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Review

Mechanisms linking obesity and cancer ☆

Sharon M. Louie [1], Lindsay S. Roberts [1], Daniel K. Nomura *

Program in Metabolic Biology, Department of Nutritional Sciences and Toxicology, 127 Morgan Hall, Berkeley, CA 94710, USA

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ABSTRACT

The incidence of obesity in US adults has been steadily increasing over the past few decades. Many comorbidities associated with obesity have been well-established such as type 2 diabetes and cardiovascular diseases. However, more recently an epidemiological relationship between obesity and the prevalence of a variety of cancers has also been uncovered. The shift of the paradigm surrounding white adipose tissue function from purely an energy storage tissue, to one that has both endocrine and metabolic relevance, has led to several mechanisms implicated in how obesity drives cancer prevalence and cancer deaths. Currently, there are four categories into which these mechanisms fall — increased lipids and lipid signaling, inflammatory responses, insulin resistance, and adipokines. In this review, we examine each of these categories and the mechanisms through which they drive cancer pathogenesis. Understanding the relationship(s) between obesity and cancer and especially the nodal points of control in these cascades will be essential in developing effective therapeutics or interventions for combating this deadly combination. This article is part of a Special Issue entitled Dysregulated Lipid Metabolism in Cancer.
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1. Introduction

The incidence of obesity has been steadily increasing over the past few decades. In 2007–2008, the prevalence of obesity among US adults was 33.8% and of overweight 68.0%, after adjusting for age [1]. These epidemic proportions of obesity are not only mirrored in the rest of the developed world, but also now in many developing countries, making obesity one of the most serious health problems worldwide [2]. While there are many comorbidities associated with obesity, such as the well-established relationship with type 2 diabetes and cardiovascular diseases, a clear epidemiological relationship between obesity and the prevalence of a variety of cancers has also been uncovered [3,4].

Cancer is currently the leading cause of death in developed countries and second in developing countries [5]. Several studies have shown significantly elevated risk for leukemia, lymphoma and myeloma with high body-mass index (BMI) in a dose-dependent manner [6], as well as an increased risk for pancreatic [7], prostate [8], breast [9], colon, endometrial, liver, kidney, esophagus, gastric, and gallbladder cancers [10] in obese adults. Furthermore, as childhood obesity rates continue to follow those of adults [11], their risks for cancers later in life are significantly higher [12]. Although the epidemiological associations between cancer progression and prognosis are firmly established, the link between obesity and cancer initiation and the molecular mechanisms underlying these associations are still being elucidated.

White adipose tissue has traditionally been considered an inert tissue almost exclusively for energy storage. Recently, white adipose has emerged as an important endocrine and metabolic organ as well as a key player in immunity and inflammation [13]. With this new understanding of adipose tissue function, researchers have delved into the relationship of these secondary effects of obesity, which may in fact be responsible for the increased propensities for various cancers. Considering the prevalence of obesity, the lethality of cancer, and the rise in childhood obesity, there is an imminent need for research to delineate the underlying mechanism(s) through which obesity drives cancer and to exploit those findings to develop interventions and potential therapeutics to combat this deadly combination. This review focuses on the mechanisms that have been proposed to underlie how obesity drives cancer pathogenesis, with emphasis on elevated lipids and lipid signaling, inflammation, insulin signaling, and adipokines (Fig. 1).

2. Elevated lipids in cancer

Obesity is primarily characterized by excess fat storage, adipocyte mass, and coordinate increases in certain types of lipids. We will first discuss the evidence for how fat from sources including cancer cell de novo lipogenesis, from the breakdown of adipose tissue in cachexia, or from neighboring adipocyte lipid-transfer, can be utilized as oncogenic signaling lipids by the cancer cells and thereby influence cancer pathogenicity. This then sets the stage for potential mechanisms through which lipid stores in obesity may also influence cancer pathogenicity.

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* Corresponding author. Tel.: +1 5107989647.
E-mail address: dnomura@berkeley.edu (D.K. Nomura).
[1] These authors contributed equally.

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2.1. Fatty acid synthase

One piece of supporting evidence for the utilization of lipids by cancer cells is the upregulation of fatty acid synthase (FASN), an enzyme that makes endogenous fatty acids, which can be modified and packaged into structural lipids required for cell division. Elevated FASN enzyme, mRNA, and enzymatic activity have been seen in human breast cancer cell lines [14], ovarian tumors, [15] prostate tumors [16] and cancer precursor lesions in the colon, stomach, esophagus and oral cavity [17]. The increase in FASN seems to be necessary for eliciting the malignant effects, such as proliferation and survival, though this itself is not the cause of malignancy [18]. One study found FASN inhibition as an off-target effect of the weight-loss drug Orlistat. This FASN inhibition induced an antiproliferative effect in prostate cancer cells in culture, which was rescued by addition of palmitate, the product of FASN [19]. Furthermore, when FASN was chemically inhibited in both breast and prostate cancer tumor xenografts, there was a significant antitumor effect [17]. These data together show the importance of FASN in cancer cell growth, survival and proliferation in vitro and in vivo.

This FASN overexpression in cancer is also mirrored in a variety of tissues in obesity, and one may postulate that the fatty acids formed through FASN in other tissues may also provide fatty acid sources to the cancer [20]. Additionally, in a study examining FASN polymorphisms and the risk of prostate cancer, one of the polymorphisms associated with prostate cancer was also significantly, positively correlated with BMI [16]. Between increases in FASN in obesity and a heightened propensity for an unfavorable FASN polymorphism, there is also evidence that FASN plays an important role in the way through which obesity may drive some cancers.

2.2. MAGL

The increased activity of FASN in cancer cells is also matched by an increase in lipolytic enzymes, such as monoacylglycerol lipase (MAGL), to promote the mobilization of lipid stores for remodeling of cellular lipids and generation of pro-tumorigenic signaling lipids. The MAGL pathway is upregulated in multiple types of aggressive human cancer cells and high-grade primary tumors [21] and releases FFAs, which in-turn fuel the generation of fatty acid-derived lipid signaling molecules such as lysophosphatidic acid and prostaglandins. Impairments of MAGL-dependent tumor growth are rescued by a high-fat diet in vivo, suggesting that exogenous sources of fatty acids can also contribute to cancer malignancy. Thus, elevated levels of fatty acids, derived either from the cancer cell or exogenous fat sources, may promote a more aggressive tumorigenic phenotype [21].

2.3. Cachexia

In subjects, with late-stage, highly malignant cancer these exogenous sources of fats may be derived from the breakdown of fat mass. Cachexia commonly accompanies late-stage cancers and causes subjects to lose both muscle and fat mass through catabolic processes. In cachectic subjects, there is a marked increase in adipose triglyceride lipase (ATGL) [22] an enzyme that breaks triglycerides into diglycerides as well as hormone-sensitive lipase (HSL), an enzyme that breaks diglycerides into free fatty acids [23]. This then leads to increased levels of circulating free fatty acids, which can be repackaged into important oncogenic signaling lipids as well as membrane structural lipids necessary for cell proliferation [24]. Moreover, there is evidence that the lipids released in these processes can be directly utilized by the cancer cells for fuel [25]. While cachexia contrasts obesity in that it is a condition marked by muscle and adipose catabolism, it provides additional evidence that cancer cells can utilize free fatty acids for both fuel and oncogenic signaling lipids. In a state of obesity, however, the free fatty acid substrates for fuel or signaling molecules must be derived from adipocyte stores.

2.4. Transfer of lipids from adipocytes to tumor

One study did show that cancer cells can access and use lipids from neighboring adipocyte stores in vitro by co-culture of ovarian cancer

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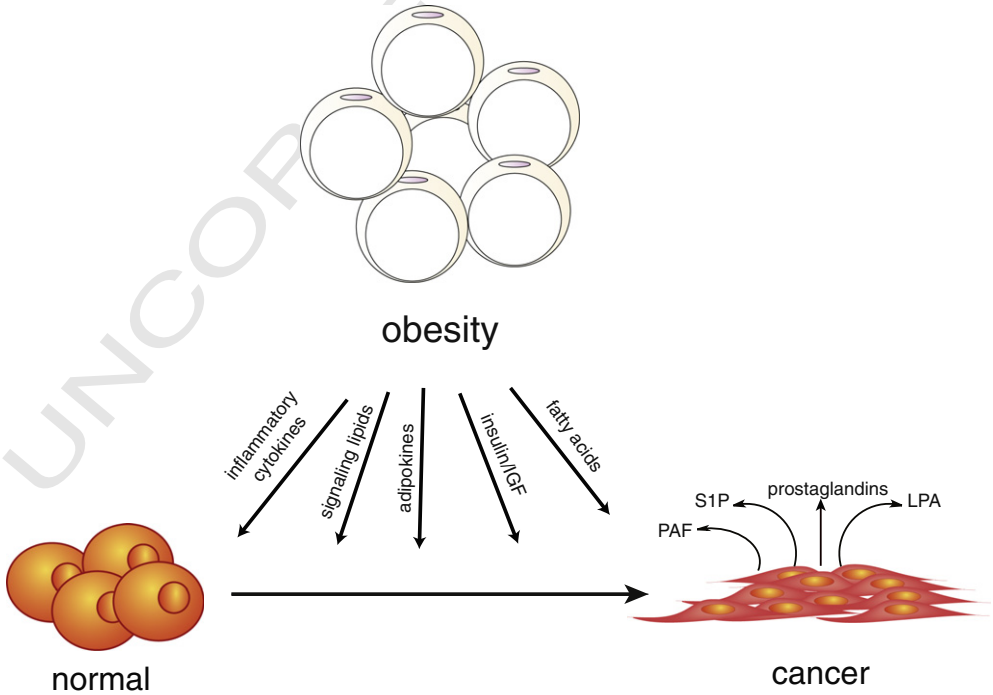

Fig. 1. Obesity-related mechanisms underlying cancer. Cancer cells have heightened de novo lipogenesis through elevated fatty acid synthase (FASN) and both obesity or cancer cell-derived lipolytic enzymes generate free fatty acids to the tumor to provide structural and oncogenic lipid signaling molecules such as platelet activating factor (PAF), sphingosine-1-phosphate (S1P), lysophosphatidic acid (LPA), and prostaglandins. Obesity also causes a low-grade inflammation and the release of inflammatory cytokines. Obesity can also lead to type II diabetes and hyperinsulinemia and insulin signaling which can fuel cancer. Furthermore, obesity leads to dysregulation in adipokines including elevated leptin and reduced adiponectin levels which can collectively stimulate tumor growth.

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cells and adipocytes. This led to the direct transfer of lipids from the adipocytes to the cancer cells, which induced lipolysis in the adipocytes and β-oxidation in the cancer cells. This indicates that cancer cells can directly use these transferred lipids as an energy source, which in-turn promotes tumor growth [26]. These data are of particular importance in considering the implications of obesity, mainly excess adipocyte mass, on cancer prevalence and aggressiveness and the synergistic interplay of adipocytes and cancer cells.

2.5. Adipose stromal cells

In another study using a mouse model, obesity was shown to facilitate tumor growth irrespective of diet, suggesting a direct role of adipose tissue in cancer progression [27]. White adipose tissue-derived mesenchymal stem cells, termed adipose stromal cells (ASC), may represent a cell population linking obesity to the increased incidence of cancer. When transplanted into mice, adipose stromal cells can promote tumor growth by serving as perivascular adipocyte progenitors. ASCs were shown to traffic from endogenous white adipose tissue (WAT) to tumors, where they can be incorporated as pericytes into blood vessels and differentiate into adipocytes [27]. Intratumoral adipocytes were shown to be associated with an increase in tumor vascularization and an increase in proliferation of adjacent malignant cells [27]. These results suggest that ASCs recruited from adipose tissue have a direct role in inducing tumor development.

3. Lipid signaling

Another mechanism through which obesity may drive cancer pathogenesis is through converting high-fat diet supplied fatty acids or de novo synthesized fatty acids into protumorigenic signaling lipids. Signaling lipids derived from other cell types or from the cancer cell itself can then signal onto the cancer cell through paracrine or autocrine interactions. Studies have shown that aggressive cancer cells upregulate MAGL to generate fatty acids to be incorporated in oncogenic signaling lipids that in-turn drive cancer pathogenicity. However, the function of MAGL can be supplanted also by exogenous fatty acid sources that arise from high-fat diets [21]. The enzymes that synthesize or break down these signaling lipids are also often-times dysregulated in cancer to promote their signaling. There are a wide-range of lipid signaling molecules that have the capacity to trigger oncogenic responses, including proliferation, motility, invasiveness, tumor growth, immunological responses, and metastasis. Imbalances in these lipid-signaling pathways can fuel various aspects of cancer [28].

3.1. LPA

Lysophosphatidic acid (LPA) is a bioactive phospholipid that stimulates cell proliferation, migration, and survival by acting on G-protein coupled receptors [29]. LPA and LPA receptors are highly expressed in multiple cancer lines including ovarian [30], breast [31], and colon [32]. Interestingly, autotaxin (ATX), the primary enzyme producing LPA, is upregulated in highly aggressive metastatic breast cancer [31], indicating that LPA is a key contributor to the aggressive phenotypes of cancer.

LPA functions by activating G-protein coupled receptors, which in turn can feed into multiple effector systems. LPA activates G_q, which stimulates the effector molecule phospholipase C, thereby generating multiple second messengers leading to activation of protein kinase C [33]. The LPA-dependent activation of PKC mediates the activation of the β-catenin pathway, leading to its cell proliferative effects in colon cancer cells [32]. LPA also activates G_i, leading to inhibition of adenylyl cyclase and therefore inhibition of cAMP accumulation. G_i also stimulates the mitogenic Ras-MAPK cascade and also the PI3K pathway, contributing to cell proliferation and migration [34–36]. LPA has also been shown to mediate cell proliferation, invasion, and migration in human breast cancer through activation of G_i protein, which activates the ERK 1/ERK2 pathway [37].

Debio-0719, a specific inhibitor of the LPA receptor 1, suppressed development of metastasis from the breast to the liver in the 4T1 breast cancer model [38]. Pharmacological or genetic blockade of MAGL lowers LPA levels indirectly through lowering the levels of fatty acids required for acylation of glycerol-3-phosphate through the de novo LPA synthesis pathway, leading to impaired cancer cell migration, invasion, and tumor growth [21]. Furthermore, knockdown of β-catenin by RNAi abolished LPA induced proliferation in colon cancer cells [32], suggesting a critical role for LPA in the initiation and progression of cancer.

3.2. Prostaglandins

Prostaglandins play a role in regulating the migratory and invasive behavior of cells during development and progression of cancer. Many human cancers exhibit high prostaglandin levels due to upregulation of cyclooxygenase-2 (COX-2) and prostaglandin E_2 synthase-1 (PGE2-1), key enzymes in eicosanoid biosynthesis. Prostaglandins are derived from the 20-carbon chain fatty acid, arachidonic acid. COX-2 is highly expressed in metastatic breast cancer [39] and knocking out COX-2 in mice reduced mammary tumorigenesis and angiogenesis [40]. High COX-2 and PGE2 levels have been implicated in the loss of e-cadherin, and subsequently, cell migration as cells become more migratory during epithelial to mesenchymal transition [41]. The expression of COX2, along with the epidermal growth factor receptor ligand epiregulin and the matrix metalloproteinases 1 and 2, can collectively facilitate mammary tumor metastasis into the lungs by the assembly of new tumor blood vessels and the release of tumor cells into circulation [42]. In mice with orthotopically implanted mammary tumors, pharmacological intervention with anti-EGFR antibody, metalloproteinase inhibitor, and a COX2 inhibitor showed reduced rates of primary tumor growth [42]. In addition, overexpression of COX-2 in transgenic mice induced increases in microvessel density and tumor growth, suggesting the role of prostaglandins in the upregulation of angiogenic factors [43]. Furthermore, prostaglandin E_2 promotes colon cancer growth through the G-protein coupled receptor, EP2, by signaling the activation of PI3K and Akt, which subsequently inactivates glycogen synthase kinase and activates the β-catenin signaling pathway [44].

The hydrolytic pathways that release the arachidonic acid from complex phospho- or neutral-lipid stores to generate prostaglandins have also been implicated in cancer progression. Phospholipase A2 (PLA_2) is an enzyme that releases fatty acids from phospholipids, generating arachidonic acid and lysophospholipids [45]. Mice deficient for cytosolic phospholipase A_2 are protected against the development of lung tumors, suggesting that PLA_2 plays a key role in tumorigenesis by altering cytokine production [46]. MAGL blockade also leads to reduced prostaglandins by reducing the arachidonic acid precursor pool required for generating prostaglandins, leading to impaired cancer cell pathogenicity [21]. These mechanisms suggest a profound role for prostaglandins in promoting cancer development and growth.

3.3. Sphingosine-1-phosphate

Sphingolipids play an important role in modulating growth and survival. Sphingosine-1-phosphate (S1P) is a biologically active lipid that plays a role in regulating growth, survival, and migration. S1P is generated by the conversion of ceramide to sphingosine by the enzyme ceramidase, which is subsequently catalyzed by sphingosine kinase-1 (SK-1) to S1P [47]. High expressions of SK-1 and S1P have been implicated in various types of cancers, including ovarian [48], gastric [49], and colon [50] cancers. SK-1 plays a critical role in determining

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the balance between pro-apoptotic ceramide and pro-survival S1P. Increased SK-1 expression and subsequently S1P levels reduce sensitivity to ceramide-mediated apoptosis and overexpression of pro-survival protein Bcl-2 in human melanoma cells [51]. Overexpression of SK-1 also activates the proliferative and anti-apoptotic PI3K/Akt pathways [52]. In addition, SK-1 promotes tumor progression in colon cancer by regulation of the focal adhesion kinase pathway, which stimulates cell motility, and thus cell invasion and migration [53]. Accordingly, S1P stimulates migration and invasion in OVCAR3 ovarian cancer cells [48]. Furthermore, S1P lyase, which degrades S1P, has been shown to be downregulated in colon cancer and S1P expression promotes apoptosis [54]. Taken together, the upregulation of SK-1, which generates S1P, stimulates proliferative pathways, contributing to the growth and survival of cancers.

3.4. PAF

Platelet-activating factor (PAF) is a proinflammatory lipid signaling molecule that can be generated by the remodeling of phosphatidylcholine, a membrane lipid, to PAF by the action of lysophosphatidylcholine acyltransferase (LPCAT) [55]. PAF activity has been implicated in several cancers, including thyroid [56] and breast [57] cancers. PAF promotes proliferation, migration, and angiogenesis in human breast cancer cells [57]. One mechanism for the tumorigenic properties of PAF is through the overexpression of cAMP-response element binding protein (CREB). PAF has been shown to activate CREB, which modulates gene expression in response to cAMP and cell stimulation with growth factors. Addition of PAF to melanoma cells stimulates CRE-dependent transcription and metastasis [58]. Taken together, PAF contributes to the onset and development of tumors through inducing angiogenesis and metastasis.

3.5. Phosphoinositides

Phosphatidylinositols can be reversibly phosphorylated at three distinct positions on the inositol headgroup, generating unique phosphoinositides that have diverse roles in signaling [28]. Phosphoinositides signal through cytosolic effector proteins to activate downstream signaling molecules. The plasma membrane localized phosphatidylinositol-4,5-bisphopshate (PtdIns(4,5)P_2) serves as the substrate for two phosphoinositide-dependent signaling events. Cleavage of PtdIns(4,5)P_2 by phospholipase C generates two second messengers, membrane-bound diacylglycerol (DAG) and the soluble inositol-1,4,5-trisphosphate (IP_3) [28]. In addition, PtdIns(4,5)P_2 can alternatively be converted to phosphatidylinositol-3,4,5-trisphosphate (PtdIns(3,4,5)P_3) by phosphoinositide 3-kinase (PI3K) [28]. PtdIns(3,4,5)P_3 is another second messenger involved in cell growth signaling and elevated levels have been implicated in cancer [59]. PI3K, the enzyme that generates PtdIns(3,4,5)P_3, plays a key regulatory function in cell survival, proliferation, migration, and apoptosis [60]. PI3K has been shown to play a mitogenic and anti-apoptotic effect in endometrial cancer [61]. Furthermore, inhibition of the enzyme blocks growth and promotes apoptosis in small-cell lung cancers [62]. Altogether, phosphoinositides have been implicated to play a profound role in the promotion of tumorigenesis.

4. Inflammation

In addition to simply storing excess fat, the state of obesity induces a low-grade, chronic, metabolically-linked, inflammatory state, different from traditional inflammation, called metaflammation [63]. Although it is unclear how this inflammatory state is initiated, one proposed mechanism is through hypoxia. During weight gain and adipose tissue expansion, there are times when some cells are too distant from the organ's vasculature causing them to become poorly oxygenated and resulting in localized hypoxia [64]. This then activates hypoxia-inducible factor (HIF)-1α, which mediates the infiltration of macrophages and monocytes into the adipose tissue and finally the secretion of tumor necrosis factor-α (TNF-α) [65].

In this metaflammatory state, TNF-α has been found to be elevated in and secreted from the white adipose tissue [66]. However, other work has shown that TNF-α is actually released from macrophages and monocytes, which have increased infiltration into the adipose tissue in obese subjects [67]. While TNF-α was originally found to mediate endotoxin-induced tumor necrosis [68], it has also been implicated in cancer angiogenesis [69] and metastasis [70] as well as cell survival [71], growth, and differentiation [72,73]. One proposed mechanism of TNF-α-induced carcinogenesis is through activation of the nuclear transcription factor NF-κB by inhibiting the inhibitor of NF-κB (IκB). This pathway has been shown to be involved in the development of lymphoma [74], pancreatic [75] and liver [76] cancers. Activated NF-κB prevents apoptosis allowing enhanced cell survival [71] and eventually inflammation-associated cancer [76]. However these effects may differ in different cell-types and experimental conditions [77]. Moreover, activation of NF-κB in cancer cells can activate cell cycling through c-Myc [71] and cyclin D1 [72] leading to increased cell growth and proliferation. While both the relationship between obesity-induced inflammation and the activation of NF-κB by TNF-α are well-established, whether there are other roles of NF-κB in obesity-associated cancers remains unknown.

Interleukin-6 is another cytokine shown to be elevated in obesity and IL-6 levels are positively correlated with BMI [78]. IL-6 secretion from the white adipose tissue is induced by TNF-α [66] as well as the hypoxic conditions of the adipose [79]. Circulating IL-6 signals through the Janus kinase-signal transducer and activator of transcription-3 (JAK-STAT3) signal cascade [80]. IL-6 induced JAK-STAT3 signal transduction stimulates cell proliferation, differentiation [81] and metastasis [82]. In animal models lacking endogenous IL-6, the effect of obesity on tumorigenesis was not seen [83]. IL-6 mediated cell proliferation has been proposed to act through the mitogen-activated protein kinase (MAPK) pathway. Upon inhibition of MAPK, there was no proliferation in the presence of IL-6 [84] indicating the integral role of IL-6 in cell proliferation in inflammation.

In addition to TNF-α and IL-6, there are other cytokines produced during the obesity-induced inflammatory state such as plasminogen activator inhibitor-1 (PAI-1). PAI-1 inhibits plasminogen activators such as urokinase and tissue plasminogen activator. These plasminogen activators convert plasminogen, a zymogen, to the active enzyme, plasmin. Plasmin is a serine protease, which breaks down the extracellular matrix, a critical step in cancer invasion and metastasis [85]. After the extracellular matrix is broken down and as the cancer becomes more aggressive, PAI-1 is upregulated to inhibit the aberrant activity of plasmin. Therefore, elevated PAI-1 levels are observed in subjects with poor cancer prognoses, (rates of relapse, death, etc.) [86]. PAI-1 has also been shown to inhibit cell-adhesion to vitronectin and promote migration from vitronectin to fibronectin, where it has a stimulatory effect on vascularization, thus promoting angiogenesis [87]. Moreover, the absence of PAI-1 prevents invasion and tumor vascularization, both of which can be rescued upon injection of an adenoviral vector expressing PAI-1 [88]. These inflammatory response data indicate the multi-faceted importance of elevated cytokine levels in cancer malignancy, their measured levels as potential cancer malignancy biomarkers, and their inhibition as a novel cancer or obesity-induced cancer drug target.

Some of these inflammatory pathways stimulated as a result of obesity intersect with other seemingly unrelated pathways altered in obesity. This interplay may lead to a synergistic effect of multiple mechanisms through which obesity drives cancer. For example, TNF-α overexpression in white adipose tissue has also been shown to play an important role in mediating insulin resistance in obesity [89] and a lack of TNF-α function results in improved insulin sensitivity in mice [90].

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5. Insulin signaling

Obesity is associated with an increased risk of developing insulin resistance. Insulin resistance is a major metabolic abnormality in most patients with type 2 diabetes characterized by elevated levels of circulating insulin [91]. Insulin resistance develops with the accumulation of fatty acid metabolites within insulin responsive tissues. Besides the overall increase in adiposity, distribution of body fat is a critical determinant of insulin sensitivity. Lean individuals with a more peripheral distribution of fat are more insulin sensitive than lean individuals who have their fat distributed predominantly centrally in the abdominal and chest areas [92–94]. Insulin resistance is a pathological condition characterized by a decrease in the efficiency of insulin signaling for blood sugar regulation. A recent meta-analysis of observational studies has revealed that insulin resistance is a significant risk factor for endometrial cancer [95]. Furthermore, cancer patients with preexisting type 2 diabetes have a worse cancer prognosis than matched patients without diabetes [96,97]. In addition, patients with HER2-positive breast cancer with expression of the IGF-1 receptor are more likely to be resistant to the preoperative chemotherapeutic drugs, trastuzumab and vinorelbine, compared to matched patients without expression of the IGF-1 receptor [98]. These data suggest that insulin resistance may promote a poorer response to cancer treatment or a more aggressive cancer phenotype in patients with preexisting diabetes. The dysregulation of insulin signaling is a major contributor to the increased risk of cancer associated with obesity.

In the obese state, characterized by insulin resistance, tissues are exposed to elevated levels of insulin and insulin signaling. In fed rats, acute elevation of insulin stimulates lipid synthesis and acetyl-CoA carboxylase activity in liver and adipose tissues [99]. Similarly, insulin also stimulates fatty acid synthesis in human breast cancer cells [100]. In addition, many groups have demonstrated the proliferative effects of elevated insulin. Insulin promotes proliferation in the human breast cancer line MCF-7 by facilitating the transit of cells through G1 [101]. More recently, insulin has been shown to induce proliferation in hepatocellular carcinoma cells by upregulating AKR1B10, a tumor marker that plays a critical role in tumor development and progression by promoting lipogenesis [102]. Furthermore, Wang et al. recently showed that insulin has mitogenic and anti-apoptotic effects on endometrial cancer [61].

In addition to insulin, insulin-like growth factors, IGF-1 and IGF-2, also play a role in insulin signaling. IGF-1 and IGF-2 are hormones that are primarily produced in the liver and share sequence homology with insulin [103], hyperinsulinemia has been shown to increase production of IGF-1 in the liver [104]. IGF-1 and IGF-2 bind to IGF receptors, which can heterodimerize with insulin receptors. Activation of the receptors results in phosphorylation of IRS proteins, which activate the oncogenic Ras-MAPK and PI3K-Akt pathways [105,106]. The PI3K/Akt signaling pathway is frequently activated in human cancers where it induces cell proliferation [107]. One downstream effector of Akt is mTOR, which promotes protein translation and cancer growth [108]. Furthermore, tumors with constitutive activation of the PI3K pathway are insensitive to dietary restrictions, which can normally delay the incidence and decrease growth of various types of tumors by reducing the levels of circulating insulin and IGF-1, suggesting a link between obesity and cancer [109]. IGF-1 has also been shown to mediate PTEN suppression and enhances cell invasion and proliferation via activation of the PI3K/Akt signaling pathway in pancreatic cancer cells [110]. Thus, the effect of obesity on the elevated levels of IGFs plays a crucial role in determining the proliferative effects of the oncogenic signaling pathways on cancer growth.

The aggressive phenotypes of various types of cancers have been linked to the IGF family. Increased expression of IGF-1, IGF-2, and/or IGF-1R have been shown in gliobaslatomas, neuroblastomas, meningiomas [111], medulloblastomas [112], breast cancer [113], and prostate cancer [114]. Several groups have documented the role of the IGF family in cancer metastasis as well. Barozzi et al. [115] found that the overexpression of IGF-2 was predictive of liver metastasis. Hakam et al. [116] also showed an increase in the expression of IGF-1R during progression from colonic adenomas toward primary colorectal adenocarcinomas and metastases. The combined effects of insulin and the insulin-like growth factors on cell proliferation and metastasis may increase the risk for cancer in the hyperinsulinemic state that is associated with obesity. Somewhat controversially, one cross-sectional study did find a negative correlation between IGF-1 levels and both insulin resistance and BMI [117]. These results, however, only consider total IGF-1 not the relative amounts of bound and free IGF-1. Another study [118] found that in obesity total IGF-1 is unchanged compared to normal weight controls, however, free IGF-1 is significantly increased and IGF binding proteins reduced. The ratio of free to bound IGF-1 may be an important factor in IGF-1-driven carcinogenesis, and this change may be induced by perturbations of the IGF-1 production and signaling pathway as a result of chronic hyperinsulinemia.

In accordance with the correlative studies, transgenic expression of IGF-1, IGF-2, or IGF-1R in mice drives development of various cancers. The transgenic overexpression of IGF-1 in mice enhances development of breast cancer [119], prostate cancer [120], and skin cancer [121]. The transgenic overexpression of IGF-2 drives development of lung cancer [122] and breast cancer [123]. Overexpression of IGF-1 receptor drives development of salivary and mammary adenocarcinomas [124] and pancreatic cancer [125]. These transgenic overexpression studies suggest that increased signaling through the IGF-1R pathway can drive cancer development, even in the presence of physiological levels of insulin.

The role of the IGF system in driving tumor development and progression in the obese state has also been explored in genetic models of obese mice with liver-specific deletion of IGF-1. IGF-1 deficiency in the mice abolished the obesity-associated enhancement of subcutaneous tumor growth where tumors in the IGF-1 deficient mice were smaller than tumors in the control mice. Furthermore, IGF-1 deficiency in the liver showed a reduction of liver metastases of a colorectal cancer cell line that was injected into the venous circulation [126].

6. Adipokines

6.1. Leptin

In addition to its fat-storing capacity, adipose tissue is the largest endocrine organ, secreting adipokines. Adipokines are adipocyte-derived hormones that play a role in maintaining energy homeostasis. Leptin, one such adipokine, is a central mediator that regulates appetite and energy homeostasis. By secreting leptin from adipocytes, the change in leptin level communicates body energy status to the brain, which responds by activating the leptin receptor and adjusting food intake [127]. Several groups have shown an overexpression of leptin receptors in various cancers, including cancers of the breast [128], prostate, and colon [129].

Obesity can lead to alterations in leptin regulation. Chronic overexpression of leptin induces leptin resistance, resulting in increased circulating leptin, similar to the increased insulin levels seen in insulin resistance that is associated with increased adiposity [130,131]. The close association between adiposity and leptin levels may suggest a role for this neuroendocrine hormone in the increased incidence of cancer in obesity. Elevated circulating leptin has been shown to increase the risk of prostate [132], breast [133], colon [134], thyroid [135], and ovarian [136] cancer.

Elevated leptin in cancer has been suggested to have several protumorigenic effects. Leptin has been shown to have mitogenic

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action in cancers of the breast [137], colon [134], and endometrium [138] and have mitogenic and anti-apoptotic effects in cancers of the ovarian [136] and prostate [132]. Increases in cell migration have also been shown by elevated circulating leptin in thyroid cancer [135] and endometrial cancer [138].

Several mechanisms have been explored by which leptin contributes to tumor development and progression. Leptin signals through a transmembrane receptor (LRb) that contains intracellular tyrosine residues that become phosphorylated to mediate downstream LRb signaling, which controls STAT3 and ERK activation [139]. STAT3 signaling is required for proper leptin regulation of energy balance [140]. Leptin induces STAT3 phosphorylation in the human breast cancer line, MCF7, and blocking phosphorylation with the specific inhibitor AG490 abolished leptin-induced proliferation [137]. Furthermore, leptin increases HER2 protein levels through a STAT3 mediated upregulation of Hsp90 in breast cancer cells. Inhibition of the STAT3 signaling cascade by AG490 abrogated leptin induced HER2 expression [141]. In gastrointestinal epithelial cell specific knockout of SOCS3, leptin production was enhanced and activated STAT3 signaling to increase development of gastric tumors in mice. Administration of an anti-leptin antibody to the knockout mice reduced hyperplasia of gastric mucosa, the initiation step of gastric tumor [142]. These studies suggest that enhancement of leptin receptor signaling by STAT3 contributes to tumor development and progression.

These signaling pathways stimulate leptin to have proliferative and mitogenic effects, contributing to the initiation and progression of cancers. Activation of leptin receptors leads to phosphorylation of MAPK and increased proliferation in MCF7 breast cancer cells [143] and in HT29 colon cancer cells [144]. Treatment with leptin and inhibitors of MAPK and PI3K inhibited the proliferative effects on prostate cancer cells [132]. Chronic elevation in leptin also caused ERK1/2 [145] activation in human breast cancer cells and ERK1/2 and Akt phosphorylation in human prostate cancer cells [132]. Activation of these pathways induces cell proliferation, which plays a critical role in tumor progression.

Additional in vivo studies support the pro-tumorigenic effects of elevated leptin levels. Mammary tumors transplanted into obese leptin receptor deficient (db/db) mice grow to eight times the volume compared to tumors in the wild-type mice, suggesting the role of obesity in increased tumor growth [146]. Surprisingly, tumors transplanted into leptin-deficient (ob/ob) mice showed a reduction of tumor outgrowth compared to wildtype or db/db mice. Residual tumors from ob/ob mice showed reduced tumor initiating activity, suggesting fewer cancer stem cells. In contrast to the obese db/db mice, the obese ob/ob mice were leptin-deficient, suggesting that leptin deficiency is sufficient to suppress obesity induced tumor growth. The reduced outgrowth and tumor burden in leptin-deficient mice indicates that leptin can promote increased tumorigenesis in an obese state [146].

Although db/db or ob/ob mice have been used to study the role of leptin in obesity-associated cancers, these leptin receptor or leptin deficient mice suffer from defective development of the ductal epithelium, resulting in models unsuitable to address mammary tumorigenesis. Park et al. focused on the role of peripheral leptin signaling in breast cancer progression through transgenic overexpression of the leptin receptor in neurons of db/db mice and crossing the brain-specific long form of leptin receptor transgenic mice into the background of the mouse mammary tumor model MMTV-PyMT, thus generating peripheral LEPR-B mutants [147]. The rate of tumor growth in the peripheral LEPR-B mutants was reduced by twofold compared to PyMT mice. Furthermore, the lack of peripheral leptin receptors reduced tumor progression and metastasis through ERK1/2 and Jak2/STAT3 mediated pathways. Under obese conditions, tumor cells exhibit high local levels of leptin, leading to an increase in LEPR-B mediated pathways, which increases tumor progression. Globally, the effects of elevated leptin in obesity can drive tumor growth and development.

6.2. Adiponectin

Adiponectin is another adipokine that is associated with cancer risk. Adiponectin is a key mediator in development and progression of several types of cancers [148] and circulating adiponectin levels are decreased in patients with diabetes and obesity-associated cancers [149].

The two classical adiponectin receptors are seven transmembrane proteins [150] that activate the downstream target AMPK. Expression of the adiponectin receptors, AdipoR1 and AdipoR2, is decreased in obesity, diminishing adiponectin sensitivity [151].

Epidemiological studies have suggested a link between circulating adiponectin levels and cancer. Adiponectin levels were inversely correlated with the risk of colorectal cancer [152], endometrial cancer [153], esophageal cancer [154], prostate cancer [155], and breast cancer [156].

Several studies have explored the mechanisms by which adiponectin inhibits carcinogenesis. Adiponectin negatively influences growth of most obesity-related cancer types, such as prostate [157] and colon [158] cancers. A study on breast cancer also proved a negative effect of adiponectin on migration [159]. MMTV-PyVT transgenic mice with reduced adiponectin expression developed mammary tumors by downregulating PTEN and upregulating PI3K/Akt signaling [160]. Thus, the proliferative effects of reduced adiponectin may be mediated through the PI3K/Akt signaling cascade. Furthermore, binding of adiponectin to its receptors provokes activation of AMPK, a critical regulator of proliferation in response to energy status [161]. AMPK plays a role in regulation of growth arrest and apoptosis by stimulating p21 and p53 [162] and is also an inhibitor of mTOR, thus suppressing cell proliferation [163]. Adiponectin has also been shown to activate PPAR-alpha, thus enhancing fatty acid combustion and energy consumption, leading to a decrease of triacylglycerides in the liver and skeletal muscle, reversing the accumulation of adiposity [150]. Recently, a new mechanism has been shown whereby the balance between ceramide and S1P mediates many of the effects of adiponectin. AdipoR1 and AdipoR2 enhance ceramidase activity [164]. An accumulation of ceramide promotes an array of activities related to metabolic diseases, often in direct opposition to adiponectin [165]. The activity of ceramidase converts ceramide to S1P, a potent inducer of proliferation and inhibitor of apoptosis [166]. Contrary to the proliferative effects of S1P, it has also been shown to activate AMPK [167]. Thus, ceramidase is an essential initiator of adiponectin actions by generating S1P, which activates AMPK. Although S1P has proliferative effects, it is degraded in the liver, the primary target tissue where adiponectin plays a role in insulin sensitization. Many of the effects of adiponectin are mediated by ceramidase activity and the resulting alteration of the ratio of ceramide to S1P plays a role in cell growth [168].

Although adiponectin levels have been shown to inversely correlate with the risk of several types of cancers, it is noteworthy to suggest that the protective effect of adiponectin may be specific to certain types of cancers and stage of tumor progression. A study comparing rates of tumor growth in the mouse mammary tumor model MMTV-PyMT and adiponectin-null mice showed defects in angiogenesis and reduced rates of tumor growth in adiponectin-null mice in early stages of tumorigenesis [169]. Despite the defects in angiogenesis, tumor growth in the adiponectin knockout mice persisted and developed into late stages of carcinoma, at which point the antiangiogenic stress at early stages led to an adaptive mechanism to bypass the dependence of adiponectin-driven angiogenesis. This study suggests a proangiogenic contribution of adiponectin toward mammary tumor growth in vivo in the early stages of tumorigenesis, but not in late stages [169].

Since adiponectin levels are inversely correlated with obesity [170], studies implicating a protective effect of adiponectin in tumorigenesis and the analysis of the PyMT tumor model by Landskroner-Eiger et al. showing a pro-angiogenic role of adiponectin at early stage tumors indicate the complex role of adiponectin in tumorigenesis, and possibly a biphasic effect of adiponectin at early stages [169].

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Overall, the above studies suggest that leptin plays a role in tumor development and progression, whereas adiponectin plays a role in tumor inhibition. In one prostate cancer model, adiponectin reduced cell proliferation and this effect was blocked by treatment with leptin [171]. Thus, leptin and adiponectin have been suggested to have opposing roles in cancer development and progression.

7. Conclusion

Several mechanisms have been suggested to explain the association between cancer and obesity, involving elevated lipid levels and lipid signaling, inflammatory responses, insulin resistance, and adipokines. However, it remains unclear how the convergence of these pathways drives obesity-linked cancer. Thus, whether therapeutic interventions can prevent the effect of obesity on cancer is still controversial.

One potential therapeutic intervention for patients with obesity and type 2 diabetes is to take insulin, drugs that increase insulin secretion like sulphonylureas, or insulin-sensitizing drugs, such as metformin or thiazolidinediones (TZDs). Data suggest that patients who take insulin or drugs that increase insulin secretion have a higher risk of cancer than patients taking insulin-sensitizing drugs [172,173]. In addition, patients taking insulin or insulin secreting drugs have a worse cancer outcome than those taking insulin-sensitizing drugs [174,175]. Epidemiological data also show that taking metformin or TZDs may be associated with lower cancer incidence, possibly due to a reduction in circulating insulin levels [176]. Although not all data sets have shown this association, the association between high circulating insulin levels and cancer risk is evident.

Another potential therapeutic implication is through lowering inflammation as a strategy for chemoprevention. Epidemiological data showed that in patients with higher BMI, aspirin is more effective in preventing colorectal cancers [177], possibly by reducing circulating cytokines. Although this effect was not seen at lower doses [177], there seems to be a therapeutic potential in modulating inflammation. Although the effectiveness of therapeutic interventions is controversial, the growing incidence of obesity suggests that lifestyle changes and therapeutics may reduce or prevent adiposity that could additionally reduce the incidence and mortality from cancer.

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