involving growth hormone, other hormones, growth factors, and IGFBPs. In particular, IGFBP-3 is the most abundant IGFBP in circulation and is critical in determining the unbound IGF-1, the most bioactive form and the one most associated with cancer-promoting activity.[4,62]

There is increasing evidence that reduction in serum levels of IGF-1 mediates many of the antiproliferative, proapoptotic, and anticancer effects of CR through its role in an evolutionarily conserved regulatory pathway that is responsive to energy availability.[49,57,58] CR is a dietary strategy for reducing energy intake (typically in the range of 20% to 40% relative to the energy intake of a control group) to prevent or reverse obesity.[49] It is arguably the most potent, broadly acting dietary intervention for decreasing cancer progression in experimental models of cancer, and the anticancer effects of CR have been associated with decreased growth factors such as IGF-1.[49] Conversely, we have shown that diet-induced obesity can lead to insulin resistance, with increased IGF-1 and decreased IGFBP-1, which can result in enhanced IGF-1 signaling.[59,60] Restoration of IGF-1 levels in mice undergoing CR, or use of genetic models with constitutive IGF-1 production, has been shown to abolish the antitumor effects of CR in multiple preclinical models.[57,58,63,64] Recent reports of extended lifespan and delayed cancer development in response to CR in rhesus monkeys[65] and observations that CR resulting as a consequence of natural experiments, such as the long-term reduction in energy intake experienced by the Okinawan population relative to inhabitants of mainland Japan,[66] suggest the anticancer effects of CR reported in rodent models extend to primates, including humans.

As noted, downstream targets of IR, IGF-1R, or hybrid IR/IGF-1Rs comprise a signaling network that regulates cellular growth and metabolism predominately through induction of the PI3K/Akt pathway.[67-69] The importance of this signaling cascade in human cancers has recently been highlighted by the observation that it is one of the most commonly altered pathways in human epithelial tumors.[67-71] Engagement of the PI3K/Akt pathway allows both intracellular and environmental cues, such as energy availability and growth factor supply, to affect cell growth, proliferation, survival, and metabolism.

Activation of receptor tyrosine kinases and/or the Ras proto-oncogene stimulates PI3K to produce the lipid second messenger, phosphatidyl-inositol-3,4,5-trisphosphate, which recruits and anchors Akt to the cell membrane where it can be additionally phosphorylated and activated.[68] Akt is a cyclic AMP–dependent, cyclic guanosine monophosphate–dependent protein kinase C superfamily member, which when constitutively active is sufficient for cellular transformation by stimulating cell-cycle progression and cell survival as well as inhibiting apoptosis.[69,70] Frequently associated with the aberrant Akt signaling commonly seen in human cancers is an elevation in mTOR signaling.[71] mTOR is a highly conserved serine/threonine protein kinase that is activated by the Akt pathway and also inhibited by an opposing signal from AMPK.[71-74] At the interface of the Akt and AMPK pathways, mTOR dictates translational control of new protein synthesis in response to both growth factor signals and nutrient availability through phosphorylation of its downstream mediators, S6K and 4EBP-1.[71-74] Ultimately, activation of mTOR results in cell growth, cell proliferation, and resistance to apoptosis.

An important convergent point for these signaling cascades is the tumor suppressor tuberous sclerosis complex (TSC).[73,75,76] TSC is a Rheb G-associated protein that keeps Rheb in an inactive guanosine diphosphate–bound state by stimulating its GTPase activity. On phosphorylation by Akt, the inactivation and release of TSC allows Rheb to bind guanosine triphosphate and become active to stimulate mTOR. In contrast, AMPK inhibits mTOR via activation of the TSC complex. The TSC1/TSC2 heterodimer forms the TSC complex that negatively regulates mTOR signaling.[76] Phosphorylation of TSC2 by AMPK activates this tumor suppressor to repress mTOR and protein synthesis.

Briefly, the TSC binds to and sequesters Rheb, a G-protein required for mTOR activation, thus inhibiting mTOR and downstream targets. However, phosphorylation of the TSC elicits inactivation, and Rheb is released, allowing for direct interaction with guanosine triphosphate and subsequent activation of mTOR.[75] Alternatively, when TSC is inhibited, Rheb is able to phosphorylate and activate mTOR.

Energy balance can influence both the Akt and AMPK pathways of mTOR activation.[8,74-77] For example, overweight and obese states are positively associated, as previously mentioned, with high serum levels of insulin and/or IGF-1. We and others have found that obesity is associated with enhanced induction of the PI3K/Akt/mTOR pathway.[59,78,78a] In contrast, CR reduces steady-state PI3K/Akt/mTOR signaling as a result of decreased circulating levels of IGF-1.[59,79] Furthermore, genetic reduction of circulating IGF-1 mimics the effects of CR on tumor development and PI3K/Akt/mTOR signaling.[63] Additionally, the literature suggests that elevated cellular amino acid, glucose, and adenosine triphosphate concentrations, as present during high-energy conditions, signal for mTOR activation.[8,78] Conversely, it has been shown that low glucose availability, high AMP/adenosine triphosphate ratios, and decreased

amino acids, as achieved during CR, can lead to growth arrest, apoptosis, and autophagy through AMPK-induced repression of mTOR.[8,78]

Another consequence of increased steady-state signaling through the Akt/mTOR pathway associated with the obese state is enhanced resistance to multiple cancer therapies.[80] For example, clinical studies strongly suggest that obesity is associated with worse outcome in patients with breast cancer receiving endocrine therapy.[81,82] In addition, our preliminary animal model studies demonstrate a significant decrease in mammary tumor response to endocrine therapy agents in obese mice compared with mice in the control group (unpublished data). These findings suggest that a worse prognosis in the obese patient with breast cancer may be related to obesity-induced alterations in tumor biology resulting in resistance to therapy. Uterine and prostate cancers provide additional examples of hormone-responsive tumors showing worse prognosis in obese patients.[1] An emerging issue in this area is the relative effects of nature versus nurture (ie, the contributions of systemic factors [lsbq]which have been the focus of this review] in the context of cell autonomous effects). The recent observations by Kalaany et al[83] that cancer cells with constitutively activated *PI3K* mutations are proliferative in vitro in the absence of insulin or IGF-1 and that they form CR-resistant tumors in vivo illustrate this issue. These findings suggest that cell autonomous alterations, such as certain types of activating *PI3K* mutations, may influence the response of cells to energy balance–related host factors, additionally illustrating the complexity of the relationships between energy balance, host factors, and cancer prognosis.

SIRTUINS

Sirtuins comprise a family of proteins that has been implicated in the regulation of aging,[84] endocrine signaling,[85] transcription,[86] and most recently metabolic changes associated with obesity.[87] Sirtuins were originally studied in the budding yeast *Saccharomyces cerevisiae*[88,89] and nematode *Caenorhabditis elegans*,[90] in which CR was shown to increase lifespan as well as increase the levels and activity of the Sir2 protein. In mammals, it has been shown that the levels of sirtuin 1 (SIRT1), a mammalian homolog of Sir2, also rise during CR and promote long-term survival of cells.[86] SIRT1 is a nicotinamide adenine dinucleotide–dependent deacetylase that acts on Ku70, which in turn sequesters the proapoptotic factor Bax from the mitochondria, thus inhibiting stress-induced apoptotic cell death.[86] Additionally, SIRT1 has been shown to repress peroxisome proliferator–activated receptor–γ by docking with its cofactors and thereby ultimately repressing genes responsive to this receptor protein. This results in lipolysis on CR and SIRT1 upregulation.[91] Decreases in sirtuin levels during obesity, specifically SIRT1 levels, have been shown to regulate many other metabolic alterations linked to obesity. SIRT1 has been shown to play a role in regulation of adiponectin,[92,93] insulin secretion, plasma glucose levels, and insulin sensitivity[94,95] and regulation of oxygen consumption and mitochondrial capacity.[96,97] Another yeast Sir2 homolog, mammalian SIRT3, has been shown to be selectively downregulated at both the gene and protein levels in a mouse model of type 2 diabetes but not in a model of insulin deficiency without diabetes.[98] In this study, insulin-deficient mice lacked muscle insulin receptor but maintained normal levels of insulin, glucose, and insulin-regulated genes. However, the same mice with streptozotocin-induced diabetes modeled the metabolic changes associated with type 2 diabetes, including downregulation of SIRT1.[98] These findings suggest that sirtuins may be involved in the control of important downstream transcriptional regulatory mechanisms involved in glucose metabolism.

Although CR has long been shown to have a dramatic effect on lifespan and tumor suppression in almost every tumor type tested, the specific role of sirtuins in cancer development and progression has yet to be elucidated. Studies have presented conflicting data as to whether SIRT1 can act as a tumor suppressor gene or an oncogene.[99] SIRT1 is upregulated in several tumor types and can inhibit apoptosis and downregulate the expression of tumor suppressor genes to extend the longevity of epithelial cancer cells.[100] SIRT1 is upregulated in tumors and cancer cells lacking the tumor suppressor gene *HIC1*[101] and upregulated in mouse and human prostate cancers.[102] In addition, the repression of SIRT1 mediated by the protein deleted in breast cancer–1 has been shown to increase p53 function.[103,104] However, there is also evidence that SIRT1 can act to suppress polyp formation in the APC^{Min} intestinal tumor model.[105] Additionally, preclinical studies of resveratrol, a phytochemical shown to activate sirtuins, suggest that activation of SIRT1 may be a viable cancer prevention or therapy strategy.[106]

METABOLIC SYNDROME

It has recently been agreed by consensus that metabolic syndrome, originally identified as a group of conditions collectively associated with increased risk of cardiovascular disease,[107] consists of central obesity, raised blood pressure, raised fasting blood glucose, and dyslipidemia, the latter comprising raised triglyceridemia and lowered high-density lipoprotein cholesterol.[108] Metabolic syndrome is frequently accompanied by increases in many cancer-promoting factors, including insulin, IGF-1, adipokines, inflammatory cytokines, and ROS.[108,109] Thus, in addition to the growth-promoting effect of any of these individual energy balance–associated factors, obese patients with cancer with metabolic syndrome may be subject to a multitude of these factors acting in concert to promote tumor progression.[110,111] Metabolic syndrome has been associated with colon,[109] postmenopausal breast,[110] and other cancers.[111] From a therapeutic viewpoint, the combination of multiple factors stimulating tumor-cell growth suggests that blocking the effects of any one factor may be insufficient to control the effects on tumor progression. These observations emphasize the importance of controlling metabolic syndrome as an entity and/or identifying strategies to interrupt critical downstream points of convergence such as mTOR, which serves as a central focus for mediating the cell growth and proliferative effects for many of these factors.

FUTURE RESEARCH DIRECTIONS

Because processes and disorders associated with energy balance have been shown to have profound impacts on cancer incidence, progression, and prognosis, modifying or interrupting these processes should affect cancer incidence and mortality. Continued efforts directed at weight control and increasing physical activity to improve cancer control are clearly warranted. Behavioral modifications including CR

and other dietary approaches to prevent or reduce obesity are obvious strategies but are difficult to implement and even harder to maintain. Success with these approaches will require new understanding of control mechanisms and design of behavioral modifications, probably in collaboration with neuropharmacologic interventions, to more effectively regulate appetite control. Bariatric surgery, targeted at weight reduction, has significant hormonal effects, including control of many components of metabolic syndrome.[112] Bariatric surgery has been shown to reduce cancer mortality,[113] but its ability to decrease cancer progression in obese patients with established diagnoses of cancer has not yet been evaluated.

Behavior modifications associated with increased physical activity have been shown to moderately decrease cancer incidence in animal models and people and to slow cancer progression in model systems.[114-116] Exercise may contribute to improved cancer survival by multiple mechanisms, including improved insulin resistance resulting in lower insulin levels, reduced circulating bioactive hormone concentrations resulting in increased steroid hormone BPs, and reduced inflammatory cytokines such as TNF-α.[116]

Progress in this field will clearly require better understanding of mechanisms and timing of the cancer-promoting and protective effects associated with energy balance. Thus, although lifelong weight control is the ideal, obesity at different times throughout the life course can be associated with different types of and kinetics for tumor development. For example, increased body mass index during adolescence is associated with increased risk of glioma in adulthood,[117] whereas adult weight gain is associated with increased risk of colon cancer.[118]

In terms of model systems for the study of energy balance and cancer progression, tissue culture models are reductionist systems with obvious limitations, but they have been useful in identifying molecular pathways connecting energy balance–related factors to tumor-cell growth. In particular, applications of microarray and proteomic analysis, RNA interference techniques, and other molecular approaches to in vitro systems are helping to elucidate key pathways and identify which may be most promising for interventional targeting.

Rodent models, especially those with genetic modifications, have been useful in studying the effects of obesity and specific obesity-related growth factors on initiation and progression of mouse tumors.[119] For example, *A-ZIP/F-1* fatless but diabetic mice have been used determine the effects of insulin, IGF-1, vascular endothelial growth factor, and inflammatory cytokines on tumor growth independent of increased adiposity and adipokines.[120] Liver-specific IGF-1–deficient mice, which have a deletion in hepatic IGF-1 and consequently have reduced circulating IGF-1 levels, were used to demonstrate that IGF-1 is an important tumor-growth factor in the response to energy balance interventions.[121] Ob/ob mice, with a mutation in the leptin gene, and db/db mice, with elevated leptin but a mutation in the leptin receptor, both develop severe obesity[122] and have been useful in demonstrating the role of leptin in breast cancer progression (S.D. Hursting, personal communication, July 2010). *PEPCK-C^{mus}* transgenic mice with a lifelong enhanced exercise phenotype[123] have been useful in demonstrating a role for exercise in reducing cytokine levels, in association with delayed tumor progression. These and similar studies suggest that it would be useful if behavioral alterations targeted at cancer control were designed to modulate levels of hormones, cytokines, and other molecular mediators, including insulin, IGF-1, leptin, and others discussed in this article.

Another understudied area is the potential role of cancer stem cells in the response to energy balance–related host factors. The cancer stem cell hypothesis proposes that solid tumors arise from stem or progenitor cells that maintain cancer stem cell properties and continually repopulate the tumor. Cancer stem cells (particularly in breast cancer) have been shown to foster blood vessel formation and promote cell motility, have been implicated in cancer metastasis, and have marked therapeutic resistance.[124-127] It is currently unclear what role, if any, cancer stem cells play in the response to energy balance modulation.

Xenograft models in which human tumor cells are transplanted in immunodeficient mice are useful in evaluating the effects of pharmacologic interventions on tumor progression.[128] However, immunodeficient mice have several metabolic defects associated with altered immune and inflammatory responses and are resistant to developing obesity, precluding the use of these models to evaluate the effects of diet, physical activity, and/or pharmacologic manipulation of energy balance on human tumor xenograft progression.

Animal models have tremendous use in evaluating chemotherapeutic agents in combination with agents targeted at interfering with obesity-related growth factors. Because many of the obesity-related growth factors function through membrane receptor tyrosine kinases, it should be possible to develop blocking antibodies and/or selective tyrosine kinase inhibitors as has been done for the epidermal growth factor receptor in non–small-cell lung and colon cancers[129] and human epidermal growth factor receptor 2/neu in breast cancer.[130] The clinical development of blocking antibodies or small molecule inhibitors of IGF-1 or the IGF-1 receptor is currently an active area of research. Everolimus, an inhibitor of mTOR, is currently in clinical use for treatment of renal cell cancer.[131] Another analog, temsirolimus, has been shown to be effective in treating mantle-cell lymphoma,[132] and mTOR inhibitors are undergoing evaluation for other tumor types.

More agents are clearly needed and are in development to target the downstream intracellular pathways associated with obesity-associated growth factors, especially the P13K/Akt/mTOR pathway and inflammatory pathways, and these agents need to be evaluated in clinical trials in combination with other chemotherapeutic approaches.[133] Of particular promise is metformin, in widespread use as an insulin sensitizer for patients with type 2 diabetes mellitus.[134] Metformin activates AMPK, resulting in inhibition of the mTOR pathway, thus reducing tumor cell growth and proliferation.[135] In a recent study of patients receiving neoadjuvant chemotherapy for breast cancer, a group of women who were also treated with metformin for coexisting diabetes showed a greater rate of pathologic response.[136] Agents such as metformin that indirectly target the mTOR complex hold great promise, because mTOR serves as a central regulatory point connecting many energy balance pathways to growth.

There exists an important development need for anti-inflammatory agents capable of safely blocking obesity-related inflammatory pathways. Nonsteroidal anti-inflammatory drugs have been shown to lower the risk of colon cancer,[137] but their use has been limited by adverse cardiovascular and/or GI effects.[138,139] Additional research is needed to identify different targets and classes of agents to interfere with inflammatory pathways without causing cardiovascular or other toxicities.

In conclusion, this review considers the key metabolic factors and their pathways underlying the link between obesity and cancer progression, particularly components of the IGF-1/Akt/mTOR, adipokine, inflammatory, and the sirtuin pathways. Clearly, no single pathway accounts for all of the effects of obesity on cancer prognosis, as illustrated by the metabolic syndrome discussion. As with most chronic disease intervention strategies, combination approaches that target multiple pathways (and maximize efficacy and minimize adverse effects) will likely be most successful in offsetting the impact of obesity on cancer outcomes. Future studies that exploit emerging mechanistic information to target energy balance–responsive pathways through combinations of lifestyle (particularly diet and physical activity) and pharmacologic approaches will facilitate the translation of this research into effective cancer prevention and control strategies in humans.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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