Interacting Inflammatory and Growth Factor Signals Underlie the Obesity–Cancer Link\textsuperscript{1,2}

Laura M. Lashinger,\textsuperscript{3} Nikki A. Ford,\textsuperscript{3} and Stephen D. Hursting\textsuperscript{3,4*}

\textsuperscript{3}Department of Nutritional Sciences, University of Texas, Austin, TX; and \textsuperscript{4}Department of Molecular Carcinogenesis, University of Texas–MD Anderson Cancer Center, Smithville, TX

Abstract

The prevalence of obesity, an established risk factor for many chronic diseases (including diabetes, cardiovascular disease, stroke, and several types of cancer), has risen steadily for the past several decades in the United States and many parts of the world. Today, ∼70% of U.S. adults and 30% of children are at an unhealthy weight. The evidence on key biologic mechanisms underlying the obesity–cancer link, with an emphasis on local and systemic inflammatory processes and their crosstalk with energy-sensing growth factor signaling pathways, will be discussed. Understanding the influence and underlying mechanisms of obesity on chronic inflammation and cancer will identify promising mechanistic targets and strategies for disrupting the obesity–cancer link and provide important lessons regarding the associations between obesity, inflammation, and other chronic diseases. J. Nutr. doi: 10.3945/jn.113.178533.

Introduction

In the past 3 decades, the prevalence of obesity (BMI > 30 kg/m\textsuperscript{2}) has sharply increased in the United States (1) and many other parts of the world (2). As the incidence of obesity has risen, so has the incidence of several chronic diseases, such as type 2 diabetes, cardiovascular disease, and certain types of cancer (3). Appreciation for the obesity–cancer link has increased since a large prospective study by Calle et al. (3) found that elevated adiposity increases the incidence and mortality rates of most types of cancer, including endometrial cancer, colorectal cancer, postmenopausal breast cancer, esophageal adenocarcinoma, thyroid cancer, renal cancer, multiple myeloma, gallbladder cancer, leukemia, pancreatic cancer, non-Hodgkin lymphoma, and ovarian cancer (4). In fact, the authors estimated that, in the United States, 14% of cancer deaths in men and 20% of cancer deaths in women could be attributed to obesity (3). Although overall risk is increased, there is an organ-specific hierarchy of susceptibility to the protumorigenic effects of obesity.

Adipose tissue serves not only as an energy depot for the body but also as an endocrine and metabolic organ that has systemic effects. In response to nutrient status and cues from other organs, adipocytes release FFAs, hormones such as leptin and adiponectin, and cytokines such as tumor necrosis factor (TNF)\textsuperscript{5-α} and interleukin (IL)-6. These biologic consequences maintain homeostasis by providing a systemic energy source and regulating lipid metabolism and insulin sensitivity (5). However, in a state of chronic positive energy balance, the excessive release of these factors has pathologic consequences, particularly development of insulin resistance and hyperinsulinemia and elevated levels of insulin-like growth factor-1 (IGF-1), vascular endothelial growth factor, TNF-α, and IL-6. Collectively, the systemic circulation contains a higher level of growth factors and proinflammatory mediators, aberrations that are considered to be “hallmarks of cancer” (6). Although inflammation is crucial for warding off pathogens and healing injured tissue in acute scenarios, a chronic inflammatory state (such as occurs with obesity) can contribute to chronic diseases, such as cancer. This review will discuss the role of inflammation and the inflammatory crosstalk that exists with energy-sensing growth factor signaling pathways underlying obesity-associated increases in cancer development and progression.

Chronic Inflammation and Cancer

Inflammation and cancer. Chronic inflammation was recognized as a putative risk factor for cancer development >100 y ago when Rudolph Virchow observed an abundance of leukocytes in tumor tissue (7). Now, it has been established that chronic inflammation is a precursor to multiple cancers, with an estimated 15–25% of cancer-related deaths worldwide attributable to infections and chronic inflammatory responses (8,9). Regardless of origin (extrinsic inflammatory conditions that increase risk or intrinsic genetic alterations that initiate inflammation), all tumors display evidence of a “smoldering” inflammation and, in fact, are considered to be inflammatory sites because they comprise not only cancerous epithelial cells but also fibroblasts, lymph and vascular cells, and cells of the innate and adaptive immune system (including neutrophils, dendritic...
cells, macrophages, mast cells, and lymphocytes) that can produce a tumor-specific array of cytokines, prostaglandins/leukotrienes, proteases, and other inflammation-related molecules (9,10). The profile of cytokines and chemokines generated from recruited immune cells, particularly macrophages, dictate tumor growth, proliferation, angiogenesis, and metastatic potential (9). These cell types and their resultant immune mediators can thus perpetuate a proinflammatory, protumorigenic environment (7), the inhibition of which with nonsteroidal anti-inflammatory pharmacologic agents can reduce incidence and mortality rates of multiple cancer types (10).

**Cellular fraction.** Although phagocytic monocytes could conceivably exert an antitumor response, evidence supports that there is a preponderance of tumor-associated macrophages (TAMs) that favor establishment of a proinflammatory tumor environment. These are primarily recruited by chemokines of the monocyte chemoattractant protein (MCP) family, particularly in ovarian, breast, and pancreatic cancer (11), as well as other factors, such as TGF-β, TNF-α, and interleukin (IL)-1β (9). TAMs produce cytokines and chemokines that influence inflammatory and immune cells, growth factors that affect tumor epithelial cell growth, proliferation, angiogenesis, and survival, and proteases that contribute to angiogenesis via degradation and restructuring of connective tissue. In response to secreted factors in the tumor tissue microenvironment, macrophages typically conform to either a classical M1 activation (cytotoxic) subtype or an alternative M2 activation (immunosuppressive) subtype, in much the same way that T cells conform to a T-helper cell 1 or 2 phenotype. Tumor tissue predominately comprises M2-type macrophages (7) that produce a signature cytokine/chemokine/growth factor profile that supports tumor proliferation, facilitates tissue remodeling and angiogenesis, and suppresses antitumoral adaptive immunity (10).

**Cytokine and growth factor signaling.** Proinflammatory mediators in the tumor environment, generated from both infiltrating immune cells and the tumor itself, exert biologic outcomes through activation of cascades that involve transcription factors and signal transducers known to be involved in cancer progression (9,12). For instance, enhanced liver and colon cancer development has been attributed to an increase in stromally derived TNF-α, the blockade of which by a TNF-α antagonist or genetic deletion prohibited progression of hepatocellular carcinoma (9,12). IL-6, primarily secreted by macrophages and macrophages at the site of inflammation, is a cytokine that promotes cell growth and inhibits apoptosis and is associated with the development of cancers, such as Kaposi’s sarcoma, multiple myeloma, and Hodgkin’s lymphoma. Systemic levels of IL-6 are also elevated in inflammatory bowel disease and increase the risk of developing colon carcinogenesis (13). Both TNF-α and IL-6 can function physiologically to drive the acute inflammatory response to injury and infection and pathophysiologically to perpetuate a chronic inflammatory state through activation of the immunomodulating transcription factor NF-κB (12). Animal models and in vitro analyses highlight the crucial role this transcription factor plays in tumor progression and provides a mechanistic link between inflammatory mediators (such as TNF-α and IL-6) and cancer promotion (7,12). NF-κB remains sequestered in the cytosol through an interaction with the inhibitor of κB (IκB), a scaffolding protein that is flagged for degradation during activation of the IκB kinase by stimuli such as bacterial and viral contaminants, inflammatory molecules such as TNF-α, IL-6, and IL-1β, and growth factors. Activation results in translocation of NF-κB to the nucleus, transcription of NF-κB-responsive genes, and ultimately increased expression of proteins that regulate proliferation, apoptosis, inflammation, metastasis, and angiogenesis. For example, NF-κB mediates transcriptional programs (and hence the protumorigenic nature) of TAMs (7). Furthermore, this pathway is constitutively activated in many human cancers and potentiates malignancy through promotion of cancer cell survival (enhanced proliferation and diminished apoptosis) and production of proinflammatory cytokines from tumor-associated inflammatory cells (12).

In addition to NF-κB, the inducible immunomodulating enzyme cyclooxygenase-2 is another molecule at the intersection of inflammation and cancer. Indeed, its expression is elevated in tumor biopsies and is observed clinically as an indicator of poor prognosis in multiple cancer types (14). Chronic use of nonsteroidal anti-inflammatory drugs and selective cyclooxygenase-2 inhibitors (such as celecoxib) have been shown in clinical trials to decrease risk of colon cancer by 50%, gastric and esophageal cancer by 40%, and breast cancer by 20% (15).

**Obesity-Related Hormones and Growth Factors and Inflammation**

**Adipocytes, macrophages, and inflammatory cytokines.** When adipocytes enlarge past the point of sufficient oxygen diffusion, adipokine/chemokine secretion increases proportionally to the size of the adipocyte, resulting in inflammation, hypoxia, and increased macrophage infiltration (16). Once adipocyte expansion has reached capacity, circulating FFAs accumulate in other tissues and result in diabetes, hypertension, and fatty liver disease. Typically, expansion of visceral adipose tissue occurs via this scenario, further worsening insulin resistance, peripheral lipolysis, and cytokine secretion, and is thus highly correlated with obesity-related comorbidities and mortality (17).

As mentioned previously, adipose tissue expansion results in enhanced production of inflammatory cytokines, such as TNF-α, IL-6, IL-1β, and MCP-1, all of which have been shown to be elevated both locally and systemically (18). More specifically, FFAs secreted from engorged adipocytes increase expression of TNF-α, IL-1β, and cyclooxygenase-2 in human monocyte-derived cells (19).

Although these cytokines are beneficial for the antipathogenic response and wound healing in an acute inflammatory scenario, they become detrimental in a chronic, “smoldering” inflammatory condition such as obesity. As a result of excessive cytokine expression, macrophages are recruited and further exacerbate the proinflammatory milieu. In fact, adipose tissue from obese individuals, relative to normoweight individuals, has many more adipose-derived macrophages, a finding that correlates with BMI (18).

In addition to its function as immunomodulator, TNF-α contributes to insulin resistance by downregulating activity of the insulin receptor and ultimately minimizing the translocation of glucose transporters to the cell membrane. Along with TNF-α, IL-6 facilitates development of systemic insulin resistance. Plasma IL-6 levels are higher in the portal vein than in peripheral arterial blood in obese individuals, suggesting that the presence of these cytokines increase primarily in response to enlarged visceral versus subcutaneous fat (18). IL-6 and leptin, an adipokine that works in part through an IL-6-dependent mechanism, were also shown to elicit a proliferative effect on preneoplastic colon.
epithelial cells (20), suggesting a link between cancer development, adipose-derived hormones, and inflammatory cytokines. Studies in transgenic mice in which increased tumor growth is associated with elevated growth factors and/or inflammatory factors in the absence of increased weight or adiposity indicate that components of these growth and inflammatory signaling pathways represent key targets for breaking the obesity–cancer link (18).

**Energy balance–responsive hormones.** Adiposity is positively correlated with circulating levels of energy balance–related hormones and growth factors, including leptin, which is secreted from adipocytes and acts as a biomass indicator, insulin, which is secreted from the pancreas to regulate blood glucose levels, and IGF-1, which is secreted from hepatocytes in association with rising insulin levels (18). Inversely proportional to the level of adiposity is the amount of circulating adiponectin, a hormone that is secreted in smaller amounts from expanding adipocytes.

In addition to effects on hypothalamic pathways, leptin has direct effects on peripheral tissues that affect cellular proliferation, immunomodulation, and angiogenesis. In fact, the leptin receptor has sequence homology to class I cytokines that signal through the janus kinase/signal transducer and activator of transcription pathway that is often dysregulated in cancer (18). Although epidemiologic studies have been inconsistent regarding the association of leptin and cancer, in vitro studies have shown that leptin has a proliferative effect on human esophageal, breast, and prostate cancers (18). Additionally, Jaffe and Schwartz (21) demonstrated that leptin promoted cell motility and invasiveness in human colon cancer cell lines. Leptin, being an immunomodulator, has also been shown to stimulate activation of NF-κB in human preneoplastic and neoplastic colonic epithelial cell lines (20,22).

Many types of cancers, including breast, colorectal, kidney, endometrial, and pancreatic, are associated with hyperinsulinemia and type 2 diabetes (18). Insulin resistance is associated with enhanced NF-κB activation secondary to increased systemic TNF-α (23), and, conversely, insulin is an activator of NF-κB signaling (24). These findings suggest a positive feedback loop between hyperinsulinemia and NF-κB activity. Additionally, insulin can exert a protumorigenic effect by initiating activation of the extracellular signal-regulated kinase, phosphotidylinositol-3 kinase, and mammalian target of rapamycin (mTOR) pathways (25). The proliferative/survival effects of hyperinsulinemia can also be attributed to an indirect mechanism involving increased levels of bioavailable IGF-1 (25). Elevated IGF-1 has been identified as a risk factor in many cancer types (18). In a genetically engineered mouse model of liver-specific IGF-1 deficiency, circulating IGF-1 was reduced by ~75%, causing a significant decrease (relative to a wild-type control) in either tumor multiplicity or volume in mouse models of colon (26), mammary (27), or pancreatic (28) cancer. Liver-specific IGF-1 deficiency mice, relative to wild-type mice, also show reduced serum cytokine levels, and this has been linked to an IGF-1/NF-κB interaction (26). Moreover, IGF-1 receptor activation has been shown to increase cyclooxygenase-2 mRNA or protein expression in colon and pancreatic cancer (29,30), and treatment with IGF-1 has been shown to circumvent the apoptotic effects of celecoxib (selective cyclooxygenase-2 inhibitor) in a pancreatic cancer model (31). More specifically, IGF-1 causes nuclear localization of the p65 subunit of NF-κB and subsequently increases NF-κB DNA binding activity comparable with that of TNF-α and induces expression of protumorigenic downstream gene targets that encode proteins, such as FLICE-like inhibitory protein, X-linked inhibitor of apoptosis, cellular inhibitor of apoptosis protein-2, bcl-2-related A1 protein, and survivin, in colon cancer and multiple myeloma cells (32,33). These downstream effects of IGF-1 receptor engagement are thought to occur via activation of downstream signaling pathways, such as extracellular signal-regulated kinase and phosphotidylinositol-3 kinase/Akt/mTOR, that modulate transcription factors that control prosurvival, proinflammatory gene expression related to cancer development and progression.

Adiponectin acts to counter the metabolic perturbations coincident with obesity by improving glucose metabolism, fatty acid oxidation, and insulin sensitivity and decreasing proinflammatory cytokine production (18). In multiple case-control studies, an inverse relation between systemic adiponectin concentrations and risk of several cancer types has been observed in colon, prostate, and endometrial cancers (18). The potential mechanisms through which adiponectin exerts its anticancer effects include increasing insulin sensitivity and minimizing survival signaling through the mTOR pathway via modulation of the key nutrient-sensing protein 5′AMP-activated protein kinase. Moreover, adiponectin influences inflammation by decreasing activation of the NF-κB pathway and thus diminishing the production of proinflammatory cytokines (18).

**Targeting Inflammation for Cancer Prevention**

**Calorie restriction.** Over the past 30 y of calorie restriction (CR), an experimental dietary regimen in which subjects are administered a low-calorie yet isonutrient diet, ranging from a 20–40% reduction relative to an ad libitum-fed control, has been studied for its ability to delay aging and inhibit inflammation and cancer (34). This strategy has emerged as the most potent, broadly acting dietary intervention for preventing or dampening cancer outcomes in many different tumor models, including transplanted, chemically or genetically induced, and including rodents and primates (34). Although most work has been performed with rodents, recent reports of extended lifespan and delayed cancer development in response to CR in rhesus monkeys and decreased postmenopausal cancer risk in response to CR during the premenopausal years in women suggest the anticancer effects of CR reported in rodent models extend to primates, including humans (34). Consistently, CR creates an opposing environment to that of the obese state, including reduced circulating levels of adipokines (leptin, TNF-α, and IL-6), IGF-1, and insulin and improved insulin sensitivity (34). Consequently, CR suppresses the proinflammatory environment that is associated with obesity. The establishment of this antitumorigenic scenario has significant influence on tumor growth. Our own work has shown that CR prevents the development and severity of pancreatic cancer and its associated inflammatory cell-rich stroma (28). Using models of colon (33) and pancreatic cancer (L. M. Lashinger, unpublished data), we found that IGF-1 reduction is responsible for reduced activity of NF-κB- and mTOR-mediated cell signaling and tumor growth. We showed that rapamycin, a specific mTOR inhibitor, partially mimics the growth-prohibitive effects of CR in a transplant model of pancreatic cancer (35). Extending that finding, Athar and Kopelovich (36) found that rapamycin decreased inflammatory cell infiltration in a 12-O-tetradecanoylphorbol-13-acetate-induced model of skin carcinogenesis, suggesting that
pharmacologic agents that share targets with CR can be exploited to suppress protumorigenic inflammatory pathways.

**Resveratrol.** Like CR, resveratrol is frequently used in antiaging and anticancer studies because it is a natural polyphenolic antioxidant, prevalent in grapes and other berries proven to have beneficial effects against cardiovascular disease and several cancers. The anticancer effects of resveratrol have been partially attributed to inhibition of lipoxygenases and cyclooxygenase-1 and cyclooxygenase-2, the enzymes that convert the eicosanoid arachidonic acid into proinflammatory mediators, and IκB kinase α, the activator of the NF-κB pathway (37). The detrimental influence of the reactive oxygen species produced by macrophages is blunted by resveratrol treatment through its antioxidant properties; therefore, it diminishes the proinflammatory nature of the TAMs. Furthermore, resveratrol inhibited the production of TNF-α-induced MCP-1 in 3T3-L1 adipocytes. Finally, activity of the histone deacetylase sirtuin 1, which potentiates antitumoral and anti-inflammatory events, is upregulated by resveratrol (37). Together, these data suggest that this natural dietary agent plays a significant role in diminishing inflammation and thus protumorigenic outcomes.

**Curcumin.** Curcumin is a spice commonly used in Asia with purported antioxidant, anti-inflammatory, and anticancer effects (38,39). One of the best-characterized effects of curcumin is its ability to significantly inhibit the NF-κB pathway in multiple cell types (38). Treatment with curcumin in genetically obese mice prevented accumulation of macrophages in adipose tissue and inhibited NF-κB activation in the liver (38). Curcumin has decreased NF-κB DNA binding and cyclooxygenase-2 and prostaglandin protein levels (40), reduced proliferation of colorectal cancer cells (41), and inhibited cancer in models of tissue and inhibited NF-κB binding and cyclooxygenase-2 (38). The detrimental influence of reactive oxygen species produced by macrophages is blunted by resveratrol treatment through its antioxidant properties; therefore, it diminishes the proinflammatory nature of the TAMs. Furthermore, resveratrol inhibited the production of TNF-α-induced MCP-1 in 3T3-L1 adipocytes. Finally, activity of the histone deacetylase sirtuin 1, which potentiates antitumoral and anti-inflammatory events, is upregulated by resveratrol (37). Together, these data suggest that this natural dietary agent plays a significant role in diminishing inflammation and thus protumorigenic outcomes.

Curcumin is a spice commonly used in Asia with purported antioxidant, anti-inflammatory, and anticancer effects (38,39). One of the best-characterized effects of curcumin is its ability to significantly inhibit the NF-κB pathway in multiple cell types (38). Treatment with curcumin in genetically obese mice prevented accumulation of macrophages in adipose tissue and inhibited NF-κB activation in the liver (38). Curcumin has decreased NF-κB DNA binding and cyclooxygenase-2 and prostaglandin protein levels (40), reduced proliferation of colorectal cancer cells (41), and inhibited cancer in models of tissue and inhibited NF-κB binding and cyclooxygenase-2 (38). The detrimental influence of reactive oxygen species produced by macrophages is blunted by resveratrol treatment through its antioxidant properties; therefore, it diminishes the proinflammatory nature of the TAMs. Furthermore, resveratrol inhibited the production of TNF-α-induced MCP-1 in 3T3-L1 adipocytes. Finally, activity of the histone deacetylase sirtuin 1, which potentiates antitumoral and anti-inflammatory events, is upregulated by resveratrol (37). Together, these data suggest that this natural dietary agent plays a significant role in diminishing inflammation and thus protumorigenic outcomes.

**Conclusions**

Chronic positive energy balance can lead to obesity and its associated adipocyte dysfunction (Fig. 1). This often results in enhanced adipocyte–macrophage interactions and metabolic perturbations that contribute to increased inflammatory and growth factor signaling. Components of these interacting pathways represent promising targets for breaking the obesity–cancer link and may also be important targets for the prevention of other obesity-related chronic diseases.

**Acknowledgments**

L.M.L., N.A.E., and S.D.H. wrote the paper. All authors read and approved the final manuscript.

**Literature Cited**


