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Review article

Obesity and cancer: at the crossroads of cellular metabolism and proliferation

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Epidemiology

Obesity is associated with increased incidence and mortality of multiple cancers, with risk ratios correlating directly with body mass index (BMI) in a dose-dependent fashion. The relationship between BMI and cancer is nonlinear and amplified at high BMI: the risk ratio for mortality from endometrial cancer, among the highest of all cancers, is 1.5 for overweight women (BMI 25–30), 2.5 for women with class 1 obesity (BMI 30–35), and rises to over 6 in women with class 3 obesity (BMI $>$ 40). Obesity is a particularly strong risk factor for colon, renal, pancreatic, and esophageal adenocarcinomas as well, with similar dramatic increases in risk at high BMI. This high degree of risk translates into a substantial disease burden: obesity is estimated to be a dominant causative factor in 10%–20% of all cases of cancer [1–3].

Although obesity increases the risk of most cancers, exceptions exist. Obesity is associated with a decreased risk of lung cancer and squamous cell cancer of the esophagus [1–4], cancers for which smoking is an important risk factor, confounding analysis of the effect of BMI. Although obesity increases breast cancer risk in postmenopausal women, no such association exists in premenopausal women, in whom some data suggest that elevated BMI may exert a protective effect [2]. Data is conflicting regarding obesity's effects on prostate cancer incidence, with different studies demonstrating a weak positive effect, no effect, or a weak protective effect [5–8]. Lower androgen levels in obese men may explain an observed protective effect, and differences among studies may relate to differences in androgen sensitivity of individual prostate cancers.

Obesity not only affects cancer incidence and long-term cancer-specific mortality, but also affects survival and recurrence among those diagnosed with cancer. Despite conflicting data regarding obesity's effects on prostate cancer incidence, compelling data demonstrate decreased survival among obese patients compared to lean patients who develop prostate cancer [9–11]. Other cancers associated with worse prognosis in the obese include colon [12], lymphoma [13], and breast [14]. Treatment efficacy may underlie some of these observations. Underdosing of chemotherapy, reduced delivery of radiation therapy, and technical challenges associated with extirpative surgery leading to lower rates of R-0 resections are reported in obese patients [15–18]. Biologic effects of adipose tissue may interfere with cancer therapy; for example, aromatase inhibitor therapy is less effective at reducing serum estradiol levels in obese breast cancer patients [19], possibly related to increased aromatase activity from adipose tissue, while other data demonstrate that obesity is associated with decreased efficacy of cytotoxic chemotherapy in breast cancer patients [20]. In contrast to these findings, in some cases obesity appears to exert a beneficial effect on survival in patients diagnosed with cancer, the so-called "obesity

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paradox". Obesity is a strong risk factor for the development of renal cell cancer, but obese patients who develop renal cell cancer experience longer survival compared to lean patients [21,22]. Conflicting data suggest that obesity may be associated with more favorable outcomes in endometrial, head and neck, rectal, and esophageal cancer as well, even after controlling for tumor stage [23–26]. The mechanisms underlying such protective effects are poorly defined. Obesity may be associated with decreased chemo- and radiation-therapy toxicities, which may contribute to increased treatment efficacy in some cases [27,28]. Alternatively, limitations in BMI as a metric for obesity as well as selection bias and other statistical confounders have been proposed to discount the obesity paradox with respect to cancer survival [29,30], which therefore remains controversial.

Multiple variables regulate the obesity-cancer risk equation. Gender and ethnic differences exist; risk ratios for obesity are significantly higher in men than women for colon cancer incidence, for example, Asians suffer increased breast cancer risk at lower BMI compared to non-Asians [30]. Similar to other metabolic diseases, visceral adiposity imparts greater risk than subcutaneous adiposity. Diabetes, hyperlipidemia, and other metabolic diseases are tightly linked to obesity but nonetheless exert independent effects on cancer incidence and mortality, and confound analysis of obesity as an independent predictor of risk. Similar confounding effects are exerted by dietary factors, which are also tightly correlated with obesity but nonetheless exert independent effects on cancer incidence; for example, high fat, low fiber diet, although associated with obesity, is a well-established independent risk factor for colon cancer. Despite these epidemiologic complexities, obesity is clearly a dominant causative agent in the pathogenesis of cancer. An understanding of the diverse molecular and cellular mechanisms underlying this association will drive development of novel diagnostic and therapeutic modalities.

Inflammation, nutrient excess, and cancer

Since Virchow first observed lymphocytes populating tumors in 1863 [31], thousands of reports have implicated inflammation in the pathogenesis of cancer. Inflammatory bowel disease, primary sclerosing cholangitis, hepatitis, and pancreatitis are but a few of many chronic inflammatory diseases associated with an increased risk of cancer in involved tissues. Immune leukocytes, including macrophages, neutrophils, monocytes, T-cells, β-cells, and natural killer (NK) cells, utilize multiple cytotoxic molecules, such as reactive oxygen species, free radicals, antibodies, and cytolytic proteins, to mediate inflammatory responses. Leukocytes also secrete cytokines, which potentiate leukocyte activation, proliferation, and inflammatory responses via autocrine and paracrine effects, and exert multiple effects on nonimmune cells, including regulating proliferation and apoptosis. The specific mechanisms underlying the association between inflammation and cancer remain poorly defined, but at a conceptual level, increased mutagenesis resulting from exposure of cells to inflammatory weapons combined with increased cell turnover secondary to tropic effects of cytokines create a perfect storm for carcinogenesis.

Obesity is associated with a state of chronic systemic inflammation. The link between nutrient excess and inflammation is rooted in the chemical nature of nutrients, bioenergetic molecules capable of participating in energy-intensive reactions that are potentially damaging to cells. Cells have evolved protective systems designed to sequester and limit exposure to these molecules, including the endoplasmic reticulum (ER), a complex organelle present in all cells that meters exposure to nutrients. When inundated with nutrients beyond the capacity of the ER to manage, cells mount an ER stress response, which leads to apoptosis. An inflammatory response is in turn generated to scavenge apoptotic cells. Cells damaged by excess nutrients are thus removed, limiting nutrient-mediated injury and protecting the organism as a whole. Excess nutrients, including free fatty acids, glucose, and downstream metabolites such as diacylglycerol, ceramides, and advanced glycation end-products, directly trigger leukocyte-mediated inflammation: free fatty acids are ligands for Toll-like receptors (TLR), which are expressed on innate immune cells and trigger inflammatory responses, while advanced glycation end-products bind leukocyte receptors for advanced glycation end-products (RAGE) with similar effects. TLR and RAGE ligands represent direct molecular links between metabolism and inflammation.

Adipose tissue in health acts as a nutrient buffer, protecting other tissues by storing excess nutrients in adipocytes in the form of lipid. As adipocytes reach hypertrophic capacity in overweight and obese patients, ER stress ensues, and leukocytes are recruited to scavenge apoptotic adipocytes. The resulting adipose tissue inflammatory leukocyte infiltrate is dominated by macrophages, but also involves T-cells, β-cells, NK cells, and other immune cell subtypes. In early obesity, nutrient excess, ER stress, and inflammation remain confined to adipose tissue. With progressive obesity, adipocyte storage capacity is overwhelmed, nutrient buffering capacity is exceeded, and excess nutrients and metabolites overflow into the systemic circulation. Nutrient- and metabolite-induced cell stress spreads beyond adipose tissue, establishing a low grade inflammatory state in all tissues that underlies the pathogenesis of malignant and nonmalignant metabolic disease.

Cytokines are central mediators of the link between inflammation and cancer. Tumor necrosis factor-alpha (TNF-α, a dominant inflammatory cytokine expression of which is elevated in obesity, promotes cancers of the skin, liver and lymphoid system in murine models, while TNF-α knockout mice are protected from chemically-induced skin and colon cancers [32–36]. Similar murine models implicate interleukins 2, 6, and 8 (IL-1, IL-6, and IL-8) in cancer initiation and progression, and expression of these cytokines is also elevated in obesity. Data from humans support a role for cytokines in cancer pathogenesis: for example, IL-6 and IL-8 gene polymorphisms are linked to gastric, colorectal, and esophageal cancers [37,38]. Inflammatory cytokines have multiple downstream effects that contribute to cancer pathogenesis. Cytokines activate inducible nitric oxide synthase, increasing nitric oxide levels that induce tumor growth, metastasis, and angiogenesis in multiple animal models [39,40]. Cytokines trigger cellular NFκB signaling, which has been implicated in carcinogenesis; inhibition of nuclear factor kappa-light-chain-enhancer of activated β-cells (NFκB) is associated decreased neoplastic cell transformation and increased tumor sensitivity to chemotherapy [41–43]. Inflammation is tightly linked to angiogenesis, a critical component of tumorigenesis. TNF-α, while inducing apoptosis in cells that suffer ER and oxidative stress, promotes proliferation of stromal and endothelial cells, potentiating fibrosis and angiogenesis within the tumor microenvironment. IL-1 is similarly required for angiogenesis and tumor progression in multiple animal models [44,45]. Finally, cytokines play important roles in cell adhesion, chemotaxis, and migration, which along with other inflammatory chemokines, may contribute to tumor metastasis.

Diabetes provides an important example of the overlap between metabolism, inflammation, and carcinogenesis. Diabetes is an independent risk factor for multiple cancers, with the strongest data supporting a link with pancreatic and liver cancers [46]. Inflammation is a major contributor to the pathogenesis of diabetes independent of cancer, and anti-inflammatory agents ameliorate diabetes. Aspirin was observed as early as 1901 to improve diabetes [47], while modern anti-inflammatory agents, including salsalate, a salicylate-derivative, and anti-TNF-α and antiIL-1 antibodies, are currently in clinical trials as therapy for diabetes [48–50]. Parallel data demonstrate a cancer preventive effect of long-term therapy with aspirin and nonsteroidal anti-inflammatory drugs [51,52]. Taken together, these observations suggest that the processes that regulate inflammation, metabolism, and carcinogenesis are intertwined, and that inflammation-based therapy for metabolic disease may also demonstrate efficacy in preventing or treating cancer. Despite these exciting opportunities, enthusiasm for inflammation-based cancer therapy must be tempered by observations that suppression of immune and inflammatory responses also stimulates carcinogenesis. For example, inhibition of NFκB in certain in vitro and in vivo preclinical models is associated with tumorigenic effects depending on the context, and it is well-established than cancer risk is increased in patients treated with long-term immunosuppression. These observations speak to the narrow therapeutic window in which the “inflammatory rheostat” and immunotherapy must be tuned.

The anabolic hormonal milieu in obesity

In addition to promoting inflammation, nutrient excess establishes a state of cellular and systemic anabolism characterized by increased expression of multiple growth factors, including insulin. Insulin-like growth factor-1 (IGF-1), steroid hormones, adipokines, and gut hormones. This anabolic environment promotes proliferation of preneoplastic and neoplastic cells, and when combined with mutagenic stimuli from chronic inflammation, creates an ideal environment for neoplasia (Fig. 1). In support of a tumor-promoting anabolic state in obesity, breast cancers in obese compared to lean women demonstrate higher mitotic index, histologic grade, and tumor size, and among tumors controlled for size, express higher levels of proliferation markers [53].

Insulin plays a dominant role in promoting the anabolic state in obesity. As adipose tissue buffering capacity is overwhelmed, free fatty acids spill into the systemic circulation. Peripheral tissues, most notably skeletal muscle and liver, respond by shifting energy production away from glucose utilization and toward fatty acid oxidation, decreasing expression of insulin receptors, glucose transporters, and insulin signaling molecules and increasing expression of enzymes involved in fatty acid catabolism. This shift in energy metabolism leads to systemic hyperglycemia, to which pancreatic islet beta cells respond with a compensatory increase in insulin secretion. These responses underlie the development of peripheral insulin resistance and hyperinsulinemia, pathognomonic features of obesity.

Insulin is a potent growth factor that induces proliferation and inhibits apoptosis in a wide range of benign and malignant cells and promotes tumorigenesis in in vitro and in vivo models [54–60]. Increased insulin levels in humans are independently associated with multiple cancers, including those most strongly associated with obesity, such as colon, endometrial, pancreas, and breast [61–64]. Insulin receptor expression is increased in multiple cancers, including breast, prostate, hepatocellular, and leukemic cancers [65,66]. Insulin also promotes the expression of IGF-1, a hormone secreted primarily by the liver that stimulates the growth of numerous cancers in in vitro and in vivo models [67,68]. IGF-1 mediates its tropic effects by binding its own receptor as well as the insulin receptor, both of which are expressed on most normal cells and overexpressed in many tumors [65]. IGF-1 also induces angiogenesis which has been linked to cancer progression [69]. Similar to insulin, a preponderance of data suggest a correlation between serum IGF-1 levels and cancer in humans, and preclinical studies demonstrate a growth promoting effect of IGF-1 on cancer growth [61,62,64].

Steroid hormones contribute to obesity-related cancer. Clinical and mechanistic data strongly implicate steroid hormones in multiple cancers independent of obesity, most notably breast, endometrial, and ovarian. Serum steroid hormone levels correlate directly with the risks of these

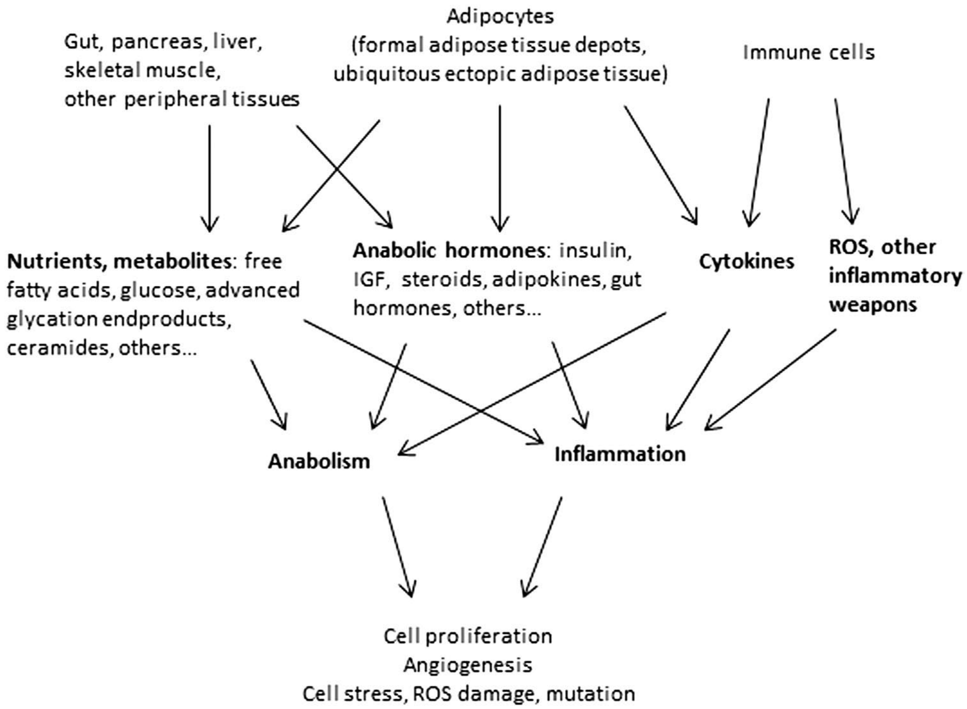

Fig. 1. Multiple factors influence carcinogenesis in obesity. Chronic anabolism and inflammation are central sequela of the many alterations in multiple organ systems observed in obesity. Direct effects of increased nutrient and metabolite delivery to cells promote cellular anabolism and proliferation, and directly stimulate the immune system via Toll-like receptors and other receptor families. Increased systemic inflammation promotes cell damage, turnover, and mutagenesis. Cytokines, adipokines, steroids, and gut hormones are elevated in obesity and similarly promote cellular anabolism and proliferation and inflammation. Adipocytes within formal adipose tissue depots, as well as ectopic adipocytes present in virtually all tissues, contribute by providing nutrients, adipokines, and cytokines to all cells via paracrine and endocrine mechanisms. Tumors, once established, recruit adipocytes and adipocyte stem cells to enhance these effects. All of these pathways trigger endoplasmic reticulum and oxidative stress pathways which in turn perpetuate one another, leading to a vicious cycle of cell stress. The combination of anabolism and inflammation creates a systemic milieu that predisposes to carcinogenesis.

cancers [70–75], while numerous in vitro and in vivo experimental models support a role for steroid hormones in tumor progression. Multiple mechanisms contribute to elevated steroid hormone levels in obesity. Elevated estradiol levels result from increased conversion of androgens to estradiol by aromatase expressed in white adipose tissue. While the ovaries are the chief source of estrogen in premenopausal women, in postmenopausal women adipose tissue becomes a dominant source, and this may also be the case in obese premenopausal women. Expression of TNF-α, IL-6, and leptin are increased in obese adipose tissue, and these cytokines and adipokines induce aromatase expression by adipocytes, exacerbating adipose tissue steroidogenesis [76,77]. Insulin, IGF-1, and glucose, also increased in obesity, inhibit expression of sex hormone-binding globulin by the liver, increasing systemic bioavailability of steroid hormones [78]. Finally insulin induces ovarian and adrenal androgen synthesis, increasing androgen levels as well as estradiol levels by providing androgen substrate for adipose tissue aromatase.

Serum levels of steroid hormones are elevated in obesity [79,80] and reduced with diet- or surgery-induced weight loss with a concomitant reduction in cancer risk [81–85]. Animal models of obesity are associated with increased incidence and growth of steroid hormone-sensitive tumors [86–89]. Breast cancer is one of the best-studied steroid-sensitive cancers and is strongly associated with obesity. Supporting a role for obesity-related aberrations in estrogen in breast cancer are observations that obesity is more often associated with estrogen receptor $(ER)^+$ breast cancers [90,91]. Furthermore, while ER^+ breast cancers generally have a more favorable prognosis than ER^- tumors, this may not be true in obese patients; in at least 1 large population-based study, mortality was substantially higher in obese patients with ER^+ tumors compared with lean patients with similar tumor histology [92], suggesting that elevated circulating estrogen in obesity may stimulate ER^+ breast cancer growth.

Adipokines are secreted primarily by adipose tissue and exert broad effects on multiple aspects of physiology via hormonal and paracrine mechanisms. Dysregulated adipokine expression contributes to the anabolic state in obesity. Leptin, secreted primarily by adipocytes, and adiponectin, secreted by both adipocytes and adipose tissue stromal cells, are dominant adipokines with pleiotropic and opposing effects. Leptin, expression of which is increased in obesity, promotes metabolic disease, insulin resistance, and inflammation, while adiponectin, expression of which is decreased in obesity, has opposite effects. A similar dichotomy is evident in the effects of leptin and adiponectin on neoplastic growth. Serum levels of leptin correlate directly, and adiponectin indirectly, with the risk of multiple cancers, including breast, colon, prostate, endometrial, gastric, colorectal, and leukemic cancers [93–99]. In vitro and in vivo models support this functional dichotomy, with leptin promoting and adiponectin inhibiting the growth of multiple types of cancer cells and tumors in preclinical models via opposing effects on cell proliferation and apoptosis [56,100,101]. Leptin promotes and adiponectin suppresses angiogenesis, effects that have also been implicated in tumorigenesis. Adiponectin inhibits angiogenesis in part via induction of endothelial cell apoptosis, and when administrated to animals with sarcomas, suppresses tumor growth [100]. Cancer cells, including hepatocellular and breast cancers, exploit the tropic effects of leptin by upregulating expression of the leptin receptor, and elevated tumor expression of the leptin receptor in breast cancer is associated with worse prognosis [102,103].

Adipokines regulate inflammation, energy homeostasis, steroid hormone metabolism, and expression of multiple growth factors. Numerous adipokines in addition to leptin and adiponectin are dysregulated in obesity, contribute to metabolic disease, and are implicated in cancer pathogenesis, including visfatin, resistin, and apelin. Targeting adipokine signaling holds promise as cancer therapy. Leptin antagonist peptides demonstrate therapeutic efficacy in preclinical models of breast endometrial and cancer [104,105], while adiponectin agonists have been studied with similar results [106].

Emerging data suggest a contribution of gut hormones to the anabolic state in obesity and in carcinogenesis. Ghrelin, an orexigenic hormone secreted by the stomach, promotes growth of gastrointestinal and prostate cancers [107–109]. Glucagon-like peptide-1 (GLP-1), a gut hormone secreted by the proximal duodenum, levels of which are decreased in obesity and increased by bariatric surgery, has beneficial effects on metabolism. GLP-1 inhibits cancer growth in in vitro and in vivo models of colon, pancreatic and cholangiocarcinoma [110,111], although separate data suggest that GLP-1 agonists may increase cancer risk [112]. Multiple other gut hormones are dysregulated in obesity and exert tropic and other cancer-promoting effects on cells. Like the adipokines, gut hormones engage in crosstalk with insulin, IGF, and steroid hormones, and also regulate inflammation. The role of this family of hormones in mediating carcinogenesis is an active area of research.

Adipocyte-tumor crosstalk

Emerging data suggest that adipocytes participate in crosstalk with preneoplastic and neoplastic cells that promotes cancer initiation and progression. Adipocyte infiltration of the pancreas and breast predisposes to cancers in these organs [113–115], while histologic evidence of peritumor adipocytes predicts a poor prognosis in multiple cancers [116–118]. Robust preclinical data demonstrate that adipocytes potentiate tumor cell proliferation and invasion in in vitro and in vivo models in multiple cancers [119–126].

The anatomic basis of adipocyte-tumor crosstalk is complex. Adipocytes influence preneoplastic and neoplastic cells via endocrine and paracrine mechanisms. Adipokines and steroid hormones secreted directly from canonical adipose tissue depots, as well as secondary endocrine effects of increased adipose tissue mass (e.g., hyperinsulinemia), discussed above, exert tropic endocrine effects on multiple target tissues and have been implicated in carcinogenesis. Many tumors associated with obesity reside near canonical anatomic adipose tissue depots, including renal, pancreatic, hepatic, and colon, and are thus also subject to paracrine effects of adipokines and other adipocyte products. Renal and pancreatic cancers are examples of tumors that arise in tissues surrounded by retroperitoneal and visceral fat that have especially high risk ratios for elevated BMI. Independent of formal anatomic adipose tissue depots, adipocytes are central components of the stromal microenvironment of multiple tissues in which tumors arise, and thus exist in intimate association with preneoplastic and neoplastic cells. Finally, tumors not only exploit preexisting adipocytes present in stromal tissues, but also recruit adipose tissue stem cells from remote sites, which differentiate into adipocytes, fibroblasts, and endothelial cells, contributing to the tumor microenvironment and promoting neoplastic growth [127].

An important mechanism by which adipocytes promote carcinogenesis is reciprocal metabolic programming that leads to energy transfer from adipocytes to cancer cells. Adipocytes provide glutamine to leukemia cells and free fatty acids to ovarian cancer cells, promoting tumorigenesis in these cancers [128,129]. Tumor cells and adipocytes participate in crosstalk which reprograms adipocyte metabolism to enhance metabolic substrate shuttling: ovarian cancer cells, for example, inhibit lipogenesis and induce lipolysis in adipocytes, promoting free fatty acid transfer to tumor cells [128]; breast cancer cells similarly induce a dedifferentiated, fibrotic, glycolytic phenotype in adipocytes that predisposes to increased energy substrate transfer to tumor cells [130,131]. Wnt signaling represents a potential underlying mechanism of induction of adipocyte dedifferentiation and fibrosis by cancer cells. A large body of literature implicates Wnt signaling in multiple cancers, and Wnt signaling is an established negative regulator of adipocyte differentiation independent of cancer. Breast cancer-induced dedifferentiation of adipocytes is mediated by breast cancer-derived Wnt ligands [130], suggesting Wnt signaling mediators as targets for interfering in adipocyte-cancer crosstalk. Emerging research suggests other avenues for exploiting adipocytes as targets for cancer therapy.

Thiazolidinediones (TZDs) promote adipocyte differentiation; induction of a differentiated, less tumorigenic adipocyte phenotype may underlie the observed decrease in cancer incidence among patients treated with TZDs [132]. Manipulation of peritumor adipocyte phenotype to reduce fibrosis and energy substrate transfer to tumors via interference in Wnt and other signaling pathways represents a promising strategy for adipocyte-based cancer therapy.

Other factors contributing to the cancer-obesity connection

In addition to aforementioned effects on the systemic inflammatory and hormonal milieu, nutrients and metabolites directly regulate tumor cell growth in in vitro models. Saturated free fatty acids promote the growth of multiple cancer cells, while unsaturated free fatty acids promote cancer cell apoptosis [133,134], effects mediated in part via regulation of mammalian target of rapamycin (mTOR) signaling [135]. Similar data demonstrate tumor promoting effects of advanced glycation end products [136]. In addition, obesity is associated with an increased risk of a number of nutrient deficiencies that have been implicated in cancer pathogenesis, including vitamin D, selenium, and magnesium. Challenges persist in distinguishing between primary effects of nutrients and metabolites on neoplastic cells and secondary effects mediated via inflammatory and hormonal mechanisms, and the relative roles of nutrient excess and micronutrient deficiencies on cancer risk in the obese. Nonetheless, dietary modification and "nutraceutical" therapy for cancer prevention and treatment continue to generate interest and may play a particularly important role in obesity.

Another emerging focus of study is the role of the microbiome in contributing to cancer in obesity. Obesity is associated with alterations in the gut microbiome that are linked to metabolic disease [137]. These changes include an increase in gram-negative gut bacteria with increased absorption of lipopolysaccharide from the gut [138,139], potentially contributing to inflammation. Microbiome-derived metabolites, including heterocyclic amines, nitrosamines, and fecapentaenes, production of which are elevated as a result of increased dietary meat and fat, act as mutagens and may contribute to carcinogenesis. Alterations in bile acid metabolism secondary to changes in the microbiome in obesity may also contribute to oxidative damage and mutagenesis. Research into the role of the microbiome in obesity and cancer is rapidly evolving.

Cell signaling pathways linking energy homeostasis and carcinogenesis

The association between obesity and cancer is rooted in the intimate relationship between the fundamental processes that regulate energy homeostasis and survival in all cells. Cellular metabolism is tightly linked to proliferation and apoptosis, which adjust thresholds for these processes in response to nutrient delivery. Nonmalignant cells appropriately engage in anabolic processes and proliferation when nutrients are plentiful, and shift to a catabolic, nonproliferative, apoptosis-prone state when nutrients are scarce. Malignant cells, in contrast, demonstrate uncoupling of cellular metabolism and proliferation. In a sense, cancer may be considered a disorder of cellular metabolism in which the link between nutrient availability and cellular regulation of metabolism is disrupted and anabolism and proliferation predominate over catabolism and apoptosis regardless of nutrient availability.

The signaling pathways that regulate cellular metabolism and cell survival are activated by multiple aberrant stimuli in obesity and participate in robust crosstalk (Fig. 2). Protein kinase B (Akt) and adenosine monophosphate-activated protein kinase α (AMPK) are dominant signaling pathways that link metabolism and proliferation in all cells. Akt is a central signaling nexus that is activated by insulin during periods of nutrient availability and plays a dominant role in the regulation cellular glucose and lipid metabolism. In addition its metabolic functions, Akt also controls cellular survival by activating mTOR, a downstream signaling pathway that promotes cell proliferation and inhibits apoptosis. AMP-activated protein kinase (AMPK), in contrast, is a central cell signaling mediator that is activated when nutrient stores are low; increased cellular AMP levels are a dominant trigger for AMPK activation. Adiponectin, levels of which are decreased in obesity, also activates AMPK. AMPK induces a catabolic state in cells, in part by inhibiting Akt. AMPK also directly inhibits mTOR activity, thus attenuating cell proliferation. Akt and AMPK thus act as opposing forces that link cellular energy homeostasis with cell growth in response to nutrient availability. Phosphatase and tensin homolog (PTEN) and liver kinase B1 (LKB1) are intermediate signaling molecules that regulate the balance of Akt and AMPK activity, adding a another layer of regulatory control. Both PTEN, which inhibits Akt, and LKB1, which activates AMPK, are activated by nutrient depletion and induce a catabolic state in cells and, through downstream effects on mTOR, also inhibit cellular proliferation.

Similar signaling crosstalk links cellular metabolism and inflammation. Nutrient activation of TLR and RAGE trigger inflammatory responses via activation of the central signaling mediator NFκB, which, in addition to inducing a transcriptional program that activates inflammation, also regulates proliferation and apoptosis in all cells, as well as angiogenesis, processes required for the cell turnover that accompanies both sterile and nonsterile inflammatory responses. Janus kinase/Signal Transducer and Activator of Transcription (Jak/STAT) and mitogen activated protein kinases (MAPK) signaling pathways are activated by cytokines and adipokines and regulate these same

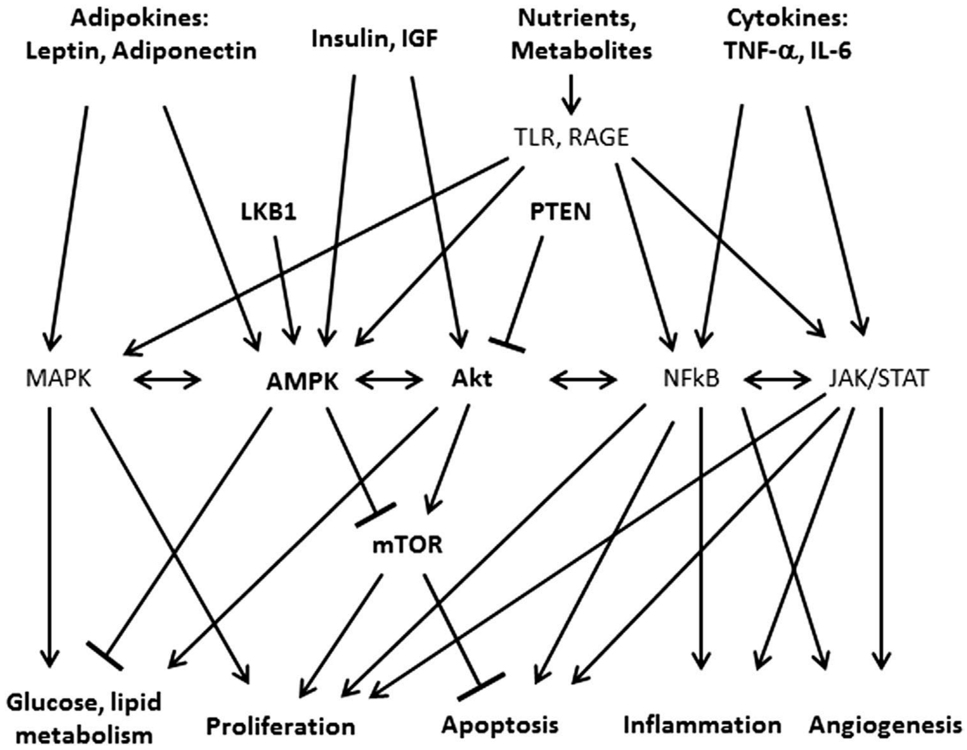

Fig. 2. Simplified schematic of major cell signaling pathways that link energy homeostasis and carcinogenesis. Primary cell stimuli include adipokines, insulin, IGF-1, nutrients and metabolites including free fatty acids, and their derivatives such as ceramide, (which activate Toll-like receptors, TLR), and advanced glycation end-products (which activate receptors for advanced glycation end-products [RAGE]), and cytokines. Adenosine monophosphate-activated protein kinase α (AMPK) and Akt are central cell signaling nexuses that control metabolism and proliferation, in part by regulating mammalian target of rapamycin (mTOR). Other pathways including mitogen activated protein kinases (MAPK), NFkB, and Janus kinase/ Signal Transducer and Activator of Transcription (JAK/STAT) signaling mediators. Intermediate signaling mediators, including liver kinase B1 (LKB1) and phosphatase and tensin homolog (PTEN), add further regulatory control. All stimuli and pathways engage in highly redundant crosstalk via cross-reactivity of intracellular signaling mediators and transcriptional programs. The resulting complex interactome mediates the link between cellular energy homeostasis and cell survival.

fundamental processes. All of these signaling pathways participate in crosstalk, share intracellular signaling mediators and exert overlapping redundant functions that together creates a highly complex interactome that controls cell homeostasis. In situations of episodic nutrient availability, these numerous interacting signals cycle on and off in response to feeding and fasting. In situations of chronic nutrient excess, in contrast, these pathways are chronically activated, promoting hyperplasia and eventual neoplasia. Neoplastic cells, once established, further exploit signaling crosstalk by selecting for mutations that uncouple inhibitory feedback pathways that in normal cells limit anabolic metabolism and proliferation when nutrients are scarce. Mutations in Akt and AMPK pathways are among the most common in all cancers. Activating mutations in Akt are present in 20%–100% of human tumors depending on the type of cancer studied [140]. The genes encoding both PTEN and LKB1 are tumor suppressor genes associated with hereditary and sporadic cancers. Mutation in the LKB1 gene underlies Puetz-Jeghers syndrome, an autosomal dominant disorder characterized by intestinal hamartomas and an increased risk of gastrointestinal cancer, while mutation in the PTEN gene is associated with Cowden's syndrome, an autosomal dominant disorder associated with benign and malignant tumors of multiple tissues. LKB1 and PTEN are also are among the most commonly mutated genes in many spontaneous cancers. These oncogenic mutations act to increase Akt activity and inhibit AMPK activity regardless of nutrient availability, uncoupling cell proliferation from nutrient status and providing a growth advantage to malignant cells.

The link between cellular control of metabolism and proliferation presents opportunities for metabolism-based cancer therapy. Recent data demonstrate that pharmacologic agents used to treat diabetes affects carcinogenesis. Data suggest that long-term treatment with insulin or insulin secretagogues (i.e., sulfonylureas) is associated with elevated cancer risk, presumably because of insulin's tropic effects on cells; conversely, treatment with metformin and TZDs attenuates cancer risk [132,141,142]. The mechanisms underlying these antineoplastic effects are likely multiple. Both metformin and TZDs reduce serum insulin levels, thus attenuating tropic stimuli delivered to preneoplastic and neoplastic cells. Metformin also activates AMPK and in doing so may recouple cell energy status to proliferation. These observations suggest that current pharmacologic agents used to treat metabolic disease may demonstrate efficacy in preventing or treating cancer. Preclinical studies exploring next generation metabolic anticancer agents are in progress, including delivery of wild-type PTEN to cancer cells via exosomes, as well as pharmacologic agents designed to up-regulate PTEN and LKB1 expression [143]. Targeting cell metabolism holds significant promise for cancer therapy.

Bariatric surgery and cancer

Both diet- and surgery-induced weight loss reduces the risk of cancer associated with obesity [144–149]. Documented reductions in inflammatory mediators, insulin, IGF, steroid, and adipokine levels likely contribute to this effect and correlate with reduction in adipose tissue mass. Bariatric surgery also induces alterations in gut hormone homeostasis and bile acid metabolism distinct from diet-induced weight loss; the contributions of these mechanisms to cancer risk reduction are currently unclear. In addition, bariatric surgery, in contrast to diet-induced weight loss, is associated with increased metabolic rate in humans and rodents, and rodent models of bariatric surgery demonstrate a shift in cellular energy homeostasis toward a catabolic AMPK-dominated signaling milieu, suggesting that surgery influences energy homeostasis at the cellular level [150–153]. These qualitative differences in metabolism after diet- and surgery-induced weight loss suggest different mechanisms of action, independent of loss of adipose tissue mass. These provocative findings reinforce the concept of cancer as a disorder of metabolism and suggest a role for bariatric and metabolic surgery in cancer prevention.

Conclusion

The association between obesity and cancer is rooted in the fundamental and intimate link between the processes that regulate cellular energy homeostasis and those that regulate cell survival, proliferation, and apoptosis. Obesity leads to dysregulation of inflammatory, endocrine, and metabolic signaling pathways, all of which engage in robust and redundant crosstalk, generating a highly complex interactome that underlies the cancer-obesity link. Chronic overnutrition promotes cell transformation in preneoplastic cells by creating an environment characterized by both anabolism and inflammation. Once neoplastic transformation occurs, mutations in cancer cells uncouple cellular nutrient availability to proliferation, promoting tumor progression. An understanding of the molecular and cellular mechanisms that underlie these processes will lead to novel metabolism-based cancer therapy.

Disclosures

The authors have no commercial associations that might be a conflict of interest in relation to this article.

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