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Cancer as a matter of fat: The crosstalk between adipose tissue and tumors

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Abstract

Obesity has been linked to the increased risk and aggressiveness of many types of carcinoma. A state of chronic inflammation in adipose tissue, resulting in genotoxic stress, may contribute to carcinogenesis and cancer initiation. Evidence that adipose tissue plays a role in cancer aggressiveness is solid and mounting. During cancer progression, tumor cells engage in a metabolic symbiosis with adjacent adipose tissue. Mature adipocytes provide adipokines and lipids to cancer cells, while stromal and immune cells from adipose tissue infiltrate carcinomas and locally secrete paracrine factors within the tumor microenvironment. This review focuses on the cross-talk between adipose tissue and tumor cells that promotes tumor growth and increases cellular lipid metabolism, metastasis, and chemoresistance.

The Cancer-Obesity Link – Epidemiologic Evidence

Obesity results from the expansion of white adipose tissue (WAT), commonly referred to as fat [1]. About 66% of all adults in the United States are overweight and 22% are diagnosed with obesity, as defined as a body mass index (BMI) exceeding 30 kg/m^2 [2]. The association of obesity with cardiovascular disease, as well as with glucose intolerance, dyslipidemia, lipotoxicity, and other components of type-2 diabetes and the metabolic syndrome, is well established. In the past few years, it has also become apparent that an

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estimated 40% of all cancer deaths in the United States are attributable, in large part, to obesity [3]. An association has been established between obesity and increased mortality from cancer of the prostate and stomach in men; the breast (postmenopausal), cervix, and uterus in women; and the kidney (renal cell), colon, esophagus (adenocarcinoma), pancreas, gallbladder, and liver in both sexes [4]. More recently, reports from the Metabolic Syndrome and Cancer Project, a European cohort study of ~ 580,000 adults, also confirmed associations between obesity and risks of colorectal, and thyroid cancers [5]. A link between obesity and cancer is further supported by epidemiological studies that have provided evidence that intentional weight loss and bariatric surgery reduces cancer incidence [6]. Moreover abdominal (central) obesity, resulting from the overgrowth of visceral WAT, has been specifically linked with cancer progression [7]. When considering these associations, it is important to separately consider the stimulatory effects of obesity on carcinogenesis, resulting in higher cancer incidence, and on cancer progression, resulting in increased mortality. For example, while obesity is associated with an increased risk of post-menopausal breast cancer, menopausal status is not a factor in the negative effects of obesity on prognosis [8]. By 2025, the global obesity rate is projected to reach 21% in women which, since 55% of all female cancers currently diagnosed are obesity-associated, is particularly concerning. A number of mechanisms have been proposed to explain the role of obesity in cancer risk and progression. These include chronic inflammation, hyperinsulinemia, and changes in circulating levels of steroid hormones, glucose and lipids, as well as cytokines and growth factors such as IGF-1, leptin and adiponectin [9, 10]. Detailed descriptions of these circulating molecules, and their functions in the setting of cancer, have been previously published [8–12] and are beyond the scope of this review. While diet is important in considering the obesity-cancer link, studies in animal models have shown that WAT overgrowth directly promotes cancer progression irrespective of diet [13, 14].

The Role of Activated Adipose Tissue in Cancer

Adipose tissue (AT) is a complex organ important for the regulation of the body’s energy balance [15]. The primary function of WAT is to store energy as lipids in adipocytes and to release them in response to physiological energy demand [1]. However, in addition to adipocytes, WAT is composed of a number of other cell types within the stromal-vascular fraction, which have diverse functions [11]. Mesenchymal stromal cells of WAT, also termed adipose stromal cells (ASC), are perivascular cells supporting the endothelium and serving as adipocyte progenitors [16, 17]. A heterogeneous palate of innate and adaptive immune cells, including macrophages, dendritic cells, mast cells, eosinophils, neutrophils, and T and B lymphocytes are contained in WAT as well [18]. Collectively, adipocytes and other stromal cells of WAT serve as a source of bioactive molecules regulating important signaling pathways implicated in cancer initiation and progression.

WAT composition and physiology predetermine susceptibility to the metabolic syndrome and its complications. Studies in mouse models have shown that, upon reaching a certain overgrowth threshold, WAT becomes inflamed and fibrotic [19], and it has been proposed that tumorigenesis and cancer progression are promoted by WAT dysfunction and chronic inflammation [10]. Factors, including the anatomic location of AT, sex, age, and metabolic

status can alter the tissue milieu and characteristics in ways we are only just beginning to understand [20]. A growing body of evidence indicates that WAT accretion and deregulation in obesity, rather than the lifestyle responsible for obesity onset, is the key determinant of cancer initiation and progression [11].

In addition to storing energy, WAT functions as an endocrine organ, secreting bioactive molecules termed adipokines [9]. Currently, more than 50 different adipokines have been identified, the majority produced by adipocytes [21]. In obesity, with an increase in WAT mass and cellularity, circulating adipokine levels are altered. Leptin and adiponectin are the most thoroughly studied of the adipokines specifically produced by adipocytes. While leptin levels increase in obesity, adiponectin levels decrease, and this altered leptin/adiponectin ratio has been found to correlate with cancer aggressiveness [22]. Other growth factors and cytokines implicated in the progression of obesity-related cancers include TNFα, IL-6, and IGF-1 [12]. Recently, a cancer-promoting role for chemokine CXCL12 (SDF1α), secreted by WAT, has been revealed [23]. Non-peptide WAT-endocrine factors, including steroid hormones and lipids, also modulate processes ranging from extra-cellular matrix (ECM) remodeling to cancer cell signaling and metabolism [21]. Collectively, adipokines promote tumor growth either via oncogenic signaling or through indirect mechanisms, such as angiogenesis and immunomodulation [9, 12, 21].

Since the role of fat tissue in cancer was first investigated, it has been assumed that all of the body's WAT depots stimulate cancer progression through the systematic circulation of these endocrine factors. However, the observation that cancers that are not surrounded by WAT are not linked with obesity suggests that carcinomas are fueled by direct local exposure to proximal adipose cells. Adipocytes are typically absent within the normal parenchyma of epithelial glands. However, in invasive carcinomas, adipocytes come in direct contact with tumors, especially in the reproductive (prostate, uterus, breast) and digestive organs [4]. Several epithelial cancers (gastric, colon, serous endometrial, and ovarian) disseminate within the abdominal cavity to the omentum, a WAT pad of approximately 20×20×3cm, which drapes from the stomach over the gastrointestinal tract [24]. Tumor-associated WAT has been found to play a role in breast cancer progression [25–27] and in aggressive prostate cancer, extraprostatic extension of the tumor into WAT beyond the confines of the gland is a key determinant of disease aggressiveness [28, 29].

Once the cancer cells become intermingled with adipocytes and other cells of WAT, a crosstalk ensues. Mechanistically, it is mediated by paracrine and contact-dependent signaling from adipocytes, and the adipose stroma [21, 24, 30]. Inflammation-associated changes in WAT and tumor ECM also appear to play a role in cancer initiation and promotion [18]. In obesity, inadequate oxygenation of hypertrophic adipocytes results in cell death, which triggers a dynamic activation of innate and adaptive immune populations. Infiltrating and resident immune cells are a potent source of pro-inflammatory cytokines and chemokines, growth factors, and matrix-degrading enzymes, such as matrix metalloproteases (MMPs), which remodel the tissue and induce chronic low-grade inflammation [19]. In the WAT of obese patients, activated adipocytes, ASC, as well as monocytes/macrophages and other leukocytes infiltrating from WAT, stimulate molecular mechanisms that promote successive stages of cancer progression (Figure 1, Key Figure).

Adipose Tissue Inflammation and Cancer Initiation

Inflammation is a hallmark of cancer that underlies obesity-linked carcinogenesis. Tumors can be considered as wounds that “do not heal” due to chronic inflammation induced by immune cells [31]. In WAT, innate and adaptive immune cells constitute almost half of the population of lipid-free cells in the stromavascular fraction. In healthy WAT, immune cells maintain tissue homeostasis and a immunosuppressive microenvironment by clearing apoptotic cells, regulating angiogenesis, and remodeling the ECM [32]. In obesity, the ability of immune cells to perform these functions is often altered, promoting inflammation, which is critical to the development of WAT fibrosis [18, 19]. The increased tissue stiffness and mechanotransduction of fibrotic tissue may be an important contributor to tumorigenesis [33]. Adipocytes and ASC secrete ECM molecules, including fibronectin, laminin, and collagens. A cleavage product of collagen VI, the most abundant WAT ECM molecule, has been implicated in both breast cancer tumorigenesis and progression [34].

However, while the effect of WAT on cancer progression is well established, and many studies have implicated WAT in tumorigenesis, it is still being debated whether WAT actually promotes cancer initiation and if it does what mechanisms are involved. Because ECM, adipokines, and other WAT-secreted molecules are not known to be directly mutagenic, mechanisms underlying obesity-cancer risk have remained uncertain. It is possible that WAT deregulated in obesity accelerates cancer growth merely by enhancing mitogenic signals in epithelial cells already containing carcinogenic mutations. However, a direct carcinogenic role for WAT cannot be ruled out. Mutations are known to result from oxidative stress which produces reactive oxygen and nitrogen species (ROS/RNS) and other types of metabolites that cause DNA double strand breaks and other lesions [35]. Obesity leads to increased DNA damage and reduced DNA repair in both animal model systems and humans [36, 37]. In obesity-associated inflammation, activated myeloid cells appear to be a major source of ROS [38]. The evolving paradigm is that the inflammatory WAT milieu creates an environment in which ROS production is elevated to a level at which genomic instability ensues. Indeed, obese children have higher levels of double strand breaks, supporting an increased potential for cancer causing mutations in obesity [39, 40]. Until there is direct evidence showing an increase in DNA damage and/or higher genetic instability in tumors at proximity to obese AT, however; the role of WAT-generated ROS in tumor initiation remains hypothetical.

Leukocyte-Cancer Cell Interactions

WAT contains various types of immune cells that play an important role in cancer and become part of the tumor organ [41]. Macrophages are the most highly represented immune cells in WAT and with obesity their numbers increase considerably in both visceral and subcutaneous adipose tissue [18]. While WAT-resident leukocytes may drive cancer by releasing cytokines systemically, it is likely that they are also recruited to tumors from WAT and act locally [42]. It is posited that they are transformed from the activated macrophages found in obese AT to tumor-associated macrophages (TAMs) and accumulate in tumor tissue. In fact, WAT macrophages and TAMs display overlapping phenotypic markers and functions [19]. A change in the macrophage landscape from anti-inflammatory to pro-

inflammatory underlies changes in lipid processing and the creation of a low-grade inflammatory state, which contributes to the metabolic syndrome and is observed in both WAT and tumors during cancer progression. Cytokines released by macrophages contribute to tumor malignancy through a variety of mechanisms, including growth promotion, matrix degradation, and tumor angiogenesis. Fibrosis, elevated ECM stiffness, angiogenesis, and regional hypoxia are among the processes driven by both WAT macrophages and TAMs. The presence of “crown-like structures” in mammary WAT, which are conglomerates of macrophages and other immune cells around dead adipocytes, is associated with increased aromatase expression and inflammation, which might increase breast cancer development [43, 44]. A decrease in anti-inflammatory macrophages may also contribute to cancer initiation and promotion.

Lymphocytes also become ‘educated’ and “activated” by inflamed WAT [18]. Pro-inflammatory cytokines released by T lymphocytes include the TNF superfamily, IL-1β, IL-6, CXCL2, MCP-1, COX-2, 5-lipooxygenase, MMPs, VEGF-C, and a number of cell surface adhesion molecules. CD4+ helper T (Th) cells and CD8+ cytotoxic T (Tc) cells, including pro-inflammatory effector Th1 cells and immunoregulatory Th2 cells, as well as Th17, γδT, and the cytotoxic natural killer (NK) cell subsets, regulate the inflammatory tone of WAT and the tumor microenvironment [42]. CD4+ cells direct the proliferation and function of CD8+ Tc cells and antigen-presenting cells (APC), such as macrophages and dendritic cells. CD8+ Tc cells are a critical component of antitumor immune defense that can directly kill tumor cells as well as stimulate APC function. In contrast, regulatory T cells (Tregs) act to suppress CD8+ Tc cells, APCs, and NK cells, through production of immunosuppressive cytokines including IL-10 and TGF-β. These counter-regulatory interactions in the tumor microenvironment suppress immunosurveillance and lead to immune tolerance [42]. Current immunotherapeutic approaches are based on the concept of “exhausted” T cells that arise due to long-term activation. Exhausted T cells express the inhibitory “checkpoint” protein, Programmed Death-1 (PD-1), which incapacitates T cell leading to a failure to kill cancer cells. Monoclonal antibodies blocking PD-1 receptor activation have shown efficacy in cancer treatment [45]. Interestingly, obesity appears to regulate PD-1 activation: TAM-specific expression of PD-L1 (the ligand for PD-1 on T cells) is promoted by HIF-1α in hypoxia [46] and T-cells in obese adipose tissue have high expression of PD-1 [47]. Furthermore, CD4+ T cells expressing PD-1 are increased in the WAT of obese mice [47]. However, until there is an established link between PD-1 expression and obesity in patients, an impact of the adipose microenvironment on the efficacy of immunotherapy remains speculative.

Adipose Stromal Cell-Cancer Cell Interactions

Tumor stroma, composed of a mixture of various non-malignant cell types, has been identified as one of the drivers of cancer progression [11, 48]. While the pool of tumor leukocytes is maintained by hematopoietic progenitors, cancer-associated fibroblasts (CAF), a major component of the tumor stroma, are of mesenchymal origin [49, 50]. This mixed population is partly derived from ASC, which have been found to play an important role in tumor growth in animal models [51]. ASC, which are abundant in WAT and proliferate in obesity, become mobilized, migrate from WAT to tumors, and promote cancer progression

[14, 51, 52]. Adipocyte-secreted matricellular protein, SPARC, binding to β1 integrin on the ASC surface, is a molecular trigger of ASC mobilization [53]. Chemokines CXCL1 and CXCL8 signaling upon their receptors, CXCR1 and CXCR2, mediate the homing of ASC to tumors [54, 55]. Poor survival of obese patients with prostate cancer has been linked to ASC trafficking from WAT to tumors, which is mediated by CXCL1 secreted from malignant epithelium and signaling on ASC via its receptor CXCR1 [55]. It was also found that the secretion of CXCL1 by tumors in the setting of obesity is induced by WAT leukocyte-derived IL-22 signaling through IL-22R on cancer cells [56].

In these and other reports, the molecular mechanisms through which tumor-recruited ASC promote cancer progression are now being unraveled. Chemokines secreted by ASC recruit macrophages, which have a tumor promoting role as discussed above [57]. However, ASC within the tumor microenvironment also directly contribute to carcinoma progression. Intratumoral adipocytes, differentiating from infiltrating ASC, stimulate the proliferation of adjacent cancer cells [14]. ASC are a major source of the ECM that drives tumor desmoplasia [33] and they also secrete trophic factors that stimulate vascularization [14, 51]. Moreover, some of the cancer-promoting effects of ASC may be contact-dependent [58]. In a recent study, a role for CXCL12, an ASC-secreted chemokine, in prostate tumor growth and invasiveness has been demonstrated [23]. In addition, roles for ASC in therapy resistance [59] and metastasis [60, 61] have also surfaced. As an illustration of metabolic symbiosis, ASC increase nitric oxide synthesis in cancer cells, leading to their decreased mitochondrial respiration, increased glycolysis, and chemoresistance [62]. Bone marrow mesenchymal stromal cells mute anti-tumor immune response through their effects on T cells [63]. It remains to be determined if ASC have similar immunosuppressive properties. Recently, it has been shown that bone marrow mesenchymal stromal cells induce the epithelial-mesenchymal transition (EMT), an important step in the progression of carcinomas to a chemoresistant and invasive phenotype [64]. The role of ASC in EMT induction and cancer aggressiveness also remains to be proven.

Adipocyte-Cancer Cell Interactions

Breast carcinomas invade adjacent mammary AT, prostate carcinomas invade the peri-glandular AT, and ovarian carcinomas invade omental AT [24, 65]. It is, therefore, not surprising that adipocytes engage in a direct interaction with cancer cells at the invasive front of tumors [28]. An analysis of peritumoral WAT in patients revealed that adipocytes adjacent to malignant cells have smaller lipid droplets than adipocytes further away from the tumor [24]. Adipocytes co-cultured with breast cancer cells also progressively lose lipid droplets and eventually become indistinguishable from ASC [25–27].

With hypoxia, cancer cells undergo metabolic reprogramming to increase lipid utilization [66]. Lipid metabolism has a particular clinical relevance for carcinomas, and increased use of lipids, as opposed to glucose, is a hallmark of cancer aggressiveness [67]. Fatty acids (FA), which produce about twice the energy of glucose, are the primary forms of lipids used by tumors as a source of energy through β-oxidation [68]. In addition, FA derivatives including phospholipids, sterols and sphingolipids, as well as important signaling molecules are integral components of the cancer cell and mitochondrial membrane [69]. Examples of

signaling lipid derivatives include sphingosine-1-phosphate and lysophosphatic acid, which regulate the migration, proliferation, and invasion of cancer cells [70]. FA are also used for the lipid modification of proteins. Unsaturated FA have been specifically implicated in cancer cell aggressiveness [71]. Tumor cells synthesize most FAs *de novo* in spite of a sufficient dietary lipid supply [70] and increased lipogenesis is a hallmark of many aggressive cancers [72]. However, in aggressive cancers endogenous lipogenesis becomes insufficient and cancer cells switch to the uptake of extracellular FA. Indeed, lipogenesis inhibitors reduce the viability of cancer cells only in the absence of exogenous lipids [73].

Adipocytes undergoing lipolysis serve as a source of lipids for cancer cells [74, 75]. Indeed, adipocyte lipolysis-derived FA increase proliferation and invasiveness of breast cancer cells in co-culture settings [27, 76, 77]. In cancer-associated adipocytes, triglycerides are hydrolyzed to release free FA by the sequential action of adipose triglyceride lipase, hormone sensitive lipase and monoacylglycerol lipase [69]. Cancer cells can induce the expression of lipoprotein lipase that processes chylomicrons, triglycerides and phospholipids, and hence enables their uptake of exogenous FAs [78]. The downstream molecular complex that facilitates intercellular cholesterol and FA transport relies on CD36, also known as FA translocase [79]. CD36 is particularly important for the uptake of long chain FA, which are subsequently transported by the FA-binding proteins, FABP3 and FABP4. Overexpression of CD36 is associated with tumor progression and metastasis [80]. Hypoxia, through HIF-1α, increases lipid uptake in cancer cells by inducing the expression of FABP3/4, as well as adipophilin, a lipid droplet structural protein [81]. Cancer cells can transiently store excess triglycerides in lipid droplets and, as energy is needed, will undergo lipolysis to free up FA [25, 82]. In addition to serving as an energy source, imported FAs are utilized for membrane lipid synthesis along with cholesterol [83] and affect cellular signaling. Increased FA load leads to passive mitochondrial uncoupling that reduces lipotoxicity in cancer cells [25]. More aggressive cancer cell lines display higher exogenous FA incorporation into oncogenic signaling lipids, as opposed to oxidative pathways [84]. It has been reported that inhibition of lipolysis, lowering free FA levels, reduces cancer pathogenicity, an observation that may have a therapeutic implication [69]. Other potential therapeutic targets are fatty acid receptors, such as CD36 and fatty acid transport proteins (FABP4/5).

The Role of Adipose Tissue in Therapy Resistance

There is emerging evidence that WAT-derived cells and factors contribute to the therapy resistance of various cancers [59, 62, 85, 86]. This is in part due to the changes in the tumor matrix driven by the adipose microenvironment. In pancreatic tumors from both patients and animal models, obesity-induced fibrotic tissue deposition prevents uniform tumor vascularization, which jeopardizes drug delivery. Interestingly, metformin, a common antidiabetic agent can inhibit desmoplasia in pancreatic cancer by reducing ECM remodeling, EMT, and metastasis [87]. Recent data suggest that ASC and adipocytes in the tumor microenvironment promote EMT, early metastasis, and chemoresistance. While the role of EMT in metastatic dissemination is controversial [88, 89], acquisition of ‘cancer stem cell’ properties and resistance to therapy is undoubtedly a hallmark of EMT [49, 90, 91]. Indeed, acquisition of therapy resistance has been linked with the activation of lipid

metabolism in cancer [71, 92], and mounting evidence links the uptake of adipocyte-derived FA to the EMT [25]. Elevated CD36-mediated FA uptake has been reported to promote the EMT in hepatocellular carcinoma [93] and ovarian cancer [80]. CD36-positive cancer cells in tumors which upregulate lipid metabolism have ‘cancer stem cell’ properties and an increased ability to disseminate, which is associated with poor prognosis [92, 94]. CD36-expressing cancer cells also have an increased survival potential and resistance to chemotherapy [74, 92]. In addition, lipolytic changes in the adipose microenvironment, leading to FA release from adipocytes, have been linked to the invasiveness of pancreatic, prostate, and breast cancers [27, 95]. Activation of carnitine palmitoyltransferase I (CPT1), a key β-oxidation gene, by JAK/STAT3 signaling downstream of adipocyte-secreted leptin has been established as a mechanism responsible for breast cancer cell aggressiveness [96]. A recent report shows that breast cancer cells co-cultured with adipocytes are also more radioresistant due to the activation of the Chk1 signaling pathway in tumor cells by IL-6 [26].

Evidence that, in obesity, adipocytes, in response to oxidative stress, secrete protective factors enabling chemotherapy resistance, has also been observed for hematological malignancies [97]. AT creates a microenvironment that supports proliferation and resistance to chemotherapy for disseminating leukemia cells. As in carcinomas, leukemic cells engage in CD36-dependent FA transport from adipocytes, fueling β-oxidation [74]. In addition, recent studies reveal that lipids in adipocytes can sequester cancer drugs, which results in chemotherapy depotentiation [98].

Concluding Remarks

There are many questions raised in this review that remain to be addressed (see outstanding questions). Despite advances in the field, primary tumors eventually progress to aggressive, metastatic phenotypes in many types of cancer. Metastasis and the resistance of cancer to treatment remains an often insurmountable challenge. Because the prevalence of obesity is rising, further insights into the mechanisms that underlie its association with cancer risk and virulence are urgently needed. While obesity is linked with cancer development, patients with high-grade cancer are, in fact, often lipodystrophic. Indeed, advanced stages of many cancers are associated with WAT loss and body wasting (cachexia), which complicates treatment and adversely affects patient survival. This is partly because tumor growth drives lipolysis in adipocytes. As a result, cancer progression tends to eventually result in global WAT mass reduction [99]. It has been proposed that the conversion of WAT into beige/brown adipose tissue (BAT) plays a role in this process [100]. BAT adipocytes have a high capacity for uncoupled thermogenic energy dissipation through the β-oxidation of FA [15]. However, the association of BAT activation with cancer progression that is evident in rodent models has not yet been tested for clinical relevance. At this point, there is a clear need for a better understanding of the changes in WAT, and the resulting changes in other organs, that underlie cancer progression in obesity. Insulin resistance and other manifestations of the metabolic syndrome, involving other organs such as the liver, kidney and muscle, also interfere in cancer development and progression. Importantly, not all obese patients exhibit AT inflammation and metabolic complications. In the future, the comparison of cancer

initiation in those with healthy and those with unhealthy obesity will help to further uncouple the relationship between AT overgrowth and metabolic complications.

Outstanding Questions

How does increased adiposity contribute to carcinogenesis and tumor progression and can the underlying mechanism(s) be blocked?

Could targeting cells from WAT be developed as a combination treatment that improves the efficacy of conventional cancer and immuno therapies?

Could the blockade of fatty acid transfer from adipocytes to cancer cells synergize with conventional therapy?

Is WAT converted to BAT in patients with high-grade tumors and, if so, should different cells/pathways be targeted in advanced cancer patients?

Currently, obese and non-obese cancer patients are given the same treatments, but there is increasing evidence that therapies tailored to obese patients may improve their survival [11]. Targeting the processes through which WAT overgrowth appears to promote cancer initiation and progression could reduce the increased cancer risk and tumor aggressiveness associated with obesity [11, 30, 101]. Recently, experimental therapeutics targeting ASC, adipose endothelium and adipocytes have been designed and their tests in animal models of cancer have shown promise [102–105]. In the future, drugs aimed at the cellular and molecular mechanisms through which WAT cells drive chemoresistance could improve the efficacy of current anticancer treatments.

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Trends

Cancer initiation in obesity can be triggered by chronic inflammation in adipose tissue, which creates localized genotoxic stress leading to carcinogenesis.

Carcinoma growth is fueled by adipokine signaling from adipose-tissue derived cells, which can infiltrate tumors.

Cancer aggressiveness in obesity is supported by fatty acids and other metabolites secreted by adipocytes, as well as by immune system dysfunction.

Pathways mediating the switch of cancer cells to lipid metabolism are among those that could be targeted in combination with conventional therapies.

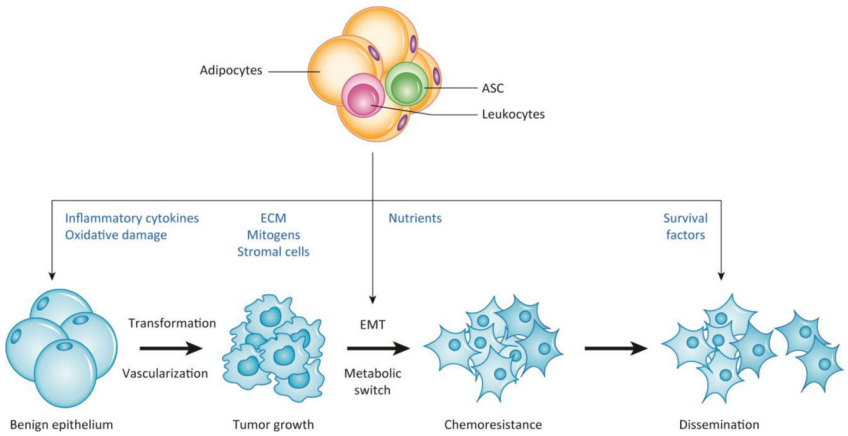

Figure 1 Key Figure.

The roles of cells from adipose tissue in the successive steps of cancer progression Interaction between AT and epithelium during cancer initiation and progression. WAT secretes factors that promote transformation of benign epithelium, induce the EMT and the switch to increased fatty acid metabolism in cancer cells, and eventually promote metastases and chemoresistance. Both endocrine WAT factors and paracrine factors from WAT-derived cells (adipocytes, ASC, and leukocytes) infiltrating tumors contribute to the steps of cancer progression.

Abbreviations: AT, adipose tissue; WAT, white adipose tissue; ASC, adipose stromal cells; BAT, beige adipose tissue; CAF, cancer associated fibroblasts; ECM, extracellular matrix; EMT, epithelial-mesenchymal transition; FA, fatty acids; MMP, matrix metalloproteases; PD-1, Programmed Death-1; ROS, reactive oxygen species; TAM, tumor-associated macrophages