

The Obesity-Cancer Link: Lessons Learned from a Fatless Mouse

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Abstract

Current dogma suggests that the positive correlation between obesity and cancer is driven by white adipose tissue that accompanies obesity, possibly through excess secretion of adipokines. Recent studies in fatless A-Zip/F1 mice, which have undetectable adipokine levels but display accelerated tumor formation, suggest that adipokines are not required for the enhanced tumor development. The A-Zip/F-1 mice are also diabetic and display elevated circulating levels of other factors frequently associated with obesity (insulin, insulin-like growth factor-1, and proinflammatory cytokines) and activation of several signaling pathways associated with carcinogenesis. In view of this information, the risk factors underlying the obesity-cancer link need to be revisited. We postulate that the pathways associated with insulin resistance and inflammation, rather than adipocyte-derived factors, may represent key prevention and therapeutic targets for disrupting the obesity-cancer link. [Cancer Res 2007;67(6):2391–3]

Introduction

The prevalence of obesity has increased dramatically in the United States (1), with nearly one third of U.S. adults now considered obese (2). Of particular concern is that these same trends have also appeared in children (3). Obesity is a well-established risk factor for several cancers. Estimates from an American Cancer Society study, the largest prospective analysis to date of the weight-cancer relationship, suggest 14% of all cancer deaths in men and 20% of all cancer deaths in women from a range of cancer types are attributable to excess body weight (4). Animal studies recapitulate this observation and show that obesity enhances tumor development (5), whereas calorie restriction inhibits a broad range of spontaneous, transplanted, and carcinogen-induced tumors (6). Although the mechanisms underlying the obesity-cancer association are not understood, obesity has been presumed to enhance tumor development through increased secretion of adipocyte-derived factors, such as leptin and adiponectin, otherwise known as adipokines.

The following is a brief review of the potential molecular pathways involved in the connection between obesity and cancer. We then discuss how the observation that the increased susceptibility of fatless mice to tumor formation suggests the need for a reevaluation of the molecular mechanisms that mediate the link between obesity and cancer (Fig. 1).

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Adipokines and Cancer Risk

Leptin, the most extensively studied adipokine, is a 16-kDa peptide synthesized by fat cells that acts on the hypothalamus to decrease food intake and increase energy expenditure (6). In the nonobese state, increasing leptin levels result in decreased appetite and increased energy metabolism through a series of neuroendocrine changes. The obese state is associated with high circulating leptin levels (6), suggesting that obese individuals are insensitive to the effects of leptin. The resistance to leptin seems to explain much of the inability of exogenous leptin administration to prevent weight gain. We and others observed that leptin can stimulate proliferation of some preneoplastic and cancer cells *in vitro* (7), but the *in vivo* role of leptin in carcinogenesis is unclear.

Adiponectin, a 225-amino-acid protein, is the most abundant transcript in adipocytes and has antidiabetic and anti-inflammatory properties (8, 9). Low levels of adiponectin are associated with an increased risk of breast cancer (9), and animal studies show that exogenous adiponectin inhibits tumor growth and tumor angiogenesis (8). Potentially, the anticancer effects of adiponectin may be mediated by its antidiabetic and anti-inflammatory properties.

The relationships between other adipokines, such as resistin and plasminogen activator inhibitor-1, and cancer have not been well characterized.

Insulin-like Growth Factor I and Cancer Risk

The involvement of insulin-like growth factor I (IGF-I) in cancer was first documented when *in vitro* studies showed that IGF-I enhances the growth of cancer cell lines (6). IGF-I acts either directly on cells via the IGF-I receptor (IGF-IR), which is overexpressed in many tumors, or indirectly by cooperation with other cancer-targeted molecules, such as the p53 tumor suppressor. Reduction in IGF-I may be also responsible for some of the antiproliferative, proapoptotic, and anticancer effects of calorie restriction through its role in an evolutionarily conserved regulatory pathway responsive to energy availability. We and others have previously established that reduced IGF-I mediates many of the anticancer effects of caloric restriction; in fact, restoration of IGF-I levels in calorie restriction mice has been shown to ablate the antitumor effects of caloric restriction in multiple models (6). In contrast, diet-induced obesity in the mouse leads to enhanced tumor growth as well as insulin resistance, increased IGF-I, and decreased IGF binding protein-1, resulting in enhanced IGF-I signaling (5, 10).

Insulin Resistance

Obesity is associated with insulin resistance, a state of reduced responsiveness of tissues to the physiologic actions of insulin, which consequently results in a compensatory increase in plasma insulin. Obesity-induced insulin resistance associated with high systemic levels of IGF-I increases the likelihood of developing type 2 diabetes and has also been linked to increased cancer risk

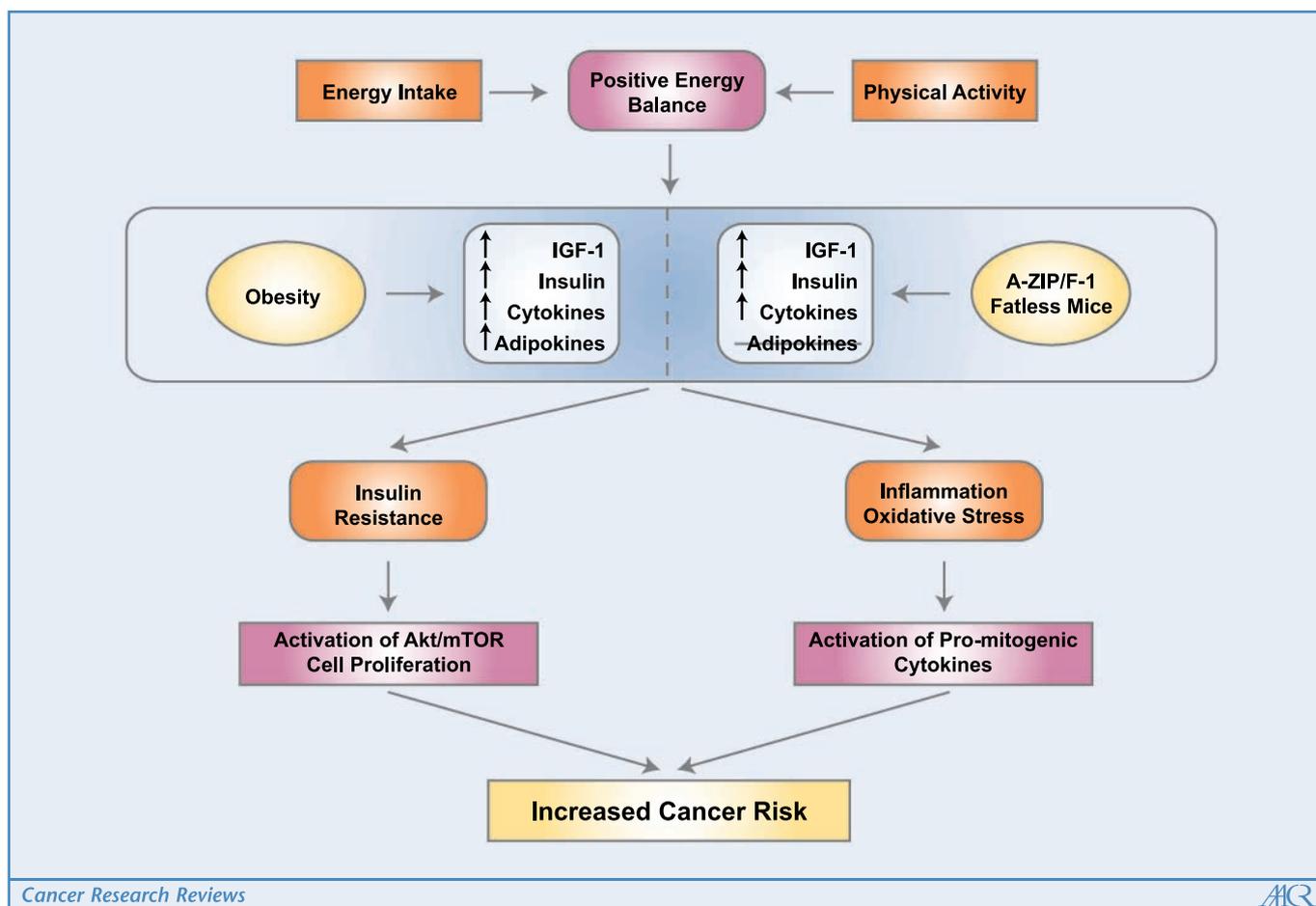


Figure 1. Schematic representation of the mechanisms underlying the obesity-cancer link. Positive energy balance due to excessive caloric intake and/or decreased energy expenditure leads to obesity. The A-Zip/F-1 mice also have increased caloric intake but have no adipose tissue or adipokines. Common metabolic consequences are insulin resistance and inflammatory stress that contribute to cancer risk. Increased cancer risk in A-ZIP/F-1 mice suggests that adipose tissue and adipokines are not required for tumor development; rather, insulin resistance and inflammation may be key to understanding the obesity-cancer link.

(10–12). Because both IGF-I and insulin are elevated, it is unclear what the relative contributions of these two factors are in the increased cancer risk associated with obesity. It is plausible that they both play a role through similar downstream signaling pathways.

Downstream Targets of Insulin/IGF-I Signaling

The phosphatidylinositol 3-kinase/Akt pathway is a critical signaling component of the insulin and IGF-I responses that regulate cellular growth and metabolism (13). Phosphatidylinositol 3-kinase activation couples extracellular signals with intracellular effectors responsible for regulation of cell growth, proliferation, survival, and metabolism. The importance of the phosphatidylinositol 3-kinase/Akt pathway in human cancers has recently been highlighted by the estimation that it is one of the most commonly targeted carcinogenesis-related pathways (14). Activation of phosphatidylinositol 3-kinase/Akt signaling is associated with activation of mammalian target of rapamycin. Mammalian target of rapamycin, a highly conserved serine/threonine protein kinase, acts as a sensor linking growth factor signals from Akt, other stress signals, and energy status to translational control of new proteins resulting in cell growth (13, 14). Together, these pathways form a sophisticated system that integrates environmental cues with metabolic cellular responses.

Inflammation

The link between chronic inflammation and increased cancer incidence is widely accepted (15). Chronic inflammation is also associated with obesity. Obesity prevention by calorie restriction or physical activity decreases both the levels of certain inflammatory markers and cancer risk (16). In general, acute inflammation is a process that benefits the host by providing protection from invading pathogens and initiating wound healing. The proinflammatory cytokines produced by activated macrophages have long-range effects that contribute to host defense mechanisms. Tumor necrosis factor- α (TNF- α) and interleukin-1 β (IL-1 β) stimulate the release of IL-6. Following the acute phase response, which involves secretion of liver-derived C-reactive protein, the production of IL-1 β and TNF- α is dampened by the release of IL-1 receptor antagonist and soluble TNF- α receptors, respectively (17).

Chronic, low-grade systemic inflammation is a condition where there is a sustained low-level (2–3-fold) increase in circulating levels of the cytokines TNF- α , IL-1 β , IL-6, IL-1 receptor antagonist, soluble TNF- α receptor, and C-reactive protein. The initial stimuli that cause chronic systemic inflammation are not well defined. One hypothesis is that the source of TNF- α production in chronic systemic inflammation associated with obesity is adipose tissue itself, although insulin resistance may also contribute to this

process (17). Additional studies are needed to determine the initiating stimuli and the role of inflammatory cytokines in chronic low-grade systemic inflammation and cancer.

Increased Cancer Risk in the Fatless A-Zip/F-1 Mouse Model

Our recent studies using the A-Zip/F-1 mice (18) that have no white adipose tissue and undetectable leptin, adiponectin, and other adipokines showed that these mice are more susceptible to papilloma formation in a classic two-stage skin carcinogenesis experiment (19), a finding confirmed in a separate report (20). Furthermore, when A-Zip/F-1 mice were crossed to the C3(1)/T-antigen mammary tumor transgenic mouse model, they developed larger and earlier tumors (19). Taken together, these findings cast a doubt on previous studies implicating leptin and adiponectin in cancer risk and suggest that adipokines may not be required for enhancement of tumor development.

However, no accelerated mammary tumor development was observed when A-Zip/F-1 mice were crossed to the mouse mammary tumor virus-Her2/neu transgenic mouse model of mammary cancer,⁵ suggesting that the fatless mice promote the growth of some genetically induced tumors but not others. These differences are reminiscent of the different responses of tumors to obesity (4). The molecular mechanisms that determine whether a particular type of tumor will grow more rapidly in the pathologic milieu of fatless or obese mice remain unknown.

What may cause the increased susceptibility to cancer in A-Zip/F-1 mice? Despite their lack of white adipose tissue, the A-Zip/F-1 mice are diabetic with high circulating levels of insulin, insulin-like growth factor-1 (IGF-1), and proinflammatory cyto-

kines (all of which also accompany diet-induced obesity), as well as activation of several carcinogenesis-related signaling pathways, particularly those downstream of the insulin, IGF-IRs, ErbB/ras, and phosphatidylinositol 3-kinase/Akt pathways (19). In addition, the A-Zip/F-1 mice have elevated levels of several cytokines typically associated with proinflammatory Th2 responses, including IL-1 β , IL-4, and IL-6, but had no detectable TNF α . It is possible that activation of these mitogenic and proinflammatory pathways, in the absence of obesity, underlies the observed accelerated tumor development in A-Zip/F-1 mice. Thus, the studies in A-Zip/F-1 fatless mice help to dissociate the role of obesity from chronic inflammation in carcinogenesis and offer an opportunity for identifying potential therapeutic and prevention targets. Unraveling this mystery will contribute to our understanding of the relationship between different cancer types, inflammation, and obesity.

Conclusion

Many studies support the role of obesity in carcinogenesis, but the role of adipose tissue itself in carcinogenesis has recently been questioned. To unravel the complexity of possible hormonal mediators and signaling pathways associated with carcinogenesis, additional studies dissociating obesity from chronic insulin resistance and inflammation in cancer risk are needed. In view of the information summarized in this review, we postulate that the pathways associated with insulin resistance and inflammation, rather than adipocyte-derived factors, may represent key therapeutic targets for disrupting the obesity-cancer link.

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