Growth Signals, Inflammation, and Vascular Perturbations
Mechanistic Links Between Obesity, Metabolic Syndrome, and Cancer

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Abstract—Nearly 35% of adults and 20% of children in the United States are obese, defined as a body mass index $\geq 30$ kg/m$^2$. 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 progression. This review 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. These interrelated pathways represent possible mechanistic targets for disrupting the obesity-cancer link. (Arterioscler Thromb Vasc Biol. 2012;32:1766-1770.)

Key Words: insulin resistance | metabolism | obesity | cancer | inflammation

The prevalence of obesity, defined as a body mass index (body weight [in kilograms] divided by height [in meters] squared) $\geq 30$ kg/m$^2$, has increased dramatically in recent decades in the United States, and nearly 35% of adults and 20% of children are now obese. 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. In obesity and metabolic syndrome, alterations also occur in the circulating levels of insulin, bioavailable insulin–like growth factor (IGF)-1, adipokines (eg, leptin and adiponectin), inflammatory factors (eg, cytokines), and vascular integrity–related factors (eg, vascular endothelial growth factor [VEGF] and plasminogen activator inhibitor [PAI]-1). Through these mediators, obesity and metabolic syndrome are linked to various chronic diseases, including cardiovascular disease, type II diabetes mellitus, and the focus of this review, cancer.

Evidence-based guidelines for cancer prevention urge avoiding obesity. Overall, 14% of all cancer deaths in men and 20% of all cancer deaths in women are attributable to overweight and obesity. 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 sexes. Although the relationships between metabolic syndrome and specific cancers are less established, first reports from the Metabolic Syndrome and Cancer Project, a European cohort study of $\approx 580,000$ adults, confirm associations between obesity (or body mass index) in metabolic syndrome and risks of colorectal, thyroid, and cervical cancer. With the increasing prevalence of obesity and metabolic syndrome, strategies to break the links between these conditions and cancer are urgently needed.

Herein, we discuss possible mechanisms underlying the links among 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 discuss, key unanswered questions remain regarding the links among obesity, metabolic syndrome and cancer and putative strategies to break them.
Dysregulated Growth Signals

Insulin and IGF-1

Insulin is a peptide hormone produced by pancreatic β-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. Sharing ≈50% sequence homology with insulin, IGF-1 is a peptide growth factor produced primarily by the liver after stimulation by growth hormone. IGF-1 regulates growth and development of many tissues, particularly prenatally. IGF-1 in circulation is typically bound to IGF binding proteins that regulate the amount of free IGF-1 bioavailable to bind to the IGF-1 receptor and elicit growth or survival signaling. In metabolic syndrome, the amount of bioavailable IGF-1 increases, possibly via hyperglycemia-induced suppression of IGF binding proteins synthesis or hyperinsulinemia-induced promotion of hepatic growth hormone receptor expression and IGF-1 synthesis. Elevated circulating IGF-1 is an established risk factor for many cancer types.

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

The phospatidylinositol-3 kinase/Akt pathway, downstream of the insulin receptor and IGF-1 receptor, is one of the most commonly altered pathways in epithelial cancers. 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-1 receptor, stimulates phospatidylinositol-3 kinase to produce lipid messengers that facilitate activation of the Akt cascade. Akt regulates the mammalian target of rapamycin (mTOR), which regulates cell growth, cell proliferation, and survival through downstream mediators. mTOR activation is inhibited by increased AMP-activated kinase under low nutrient conditions. Increased activation of mTOR is common in tumors and many normal tissues from obese and diabetic mice, and specific mTOR inhibitors block the tumor-enhancing effects of obesity in mouse models.

Leptin, Adiponectin, and Their Ratio

Leptin, 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, and estrogens all stimulate leptin release. Leptin has direct effects on peripheral tissues, indirect effects on hypothalamic pathways and modulates immune function, cytokine production, angiogenesis, carcinogenesis, and other biological processes. The leptin receptor has similar homology to class I cytokines that signal through the janus kinase and signal transducer activator of transcription pathway that is often dysregulated in cancer.

Adiponectin is a hormone mainly secreted from visceral adipose tissue. Levels of adiponectin, in contrast with 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. 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 AMP-activated kinase. Adiponectin also reduces proinflammatory cytokine expression via inhibition of the nuclear factor κ-light chain enhancer of activated B-cells (NF-κB). In vitro, animal and epidemiological evidence linking leptin or adiponectin individually to cancer risk is mixed. Associations among the adiponectin-to-leptin ratio and the metabolic syndrome and some cancers are reported. Further characterization of these links is needed.

Chronic Inflammation

Cytokines and Cross Talk Among 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. These effects are further amplified by the release of inflammatory cytokines such as interleukin-1β, interleukin-6, tumor necrosis factor-α, and monocyte chemoattractant protein-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 mellitus (through downregulation of insulin receptors and glucose transporters), hypertension, and fatty liver disease and also activates signaling molecules involved in epithelial carcinogenesis, such as NF-κB.

NF-κB is a transcription factor that is activated in response to bacterial and viral stimuli, growth factors, and inflammatory molecules (eg, tumor necrosis factor-α, interleukin-6, and interleukin-1β) and is responsible for inducing gene expression associated with cell proliferation, apoptosis, inflammation, metastasis, and angiogenesis. Activation of NF-κB is a common characteristic of many tumors and is associated with insulin resistance and elevated circulating levels of leptin, insulin, and IGF-1.

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. Now, inflammation is a recognized hallmark of cancer, and growing evidence continues to indicate that chronic inflammation is associated with increased cancer risk. 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.

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

In some cancers, inflammatory conditions precede malignant changes (as previously mentioned); whereas, in other cancer types, genetic alterations and premalignant changes precede the inflammatory microenvironment and neoplasia. Malignancies may thus be initiated or exacerbated by inflammation, and increased levels of inflammation markers may be a cause or consequence of cancer. 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.

Vascular Perturbations

VEGF

VEGF, a heparin-binding glycoprotein produced by adipocytes and tumor cells, has angiogenic, mitogenic, and vascular permeability–enhancing activities specific for endothelial cells. 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. 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.

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. 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 (ie, 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 is speculated to be associated with increased levels of VEGF (and other proangiogenic factors) produced by visceral white adipose tissue. The relative contributions of tumor–derived, versus adipocyte–derived, proangiogenic factors in tumor development, progression and metastasis remain unclear.

PAI-1

PAI-1 is a serine protease inhibitor produced by endothelial cells, stromal cells, and adipocytes in visceral white adipose tissue. Increased circulating PAI-1 levels, frequently found in obese subjects, are associated with increased risk of atherogenesis and cardiovascular disease, diabetes mellitus, and several cancers. 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. Although PAI-1 levels in obese individuals may be reduced via weight loss or tumor necrosis factor-α blockade, the role of PAI-1 in tumorigenesis remains controversial.

Summary and Some Unanswered Questions

Obesity, which is often accompanied by the metabolic syndrome, results from chronic positive energy balance attributable to excessive energy intake and decreased energy expenditure (Figure). 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, and inflammation and thereby may increase cancer development and progression. To accelerate the pace of identifying new mechanism–based intervention targets to prevent or control obesity-related cancers, additional study is required to establish the causal relationships among specific components of obesity–responsive growth signaling, inflammation and vascular integrity pathways and cancer.

Longitudinal studies indicate that successful weight loss after bariatric surgery reduces cancer rates; however, key questions remain unresolved regarding weight loss intervention for breaking obesity-cancer links. For example, how much weight loss is necessary to decrease the tumor-enhancing effects of obesity, and how long does it take to normalize cancer risk? Do the effects of weight loss in obese or metabolically dysregulated individuals vary by cancer type? Does the mode of weight loss (eg, diet, exercise, surgery, or pharmacologic regimens) differentially affect the answers to these questions, and if so, what are the mechanistic bases for differences? In a recent randomized trial, weight loss of 5% or more by calorie restriction, with or without exercise, reduced inflammatory biomarkers in overweight/obese postmenopausal women, compared with controls. Although this finding is encouraging, long-term study is needed to determine whether the changes are accompanied by reduced cancer risk.

Weight loss is often challenging. Another key question is can weight loss-independent interventions break the obesity-cancer links? Among potential therapeutics, metformin, which inhibits mTOR signaling via AMP-activated kinase activation, is associated with reduced risks of cancer incidence and mortality when used in diabetic patients. A phase 3, randomized trial is ongoing for metformin versus placebo, plus standard adjuvant therapy, to evaluate recurrence and survival in patients with early-stage breast cancer; final results are expected in 2016. Although obesity is not an eligibility criterion in the phase 3 trial, another ongoing trial (phase 2) is evaluating metformin for colorectal cancer risk reduction in patients with a history of colorectal adenomas and body mass index >30 kg/m². Additional cancer-specific, proof-of-principle studies are warranted to determine whether (and which) specific inhibitors of the IGF/insulin/Akt signaling pathway (eg, rapamycin or rapalogues), leptin/janus kinase/
signal transducer activator of transcription pathway (eg, STAT3 inhibitors), inflammatory cascade (eg, cyclooxygenase-2 or NF-κB inhibitors), or vascular integrity-related factors (eg, VEGF or PAI-1 inhibitors) reduce cancer risk or improve outcomes in the obese (or formerly obese) patient. Also, given that increased Akt signaling can contribute to resistance to multiple forms of cancer therapy, including chemotherapy and targeted therapies, does obesity, which activates the Akt/mTOR pathway, predispose to resistance to certain therapeutic agents? Progress in addressing these questions may accelerate strategies for the prevention and control of cancers related to or caused by excess body weight and the metabolic syndrome.

Conclusion

Multiple hormones, growth factors, cytokines, and other mediators associated with the obese state and the metabolic syndrome enable cross talk between macrophages, adipocytes, endothelial cells, and epithelial cells and contribute to cancer-related processes (including growth signaling, inflammation, and vascular alterations). Components of these interrelated pathways represent promising mechanism-based targets (analogous to reducing cholesterol levels to reduce heart disease risk) for lifestyle or pharmacological interventions to prevent or control cancer in obese or otherwise metabolically dysregulated individuals.

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None.

References


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