
Obesity, Energy Balance, and Cancer: A Mechanistic Perspective

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Abstract

Nearly 36 % of adults and 20 % of children in the USA are obese, defined as a body mass index (BMI) ≥ 30 kg/m². Obesity, which is accompanied by metabolic dysregulation often manifesting in the metabolic syndrome, is an established risk factor for many cancers. Within the growth-promoting, proinflammatory environment of the obese state, cross talk between macrophages, adipocytes, and epithelial cells occurs via obesity-associated hormones, cytokines, and other mediators that may enhance cancer risk and/or progression. This chapter synthesizes the evidence on key biological mechanisms underlying the obesity–cancer link, with particular emphasis on obesity-associated enhancements in growth factor signaling, inflammation, and vascular integrity processes, as well as obesity-dependent microenvironmental perturbations, including the epithelial-to-mesenchymal transition. These interrelated pathways represent possible mechanistic targets for disrupting the obesity–cancer link.

Keywords

Obesity • Inflammation • Growth factor signaling • Vascular perturbations • Insulin resistance

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Abbreviations

AMPK	AMP-activated kinase
BMI	Body mass index
CR	Caloric restriction
COX-2	Cyclooxygenase-2
DIO	Diet-induced obesity
EMT	Epithelial-to-mesenchymal transition
FGF-2	Fibroblast growth factor-2
IGF-1	Insulin-like growth factor-1
JAK	Janus kinase
mTOR	Mammalian target of rapamycin
MCP-1	Monocyte chemoattractant protein-1
NF- κ B	Nuclear factor kappa-light-chain-enhancer of activated B cells
PAI-1	Plasminogen activator inhibitor-1
PI3K	Phosphatidylinositol 3-kinase
STAT	Signal transducer activator of transcription
TNF- α	Tumor necrosis factor-alpha
tPA	Tissue-type plasminogen activators
uPA	Urokinase-type plasminogen activators
VEGF	Vascular endothelial growth factor
ZEB1	Zinc finger E-box-binding homeobox 1

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1 Introduction

The prevalence of obesity, defined as a body mass index (BMI, body weight [in kilograms] divided by height [in meters] squared) $\geq 30 \text{ kg/m}^2$, has increased dramatically in recent decades in the United States, and nearly 36 % of adults and 20 % of children are now obese [1]. Among obese adults, approximately 60 % meet the criteria for the metabolic syndrome, a state of metabolic dysregulation characterized by insulin resistance, hyperglycemia, dyslipidemias (particularly hypertriglyceridemia), and hypertension [2]. In obesity and/or metabolic syndrome, alterations also occur in circulating levels of insulin, bioavailable insulin-like growth factor (IGF)-1, adipokines (e.g., leptin and adiponectin), inflammatory factors (e.g., cytokines), and vascular integrity-related factors (e.g., vascular endothelial growth factor [VEGF] and plasminogen activator inhibitor [PAI]-1) [3, 4]. Through these mediators, obesity and metabolic syndrome are linked to various chronic diseases [3, 5] including cardiovascular disease, type 2 diabetes, and the focus of this review, cancer.

Evidence-based cancer prevention guidelines urge avoiding obesity [6]. Overall, 14 % of all cancer deaths in men and 20 % of all cancer deaths in women are attributable to overweight and obesity [7]. Obesity is associated with increased mortality from cancer of the prostate and stomach in men; breast (postmenopausal), endometrium, cervix, uterus, and ovaries in women; and kidney (renal cell), colon, esophagus (adenocarcinoma), pancreas, gallbladder, and liver in both genders [7]. While the relationships between metabolic syndrome and specific cancers are less well established, first reports from the Metabolic Syndrome and Cancer Project, a European cohort study of approximately 580,000 adults, confirm associations between obesity (or BMI) in metabolic syndrome and risks of colorectal, thyroid, and cervical cancer [8]. With the increasing prevalence of obesity and metabolic syndrome, strategies to break the links between these conditions and cancer are urgently needed [3].

Herein, we discuss possible mechanisms underlying the links between obesity, metabolic syndrome, and cancer, with emphasis on obesity-associated enhancements in growth signaling, inflammation, and angiogenic processes and on the cross talk between macrophages, adipocytes, endothelial cells, and epithelial cells in many cancers. Specifically, we describe the dysregulation of growth signals (including insulin, IGF-1, downstream signaling pathways, and adipokines), cytokines and cellular cross talk, and vascular integrity factors in the obese state that may contribute to multifactorial enhancement of cancer processes. Components of these interrelated pathways offer possible mechanism-based targets for the prevention and control of cancers related to, or caused by, excess body weight and the metabolic syndrome. However, as we also discuss, key unanswered questions remain regarding the links between obesity, metabolic syndrome, and cancer and putative strategies to break them.

2 Dysregulated Growth Signals

2.1 Insulin and IGF-1

Insulin is a peptide hormone produced by pancreatic beta cells and released in response to elevated blood glucose. Hyperglycemia, a hallmark of metabolic syndrome, is associated with insulin resistance, aberrant glucose metabolism, chronic inflammation, and the production of other metabolic hormones such as IGF-1, leptin, and adiponectin [9]. Sharing ~50 % sequence homology with insulin, IGF-1 is a peptide growth factor produced primarily by the liver following stimulation by growth hormone. IGF-1 regulates growth and development of many tissues, particularly prenatally [10]. IGF-1 in circulation is typically bound to IGF-binding proteins (IGFBPs) that regulate the amount of free IGF-1 bioavailable to bind to the IGF-1 receptor (IGF-1R) and elicit growth or survival signaling [10]. In metabolic syndrome, the amount of bioavailable IGF-1 increases, possibly via hyperglycemia-induced suppression of IGFBP synthesis and/or hyperinsulinemia-induced promotion of hepatic growth hormone receptor expression and IGF-1 synthesis [9]. Elevated circulating IGF-1 is an established risk factor for many cancer types [10, 11].

2.2 Signaling Pathways Downstream of the Insulin Receptor and IGF-1R

The phosphatidylinositol 3-kinase (PI3K)/Akt pathway, downstream of the insulin receptor and IGF-1R, is one of the most commonly altered pathways in epithelial cancers [12]. This pathway integrates intracellular and environmental cues, such as growth factor concentrations and nutrient availability, to regulate cellular survival, proliferation, protein translation, and metabolism. Activation of receptor tyrosine kinases, such as the insulin receptor or IGF-1R, stimulates PI3K to produce lipid messengers that facilitate activation of the Akt cascade. Akt regulates the mammalian target of rapamycin (mTOR) [13], which regulates cell growth, cell proliferation and survival through downstream mediators. mTOR activation is inhibited by increased AMP-activated kinase (AMPK) under low nutrient conditions [14]. Increased activation of mTOR is common in tumors and many normal tissues from obese and/or diabetic mice [15], and specific mTOR inhibitors block the tumor-enhancing effects of obesity in mouse models [16, 17].

2.3 Leptin, Adiponectin and Their Ratio

Leptin is a peptide hormone produced by adipocytes, is positively correlated with adipose stores and nutritional status, and functions as an energy sensor to signal the brain to reduce appetite. In the obese state, adipose tissue overproduces leptin,

and the brain no longer responds to the signal. Insulin, glucocorticoids, tumor necrosis factor- α (TNF- α), and estrogens all stimulate leptin release [18]. Leptin has direct effects on peripheral tissues, indirect effects on hypothalamic pathways and modulates immune function, cytokine production, angiogenesis, carcinogenesis, and other biological processes [18]. The leptin receptor has similar homology to class I cytokines that signal through the Janus kinase and signal transducer activator of transcription (JAK/STAT) pathway that is often dysregulated in cancer [19].

Adiponectin is a hormone mainly secreted from visceral adipose tissue. Levels of adiponectin, in contrast to leptin, negatively correlate with adiposity. Adiponectin functions to counter the metabolic program associated with obesity and hyperleptinemia by modulating glucose metabolism, increasing fatty acid oxidation and insulin sensitivity, and decreasing production of inflammatory cytokines [20]. The possible mechanisms through which adiponectin exerts anticancer effects may include increasing insulin sensitivity, and decreasing insulin/IGF-1 and mTOR signaling via activation of AMPK. Adiponectin also reduces proinflammatory cytokine expression via inhibition of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) [21–23].

In vitro, animal and epidemiologic evidence linking leptin [23–25] or adiponectin [21, 26–28] individually to cancer risk is mixed. Associations between the adiponectin-to-leptin ratio and the metabolic syndrome [29–31] and some cancers [32–34] are reported. Further characterization of these links is needed.

3 Chronic Inflammation

3.1 Cytokines and Cross Talk Between Adipocytes, Macrophages, and Epithelial Cells

Obesity and metabolic syndrome are associated with a low-grade, chronic state of inflammation characterized by increased circulating free fatty acids and chemoattraction of immune cells (such as macrophages that also produce inflammatory mediators) into the local milieu [35–37]. These effects are further amplified by the release of inflammatory cytokines such as interleukin (IL)-1 β , IL-6, TNF- α , and monocyte chemoattractant protein (MCP)-1. Adipocytes can enlarge past the point of effective oxygen diffusion, which results in hypoxia and eventually necrosis. Free fatty acids escape the engorged/necrotic adipocytes and deposit in other tissues, which in turn promotes insulin resistance and diabetes (through down-regulation of insulin receptors and glucose transporters), hypertension, and fatty liver disease and also activates signaling molecules involved in epithelial carcinogenesis, such as NF- κ B [38].

NF- κ B is a transcription factor that is activated in response to bacterial and viral stimuli, growth factors, and inflammatory molecules (e.g., TNF- α , IL-6, and IL-1 β) and is responsible for inducing gene expression associated with cell

proliferation, apoptosis, inflammation, metastasis, and angiogenesis. Activation of NF- κ B is a common characteristic of many tumors and is associated with insulin resistance and elevated circulating levels of leptin, insulin, and/or IGF-1 [39, 40].

3.2 Inflammation and Cancer

The link between chronic inflammation and cancer development was first noticed nearly 150 years ago by Rudolph Virchow when he observed an abundance of leukocytes in neoplastic tissue [41]. Now, inflammation is a recognized hallmark of cancer, and growing evidence continues to indicate that chronic inflammation is associated with increased cancer risk [42–44]. Several tissue-specific inflammatory lesions are established neoplastic precursors for invasive cancer, including gastritis for gastric cancer, inflammatory bowel disease for colon cancer, and pancreatitis for pancreatic cancer [45, 46].

Tumor microenvironments are composed of multiple cell types including epithelial cells, fibroblasts, mast cells, and cells of the innate and adaptive immune system [46, 47]. As discussed previously, macrophages, which are activated in the obese state, infiltrate tumors and amplify the inflammatory tumor microenvironment, often through NF- κ B-dependent production of cytokines and angiogenic factors [46]. Another important cancer-related inflammatory mediator is cyclooxygenase (COX)-2, an enzyme that is upregulated in most tumors and catalyzes the synthesis of the potent inflammatory lipid metabolite, prostaglandin E₂. COX-2 overexpression is an indicator of poor prognosis in multiple cancer types [48].

In some cancers, inflammatory conditions precede malignant changes (as previously mentioned), whereas, in other cancer types, genetic alterations and pre-malignant changes precede the inflammatory microenvironment and neoplasia [44]. Malignancies may thus be initiated or exacerbated by inflammation, and increased levels of inflammation markers may be a cause and/or consequence of cancer [43, 44]. In either scenario, the inflammatory microenvironment exerts tumor-promoting effects, with dysregulated inflammation pathways implicated in genetic instability and also cell proliferation, survival, angiogenesis, and metastasis associated with cancer [42, 43, 49].

4 Microenvironmental Factors

4.1 Vascular Perturbations

VEGF, a heparin-binding glycoprotein produced by adipocytes and tumor cells, has angiogenic, mitogenic, and vascular permeability-enhancing activities specific for endothelial cells [50]. Circulating levels of VEGF are increased in obese, relative to lean, humans and animals, and increased tumoral expression of VEGF is associated with poor prognosis in several obesity-related cancers [51]. The need

for nutrients and oxygen triggers tumor cells to produce VEGF, which leads to the formation of new blood vessels to nourish the rapidly growing tumor and may facilitate the metastatic spread of tumor cells [50].

Adipocytes communicate with endothelial cells by producing a variety of proangiogenic and vascular permeability-enhancing factors. These include VEGF, IGF-1, PAI-1, leptin, hepatocyte growth factor, and fibroblast growth factor-2 [52]. In the obese, nontumor setting, these factors stimulate neovascularization in support of the expanding fat mass. These adipose-derived factors may also contribute to obesity-associated enhancement of tumor angiogenesis. Bevacizumab-based therapy (i.e., anti-VEGF therapy), in combination with conventional chemotherapy, is considered a first-line treatment option for patients with advanced colorectal cancer; however, decreased efficacy in obese patients is reported and speculated to be associated with increased levels of VEGF (and/or other proangiogenic factors) produced by visceral white adipose tissue [53, 54]. The relative contributions of tumor-derived versus adipocyte-derived proangiogenic factors in tumor development, progression, and metastasis remain unclear.

PAI-1 is a serine protease inhibitor produced by endothelial cells, stromal cells, and adipocytes in visceral white adipose tissue [55]. Increased circulating PAI-1 levels, frequently found in obese subjects, are associated with increased risk of atherogenesis and cardiovascular disease, diabetes and several cancers [4, 55]. PAI-1, through its inhibition of urokinase-type and tissue-type plasminogen activators, regulates fibrinolysis and integrity of the extracellular matrix. PAI-1 is also involved in angiogenesis and thus may contribute to obesity-driven tumor cell growth, invasion, and metastasis [4]. Although PAI-1 levels in obese individuals may be reduced via weight loss or TNF- α blockade [56, 57], the role of PAI-1 in tumorigenesis remains controversial [55].

4.2 Epithelial-to-Mesenchymal Transition

Mouse model studies of cancer typically involve xenotransplantation of human tumor cell lines into immunodeficient mice [58, 59]. However, xenograft models are extremely limited due to their lack of normal tumor microenvironment. Immunodeficient mice have aberrant mammary gland development, lack normal immune/inflammatory responses, and resist developing DIO and CR phenotypes, which prevents elucidation of the link between energy balance and cancer development/progression in this system. One approach to overcome these limitations is the development of syngeneic transplant models in immunologically intact animals for studying the energy balance–cancer link. For example, a recent publication from our laboratory describes the development and characterization of a transplant model of claudin-low and basal-like mammary cancers, which overcomes many existing limitations of xenograft models by using (a) cells derived from a spontaneous MMTV-Wnt-1 mouse mammary tumor that, like basal-like breast cancers in women, are responsive to CR and obesity, and (b) a wild-type,

syngeneic host with normal immune function, mammary gland development and metabolic responses to energy balance modulation [60].

Our findings in this model indicate a mechanistic link between energy balance, the epithelial-to-mesenchymal transition (EMT), and tumor initiating cells (TICs) in breast cancer progression [60]. We speculate that DIO prepares fertile soil (tumor microenvironment), including changes in EMT, intratumoral adipocytes, and local and systemic hormones, growth factors, and cytokines, for enhanced tumor progression, and that determinants of growth in this fertile soil include the plant variety (intrinsic breast cancer subtype) and/or the seed density (extent of TIC enrichment). In contrast, CR may discourage tumor progression by acting on the soil antithetically to DIO, including promoting epithelial differentiation, discouraging EMT, preventing intratumoral adipocytes infiltration, and decreasing systemic hormones, growth factors, and cytokines. Future studies are warranted to determine whether the tumor-enhancing effects of DIO depend on the extent of TIC enrichment in different subtypes of breast cancer, as well as other epithelial cancers, and whether CR targets different (and perhaps TIC-independent) pathways than DIO to impact breast cancer progression.

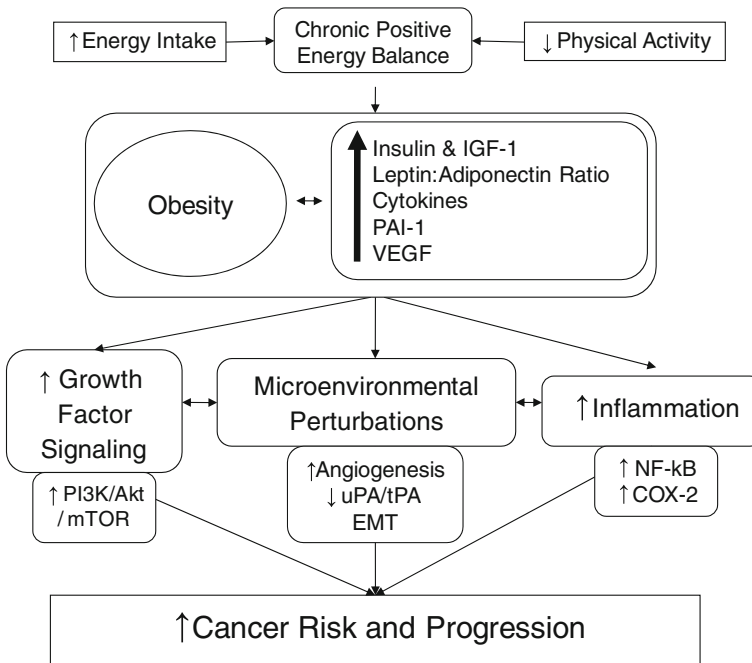


Fig. 1 Obesity and cancer: overview of mechanisms. An arrow preceding text denotes a directional effect (e.g., activity or concentration). Abbreviations: *IGF-1* insulin-like growth factor-1; *PAI-1* plasminogen activator inhibitor-1; *tPA* tissue-type plasminogen activator; *uPA* urokinase-type plasminogen activator; *VEGF* vascular endothelial growth factor; *EMT* epithelial-to-mesenchymal transition

Components of EMT may thus represent novel targets for preventing and/or controlling cancer and novel biomarkers of response to energy balance modulation or other interventions, particularly in obese women. It is plausible that energy-responsive growth signaling pathways regulate tumor cell differentiation and TIC proliferation through upregulation of obesity-associated serum hormones and cytokines, including those already described in this review. For example, increased circulating IGF-1 is associated with increased risk for pre- and postmenopausal breast cancer [61, 62] and increased tumor growth in animal models [16, 17, 63]. IGF-1 also plays a major role in stimulating expansion of normal breast stem cell populations during mammary gland development [64]. Additionally, IGF-1 receptor signaling potentiates SLUG-mediated EMT in hepatocytes [65] and increases ZEB1 mediated EMT in prostate cancer cells [66], although the relationship between IGF-1 receptor and EMT in breast cancer has not previously been reported. Metformin, a standard drug for diabetes that increases insulin sensitivity and lowers circulating insulin levels, effectively inhibits proliferation and survival of TICs [67, 68]. Obesity-associated increases in serum leptin levels have been previously shown to correlate with breast cancer risk and prognosis [69]. Leptin activates Hedgehog signaling and alters gene expression programs that may contribute to cell fate and EMT in hepatic stellate cells [70].

5 Summary and Conclusions

Obesity often results from chronic positive energy balance due to excessive energy intake and/or decreased energy expenditure (Fig. 1). Metabolic consequences include increased circulating levels of insulin and bioavailable IGF-1, and altered levels of adipokines, cytokines, and proangiogenic/vascular integrity factors. Activation of the pathways downstream of these critical systemic regulators leads to enhanced growth factor signaling, vascular perturbations, inflammation, as well as cancer-associated changes in the microenvironment, such as EMT, and thereby may increase cancer development and/or progression. **Components of these interrelated pathways represent promising mechanism-based targets for lifestyle or pharmacologic interventions to prevent or control cancer in obese or otherwise metabolically dysregulated individuals.** To accelerate the pace to identify new mechanism-based intervention targets to prevent or control obesity-related cancers, additional study is required to establish the causal relationships between specific components of obesity-responsive growth signaling, inflammation, and microenvironmental regulating pathways and cancer.

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