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Obesity, Inflammation, and Cancer

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Abstract

Obesity, a worldwide epidemic, confers increased risk for multiple serious conditions, including cancer, and is increasingly recognized as a growing cause of preventable cancer risk. Chronic inflammation, a well-known mediator of cancer, is a central characteristic of obesity, leading to many of its complications, and obesity-induced inflammation confers additional cancer risk beyond obesity itself. Multiple mechanisms facilitate this strong association between cancer and obesity. Adipose tissue is an important endocrine organ, secreting several hormones, including leptin and adiponectin, and chemokines that can regulate tumor behavior, inflammation, and the tumor microenvironment. Excessive adipose expansion during obesity causes adipose dysfunction and inflammation to increase systemic levels of proinflammatory factors. Cells from adipose tissue, such as cancer-associated adipocytes and adipose-derived stem cells, enter the cancer microenvironment to enhance protumoral effects. Dysregulated metabolism that stems from obesity, including insulin resistance, hyperglycemia, and dyslipidemia, can further impact tumor growth and development. This review describes how adipose tissue becomes inflamed in obesity, summarizes ways these mechanisms impact cancer development, and discusses their role in four adipose-associated cancers that demonstrate elevated incidence or mortality in obesity.

INTRODUCTION

Obesity is epidemic in most developed countries. According to the World Health Organization's 2014 report, >1.9 billion adults worldwide are overweight and >600 million are obese, corresponding to 39% overweight and 13% obesity rates for the world's adult population (1). In the United States, 69% of adults are overweight and 35% are obese (2). The unrelenting rise in obesity is becoming a global crisis because these individuals are at increased risk for developing many serious chronic health conditions, including multiple forms of cancer that also demonstrate worse outcomes with obesity. These combined factors prompted the 2013 decision of the American Medical Association to recognize obesity as a disease.

Lifestyle and environmental factors, rather than inherited genetic defects, regulate the development of 90–95% of all cancers (3). Lifestyle-related changes in body mass index (BMI), a measure of adiposity, are associated with increased cancer risk (4). One recent study estimated that 3.6% of all new cancer cases worldwide are attributable to excess adiposity and that uterine, postmenopausal breast, and colon cancer account for 63.6% of cancers attributable to high BMI (5). Excess body weight is also associated with increased cancer mortality and may account for 14% and 20% of cancer deaths in overweight men and women ≥50 years of age, respectively, and as much as 52% and 62% of the cancer death rate in morbidly obese (BMI > 40 kg/m^2) men and women, respectively (4). Based on these data, and the growing worldwide obesity epidemic, excess weight gain may represent one of the largest avoidable causes of cancer risk and mortality in nonsmokers.

Obesity is a state of chronic subclinical inflammation, which mediates most of its systemic complications. This inflammation also contributes to obesity-associated increases in cancer prevalence and mortality, given that chronic inflammation sets the stage for cancer. Inflammation is a central component of tumor development and progression, as multiple inflammatory cells and mediators are found in tumor microenvironments, where they can function to sustain proliferative signaling, activate migration and metastasis, and promote angiogenesis (6, 7). The cancer/inflammation relationship is also supported by the observation that chronic infections are associated with 18% of cancer cases worldwide (e.g., *Helicobacter pylori* and gastric cancer, human papilloma virus and cervical cancer, and hepatitis viruses B and C and liver cancer). However, not all inflammatory responses promote tumor development. Acute inflammation is characterized by accumulation of CD8$^+$ T cells and natural killer (NK) cells that are important for cancer immunity (8), but these cells are less abundant at sites of chronic low-grade inflammation that can promote tumor growth and progression. Correspondingly, obesity-associated inflammation appears to be a stronger predictor of cancer risk than obesity itself. Metabolic dysfunction during obesity is regulated by chronic inflammation, and metabolically healthy obese subjects have less adipose inflammation, cardiovascular risk, and risk of certain obesity-related cancers than unhealthy obese individuals with metabolic dysfunction (9). Multiple factors originating from inflamed adipose tissue are implicated in the increased cancer risk associated with obesity. The aim of this review is thus to provide an overview of the escalating cycle of adipose inflammation that characterizes obesity, describe how components of this cycle and the inflammatory complications of obesity impact the tumor microenvironment to promote cancer, and discuss how these mechanisms influence specific cancers known to be altered by obesity. Selected cancers with increased prevalence in obesity were chosen for discussion due to their origin within an adipose-rich tissue (breast cancer), direct perfusion by visceral adipose tissue [hepatocellular carcinoma (HCC)], and direct association with mesenteric adipose tissue (colorectal and pancreatic cancers) in order to highlight the molecular and cellular mechanisms by which adipose tissue promotes carcinogenesis.

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ADIPOSE INFLAMMATION IN OBESITY

Adipose tissue is the body's primary long-term energy reservoir, storing energy as lipids to maintain physiologic homeostasis. Adipose tissue is now increasingly recognized as the body's largest endocrine organ, capable of secreting over 50 different adipokines, cytokines, and chemokines, which stand at the crossroads of metabolism and immunity (10). Overnutrition, due to excess caloric intake or reduced caloric expenditure, results in adipose tissue expansion to accommodate increased energy-storage demands; however, excessive expansion during obesity substantially alters adipose tissue histology and function. As adipocytes increase in size, some become apoptotic and surrounded by macrophages to form the crown-like structures that have become a hallmark of adipose inflammation (11). Interactions among adipocytes and adipose-resident immune cells at different stages of this process enhance adipocyte lipolysis and secretion of lipids, as well as adipocyte and immune cell production of multiple proinflammatory factors (**Figure 1**). Negative effects of these factors on peripheral target tissues can subsequently induce insulin resistance and hyperinsulinemia, hyperglycemia, hyperlipidemia, and vascular injury, all of which are associated with oxidative stress and cancer development and/or progression.

Maintenance of Normal Adipose Tissue Function

Lean adipose tissue is composed of a comprehensive, balanced system of anti-inflammatory and proinflammatory mediators and immune cells that sustain normal adipose storage, endocrine function, and, importantly, systemic insulin action in order to maintain normal whole-body metabolism. Interleukin (IL)-4 is a key anti-inflammatory regulator in lean adipose tissue, as it promotes the differentiation and maintenance of three anti-inflammatory cell types associated with normal adipose function: T helper type (T_H)2 cells, alternatively activated M2-like macrophages, and regulatory T cells (Tregs). Activation of signal transducer and activator of transcription (STAT)6 by IL-4 drives expression of an M2 macrophage phenotype in adipose tissue macrophages (ATMs) of lean mice that promotes systemic insulin sensitivity (12, 13). Eosinophils are likely the major source of adipose tissue IL-4 production, because in visceral adipose tissue of lean mice ~90% of IL-4-expressing cells are eosinophils (14). Both IL-4 and IL-13 are required to sustain M2 macrophages. Eosinophils secrete both these cytokines, and eosinophil deficiency is reported to increase high-fat diet (HFD)-induced insulin resistance, suggesting that eosinophils play an essential role in adipose tissue homeostasis (14). Correspondingly, one study has reported that M2-like macrophage deficits in adipose tissue of IL-4/IL-13-deficient mice are rescued in proportion to the number of adoptively transferred wild-type eosinophils in adipose tissue (14). Further studies have found that IL-5 and IL-13 from innate lymphoid type 2 cells (ILC2s) promote adipose eosinophil accumulation (15). IL-33 expression by adipose tissue endothelial cells, adipocytes, and macrophages (16) may also play a central role in adipose homeostasis because it rapidly activates ILC2s to increase IL-5 and IL-13 expression, leading to the accumulation of eosinophils and M2-like macrophages (15). IL-25 also sustains homeostasis and activation of IL-13-producing ILC2 and type II natural killer T (NKT) cells in adipose tissue (17). Increasing adipose tissue levels of IL-13-producing ILC2 and type II NKT cells by adoptive transfer or IL-25 administration can increase adipose eosinophil and M2-like macrophage levels (17, 18). Thus, a newly defined ILC2-eosinophil-M2 axis maintains adipose tissue metabolic homeostasis.

Tregs are another important negative regulator of adipose inflammation. Tregs strongly inhibit proinflammatory responses of other immune cells. Under noninflammatory conditions, Tregs are found in nonlymphoid tissues including skin, lungs, liver, intestinal mucosa, and adipose tissue. These Tregs have unique combinations of transcription factors, immune regulatory functions,

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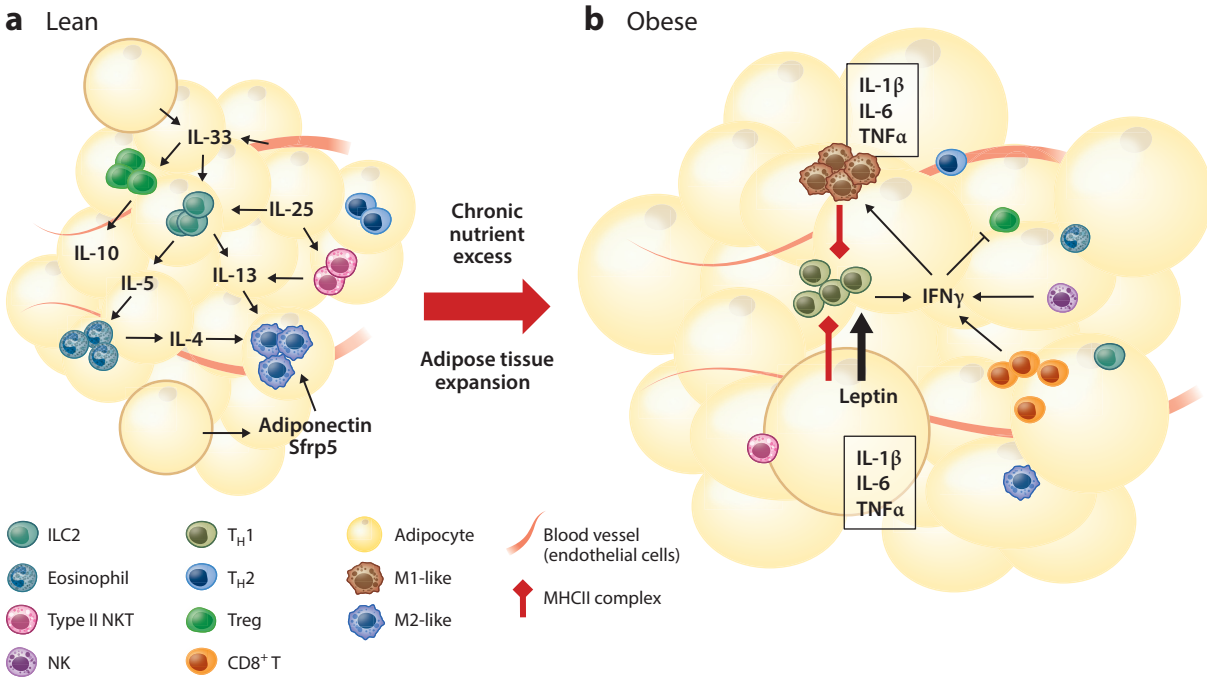

Figure 1

Regulation of inflammation in adipose tissue. (*a*) In the lean state, healthy adipose tissue is enriched with anti-inflammatory immune cells (ILC2s, Tregs, eosinophils, type II NKT and T_H2 cells, and M2-like macrophages) that attenuate adipose inflammation. Adipocyte-derived and endothelial cell–derived IL-33 maintains adipose Treg abundance and anti-inflammatory activities, including IL-10 secretion, and activates ILC2 production of IL-5 and IL-13, which sustain adipose eosinophils and M2-like macrophages, respectively. Eosinophils also produce IL-4 to maintain M2-like macrophages. IL-25 sustains ILC2s as well as IL-13-producing type II NKT cells, whereas lean adipocytes produce anti-inflammatory adipokines, including adiponectin and Sfrp5, to inhibit proinflammatory immune cell actions. (*b*) As obesity develops, adipocytes express more leptin, which, in conjunction with MHCII expression by adipocytes, myeloid cells, and other cell types, stimulates T_H1 cell activation. IFNγ secreted by activated T_H1, NK, and $CD8^+$ T cells stimulates adipocyte MHCII expression and M1 macrophage polarization and may also reduce Treg and T_H2 abundance and function, which decline as adipose expansion progresses. Both adipocytes and M1-like macrophages produce inflammatory cytokines, including IL-1β, IL-6, and TNFα, that further promote adipose inflammation. These processes parallel decreased abundance of Treg and T_H2 cells. Abbreviations: IFNγ, interferon γ; IL, interleukin; ILC2, innate lymphoid type 2 cell; MHCII, class II major histocompatibility complex; NK, natural killer; NKT, natural killer T; Sfrp5, secreted frizzled-related protein 5; T_H1, T helper type 1; T_H2, T helper type 2; TNFα, tumor necrosis factor α; Treg, regulatory T cell.

and T cell receptor repertoires that are specific to their microenvironments (19). Surprisingly, Tregs comprise 50% of $CD4^+$ adipose-resident T cells (ARTs) in visceral adipose tissue of lean mice, much higher than the 10–15% found in lymphoid tissue, but decline to approximately 15% of the $CD4^+$ ART population in obesity (20). Adipose Tregs regulate systemic insulin action, as restoration of adipose Tregs in obese, insulin-resistant mice improves insulin action (21). Tregs in visceral adipose tissue are characterized by increased IL-10 production and increased expression of chemokine (C-C motif) receptor (CCR)1, CCR2, chemokine (C-X-C motif) receptor 4, GATA family of transcription factors 3, peroxisome proliferator-activated receptor γ (PPARγ), and the lipid transporter CD36 (20). Notably, Treg-specific PPARγ deficiency decreases the abundance of adipose Tregs but not lymphoid tissue Tregs in lean mice, and administration of PPARγ ligand to obese mice increases adipose Treg abundance and systemic insulin sensitivity only in wild-type mice (22). Thus, Treg PPARγ activity appears to be a key determinant of adipose Treg abundance

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that can attenuate systemic insulin resistance linked to obesity and inflammation. Recently, IL-33 was identified as an indispensable factor for the development and maintenance of visceral adipose tissue Tregs, because genetic ablation of IL-33 or its receptor severely reduced adipose Treg abundance (23). IL-33 thus has important actions on both Tregs and ILC2s and, in addition to IL-4—which regulates T_H2 cells, Tregs, and M2-like macrophages—has emerged as a central regulator of the immune cells that maintain inflammatory balance in lean adipose tissue.

Adipocytes are an important source of other anti-inflammatory factors in addition to IL-33. Adipocytes produce IL-10 (24), a potent anti-inflammatory cytokine that promotes the phenotypic stability of Tregs, although the majority of IL-10 released by adipose tissue is attributed to the adipose stromovascular fraction, which contains all cells in adipose tissue except for adipocytes. Adiponectin is a powerful anti-inflammatory factor primarily produced by lean adipocytes with multiple effects on immune cells to increase anti-inflammatory expression of IL-10 and the IL-1 receptor antagonist (IL-1RA); reduce proinflammatory interferon γ (IFNγ) and IL-12 expression; and decrease the class II major histocompatibility complex (MHCII), CD80, and CD86 expression required by antigen-presenting cells to activate $CD4^+$ T cells (25). These adiponectin effects increase Treg abundance. Secreted frizzled-related protein 5 (Sfrp5), a Wnt signaling protein, is another important adipocyte-derived anti-inflammatory adipokine whose expression is downregulated in obese mice and humans (26). Deficiency of Sfrp5 increased adipose accumulation of proinflammatory macrophages and activity of the adipocyte c-Jun N-terminal kinase (JNK) pathway that was associated with insulin resistance and increased liver fat, whereas administration of Sfrp5 rescued these changes.

Mechanisms Leading to Adipose Inflammation and Adipocyte Dysfunction in Obesity

Normal energy storage and endocrine activities of adipocytes are profoundly altered during obesity. Chronic nutrient overload leads to adipocyte hypertrophy, mitochondrial dysfunction, and oxidative and endoplasmic reticulum stress to increase proinflammatory signaling, adipokine secretion, and cell death (27). At the tissue level, these alterations are associated with significant changes in the abundance and composition of the adipose stromovascular fraction, with drops in anti-inflammatory Treg and T_H2 cell numbers and increases in proinflammatory T_H1 and $CD8^+$ T cell numbers. Similarly, there is a shift in the ratio of M2 to M1 macrophages, as ATMs become activated to adopt a proinflammatory M1 phenotype in response to ART changes, lipid activation, and other environmental factors that change with obesity (28). However, our understanding of ATM changes in response to weight gain has been complicated by a recent study indicating that palmitate, hyperinsulinemia, and hyperglycemia can metabolically activate ATMs, but not to the full extent of classical M1 activation (29). This study used omental and subcutaneous ATMs, so more work is needed to determine whether there are differences in visceral versus subcutaneous ATM activation. In addition, a comprehensive model of obesity-associated adipose tissue changes has been complicated by conflicting results on the timing and relative contributions of changes in different cell types, which most likely arise from differences in experimental design.

Adipocytes are strong candidates for initiating the cascade of cell changes that promotes adipose inflammation, as they link storage capacity and endocrine function. Adipocytes are the predominant source of adiponectin and leptin, two highly expressed adipokines that have opposing effects on immune cell function. Leptin has multiple proinflammatory effects and increases soon after exposure to nutrient excess, whereas adiponectin has predominantly anti-inflammatory effects and decreases with increased adiposity in response to adipose inflammation. Leptin stimulates production of IL-1, IL-6, IL-12, and tumor necrosis factor α (TNFα) by innate immune cells and

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enhances reactive oxygen species (ROS) production and the secretion of leukotriene B4, cyclooxygenase 2 (COX2), and nitric oxide (25). Leptin is also reported to exert direct effects to increase T cell proliferation and T_H1 cell polarization and to inhibit Treg proliferation.

Our studies suggest that leptin plays a key role in initiation of the adipose proinflammatory cascade (30). Increases in leptin precede increases in T_H1 polarization and IFNγ, which occur prior to decreases in T_H2 cell and Treg subtype markers, and ART and ATM increases. Expression of both leptin and MHCII, the latter of which is required for $CD4^+$ T_H1 cell activation, was found to regulate this response; adipose inflammation was markedly attenuated in both leptin- and MHCII-deficient obese mice (30). Adipocytes isolated from obese versus lean humans and mice demonstrate increased expression of MHCII pathway genes required for $CD4^+$ T cell activation and greater capacity to stimulate antigen-dependent T_H1 cell differentiation and IFNγ secretion. Adipocyte MHCII increases in mice occur within 2 weeks of the start of obesogenic HFD, in parallel with T_H1 ART increases, suggesting that adipocytes regulate T_H1 ART activation early in obesogenic adipose expansion (30).

Leptin-mediated increases in T_H1 $CD4^+$ ART IFNγ secretion can promote M1 polarization, which can be opposed by IL-4 and IL-10 from T_H2 cells and Tregs (31), and from other cells, such as ILC2s and neutrophils, whose behavior during weight gain is not as well known. Both $CD4^+$ T_H1 and $CD8^+$ T cells secrete IFNγ and accumulate prior to ATMs during obesity, and their relative contributions to adipose inflammation and insulin resistance are uncertain. CD8 deficiency protects obese mice from adipose inflammation and insulin resistance, which are partially restored by adoptive transfer of $CD8^+$ T cells (32); however, $CD4^+$ ART deficits found in MHCII-deficient mice also protect mice from adipose inflammation despite high adipose $CD8^+$ ART abundance (30), implying that regulatory interactions among $CD4^+$ and $CD8^+$ ARTs impact adipose inflammation. Obesity also increases the adipose abundance of NK cells that express IFNγ in adipose tissue (33), whereas antibody-mediated NK cell depletion reduces diet-induced ATM accumulation, suggesting that NK cells may also regulate adipose inflammation and its systemic complications (33).

Proinflammatory macrophage accumulation is a central characteristic of obesity and a major component of adipose inflammation linked to systemic complications of obesity (34). Myeloid-specific mutations that attenuate macrophage inflammation or chemotaxis, as well as drugs that promote M2 macrophage differentiation, can inhibit adipose inflammation and systemic complications of obesity (35–37). For example, combined JNK1/JNK2 disruption in hematopoietic cells is reported to attenuate diet-induced hyperglycemia, hyperinsulinemia, insulin resistance, and proinflammatory accumulation of M1-like ATMs, despite similar adiposity in JNK1/JNK2 knockout and control mice (37). Conversely, mice with macrophage-specific deletion of interferon regulatory factor 4, which is normally highly expressed to attenuate macrophage inflammation, are more insulin resistant than wild-type mice and have more M1-like ATMs (38). Multiple studies have also identified factors implicated in macrophage accumulation in adipose tissue and their regulation in obesity (39). B cells, mast cells, NK cells, and neutrophils also regulate the adipose inflammatory milieu, impacting subsequent systemic metabolic changes (27).

ADIPOSE TISSUE AND THE TUMOR MICROENVIRONMENT

Classically, cancer cells were thought to exert most if not all of the actions required for tumor development—the hallmarks of cancer—including abilities allowing these cells to sustain proliferative signaling, evade growth suppression, resist cell death, develop replicative immortality, induce angiogenesis, and stimulate invasion and metastasis (40). Mounting evidence, however, now indicates that other cell types present in the tumor microenvironment also play key roles in

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these processes as well as in cancer cell metabolism and immune clearance (7). Thus, the tumor microenvironment is a critical determinant of the initiation and progression of cancer and is characterized by a complex interplay among multipotent stromal/stem cells, fibroblasts, blood vessels, adipocytes, inflammatory and immune cells, cytokines, and extracellular matrix. Under normal conditions, these stromal components suppress carcinogenesis, which correlates with organismal survival (41); however, in a tumor-associated neighborhood, the stroma becomes transformed by a variety of stimuli to promote tumor progression. Cancer cells themselves can modify the stroma to synthesize cytokines, chemokines, growth factors, and proteinases that accelerate disease. Infiltration of immune cells is another stimulus that alters these stromal factors, modulates the inflammatory environment, and promotes angiogenesis. Inflamed adipose tissue can also profoundly impact the tumor microenvironment, which likely explains the strong relationship between adiposity and a variety of tumors.

Virchow linked chronic inflammation and cancer development over 100 years ago when he observed an abundance of leukocytes in neoplastic tissue (42). Since then, the role of chronic inflammation as a precursor of cancer development has been observed in multiple cancer types (43). Chronic inflammation, in part through production of injurious ROS, produces mutations and proliferation of mutated cells; activates transcription factors such as nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), STAT3, and activator protein 1 in premalignant cells to enhance cell proliferation and survival; and promotes angiogenesis in conjunction with hypoxia. Tumor-promoting cytokines include IL-6, IL-11, TNFα, IL-1β, IL-23, and others, the impact of which varies according to the specific tumor type and its stage. In addition, inflammation promotes several steps in the process of metastasis, which is a major mechanism of cancer death (40). Depending on the tumor, these steps can include epithelial-mesenchymal transition, entry into blood vessels and lymphatics, and seeding and proliferation in new areas, where there is interaction with immune and stromal cells.

Once tumors are established, they can educate immune cells to become protumoral, substantially altering the tumor microenvironment (44). The tumor microenvironment contains increased levels of cytokines and growth factors that decrease proinflammatory T_H1 cells and increase T_H2 cells and Tregs. Under these conditions, in which there are high levels of IL-4, transforming growth factor β (TGF-β), and arginase 1, the continued recruitment of monocytes from the circulation by colony-stimulating factor 1 leads to increased tumor-associated macrophages (TAMs) in the tumor microenvironment. The TAMs strongly promote angiogenesis by secreting vascular endothelial growth factor (VEGF), TGF-β, and fibroblast growth factor (45); increase the invasive capacity of tumor cells; and even help escort malignant cells out of the bloodstream to form metastases. In conjunction with immunosuppressive myeloid lineage cells (immature dendritic cells, neutrophils, monocytes, and early myeloid progenitors), TAMs inhibit both effector $CD8^+$ T cells, by secreting human leukocyte antigen G—which causes the T cells to acquire an immunosuppressive phenotype—and effector $CD4^+$ T cells, by expressing ligands to the inhibitory receptors programmed death 1 and cytotoxic T-lymphocyte-associated protein 4—which are upregulated in T cells, B cells, and NKT cells to control the intensity of the immune response and resolve inflammation. Finally, TAMs help to recruit Tregs to the tumor microenvironment and, through their secretion of IL-10 and TGF-β, induce T cells in the microenvironment to become Tregs. Thus, there is an escalating immunosuppressive milieu that inhibits the host from fighting the tumor. Furthermore, secreted proteases may liberate membrane-bound growth factors and degrade extracellular matrix to attenuate contact-dependent growth arrest, release extracellular matrix fragments with promigratory properties, and remodel the local environment to permit tumor metastasis.

Excess adipose tissue and its proinflammatory capacity can potently impact the tumor microenvironment (**Figure 2**). Obesity alters adipose tissue secretion of adipokines and cytokines,

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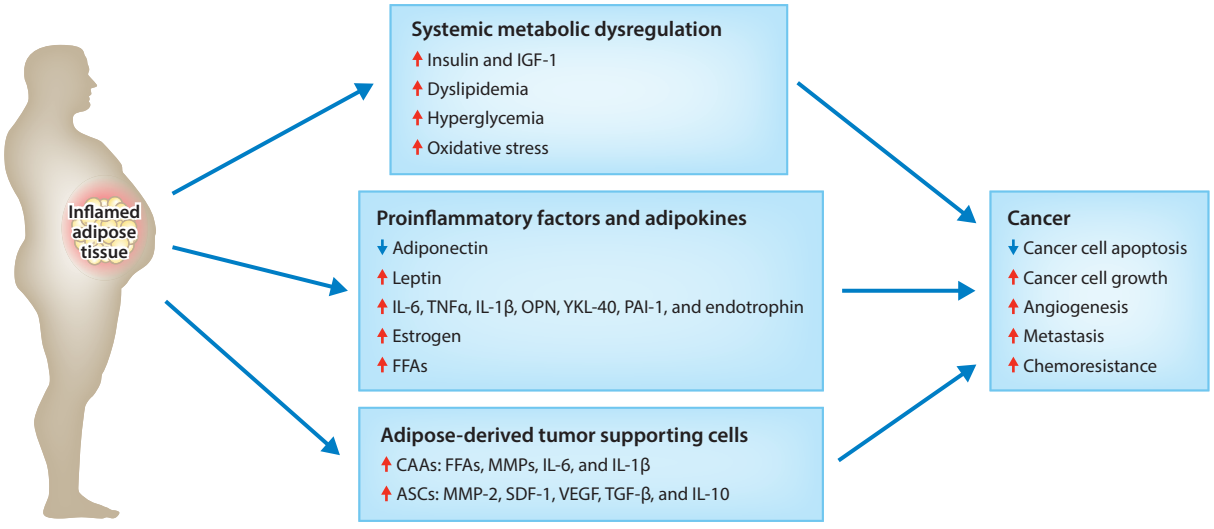

Figure 2

Mechanisms linking obesity to cancer. The dramatic expansion of inflamed adipose tissue during obesity has several effects that impact cancer development. Inflamed adipose tissue is an important endocrine organ, producing adipokines and other factors that promote tumor growth and metastasis while also inducing metabolic dysregulation that impacts these processes. Adipose tissue is also a source of cells that can alter the tumor microenvironment, including CAAs that release FFAs and inflammatory cytokines and ASCs that can contribute to the remodeling of the tumor microenvironment. Adipose-derived proinflammatory factors also promote a tumor-favorable environment indirectly by affecting systemic metabolism and tumor supporting cells. Abbreviations: ASCs, adipose-derived stem cells; CAAs, cancer-associated adipocytes; FFAs, free fatty acids; IGF-1, insulin growth factor-1; IL, interleukin; MMP, matrix metalloproteinase; OPN, osteopontin; PAI-1, plasminogen activator inhibitor-1; SDF-1, stromal-derived factor-1; TGF-β, transforming growth factor β; TNFα, tumor necrosis factor α; VEGF, vascular endothelial growth factor.

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which subsequently affects multiple systemic processes, including the tumor microenvironment. In particular, adiponectin, leptin, IL-6, TNFα, chitinase-3-like-protein-1 (also known as YKL-40), osteopontin, and plasminogen activator inhibitor-1 (PAI-1) are all produced and secreted by adipocytes and promote various aspects of tumor growth, development, and metastasis. In addition to releasing anti- and proinflammatory cytokines, cells from adipose tissue can invade the tumor microenvironment. When cancer-associated adipocytes (CAAs) are present in the microenvironment of tumors adjacent to adipose tissue, e.g., breast cancer, they enhance cancer progression through multiple mechanisms. Adipose tissue is also a rich source of adipose-derived stem cells (ASCs) that can become cancer-associated fibroblasts to promote both cancer and angiogenesis. Finally, the proinflammatory state of adipose tissue in obesity, as well as excess lipolysis, leads to systemic insulin resistance, resulting in elevation of circulating insulin and insulin-like growth factors that impact tumor growth and progression. Moreover, the systemic deranged metabolism associated with dyslipidemia and hyperglycemia can further affect development and progression of tumors and their microenvironment.

ADIPOSE-DERIVED FACTORS IMPACT CANCER

Adipokines Associated with Cancer Risk

Adipose tissue was long considered to function primarily as an energy storage depot, but this view has evolved on the basis of evidence that it also functions as an important endocrine organ that produces numerous adipokines to regulate systemic metabolism and inflammation. Adipose

composition changes with increased adiposity owing to increased influx of and phenotypic changes in multiple immune cell types. Altered interactions among adipocytes, adipose-resident immune cells, and other cell types can dramatically change adipokine production during excess weight gain. Notably, as discussed below, several of these adipokine changes are associated with increased cancer risk or implicated in cancer development or progression.

Adiponectin. Adiponectin is the most highly secreted of all factors expressed by adipose tissue and appears to have antineoplastic activity due to its actions to attenuate inflammation and cell proliferation. However, circulating adiponectin levels decline in obesity, enhancing adipose and systemic inflammation. Low adiponectin levels are associated with increased risk of multiple cancers, as are changes in the high-molecular-weight form of adiponectin and mutations in adiponectin and its two receptors, *ADIPOR1* and *ADIPOR2* (46). Correspondingly, adiponectin administration to murine cancer models has been shown to have multiple cancer-inhibitory effects: reducing proliferation; increasing apoptosis; and decreasing vascularity, growth, and invasion (47).

Leptin. Leptin is a critical adipose-derived satiety hormone that acts through its cognate receptor in the arcuate nucleus of the hypothalamus to suppress appetite, and thus caloric intake, in order to control energy homeostasis. The development of hyperleptinemia and leptin resistance is closely linked with chronic overnutrition and excess weight gain. Leptin has been reported to increase cell proliferation, migration, and invasion responses in several in vitro and in vivo cancer model systems through activation of the Janus kinase/STAT pathway, which modulates phosphoinositide 3-kinase (PI3K)/Akt and extracellular signal–regulated kinase (ERK) signaling to increase inflammatory cytokines (IL-6 and TNFα), promote tumor vascularization by stimulating increased VEGF and hypoxia-inducible factor 1α (HIF-1α) expression (47), and inhibit apoptosis. Systemic leptin and adiponectin levels thus appear to exert almost diametrically opposing effects on tumor development, corresponding to observations that higher adiponectin-to-leptin ratios are associated with decreased cancer risk (48).

Estrogen. Estrogen is primarily produced by aromatase activity in ovarian and placental tissue in premenopausal women; however, after menopause, aromatase activity in adipose tissue and the epidermis plays a significant role in regulating systemic estrogen levels. Aromatase activity is stimulated by multiple adipose-derived proinflammatory factors (IL-1β, IL-6, prostaglandin E2, and TNFα) and liver-derived insulin growth factor-1 (IGF-1), all of which increase with weight gain, whereas corresponding adipose-associated increases in insulin reduce hepatic production of sex hormone–binding globulin (SHBG), which binds estradiol in a biologically inactive state (49). Excess weight gain in men and postmenopausal women is thus associated with significant increases in adipose-derived aromatase activity, estrogen production, and systemic estrogen bioavailability, which may partly explain the increased risk of several gynecological cancers associated with obesity in postmenopausal women.

IL-6. IL-6 has been strongly implicated in the development and growth of a variety of cancers (50). IL-6 modulates the Janus kinase/STAT pathway to promote cancer cell proliferation and survival and angiogenesis. Plasma levels of IL-6 correlate with disease aggressiveness and poor prognosis (51).

Tumor necrosis factor α. Circulating TNFα levels are increased in obesity due to secretion by adipocytes and other immune cells. Similar to IL-6, TNFα has been linked to cellular transformation, proliferation, invasion, angiogenesis, and metastasis (52, 53).

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IL-1β. IL-1β gene polymorphisms are associated with increased cancer risk, and increased tumor expression of IL-1β is associated with poor prognosis (54, 55). NOD-like receptor family, pyrin domain containing 3 (NLRP3) inflammasome activity, which directly regulates IL-1β production, is stimulated by multiple factors that increase with obesity, including free fatty acids (FFAs), cholesterol, hyperglycemia, and ROS (56).

Osteopontin. Osteopontin is a phosphoprotein expressed by adipocytes and multiple other cells, and circulating levels are increased in obesity (57). Osteopontin can increase neoplastic transformation and survival of cancer cells and progression of metastasis (58).

YKL-40. YKL-40 is expressed in higher levels in obesity and type 2 diabetes mellitus (T2DM) (59). It is also increased in some tumors, where it contributes to inflammation, cancer cell proliferation and survival, angiogenesis, and extracellular matrix remodeling (60).

PAI-1. PAI-1 is a serine protease inhibitor produced by many cell types—including adipocytes, where expression is increased in obesity (61). PAI-1 can enhance cancer cell invasion and metastasis and is a poor prognostic indicator for some tumors, including breast and colon cancer (61).

Endotrophin. Endotrophin is a C-terminal cleavage product of collagen VI, which is highly expressed in adipose tissue of obese mice and prominently accumulated in crown-like structures of adipose tissue (62). Endotrophin stimulates tumor cell growth and metastasis by activating TGF-β signaling and may play a crucial role in obesity-associated tumor development (62).

Adipose Cells Associated with the Cancer Microenvironment

Several cancers develop either adjacent to adipocytes (e.g., breast cancer) or at anatomical sites where they are in close proximity to adipose tissue (e.g., gastric, colorectal, and ovarian cancers). Conditioned media from differentiated primary adipocytes and adipocyte cell lines have been reported to promote cancer cell survival and migration, and cancer cells cocultured with adipocytes reveal enhanced in vitro and in vivo invasion activity, suggesting that adipokines can directly regulate tumor growth and metastasis (63). However, cancer cells can also reprogram adjacent adipocytes to adopt a CAA phenotype, characterized by a dramatic decrease in lipid content and several adipocyte differentiation markers, and significantly heightened expression of matrix metalloproteinase (MMP)-11/stromelysin-3 (increased in adipose tissue surrounding invasive tumors), IL-6, and IL-1β to further impact tumor development (64). Notably, mounting evidence indicates that cytokines secreted from adjacent cancer cells promote adipocytes to release high-energy FFAs, stimulating cancer metabolism to support rapid tumor growth of multiple invasive cancers (63).

Adult adipose tissue is also a rich source of multipotent stem cells, which can regulate tumor cell invasion, growth, and vascularization (65). ASCs promote tumor invasion by secreting MMP-2 and stromal-derived factor-1 or several other chemoattractant factors. Conversely, ASCs can migrate into established tumor microenvironments in response to a PDGF gradient and secrete VEGF to promote angiogenesis in response to local hypoxia. Exposure to factors in the tumor microenvironment also causes ASCs to differentiate into cancer-associated fibroblasts, which interact with CAAs and cancer cells to promote tumor progression. Finally, ASCs isolated from cancer versus control subjects have been reported to express more TGF-β1 and IL-10, and conditioned media of ASCs from cancer patients preferentially increase Treg markers in cultured leukocytes, suggesting that ASCs may also exhibit activity to prevent tumor clearance by adaptive immune responses.

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Increased adipose tissue volume is associated with a higher number of ASCs, which are increased in the blood of obese subjects (66). In addition, ASCs from obese women have enhanced leptin expression and increased potential to traffic to tumors compared with those from lean women, and may alter genes involved in the cell cycle, cell survival, angiogenesis, and metastasis (67).

METABOLIC DYSREGULATION ENHANCES CANCER RISK

Central adiposity is characterized by inflammation and metabolic dysfunction that confer increased risk for insulin resistance, dyslipidemia, and hyperglycemia, leading to increased cardiovascular disease risk, cancer risk, and other life-threatening obesity-related conditions. Waist circumference functions as a surrogate marker for the extent of central obesity and is a reported predictor of cancer risk (68, 69) even after adjustment for BMI, indicating that visceral adiposity is more closely associated with cancer risk than is whole-body adipose mass. Visceral adipose tissue is primarily associated with mesentery and omentum within the abdominal cavity and drains directly into the hepatic portal vein. Compared with subcutaneous adipocytes, visceral adipocytes appear to have greater lipogenic and lipolytic capacity (70) and produce more proinflammatory factors. Consistent with a more pathogenic phenotype, increased visceral adipose tissue correlates with increased metabolic risk.

Insulin Resistance and Hyperinsulinemia

During excess weight gain, enhanced hepatic glucose production coupled with decreased glucose uptake by insulin-resistant skeletal muscle leads to compensatory hyperinsulinemia. This chronic hyperinsulinemia can increase IGF-1 and decrease hepatic expression of IGF-binding proteins and SHBGs to increase IGF-1 and estrogen bioavailability (71). Both insulin and IGF-1 can stimulate in vitro tumor cell proliferation, and epidemiological studies indicate that elevated insulin and IGF-1 levels favor aggressive growth of colorectal, pancreatic, liver, postmenopausal breast, and endometrial cancers (72–74). Insulin stimulates both ERK and PI3K signaling pathways to promote tumor growth, loss of epithelial integrity, migration, and metastasis. IGFs promote tumor growth, migration, and invasion, and IGF-1 also stimulates HIF-1α, which correlates with metastasis of some tumors and inhibits p53 to prevent tumor apoptosis.

Dyslipidemia

Excessive adipose expansion results in proinflammatory responses that stimulate lipolysis and secretion of FFAs, which accumulate in multiple tissues to cause lipotoxicity, insulin resistance, inflammation, and metabolic derangements (75). FFA deposition in liver can lead to insulin resistance, increased hepatic glucose production, inflammation, altered hepatic triglyceride and cholesterol metabolism—resulting in dyslipidemia—and, ultimately, nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), and cirrhosis, which set the stage for HCC (76–78). Lipid accumulation in pancreatic islets is lipotoxic, giving rise to β cell apoptosis, impaired insulin secretion and T2DM, and increased risk of pancreatic cancer. In skeletal muscle, lipid accumulation causes insulin resistance and compensatory hyperinsulinemia.

Obesity-associated dysregulation of lipid storage and metabolism has also been reported to impact cancer risk in tissues that do not play major roles in the regulation of metabolic homeostasis, including breast, prostate, and colorectal tissues (79–81). Cholesterol increases associated with dyslipidemia appear to play important roles in breast cancer growth and metastasis (81) and regulate hepatic inflammation linked to NAFLD progression to NASH (82). Lipid dysregulations

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associated with obesity can also enhance the production of signaling lipids that promote tumor growth and metastasis. Monoacylglycerol lipase (MAGL) is upregulated in aggressive human tumors to generate lipid-signaling molecules that promote migration, invasion, survival, and tumor growth (83). MAGL inhibition impairs tumor growth, but tumor growth is restored in obese mice, indicating that obesity-associated changes in lipid metabolism can promote tumorigenesis (83).

Hyperglycemia

The inability of insulin production to overcome insulin resistance leads to hyperglycemia and T2DM. Cancer cells demonstrate increased glucose uptake and glycolysis, so that hyperglycemia might be expected to support increased proliferation. Although it is not clear that glucose availability is a rate-limiting step during in situ tumor growth, high fasting serum glucose levels have been linked to increased cancer incidence and mortality, which is enhanced in diabetic patients, who are twice as likely to die from cancer as nondiabetic patients (84, 85). Hyperglycemia is associated with multiple actions that impact cancer risk (86). Chronic increases in mitochondrial glucose metabolism driven by hyperglycemia induce mitochondrial dysfunction and ROS generation while also increasing glucose conversion to sorbitol, with accompanying decreases in nicotinamide adenine dinucleotide phosphate and glutathione levels (87). Hyperglycemia thus results in reduced antioxidant capacity in the face of enhanced intracellular ROS production. Normalizing mitochondrial superoxide production during hyperglycemia has been shown to attenuate sorbitol accumulation, the production of reactive end products, and the activation of proinflammatory signaling pathways (88). Similarly, in a human study, oxidative stress induced in response to acute hyperglycemia was found to increase circulating levels of IL-6, IL-18, and TNFα (89), which may impact tumor development and progression. Finally, chronic exposure of primary cancer cells to hyperglycemic conditions in vivo or in vitro can induce epigenetic modification of cancer pathway genes, which persists even after a return to normoglycemic conditions, to promote aggressive tumor growth (90).

Oxidative Stress

ROS play important roles in signaling events required to maintain cellular homeostasis; however, excess ROS production, which is associated with weight gain, can promote tumor initiation, progression, and vascularization (91). Exposure to high glucose and FFA levels associated with excess weight gain can induce mitochondrial dysfunction, enhancing ROS production in the face of reduced antioxidant capacity to stimulate expression of proinflammatory factors and increase mitochondrial and nuclear DNA damage (92). Enhanced renin-angiotensin system activity due to adipocyte overexpression of angiotensinogen in obesity can also enhance intracellular ROS production by increasing angiotensin II–induced nicotinamide adenine dinucleotide phosphate oxidase activity, raising superoxide levels to promote DNA damage, mitochondrial dysfunction, and signaling events favoring tumor development and progression (92).

BREAST CANCER

Epidemiology

Breast cancer is the most common cancer among US women, with a 12% lifetime risk, and the second most common cause of cancer death, responsible for approximately 3% of mortality (93). Overweight and obesity are associated with increased breast cancer risk in postmenopausal women, decreased risk in premenopausal women (94), and increased risk for breast cancer–specific

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mortality in both pre- and postmenopausal women (95). In obesity, dysregulated systemic metabolism and inflammation induce hyperinsulinemia, hyperglycemia, and dyslipidemia; enhance postmenopausal sex hormone production; and increase proinflammatory adipokine secretion, most notably leptin, to impact breast cancer development and progression.

Nonadipokine Factors

Cancer cells exposed to hyperglycemia can acquire aggressive growth characteristics that persist after return to euglycemia, and hyperglycemia is a reported risk factor for cancer progression (86). One recent study identified 25 genes in primary mouse breast tumors that revealed epigenetic modifications after exposure to transient in vivo hyperglycemia, including 2 genes involved in receptor tyrosine kinase signaling: the human epidermal growth factor receptor 3 ligand neuregulin-1 (Nrg1) and the VEGF receptor Kdr (kinase insert domain receptor) (90). Nrg1 has been reported to enhance proliferation, survival, invasion, and angiogenesis (96). Nrg1 gene knockdown was found to attenuate aggressive cancer growth induced by prior hyperglycemic exposure, whereas human epidermal growth factor receptor 3 was induced during hyperglycemia (90), suggesting that autocrine Nrg1 signaling and, potentially, increased VEGF sensitivity may mediate part of the hyperglycemia effect to promote aggressive breast cancer growth.

Dyslipidemia and hypercholesterolemia are also linked to aggressive breast cancer growth. Recent work has indicated that 27-hydroxycholesterol, which is synthesized by cytochrome P450 (CYP)27A1 and hydrolyzed by CYP7B1 and increases with hypercholesterolemia, acts as an important estrogen receptor (ER) ligand to promote the growth of ER^+ tumors. Liver is most likely the major source of circulating 27-hydroxycholesterol due to its abundant CYP27A1 expression, but CYP27A1 was also highly expressed in normal breast tissue and ER^+ breast tumors and tumor-infiltrating macrophages, and although CYP27A1 expression was similar in normal breast tissue and ER^+ tumors, CYP7B1 expression was reduced in ER^+ breast tumors, and this decrease correlated with reduced survival (97, 98). CYP7B1 knockout, and high-cholesterol diet, also dramatically reduced tumor latency and increased tumor growth rates in mouse models of ER^+ breast cancer (98). MAGL-regulated alterations in lipid metabolism of aggressive tumors, including breast tumors, have also been shown to promote tumor growth and migration, and reduced tumor growth resulting from MAGL suppression can be rescued by HFD.

Adipose tissue is a major source of circulating estrogen in obese postmenopausal women due to androgen-to-estrogen conversion by adipose aromatase activity, which increases with adipose mass and adipose inflammation (99). Systemic estrogen bioavailability is also enhanced by reduced serum SHBG levels associated with obesity (49), and increases in breast tumor ERα expression suggest an obesity-associated increase in breast cancer estrogen signaling (100).

Adipokines and Cytokines

Because adipocytes compose ~90% of normal breast volume, breast neoplasms develop in close proximity to mammary adipose tissue. Although little is known about the adipokine expression and cellular composition profiles of normal mammary adipose tissue with obesity, visceral and mammary adipose tissue appear to share proinflammatory mechanisms that can regulate tumor growth. Moreover, adjacent adipose tissue serves as a ready source of accessory cells (CAAs and ASCs) that advance aggressive tumor invasion and growth. Mounting evidence demonstrates that adipose tissue inflammation is a key driver of estrogen production in obese postmenopausal women and plays an important role in ER^+ breast cancer, at least in part through its actions to increase aromatase expression in mammary and other adipose tissue depots that subsequently increase

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systemic estrogen bioavailability. In addition, proinflammatory and inflammation-induced factors derived from mammary adipose tissue, the tumor microenvironment, and the tumor itself also impact tumor growth and progression.

Leptin is a key regulator of obesity-associated adipose inflammation (as discussed above) and breast tumor development, during which it increases expression of genes associated with proliferation and angiogenesis and promotes tumor growth (101). In addition to conventional mechanisms governing its expression during nutrient excess, leptin production can also be induced by elevated local concentrations of estrogen and cytokines, including IL-1 and TNFα, that increase with obesity. Conversely, increases in leptin both induce aromatase-mediated estrogen production and transactivate ER signaling in MCF7 breast cancer cells, as well as stimulate leukocyte secretion of IL-1, IL-6, IL-12, TNFα, IFNγ, and nitric oxide, which may create a regulatory feedback cascade to promote tumor growth and leukocyte invasion. Leptin can also increase tumor production of several proangiogenic factors, including MMP-2, MMP-9, and VEGF, although leptin has itself been reported to promote angiogenesis through actions on VEGF receptor signaling and Notch expression (101, 102). Finally, recent studies suggest that leptin may promote breast cancer epithelial-mesenchymal transition and cancer stem cell renewal (101, 103).

Tumor-Intrinsic Inflammation

Numerous proinflammatory cytokines expressed by mammary adipose tissue, breast tumor cells, and cells of the tumor microenvironment can induce tumor progression, although to what extent obesity influences expression of many of these factors in various cells of the tumor microenvironment is not known, nor are the contributions of cytokine secretion by various compartments. Similarly to other adipose tissue depots, obesity increases the crown-like structure density in mammary adipose tissue, with corresponding increases in adipose expression of multiple proinflammatory factors, including IL-1β, IL-6, TNFα, and prostaglandin E2, all of which can induce aromatase activity (49) in addition to exerting effects on other protumorigenic mechanisms. IL-1 is expressed by many breast tumor–associated and –adjacent cell populations, and its tumor expression is linked to increased cell proliferation, survival, invasion, and angiogenesis; IL-1 is expressed primarily by ER^- tumors, but both ER^+ and ER^- tumors express IL-1 receptors (104). IL-6 is expressed by adipocytes, breast cancer tissue, and stromal cells and can induce genes associated with epithelial-to-mesenchymal transition, tumor migration and invasion, and stem cell recruitment, but can also inhibit cell proliferation in an ER-dependent fashion, with tumor IL-6 expression showing linkage to early-stage breast tumors and increased survival outcomes (105). IL-1, IL-6, and TNFα have also been reported to induce breast tumor cells to express chemokine (C-C motif) ligand 22, stimulating Treg chemotaxis and accumulation, which is associated with poor cancer prognosis through action to reduce the cytotoxic activity of invasive $CD8^+$ T cells (101).

LIVER CANCER

Epidemiology

Liver cancer, primarily HCC, is the third-ranking cause of cancer mortality worldwide (93). Chronic hepatitis infection is still a major contributor to HCC risk, but obesity is likely the primary risk factor in the absence of viral infection, which will decrease with global vaccination. HCC is more common in men, among whom the age-adjusted HCC risk has increased threefold in the past two decades and now ranks as the fourth most common cause of male cancer mortality (106). Further, large population studies in North America and Sweden have found that male obesity is associated with 4.5- and 3.1-fold HCC risk increases, respectively. Obesity is strongly associated

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with NAFLD, which is relatively benign but can progress to NASH, a more proinflammatory condition, which can in turn progress to cirrhosis and HCC (106, 107). NAFLD patients are proposed to be at greater risk for HCC in the absence of other factors. Estimates suggest that 25–30% of the US adult population may have NAFLD, and epidemiological studies suggest that NAFLD may explain up to 22% of HCC cases in industrialized countries (107).

Adipokines and Cytokines

The liver is the first tissue to encounter factors released by visceral adipose tissue, which drains into the portal vein, and obesity-associated changes in adipokine and FFA secretion have been shown to impact liver inflammation. Leptin activates hepatic stellate cells, increasing monocyte chemoattractant protein-1, VEGF, collagen α1, and tissue inhibitor of metalloproteinase 1 (TIMP1) expression while decreasing MMP-1 expression and activating HIF-1α. These changes stimulate hepatic inflammation, fibrosis, and angiogenesis to promote development of NASH, cirrhosis, and increased HCC risk (108). Similar proinflammatory and profibrotic leptin effects have been reported for hepatic Kupffer cells, macrophages, and sinusoidal endothelial cells. Leptin also exhibits actions to promote HCC proliferation, survival, migration, and invasion, which can be antagonized by adiponectin, and increases telomerase expression and activity to attenuate senescence. Adipose-derived IL-6 and TNFα have also been implicated in liver inflammation, associated with increased HCC risk (109).

Obesity increases adipose tissue lipolysis, increasing FFA levels to directly promote NAFLD and hepatic inflammation, at least partly through effects to induce hepatic mitochondrial dysfunction, endoplasmic reticulum stress, and Toll-like receptor signaling (109). NAFLD with low-level chronic inflammation is a prominent feature of obesity and can mimic several of its complications, as elegantly demonstrated in a study of lean mice with hepatic-specific overexpression of I kappa B kinase β (IKKβ) (110). These mice revealed many of the characteristic phenotypes associated with diet-induced obesity, including systemic insulin resistance, hyperglycemia, and increased hepatic expression of several cytokines linked with tumor development (IL-1β, IL-6, and TNFα). Notably, IL-6 or TNFR1 knockout almost completely blocked obesity-promoted HCC, suggesting that elevated hepatic IL-6 and TNFα play an important role (111).

Tumor-Intrinsic Inflammation

Signaling pathways regulating NF-κB, JNK, and STAT3 are activated during obesity and implicated in tumorigenesis. Disruption of NF-κB activation by selective ablation of IKKβ in both hepatocytes and immune cells reduces HCC numbers and size after diethylnitrosamine treatment. Hepatocyte-specific IKKβ deficiency increases HCC incidence due to enhanced ROS production and increased JNK activation that promote cyclin D1–driven hepatocyte proliferation (110, 112, 113). Correspondingly, JNK1-deficient mice are much less susceptible to diethylnitrosamine (112). STAT3 activation, which promotes cell growth and differentiation and inhibits apoptosis (50), is detected in ∼60% of human HCC samples, where it is associated with more aggressive phenotype and poor prognosis (114). Both leptin and IL-6 can activate STAT3, suggesting that systemic and local increases linked with obesity and tumorigenesis may impact HCC development.

Immune Microenvironment

Myeloid and lymphoid cells are abundant in the HCC microenvironment. For example, TAMs secrete IL-6, TNFα, VEGF, chemokine (C-X-C motif) ligand 12 and several other factors

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to promote HCC growth, angiogenesis, metastasis, and Treg activity (115), and elevated Treg-to-$CD8^+$ T cell ratios are associated with increased mortality and reduced survival time (116). Two adipokines altered in obesity, adiponectin and leptin (25), regulate myeloid and lymphoid activities associated with tumor development, but little is known about the relative effects of specific cytokines. Serum IGF-1 increases linked with obesity may facilitate the growth of hepatic metastases, given that obese IGF-1-deficient mice have a reduced incidence of liver metastasis, paralleling reductions in hepatic macrophages and markers of macrophage (TNF-α, IL-1β, monocyte chemoattractant protein-1, and IL-18) and endothelial cell (P-selectin, intercellular adhesion molecule 1, and vascular cell adhesion molecule 1) activation consistent with a less tumorigenic microenvironment (117).

COLORECTAL CANCER

Epidemiology

Visceral adiposity and metabolic syndrome are independent predictors for development of adenomatous polyps and malignant transformation to colorectal cancer (CRC) (118). Obesity also portends a poorer prognosis (119). Inflammatory bowel diseases independently increase CRC risk commensurate with disease duration (120), and these colitis-associated cancers (CACs) are especially aggressive with regional spreading and have high mortality (120). Collectively, human and experimental murine data link obesity and chronic inflammation to CRC initiation and aggressive tumor progression.

Inflammation and Initiation

Many CRCs, including CAC tumors, follow an adenoma-carcinoma sequence model characterized by biallelic mutation of the *APC* tumor suppressor, accumulation of the oncogene β-catenin (CTNNB1), and formation of an adenomatous polyp, the precursor lesion of CRC. Subsequent mutations in oncogenes such as *KRAS* increase polyp numbers and promote early carcinomas. From early adenomas to frank carcinoma, progressive overexpression of COX2, an enzyme that catalyzes synthesis of prostaglandins and other eicosanoids in response to inflammatory stimuli, plays a key role in CRC carcinogenesis and development (121). Importantly, long-term use of aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) blocks COX2 activity and reduces the risk of CRC initiation; prescription of NSAIDs also improves outcomes of progressed CRCs (122). A genome-wide association study (GWAS) identified two single-nucleotide polymorphisms, relating to the genes encoding IL-16 and microsomal glutathione S-transferase 1, that predict benefit of aspirin for CRC prevention (123). Both IL-16 and microsomal glutathione S-transferase 1 are implicated in chronic inflammatory diseases, but their mechanistic relationship to obesity-related inflammation and CRC tumorigenesis is uncertain.

The WNT/CTNNB1 pathway has substantial roles in adipogenesis, impaired glucose metabolism, and metabolic diseases, and its dysregulated activation (most commonly from loss of the *APC* tumor suppressor) plays a critical role in CRC carcinogenesis. Elevated BMI and reduced physical activity are associated with greater risk of WNT/CTNNB1-negative but not WNT/CTNNB1-positive CRC (124), suggesting that obesity-related CRC carcinogenesis does not require WNT/CTNNB1 activation. Accumulating evidence suggests that increased bioavailability of IGF-1 and its axis is a mediator of the causal link between obesity and CRC (72, 119). IGF-1 promotes cancer cell survival and proliferation, and IGF1R expression is high in CRC

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cells lacking CTNNB1 mutations (125). Further studies are warranted to elucidate a possible obesity-related IGF-1 CRC mechanism.

Adipokines and Adipocytokines

Epidemiological and experimental evidence suggests that leptin and adiponectin mechanistically link obesity-related inflammation to colorectal carcinogenesis (126). Decreased adiponectin concentrations are associated with adenoma development and CRC pathogenesis (127), and leptin directly correlates with CRC risk and more aggressive tumor phenotype, as demonstrated by association with tumor stage (128). Experimental data suggest that HFD-related CRC carcinogenesis is mediated in part through higher serum leptin levels (129). In contrast to adiponectin, however, leptin does not appear to be involved in early-stage CRC carcinogenesis; rather, it plays a role only after tumor initiation (130). Both leptin and adiponectin receptors are expressed in CRC tumors, and these adipokines each antagonize many of the other's functional and molecular processes. Whereas leptin is a known mitogen, promotes CRC progression, and activates NF-κB to decrease apoptosis, adiponectin inhibits cell proliferation, promotes apoptosis, is antiangiogenic, and suppresses invasion; molecularly adiponectin activates AMP-activated protein kinase and antagonizes leptin's STAT3 activation (119).

Persistent obesity-related inflammation can induce CRC mutagenesis through reactive oxidative damage and epigenetic silencing (131) and, thus, promote cancer growth. In lean adipose tissue, adiponectin suppresses secretion of adipose-derived proinflammatory cytokines like IL-6 (127), whereas in obese tissue leptin increases production of TNFα, IL-6, and IL-12. In mice, administering adiponectin increases levels of anti-inflammatory cytokines in serum (132), whereas the colon tissue of adiponectin-deficient mice secretes more proinflammatory cytokines (IL-6, IL-1β, and TNFα) and develops larger CRC tumors (133). Leptin also upregulates proinflammatory cytokines secreted from colonic cells of mice and may be implicated in obesity-related carcinogenesis (134). TNFα, implicated in both CAC and obesity-related CRC risk, promotes continuous stimulation of NF-κB, which appears to regulate TAMs and fibroblasts to secrete proangiogenic factors and growth factors. IL-6 induces proliferation via STAT3, but adiponectin attenuates IL-6's action, and inactivation of STAT3 leads to ineffective angiogenesis and reduced tumor growth (135).

Immune Microenvironment

Adipokines influence innate and adaptive immunity, but their contributions to the CRC tumor immune microenvironment are less clear. The CRC microenvironment contains immunosuppressive cytokines such as TGF-β and IL-10, which limit antitumor T cell responses (136). For prognosis, a high density of $CD8^+$ T cells in the primary lesion is associated with less tumor invasion and improved survival, whereas a high density of Tregs is associated with poorer outcomes (137). Tumor-infiltrating Tregs play an important role in preventing an antitumor T cell response, and a unique latency-associated peptide $(LAP)^+$ Treg was recently discovered in CRC tumors that secretes more IL-10 and TGF-β and is more immunosuppressive than LAP^- $Foxp3^+$ Tregs (138). Dendritic cells, key players in orchestrating an immune response, are also suppressed in CRC (136). Tumor-derived IL-6, stimulated in part by leptin, promotes accumulation of myeloid-derived suppressor cells (MDSCs) (139) and upregulates dendritic cell expression of arginase (136), both processes that attenuate $CD4^+$ and $CD8^+$ T cell responses. Obesity also increases adipose-derived granulocyte-macrophage colony-stimulating factor (GM-CSF), which

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restricts T cell receptor repertoire and compromises T cell function (140). Further research into the relationships among adipokines, adipocytokines, and the CRC immune microenvironment is warranted and may have significant implications for efforts in immunotherapy.

PANCREATIC CANCER

Epidemiology and Association with Type 2 Diabetes Mellitus

Inflammation, obesity, and metabolic syndrome are each associated with an increased risk of pancreatic ductal adenocarcinoma (PDAC) and its precursor lesion pancreatic intraepithelial neoplasm (PanIN) (141). PDAC, an exocrine tumor, represents over 90% of all pancreatic malignancies and has an average survival time after diagnosis of less than one year. The obesity-related risk for pancreatic cancer is especially high in women (141). T2DM, a major comorbidity of obesity, is the single risk factor explaining most of the excess risk in obesity (142). It should be noted that diabetes can be both an early consequence of pancreatic cancer and a risk factor for future pancreatic cancer. Insulin resistance and hyperinsulinemia, independent of obesity, are risk factors for pancreatic cancer (143); hyperinsulinemia directly promotes proliferation in pancreatic cancer cells and increases the bioavailability of the tumorigenic protein IGF-1 (71). Chronic hyperglycemia, independent of obesity, is also a risk factor (143); advanced glycated end product–specific receptors mediate inflammation and autophagy within PanIN and PDACs (144). Although long-duration obesity is a significant pancreatic cancer risk factor (145), a recent (within 2–8 years) T2DM diagnosis has the strongest association with pancreatic cancer (OR = 1.79) (146), suggesting a causal relationship between newly diagnosed T2DM and pancreatic cancer risk.

Adipokines and Cytokines

The molecular crossroads linking obesity, diabetes, and inflammation to pancreatic cancer are multifaceted and implicate adipose-derived cytokines. In obesity, low adiponectin increases the risk of developing pancreatic cancer (147). Adiponectin receptors are expressed on human pancreatic β cells and pancreatic tumor cells (147) and inhibit cell proliferation and promote apoptosis (127, 148). The mechanistic basis implicating adiponectin in pancreatic cancer development is supported by GWAS identification of the gene nuclear receptor 5A2 (*NR5A2*), which activates adiponectin transcription, as an important risk factor for pancreatic cancer (149). Adiponectin may decrease pancreatic cancer risk through its regulation of glucose metabolism and insulin resistance (150). Adiponectin also suppresses synthesis of proinflammatory TNFα and IFNγ and induces production of anti-inflammatory cytokines IL-10 and IL-1RA (61).

Leptin, an adipokine whose secretion is increased in obesity, has an unclear effect on pancreatic cancer progression despite being found to enhance tumor proliferation in a variety of other cancers. Leptin decreases in vitro cellular proliferation and metabolic activity in pancreatic carcinoma (151), in contrast to other solid tumors. Human and murine pancreatic cancer cells express both the short and long forms of the leptin receptor, but loss of the long isoform results in increased growth and metastasis of murine pancreatic cancer cells (152), suggesting an antitumor effect. Recently, however, leptin receptor expression was shown to potentiate tumor growth independent of tumor cell proliferation (153). Obesity-related adipocytokines IL-6 and TNFα likely augment leptin signaling through STAT3 and/or PI3K pathways (154). More research into the effects of leptin on inflammation and pancreatic tumor progression is warranted.

Proinflammatory cytokines, secreted both from adipose tissue and from the tumor mass, play important roles in the progression of pancreatic cancer. Cytokines IL-1β and IL-6 are implicated in obesity-related inflammation, chronic pancreatitis, and pancreatic cancer (154). GWAS data

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suggest IL-1β is a predictive risk factor for pancreatic cancer (54), and a polymorphism in IL-1β exon 5 predicts survival in unresectable tumors. IL-1β is found in abundance in 60% of pancreatic cancers (155), where it is secreted by both tumor and immune cells and mediates adhesion and invasion of PDAC. Serum IL-6 is an independent prognostic factor for poor survival in high-grade pancreatic tumors (155), and serum levels of both IL-6 and IL-1β predict the efficacy of chemotherapy in patients with advanced pancreatic cancer (154). Tumor unresponsiveness to chemotherapy appears to be due in part to IL-1β-induced upregulation of COX2 (156) and activation of the NF-κB and ERK signaling pathways (157). Obese adipose tissue increases secretion of IL-1RA (25), which in turn inhibits the tumorigenic effects of IL-1 cytokines (157). Low IL-1RA levels are associated with poor prognosis (155), and experimental antagonism of IL-RA enhances tumor growth (156).

Tumor-Intrinsic Inflammation

Recent research has begun to identify important molecular mediators linking obesity-related inflammation to tumor-intrinsic changes. K-ras is mutated into a constitutively active form in most (93%) PDACs (158) and is the primary promoter of the early stages of PDAC (159). Evidence suggests that HFD initiates a positive feedback inflammatory loop in which a HFD elevates K-ras activity, which increases COX2 expression. This theory is consistent with observations that within K-ras-overexpressing pancreatic tumors, TNFR1 signaling increases infiltration of inflammatory cells and levels of TNFα, IL-1β, and IL-6 cytokines while promoting PanIN lesions and pancreatic fibrosis and insufficiency (160). K-ras-mediated inflammation also activates the transcription factors STAT3 and NF-κB, which regulate many features of tumor survival and invasion (154). STAT3 and NF-κB reciprocally promote the positive feed-forward loop of KRAS–STAT3 through autocrine and paracrine IL-6 and IL-11 production (154), and NF-κB through TNFα and IL-1α (161).

Immune Microenvironment

PDAC is characterized by a dense stroma of inflammatory cells (162), and many of the previously reviewed adipokines play a role in composing the PDAC immune microenvironment, which is overwhelmingly immunosuppressive. The prominent leukocyte infiltration is dominated by TAMs, MDSCs, and Tregs, which constitute the early response and persist through invasive cancer (162). Activation of STAT3, either by stromal cells or by tumor cells downstream of K-ras activity, recruits MDSCs (163). K-ras also regulates immune cell infiltration and macrophage activation through direct promotion of pancreatic tumor secretion of GM-CSF (159), which enhances inflammation but cripples the adaptive immune response so that tumor cells escape immune surveillance (164). Increased tumor GM-CSF is associated with poor clinical outcomes. Conversely, adiponectin negatively regulates macrophage growth and function and suppresses GM-CSF (165).

EFFECTS OF WEIGHT LOSS ON INFLAMMATION AND CANCER RISK

The anti-inflammatory effect of weight loss through low-calorie diet (LCD), surgery, or exercise is of keen interest to researchers and clinical practitioners. Short-term very LCD intervention in nondiabetic premenopausal obese women resulting in an approximate decrease in body weight of 6% has been reported to decrease proinflammatory and increase anti-inflammatory gene expression in visceral adipose tissue, primarily due to changes in stromovascular cells (166). LCD-induced weight loss has been observed to reduce proinflammatory plasma markers, including C-reactive protein, IL-6, and TNFα, in obese patients ≥60 years of age, independent of exercise, which

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conferred no additional benefit (167). Similar effects of LCD and LCD plus exercise to decrease plasma and subcutaneous adipose tissue IL-6 and TNFα expression were reported in middle-aged (~40 years of age) obese women, whereas subjects in the exercise-only group, who did not lose fat mass, did not exhibit significant improvements in plasma or adipose inflammation or systemic insulin sensitivity (168).

One of the most distinct changes during weight loss, through either diet restriction or surgery, is the decreased number of infiltrating macrophages in both adipose tissue (39) and tissues of obesity-related cancers, such as colon and liver (111). A decrease in excess adipose mass appears to be required to attenuate obesity-associated adipose inflammation and its systemic complications. However, adipose inflammation may also predict weight loss and regain in response to dietary intervention. One recent study found that, among groups of subjects with similar caloric intake, those who revealed the least weight loss and subsequently regained the most weight had greater adipose inflammation, serum IL-6, and insulin resistance (169).

Weight loss and corresponding decreases in proinflammatory adipokines and obesity-linked pathologies appear to reduce or delay carcinogenesis. Diet-induced weight loss in obese individuals is reported to reduce colorectal inflammation, decreasing rectosigmoid expression of multiple proinflammatory cytokines and markers of T cell and macrophage accumulation while also attenuating several cancer-related pathways, including FOS, JUN, STAT3, and NF-κB expression (170). This is consistent with findings that calorie restriction protects mice from colonic neoplasia and reduces COX2 expression (171). Weight loss in obese, postmenopausal women has been reported to improve serum biomarkers of breast cancer risk, including SHBG, bioavailable estradiol, insulin, C-reactive protein, adiponectin, and leptin (172). Similarly, a large mixed-weight population study found that all-cause weight loss was associated with reduced colon cancer risk (173).

Bariatric surgery is increasingly used to treat obesity and its comorbidities, and can improve insulin sensitivity within days of surgery, even before substantial weight loss, possibly through gut hormonal changes and attenuation of adipose tissue inflammation (174, 175). Bariatric surgery induces remission of T2DM and dyslipidemia and decreases overall mortality in patients who achieve weight loss (176). Thus, bariatric surgery should theoretically have effects to attenuate cancer risk and mortality. Indeed, retrospective cohort studies have repeatedly observed reductions in cancer mortality or incidence (177). The Swedish Obese Subjects randomized trial compared 2,010 obese patients undergoing bariatric surgery (BMI $\geq$ 34 kg/m^2 for men and $\geq$ 38 kg/m^2 for women) with 2,037 obese patients receiving conventional treatment and found bariatric surgery was associated with reduced cancer mortality risk in obese women but not men (178). Similar results were found in a retrospective study of 9,949 morbidly obese (BMI $\geq$ 35 kg/m^2) gastric bypass patients and 9,628 matched morbidly obese controls, which found reduced mortality risk for all cancer and obesity-related cancer only in women (179). However, both studies were highly enriched in women (71% and 83–86%, respectively), which may have contributed to gender disparity in cancer risk reduction with weight loss. Most studies have not addressed specific cancers, but recent work has suggested that bariatric surgery–induced weight loss is associated with reduced endometrial cancer risk (179, 180), whereas meta-analyses have shown conflicting results of bariatric surgery with respect to increasing or decreasing CRC risk (181, 182). More prospective studies are clearly needed to determine the effects of bariatric surgery, and weight loss in general, on cancer risk and the mechanisms by which risk is decreased or increased.

CONCLUSIONS AND FUTURE DIRECTIONS

Obese US adults now outnumber those who are merely overweight (183). A carefully orchestrated balance exists between adipocytes and immune cells to maintain normal whole-body metabolism

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in the lean state. In obesity, the balance shifts to a markedly proinflammatory adipose tissue microenvironment. The obese population has significantly increased cancer risk due to obesity-associated adipose inflammation, which can increase adipose secretion of proinflammatory factors, dysregulate systemic metabolism, and alter the tumor microenvironment. Adipose-derived factors that are altered in obesity can directly regulate tumor and tumor stromal cells as well as local immune cells to influence tumor growth, metastasis, and progression, and the increased mass of adipose tissue can also supply tumor supporter cells to further regulate the development of the tumor microenvironment (**Figure 2**).

Mounting evidence, primarily from bariatric surgery studies, indicates that substantial weight loss reduces cancer risk, most likely by attenuating adipose-related inflammatory mechanisms that can regulate tumor development and progression. Some studies have also found decreased cancer risk in obese populations undergoing therapeutic interventions for adverse obesity-related phenotypes. However, not all such phenotypes are amenable to specific intervention, and the multifactorial nature of obesity may diminish the possibility of conferring a significant benefit by attenuating any one adverse phenotype. Adipose inflammation, however, appears to be strongly correlated with most obesity-related changes that increase cancer risk. Thus, approaches that attenuate adipose inflammation are likely targets for therapeutic intervention. Indeed, attenuation of systemic inflammation by NSAID administration is associated with reduced risk of obesity-related cancer, especially breast cancer (184–186), indicating that inflammation plays a prominent role. More investigation is needed to identify key inflammatory mechanisms and targets for more effective anti-cancer therapy. Better understanding of the cellular and molecular mechanisms underlying obesity-induced inflammation should define more specific and efficient means of controlling chronic inflammation in obesity to attenuate cancer risk. Elucidation of these mechanisms also holds promise for the discovery of biomarkers to permit early diagnosis of and assess therapeutic effectiveness for obesity-related cancers, which are increasing in incidence worldwide.

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DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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