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REVIEW ARTICLE

From obesity to cancer: a review on proposed mechanisms

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Nowadays, obesity is considered as a serious and growing global health problem. It is documented that the overweight and obesity are major risk factors for a series of noncommunicable diseases, and in recent years, the obesity-cancer link has received much attention. Numerous epidemiological studies have shown that obesity is associated with increased risk of several cancer types, including colon, breast, endometrium, liver, kidney, esophagus, gastric, pancreatic, gallbladder, and leukemia, and can also lead to poorer treatment.

We review here the epidemiological and experimental evidences for the association between obesity and cancer. Specifically, we discuss potential mechanisms focusing how dysfunctional angiogenesis, chronic inflammation, interaction of proinflammatory cytokines, endocrine hormones, and adipokines including leptin, adiponectin insulin, growth factors, estrogen, and progesterone and strikingly, cell metabolism alteration in obesity participate in tumor development and progression, resistance to chemotherapy, and targeted therapies such as antiangiogenic and immune therapies.

KEYWORDS

adipose tissue, cancer, mechanism, obesity

1 | INTRODUCTION

Obesity is defined as the abnormal or excess fat accumulation. It has received considerable worldwide attention as a severe health problem in recent years.[1] Obesity is associated with elevated incidence of chronic diseases including cardiovascular disease, type 2 diabetes mellitus, and hypertension and may also be an important risk factor for certain types of cancer. The imbalance between energy intake and energy expenditure is considered the main cause of overweight and obesity.[2]

The global trend of obesity is increasing: Based on the World Health Organization (WHO) estimation in 2005, nearly 1.6 billion people worldwide were overweight and at least 400 million adults were obese, and by 2015, the numbers increased to approximately 2.3 billion overweight adults and at least 700 million obese individuals.[3] In developing countries more than 115 million people are suffering from obesity-related problems. Since 1980, in the Middle East, the Pacific Islands, Australasia, and China, obesity rates have increased 3-fold or more spiked more than 3-folds. Obesity rates in Western Africa are estimated at 10%. That may not seem very high but is worrying considering that in urban West Africa, obesity has more than doubled in the last 15 years.[4,5]

Overweight and obesity are as the fifth leading risk for global deaths. Adams et al in a prospective cohort study on the more than 500 000 US men and women with 10 years' follow-up reported that risk of death increased by 20% to 40% in the overweight patients and by 2- to 3-folds in the obese compared with that in normal-weight patients.[6] On the basis of a systematic review, direct economic cost associated with obesity is estimated to be on average between 0.7% and 2.8% of a country's total health care expenditures and medical costs of obese individuals were found to be 30% greater than those of the normal-weight peers.[7]

Central obesity, dyslipidemia, hyperglycemia, insulin resistance, and hypertension together define metabolic syndrome or syndrome X, which has been shown to have a link with certain types of cancer.[8] In this review article we attempt to clarify the proposed mechanisms for the link between obesity and cancer.

2 | EPIDEMIOLOGICAL STUDIES

Case-control and cohort studies have consistently demonstrated that obesity is associated with higher risk of colorectal cancer in men and women. A gender bias has been observed with obese men more likely to develop colorectal cancer than obese women.[9] For example, in a large cohort study conducted by the American Cancer Society, people with body mass index (BMI) over 30 kg/m^2 were compared with people with BMI below 25 kg/m^2. The results estimated the

relative risk of colorectal cancer at 1.8 for obese men and 1.2 for obese women. In another study on men between 40 and 75 years old, central obesity as waist circumference measurement and waist to hip ratio ≥0.99 compared with ≤0.9 was a strong risk factor for colon cancer and adenoma.[9,10]

Also, many epidemiological studies since 1970s have assessed association between body size and risk of breast cancer. Taking menopausal status into account one study found that postmenopausal obese women had 30% to 50% increased rates of breast cancer. In other case-control studies found postmenopausal women with BMI above 27 to 28 kg/m^2 had 10% to 60% increased risk of breast cancer. While, several cohort and case- control studies among premenopausal women have illustrated modest reduction with a high BMI (≥28 kg/m^2). Also, the most informative studies showed neither waist circumference nor waist to hip ratio is related to premenopausal breast cancer risk.[10–12]

Endometrial cancer was one of the first cancers linked with obesity. A great majority of case-control and cohort studies have shown strong association between obesity and this type of cancer.[13] A 2-fold increase in endometrial cancer risk among women with BMI > 30 kg/m^2 was reported when compared with that among those that had BMI < 23 kg/m^2 in the series studies conducted in North America, northern Europe, southern Europe, and China.[10,11]

Higher risk of kidney cancer especially renal cell cancer in several studies in women than men related has been shown with overweight and obesity[14] that seems to be independent of blood pressure. Possibly, hypertension and obesity through different mechanisms can influence on renal cell cancer.[15] In a meta-analysis including 11 studies, the increase in renal cell cancer risk per unit increase in BMI was estimated at 6% and 7%, respectively, in men and women, and the risk was on average 36% higher for the overweight (BMI > 25 kg/m^2) and 84% higher for the obese (BMI > 30.0 kg/m^2).[9]

A study by Lagergren et al among Swedish patients demonstrated strong positive association between high BMI (>25.6 kg/m^2 in men and >24.2 kg/m^2 in women) and esophageal adenocarcinoma (OR = 7.6; 95% CI, 3.8-15.2) and also higher risk for people with BMI > 30 kg/m^2 relative to those with BMI < 22 kg/m^2 (OR = 16.2; 95% CI, 6.3-41.4).[9] Gastro-esophageal reflux disease has been linked with esophageal adenocarcinoma and Barrett esophagus; therefore, obesity may increase the risk of the adenocarcinomas indirectly by increasing the risk of gastro-esophageal reflux disease and Barrett esophagus, although in some studies, this indirect association has not been observed.[16]

Some cancers are likely to be obesity related. Both lower and higher risk of pancreatic cancer has been reported for high BMI subjects.[16] In a case-control study in Atlanta, overweight men and women (BMI ≥ 27.2 and ≥34.4 kg/m^2, respectively) had a 50% increased risk of pancreatic cancer compared with normal-weight subjects (BMI 17.4-23.1 and 20.5-27.5 kg/m^2, respectively).[10] However, other studies have reported either no or smaller association.[17]

Regarding liver cancer or hepatocellular carcinoma, a number of studies have found an increased risk of 1.5- to 4-fold among obese individuals.[18] In a study by N'Kontchou and colleagues, multivariate analysis revealed hepatocellular carcinoma risk factors including BMI between 25 and 30 kg/m^2 (hazard ratio [HR], 2.0; 95% CI, 1.4-2.7), BMI 30 kg/m^2 or more (HR, 2.8; 95% CI, 2.0-4.0); however, another study did not confirm these results.[9]

Similarly, adenocarcinoma of the gastric cardia has been found to be associated with obesity.[19] In a systematic review and meta-analysis on 2059 cases, the link between BMI and gastric cardia adenocarcinoma was studied. The results (men and women, overweight + obese OR, 1.5; 95% CI, 1.3-1.8; P = .38) indicate this association is not as great as for adenocarcinoma of the esophagus.[20] That is possibly because reflux mechanisms might also cause esophagus adenocarcinoma.[19]

On the other hand, for some cancers no association with BMI has been reported. For example, no association have been reported between BMI and lung cancer in nonsmoking populations if smoking is considered as a primary cause of lung cancer that can be a confounding factor in study populations was rolled out.[16]

Several studies have investigated the association between BMI and cervical cancer. In a prospective human papillomavirus cohort study in Korea on 1125 women aged 18 to 65 years and women with a normal BMI (18.5-23 kg/m^2), the multivariate ORs (95% CIs) for those overweight (23-25 kg/m^2) and have mild obesity (≥25 kg/m^2) were 1.25 (0.79-2.00) and 1.70 (1.10-2.63), respectively. In two cohort studies much lower relative risk were observed on obese women. However, in another cohort study, no association was found in Swedish women.[9,21]

For ovarian cancer, some studies have reported that obese women BMI ≥30 kg/m^2 have an increased risk of 1.69 compared with those with normal BMI (95% CI, 1.00-2.86; P trend = .06).[10] However, other studies have not found an association between ovarian cancer and obesity. Interestingly, obesity is a well-established risk factor for other hormone-related cancers in women such as breast and endometrial cancers.[22,23]

In the Prostate Cancer Prevention Trial by Gong and colleagues, men who had BMI <25 kg/m^2 in comparison with those with BMI ≥30 kg/m^2 had 18% lower risk of low-grade prostate cancer and also had 78% increased risk of high-grade (Gleason score 8-10) tumors. In another study BMI in age 20 years with prostate cancer showed men who had BMI ≥25 kg/m^2 in compared with BMI ≤19 kg/m^2 had a relative risk of 1.3 (95% CI ,0.81-2.2). On the basis of central obesity measurement, in a population-based cohort study in China, for waist to hip ratio >0.92 compared with ≤0.86, the reported OR is 2.7.[9,10]

3 | EXPERIMENTAL MODELS

Obesity in many animal models has been shown in relation with certain types of cancers. In a study on 5-week-old C57BL6/J mice, the aim was to determine whether obesity increases colon tumor development independent of the potential carcinogenic effects of ongoing intake of high-dietary fat. Mice were fed with regular chow or high-fat diet (HFD) for 8 weeks and switched in 4 experimental feeding groups: regular chow, HFD, regular chow switched to HFD, and HFD switched to regular chow. Two weeks after the dietary switch, mice were given 5 weekly injections of

azoxymethane to induce colon tumors. In this study all the obese groups showed increased tumor formation, but only mice switched from HFD to regular diet group showed enhanced apoptosis and proliferation. It seems that obesity did not affect the metabolism of this carcinogen. Obese mice switched from HFD to regular diet group before carcinogen treatment developed more adenomas than those on a regular diet, suggesting that factors associated with obesity—independent of maintained HFD and obesity—promote tumor development.[24,25]

Another study used long term (HF) diet on C57BL/6J male mice to induce hepatic steatosis and nonalcoholic steatohepatitis. Male littermates derived from the intercrosses were fed standard chow (SC) until 8 weeks of age and then had free access to SC or HF diet. Results of this study exhibited that the body weight, fasting insulin level, and leptin level had significant difference statistically, and all of them were higher compared with those of the mice fed SC diet. The HF diet for 60 weeks in the mice lead to enlarged liver compared with animals fed SC for the same duration. In addition, liver histology in HF diet group showed the typical features of nonalcoholic steatohepatitis in various stages of progression in the liver, including portal inflammation and blue wave-like bands of fibrotic tissue in portal lesions whereas in mice fed with SC had almost normal liver histology. Finally, tumors appearing as nodular lesions with various diameters on the liver surface were observed in 10% of the HF diet group after 30 weeks and in 54% of other animals after 60 weeks of the HF diet. On the contrary, no such nodular lesions were detected in the mice that were SC fed. Thus, steatosis developed in healthy livers associated with an inflammatory process triggered by the release of cytokines and oxidative stress resulted in hepatocellular degeneration, fibrosis, and tumorigenesis.[26]

In a study on 3- to 5-week-old male C57BL/6J mice, the aim was to investigate the precise effects of obesity on gastric cancer growth and its molecular mechanisms; mice received HFD and normal chow for 12 weeks. Then 24/24 mice on normal chow as lean were considered and 24/36 mice that consumed HFD and the body weight exceeded the mean plus 2-fold standard deviation of the lean mice body weight as obese and third group 12 mice on HFD, however, did not meet the mentioned criterion as nonobese. Then through subcutaneous injection of 2.0×10^6 murine forestomach carcinoma cell line (MFC) cell into the right flank in 12 obese, 12 lean, and 12 nonobese mice, in vivo gastric cancer model was created. Another 12 obese and 12 lean mice that had no difference with relative injected mice in the body weight were injected subcutaneously with 0.9% normal saline into the right flank as a control group. All mice were maintained on a normal diet or an HFD for another 2 weeks.[27]

The tumors became palpable 4 days after injection and within 2 weeks were observed in 83.3% of lean mice, 75% of nonobese mice, and 100% of obese mice. However, tumor growth rate was faster in the obese mice than in the lean and nonobese animals. Tumor weight in obese mice showed a significantly positive correlation with the body weight. This study showed obesity potentiated MFC cell migration and proliferation, decreased MFC cellular apoptosis, and accelerated cell cycle progression through endocrine mechanisms nampt/sirt1/c-myc positive feedback loop.[28]

4 | MECHANISMS OF OBESITY-RELATED CANCER

4.1 | Inflammation and angiogenesis

Angiogenesis is a process of growth and remodeling of an initial vascular system, which is modified to create an intricate branching network and matured vasculature. It is a multistep process that consists of extracellular matrix degradation, endothelial cell proliferation and migration, tubal formation, and anastomosis.[29–31]

Adipose tissue generates several angiogenic and angiostatic factors including placental growth factor, fibroblast growth factor (FGF2), angiopoietin-2, angiostatin, endostatin, leptin, thrombospondin (TSP-1), resistin, insulin-like growth factor (IGF), and hepatocyte growth factor. But most of the angiogenic activity is attributed to vascular endothelial growth factor (VEGF/VEGFR).[32] The plasticity of adipose vasculature is the result of a net balance between angiogenic factors and inhibitors. Development of preadipocytes differentiated into adipocytes and adipose tissue requires new blood vessels supply. In accordance with this, in the study, it was demonstrated that inhibition of angiogenesis by VEGFR2 blocking antibody reduced angiogenesis, tissue growth, and differentiation of preadipocytes.[33]

Similar to angiogenesis, chronic inflammation is critical for cancer initiation and progression. In chronic inflammatory conditions such as obesity often there is inadequate vascularization and oxygen delivery because of increasing cell size and number of adipose tissue.[33–35] Increased adipocyte size requires the supply of oxygen to diffuse over longer distances leading to decreased partial oxygen pressure or hypoxia that in has been observed in adipose tissue of many obese people.[36] A common stimulus for both chronic inflammation and angiogenesis is hypoxia. It induces hypoxia-inducible factor 1 (HIF1) expression[37]; this local adipose tissue hypoxia binds to the hypoxia response element of target genes and leads to angiogenic response.[38] Also, production of inflammatory cytokines such as interleukin 1β (IL-1β), TNF-α, and monocyte chemoattractant protein (MCP) which in turn increase infiltration of macrophages responding to enlarged adipocytes stress that has been investigated in tumor biology. The inflammatory state leads to adipose tissue remodeling and fibrosis.[39–41] Adipose tissue remodeling in obesity is often found as macrophages, which are localized to dead adipocytes where fuse to scavenge the residual lipid droplet and form multinucleate giant cell that it is recognized as crown-like structure, a hallmark of chronic inflammation.[42] For example, the crown-like structure-B index is defined severity of breast inflammation can be considered as a biomarker of increased breast cancer risk or poor prognosis.[43,44]

Since lysyl oxidase is a well-established HIF target that facilitates cross-linking collagens and elastins in the extracellular space and increases extracellular tensile strength, it can exert adipose tissue fibrosis and trigger increased and ultimately mediates local inflammation and insulin resistance. Hyperinsulinemia and insulin resistance can lead to promoting cell growth and inhibiting apoptosis.[45,46]

Nitric oxide (NO), a cellular signaling molecule, is produced by NO synthase (NOS) isoenzymes from L-arginine. Inducible isoform (iNOS) is involved in immune response and inflammatory condition; NO dilates vessels and stimulates its permeability that leads to immune cell

extravasation. Adhesion of immune cells to the endothelium is one of the most important steps in inflammatory process. Adhesion molecules such as E-selectin play a communication role in inflammatory process and can have a role in immune cell extravasation.[39] There are similar roles for adhesion molecules, intracellular adhesion molecule (ICAM-1), vascular cellular adhesion molecules (VCAM-1), and integrins.[47,48] Inflammatory cells also release angiogenic factors including: VEGF, angiopoietins, fibroblast growth factor (bFGF), hepatocyte growth factor, platelet-derived growth factor (PDGF), and transforming growth factor (TGF-ß), which have mitogenic and migratory effects on endothelium.[49–51] Activation of transcription factor NF-κB is considered as the primary event in inflammation. Several studies have demonstrated interplay between NF-κB and Ang-Tie2 signaling pathway. Angiopoietins (Ang-2) is an angiogenic factor that upregulates several proinflammatory pathways that can lead to leukocyte recruitment and infiltration through NF-κB signaling interaction.[52]

As mentioned above, angiogenesis, inflammation, and immune cell infiltration processes are the main features of adipose tissue expansion in obesity, and interestingly these processes also recently were suggested in obesity-related tumor biology and tumor progression.[53] In addition, it has been shown that the same processes can contribute in resistance to anti-VEGF therapy.[53–55] For instance, in metastatic kidney or colon cancer obesity is related with reduced survival in patients treated with bevacizumab an anti-VEGF antibody.[56]

Obesity is recognized as a low-grade, chronic, and systemic inflammation, and some of the adipokines such as leptin may also facilitate inflammation and immunosuppression; it is clear that obesity-associated inflammation can affect response to chemotherapeutic agents as well as targeted therapy.[28,57]

To develop a drug that can interfere with obesity-related tumor progression will be worthwhile. One such agent is metformin, which is widely prescribed as an antidiabetic drug, and because of its novel effects, it is frequently administered to diabetic pancreatic ductal adenocarcinoma patients and still is under extensive investigations.[58] A recent review article showed that it can reduce the incidence of cancer in diabetic patients. It in overweight/obese condition reprograms the fibro-inflammatory tumor microenvironment and reduces ANG II receptor I expression and PDGF/TGF-β signaling because ANG II signaling increases coagulopathy. Thus, metformin exerts beneficial effects in prevention of thrombotic events that frequently is observed in pancreatic cancer.[34,59,60] It reduces inflammation through reduction of proinflammatory cytokines production and recruitment of tumor associated macrophages and adenosine mono phosphate kinase (AMPK) activation and STAT3 signaling inhibition in macrophages.[61] In this study metformin effect in patients was found BMI dependent as both overweight and obesity. Hence, BMI as a biomarker of response to this drug should be proposed in cancer patients, of course further studies needed in this field.

4.2 | The role of hormones

4.2.1 | Leptin

In the past, adipose tissue was only considered as an organ of storage and mobilization of lipids; however, over the past decade, it came to be recognized as an active endocrine organ because of its secretion of a large amount of bioactive substances, the adipokines.[46]

Leptin, a 16-kDa peptide hormone, is predominantly produced in subcutaneous white adipose tissue and regulates energy intake through influence on neurons within the arcuate nucleus of the hypothalamus: neuropeptide Y (NPY), γ-aminobutyric acid (GABA), and proopiomelanocortin (POMC) neurons.[62,63] It acts on its target cells through binding with plasma membrane 6 receptor isoforms (Ob-Ra-f) that have identical extracellular ligand-binding domain and differ in their intracellular domain. The Ob-Rb—also known in humans as Ob-RL (long)—is the only isoform that activates the janus kinases, signal transducer, and activator of transcription (JAK/STAT) system,[64,65] it has been also shown that mediates its actions via AMPK,[65] phosphoinositide 3 kinase–protein kinase B (PI3-Akt), and mitogen-activated protein kinase (MAPK) pathways.[66,67]

Leptin is involved in maintenance of immune system function in relation with energy homoeostasis[68] as ob/ob mice are immunodeficient and reduced food intake and acute starvation in murine can lead to immune system disturbance, which is reverted by administration of exogenous leptin.[69]

Leptin resistance is recognized as decreased sensitivity to leptin action also increased production of leptin despite an inadequate response as inherited, limited tissue access such as at blood-brain barrier (BBB), intracellular suppressor of cytokine signaling-3 (SOCS-3), which inhibits

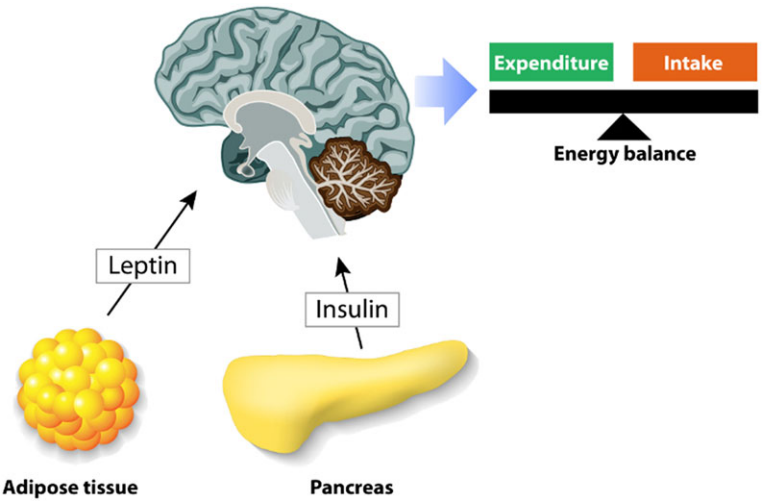

FIGURE 1 Control of food intake. Metabolic human hormones regulate the energy balance[79]

leptin JAK/STAT signaling, and extracellular circulating factors may bind leptin and alter its bioavailability and bioactivity serum leptin interacting proteins. Leptin resistance is common in obesity.[64] Furthermore, this adipokine has a structural and functional homology with proinflammatory cytokines such as IL-6 (interleukin) and C-reactive protein[70] also has been shown to upregulate other proinflammatory cytokines such as TNF-α, MCP-1, and reactive oxygen species from endothelial cells and peripheral blood mononuclear cells.[69] In addition, it promotes the production of proliferative and profibrotic cytokines and stimulates the hypertrophy and proliferation of vascular smooth muscle cells and thus contributes in a variety of proatherogenic functions.[71]

On the other hand, leptin interacts with insulin in control of food intake as been demonstrated (Figure 1). Basal plasma leptin and insulin concentration are parallel each other as increased leptin is associated with hyperinsulinemia and insulin resistance independent of BMI.[72] It is noteworthy, insulin by increasing nitric oxide (NO) availability causes vasodilatation and protective function on the endothelium; therefore, insulin resistance is associated with endothelial dysfunction, an early process in obesity.[73,74] Leptin is a potent angiogenic factor that acts through promotion of VEGF (vascular endothelial growth factor) secretion[75,76] that is in the consequence of local hypoxia and HIF-1α activates proinflammatory NF-κB signaling pathway, inflammatory cell response, and proinflammatory cytokine production.[77,78]

Thus, leptin is recognized as an adipokine with mitogenic, antiapoptotic, and proinflammatory properties contributing to carcinogenesis.

4.2.2 | Adiponectin

Adiponectin, a 30-kDa polypeptide, is most abundantly expressed and exclusively released from adipocytes of white adipose tissue.[80] It acts through 2 main receptors, AdipoR1 and AdipoR2, and activates downstream signaling pathways including the activation of AMPK and ceramidase and the inhibition of phosphatidylinositol 3-kinase; wingless type protein (Wnt)/b-catenin, extracellular regulated kinase 1 or 2 (ERK1/2); nicotinamide adenine dinucleotide phosphate oxidase, STAT3; and nuclear factor κB (NF-κB).[81,82]

Adiponectin secretion in circulation has 3 forms: trimer, hexamer, and high molecular weight (HMW) multimer. The HMW adiponectin is the major active form and mediates the insulin sensitizing effect of this adipokine. In obesity status intracellular assembly and the secretion of the HMW adiponectin are impaired.[83]

Adiponectin represents protective several effects on carcinogenesis. The HMW adiponectin through binding with 3 growth factors including platelet-derived growth factor (PDGF BB), bFGF, and heparin-binding epidermal growth factor–like growth factor (HB-EGF) can exert antiproliferative action by reducing the bioavailability of these growth factors at the prereceptor level.[84]

In the studies, it has been shown that it can mitigate the inflammatory response by inhibiting TNF-α activation of NF-κB (nuclear factor-kappa B), IL-6, and exert angiogenesis inhibition.[63,85] Also, with using of AMPK can regulate of glucose utilization and fatty acid oxidation can be insulin sensitizing.[86,87]

Expression and secretion of IL-6 are directly related to the degree of obesity and insulin resistance. The IL-6 primary source, which is adipose tissue macrophages, is infiltrated in obesity. It can, through decreased expression of insulin receptor substrate 1, induction of SOCS-3 and repression of adiponectin, an important anti-inflammatory adipokine, lead to inflammation, insulin resistance, and carcinogenesis.[88,89]

Also, adiponectin inhibits leptin and IL-6 induced cell proliferation by blocking activation JAK/STAT and NF-κB pathways. In addition, via AMPK and PI3K pathways, it acts for production of NO-eNOS and reduction of vascular smooth muscle cell proliferation.[90,91]

Taken together, the dysregulation of adiponectin production in obesity can lead to endothelial dysfunction, hypertension, myocardial damage and heart failure, which represent some disturbances of metabolic syndrome, and it is significantly associated with cardiovascular disease and cancer initiation and progression.

4.3 | Proinflammatory cytokines

4.3.1 | Tumor necrosis factor α

Tumor necrosis factor α is a 26-kDa transmembrane protein and a powerful proinflammatory adipocytokine. In recent years it has attracted much attention for its possible role in energy homeostasis because of its involvement in the pathogenesis of cachexia.[89,92]

The TNF-α can impair insulin signaling at both skeletal muscle and adipose tissue. It is a powerful proinflammatory cytokine, crucial to the transcription of numerous genes linked to the inflammatory process, the process causally related with the development of chronic inflammation, obesity, and insulin resistance eventually cancer.[63]

The TNF-α, because of its roles in chronic inflammatory diseases, has been shown in carcinogenesis particularly in the early stages of carcinogenesis via angiogenesis and invasion mechanisms,[93,94] which in Figure 2 has been illustrated.

For example, increased TNF-α level has been observed in *Helicobacter pylori*–positive gastric preneoplastic lesions.[95] However, in high concentrations this cytokine can show antitumor effect as William B. Coley used it for treatment of systemic bacterial filtrate injection in sarcoma patients,[96] although there were severe adverse effects such as hypotension and organ failure; thus, local administration is probably safer and more effective.[97] Sustained low TNF-α level has been shown to induce tumor phenotype.[98] Kwong et al showed organoid of normal human ovarian epithelial cells exposed to a prolonged high dose of TNF-α eventually develop tumors.[99]

Taken together, the pro or antitumor response of TNF-α depends on local concentration in addition to its expression site in the tumor.[100]

4.3.2 | Interleukin 6

Interleukin 6 (IL-6) is another proinflammatory cytokine well known for its role in promoting proliferation and inhibition of apoptosis when binds to its receptor (IL-6Rα) and activates specific (JAK/STAT1 and STAT3) signaling pathways.[101] The STATs belong to a family of transcription factors involved in tumorigenic processes, and this is one of the mechanisms in which IL-6 can promote proliferation.[102] Several studies have exhibited IL-6 role in multiple myeloma development as in one study blocking of the IL-6R/STAT3 pathway induced apoptosis in vitro.[103] Another study showed that IL-6 can induce tumorigenesis

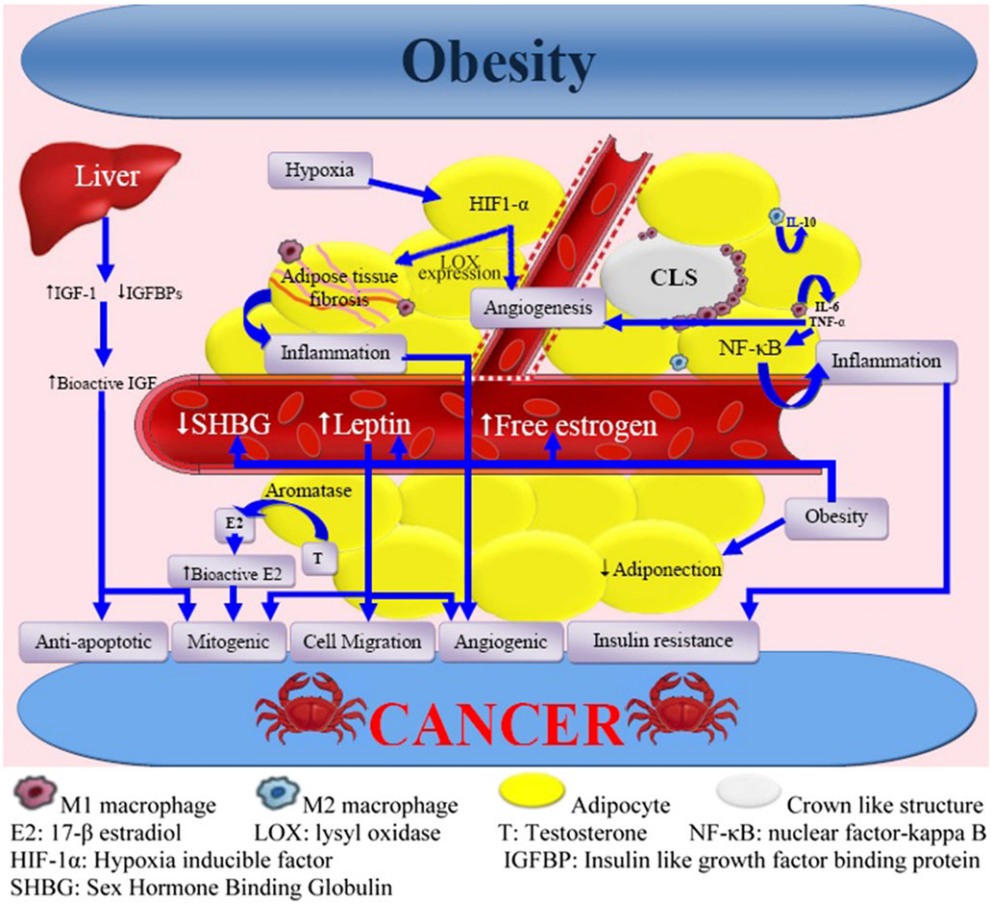

FIGURE 2 Schematic overview of several mechanisms associating obesity with cancer development

in oral squamous cell cancer lines in vitro by hypermethylation of tumor suppressor genes as well as by hypermethylation of retrotransposon long interspersed nuclear element-1 (LINE-1).[102]

Taken together, on the basis of these findings, IL-6 can be considered as a therapeutic target in cancer. At present, some antibodies against IL-6 or IL-6R are under evaluation in phase I/II clinical trials including siltuximab (CNTO 328), a monoclonal antibody against IL-6, has shown promising results for non-small cell lung cancer (NSCLC), ovarian cancer, prostate cancer, and multiple myeloma.[104–108]

4.3.3 | Transforming growth factor β

TGF-β is a pleiotropic cytokine with anti-inflammatory properties[109] that binds to its cognate type II receptor (TGF-β RII), induces type I TGF-β receptor (TGF-β R1) phosphorylation, and forms a heterotetrameric complex that activates SMAD dependent transcription.[110] SMAD transcription factors are characterized by a serine and threonine rich linker region that connects 2 MAD (mothers against dpp) homology regions.[111]

Studies on role of TGF-β in cancer have exhibited complex and paradoxical results. In early stages, TGF-β acts as a tumor suppressor, inhibiting cell cycle progression, but in later stages enhances invasion and metastasis by inducing epithelial mesenchymal transition (EMT).[112] Guasch et al observed that in a conditional TGF-β RII knock-out mice model, highly proliferative epithelia of rectal and genitalia developed spontaneous squamous cell carcinoma and progression.[113] A deficient TGF-β pathway leads to tumorigenesis, and vice versa increased TGF-β1 mRNA and protein have been observed in gastric carcinoma, NSCLC, colorectal, and prostate cancer.[114] Targeting this cytokine with TGF-β inhibitors, specifically ligand traps, antisense oligonucleotides, receptor kinase inhibitors, and peptide aptamers in cancer patients has shown promising results, although serious adverse effects of systemic TGF-β inhibitors have been reported.[115] Further studies are needed to evaluate safety, dose-effective therapy.

4.3.4 | Interleukin 10

Interleukin 10 (IL-10) is produced by almost all immune cells including T cells, B cells, monocytes, macrophages, mast cells, dendritic cells, and keratinocytes[116] that has been demonstrated in Figure 2. Tumor cells can also secrete IL-10.[117] It binds to its receptor, JAK1 and TYK2 tyrosine kinases phosphorylate, an IL-10 intracellular domain, and interact with STAT1, STAT3, and STAT5[118] similar to IL-6, IL-10 leads to a sustained STAT3 phosphorylation and whereas IL-6 induces a transient rapidly declining STAT3 phosphorylation and nuclear localization.[119] Thus, IL-10 might act as a tumorigenic agent through STAT3 activation (STATs belong to a family of transcription factors involved in tumorigenic processes) leading to Bcl-2 upregulation and apoptosis resistance.[120]

On the other hand, it can downregulate proinflammatory cytokine expression and exert an antitumoral effect; this effect has been shown in gliomas, melanomas, breast, and ovarian carcinomas through MHC-I downregulation.[121]

4.3.5 | Estrogen and progesterone

Obesity is defined as abnormal or excess fat accumulation and is associated with aromatase enzyme expression elevation in the adipose tissue that in turn converts androstenedione to estrone and testosterone to estradiol.[122] Obesity status also reduces sex hormone binding globulin (SHBG) capacity leading to increased levels of free biologically active estrogens[123] in which Figure 2 shows this mechanism. On the other hand, obesity is related with expression of proinflammatory cytokines including IL-6, TNF-α also, adipokines such as leptin. These in turn stimulate aromatase activity leading to an increase in estrogen levels.[122,124] Thus, obesity may be involved in carcinogenesis specifically for sex-dependent cancers such as breast and endometrium by increasing estrogen concentrations through the aforementioned mechanisms.[125]

Indeed, estrogens play an important role in the progression of human breast carcinoma by binding with specific receptor ERα that promotes breast cell proliferation directly and/or indirectly by altering gene transcription. In comparison with sharp mitogenic effects of estrogen on cultured breast cancer cells (in vitro models) the response to progesterone is both proliferative and inhibitory. Progesterone can upregulate many growth factor–initiated signaling pathways including insulin receptor substrate and epidermal growth factor receptor (EGFR) family members and therefore may act by sensitizing breast cancer cells to growth factors.[126,127]

In recent years mounting evidence has demonstrated that androgens are not the sole effectors in the complexity of prostate carcinogenesis. Studies on rat model have shown that brief prenatal exposure to high doses of estrogen or estrogen imprinting process via inflammation, prostatic hyperplasia mechanisms cause to prostate cancer.[128,129] In vitro studies on rat prostate models have shown that estrogen could induce genotoxicity via single strand DNA breaks and lipid peroxidation.[130] Another study demonstrated that chronic exposure to estrogen increased circulating prolactin levels in adult human whereas proliferative effects of prolactin has been well identified, and recent studies have supported the role of prolactin in breast and prostate cancers development.[131,132] On the other hand, estrogen functions are mediated by the estrogen specific receptors (ER), and multiple ERs are localized in prostate tissues that their activation has been associated with in vitro and in vivo phenotypic changes. Numerous evidences demonstrate direct estrogen signaling pathways within prostate cells that is involved in development of prostate cancer.[133,134]

In a study by Grindstad et al,[135] wide distribution of progesterone receptors (PRs) was observed in stromal and epithelial cells of benign and malignant prostate tissue in patients that had underwent radical prostatectomies for initial treatment. Results of this study indicated high progesterone density level in epithelial cells was associated with clinical failure in patients with Gleason score > 7 and progressing prostate cancer, but some other experimental investigations have reported conflicting results. This might be due to lacking of methodological standardization. To supporting this association, Check et al[136,137] conducted several studies that showed that mice with prostate cancer treated with a PR antagonist, mifepristone, had less prostate cancer complications and less mortality compared with controls. Although proliferative actions of progesterone have been reported in tumor cells of some organs, including breast, astrocytoma, and osteosarcoma, whereas an antiproliferative action of progesterone in endometrial cancer has been showed. It supports the hypothesis that progesterone actions are tissue specific.

Investigators have found the expression of all sex steroid receptors consist of estrogen receptor (ERα and ERβ), PR, and androgen receptor in lung tissue. It is well documented that sex steroids are involved in the pathogenesis of the lung disease.[138,139]

Estrogen promotes cell proliferation, and the transcription of estrogen responsive genes in NSCLC greater extent than nonneoplastic lung fibroblasts[140,141] as fulvestrant a known ER antagonist and downregulator of ERα can inhibit estrogen stimulated growth of NSCLC tumor xenografts grown in immunosuppressed mice.[142]

In addition, the aromatase enzyme is expressed in lung tissue, and its expression is significantly higher in metastatic cells than in primary cancer cells, which have been reported in tumor tissues obtained from both male and female NSCLC lung cancer patients. It is associated with high intratumoral concentrations of estrogens in lung cancer.[143]

There are contradictory data about the effects of progesterone in lung tumors; some studies indicate that low PR expression is associated with poor prognosis in NSCLC patients against; the additional studies demonstrate that both estrogen and progesterone in NSCLC cells increase the proliferation of endothelial cells by promoting expression of VEGF in the lung tumor bed and lung cancer growth and development.[144]

4.3.6 | The insulin and IGF system

The IGF system includes 3 peptides insulin—IGF-1, IGF-2 (each with its receptor besides), and IGF-binding proteins (IGFBPs)—and among these, insulin receptor and the IGF-1 receptor (IGF1R) are overstimulated in obesity.[145] The IGF-1 is produced in liver and mediated indirect effects of growth hormone on skeletal and visceral growth in fetal and postnatal period, whereas IGF-2 is a fetal growth factor. The IGFs are similar with insulin in structure and function, so they could bind with each other receptors. The IGF-1 via stimulation of proliferation, differentiation, and protein synthesis promotes its growth effect. The IGF-2 is more mitogenic than IGF-1 and is often expressed in tumors. Despite other protein/peptide hormones, IGFs bind with binding proteins (IGFBPs). Six IGFBPs have been known with different characteristic and functions, in which IGFBP3 is the predominant one circulating in serum. They are produced by the liver and enhance the half-life of the IGFs,[8,77,146] which is shown in Figure 2.

Hyperinsulinemia is associated with lower IGFBP production (particularly IGFBP3 that is upregulated by p53 and is an apoptosis promoter) and increased levels of free IGFs and receptors overstimulation lead to promoting cell growth and inhibiting apoptosis.[146]

Binding of insulin or IGFs with their related receptors are consisting α and β subunits. The β subunit possesses tyrosine kinase activity that leads to autophosphorylation, insulin receptor substrates recruitment, and activation of 2 major mitogenic signaling pathways

MAPK and metabolic and antiapoptotic PI3K pathway. Antiapoptotic effect of PI3K pathway is exerted through activation of AKt and AKt in turn activates mammalian target of rapamycin (mTOR) signaling. The process results in protein synthesis, cell growth, and promotion of cells for mitosis that all mechanisms favor tumor growth.[145,147,148]

The mTOR regulation is controlled by phosphatase and tensin homolog (PTEN), a tumor suppressor and tumor suppressor gene products tuberous sclerosis (TSC) TSC-1 and TSC-2. Signaling pathways such as PI3K, MAPK, AMPK, and hypoxia constituent input to TSC-1 and TSC-2.[147] Aforementioned mechanisms for the link between obesity and cancer are summarized in Figure 2.

4.4 | Metabolism and cancer

Metabolic reprograming profiles have been seen in many human cancers. Because cancer cells have common phenotype of uncontrolled, unlimited cell proliferation, they tend to have excess of total biomass (lipids, nucleic acid, and proteins).[149] In contrast to normal cells, most cancer cells rely on aerobic glycolysis (this is glycolysis taking place in presence of enough oxygen) instead of mitochondrial oxidative phosphorylation to supply energy for cellular processes. Exacerbated glucose uptake and glycolysis utilization leading to lactate production (termed Warburg effect) is the first step metabolism rewiring in transformed cells.[150] Alteration in lipid metabolic enzymes and the pathways involved in generation of lipid membrane plays a pivotal role in cancer-associated metabolic reprogramming.[151] Lipid components could provide energy for cancer cells in deprived conditions.[152] Steps of Warburg effect are shown in Figure 3.

Many studies have indicated that tumor cells synthesize free fatty acids and phospholipid using a de novo pathway. Interestingly, integrated studies of gene-expression data have discovered upregulated transcripts required in de novo lipogenesis and cholesterol synthesis pathways in cancer cells. Acetyl-CoA carboxylase (ACC), fatty acid synthase, and ATP citrate lyase (ACLY) that are involved in lipogenesis are highly expressed in many cancer cells such as breast and prostate tumors.[153,154] Further evidence have pointed out other enzymes involved in cholesterol related pathways (uptake, synthesis and storage) and fatty acid oxidation that are overexpressed in malignant tumors.[155] Carnitine palmitoyltransferase 1 isoform A and C (CPT1A and C) as fatty acid oxidation–limiting enzyme are upregulated in many cancers. Upregulation of CPT1C preserves tumor cells from death by hypoxia and hypoglycemia.[156] In this condition, the cells show an enhanced concentration of AMP. High concentration of AMP leads to activation of AMPK, a master metabolic regulator that upregulates CPT1C. For this reason, CPT1 knockdown might make radiotherapy and apoptosis inducer treatments more effective.[157] In low-energy status such as insulin resistance, there is a decreased uptake of glucose, and cells show an enhanced concentration of AMP. This leads to activation of AMPK, which is controlled by the tumor suppressor gene liver kinase B1 (LKB1). The AMPK can modulate anabolic and proliferative pathways including the PI3K/Akt/mTOR and glucose uptake.[158–160]

Some of tumors such as pancreatic tumors have specific alterations in their metabolic pathways especially in production of lipid messengers (phosphatidylinositol, PIs), lipid mediators (leukotrienes), and structural lipid (glycosphingolipids). Lipogenic tumors share a common phospholipid membrane phenotype such as significant increase in membrane phosphatidyl choline and phosphatidylethanolamine. However, phosphatidylcholine content is composed of saturated fatty acids, which is correlated with reduction of membrane fluidity and dynamics and causes chemotherapy resistance.[161]

Lipids can act as signaling molecules and reinforce cancer cell proliferation, angiogenesis, migration, and survival through binding to G-proteins coupled receptors.[151,152] Among these molecule, phosphatidylinositol-triphosphate (known as PI3P) are the most important that act as a second messenger and has a major role in transmission of signals to the cellular machinery.[153,154] This molecule is produced

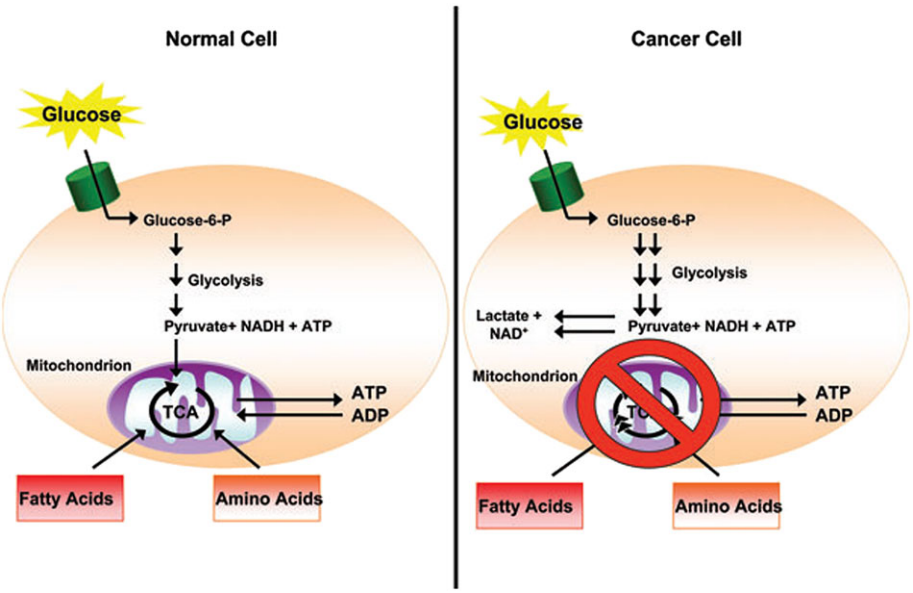

FIGURE 3 Warburg effect in cancer cells: in normal cells, aerobic glycolysis implies the conversion of glucose via pyruvate into acetyl-CoA and its complete oxidation (through tricarboxylic acid [TCA] cycle and oxidative phosphorylation) to CO_2 and H_2O (which generates 38 ATP molecules per molecule of glucose). In contrast, in tumor cells, aerobic glycolysis is overactivated instead of mitochondrial oxidative phosphorylation to supply energy for cellular processes[152]

in response to growth factor signaling. Then PI3P mediates activation of AKT that finally activates mTORs. This signaling pathway known as PI3K/AKT/mTORs, which is overactivated in cancer cells and inhibits cell death, increase cancer cell survival and proliferation. This pathway has a natural inhibitor termed PTEN, which is mutated or deleted in cancer. The PTEN dephosphorylates PI3P to PI2P which limit ability of AKTs to bind to membrane.[161,162] Glucose metabolism and growth control pathways PI3K/Akt/mTOR are tightly linked in proliferating cells as in some experimental studies have been shown that diet-induced obesity leads to activation of Akt and mTOR in a variety of epithelial tissues.[163–165]

Migration of cancer cells is one of the prominent hallmarks of metastatic cancers. Moving tumor cells require to home and are able to proliferate in the respective tissue.[166] Recent studies revealed the relationship between lipid metabolism and metastasis formation. Omentum, an abdominal fat pad, is a first-target tissue for the ovarian metastatic tumor cells. Omental adipocytes through the induction and secretion of adipokines improve the ovarian cancer cell metastasis.[167] In addition, studies demonstrated that ovarian cancer cells could provide energy for tumor growth by augmentation of lipolysis within adipocyte and using adipocyte-derived lipids for β-oxidation.[168,169] Fatty acid binding protein 4 has a main role in coupling of energy between metastatic tumor cells and their surrounding adipocytes.[170] The same results have been reported in the cases of prostate and breast cancers.[171,172]

Recent studies revealed that chemokines and signaling lipids such as diacylglycerols, lipoprotein A, and prostaglandins could induce cell migration. Overexpression of monoacylglycerol lipase, a lipase released free fatty acid from triacylglycerol, was shown in highly aggressive tumors and its inhibition disturbed cancer cell migration.[173] Interestingly, the results shown that knockdown of monoacylglycerol lipase led to inhibit tumor growth and invasion, but the exogenous addition of saturated fatty acid through diet remade the invasion ability of these cells.[174] Other results demonstrate that diet-derived lipids by altering insulin and IGF-1 levels could affect cancer cells. However, we need more detailed studies to clarify whether selective reduction of fat in diet is more effective in cancer treatment.[175]

Cancer metabolism has now been accepted as an effective part involved in advent and progression of cancer. In this regards, lipid metabolism is considered as new and potential target for anticancer therapy. Down regulation of rate-limiting enzyme involved in lipogenesis such as FAS, ACC, and ACLY by siRNA expression or chemical inhibition reduced cancer progression.[176,177] Additionally, uses of statins that are commonly prescribe for cardiovascular disease can improve efficacy of chemotherapy.[178,179] Recent research demonstrated that metformin, an antidiabetic drug associated with reduction of insulin resistance, inhibits transformation of cells. Patients used this drug has shown an increased tumor response to chemotherapy especially in the case of breast cancer. This effect of metformin may be free from blood glucose levels. It appears that anticancer effect of metformin is through inhibiting mitochondrial complex I in the liver, interfere with ATP production , then induced energy stress and apoptosis. Although there are many studies, it still remains unclear whether metformin acts directly on tumor by promoting apoptosis or acts indirectly by decreasing insulin levels and insulin-related growth factor.[180,181]

5 | CONCLUSION

Regarding continued growth of the overweight and obese population worldwide and its association with several cancer types including of breast and pancreas, this review describes underlying mechanisms, in particular metabolism modification, that occurs in obesity setting and thereby promotes cancer development. Thus, the adoption of preventive strategies to obese persons is essential to reduce cancer incidence. Furthermore, investing on research in this challenging field is noteworthy to discover new therapeutic targets against cancer in a more and more efficient manner to help cancer patients and improve their quality of life.

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