Obesity and Breast Cancer: Molecular and Epidemiological Evidence

Nehad M. Ayoub[1,*] and Amal Kaddoumi[2]

[1]*Department of Clinical Pharmacy, Faculty of Pharmacy, Jordan University of Science and Technology, Irbid 22110, Jordan*

[2]*Department of Basic Pharmaceutical Sciences, School of Pharmacy, University of Louisiana at Monroe, Monroe, Louisiana 71201, USA*

Abstract: Carcinoma of the breast is a leading cause of cancer deaths among women world-wide. Obesity is recognized as a well-established risk factor for epithelial tumors including the mammary epithelium. Adipose tissue is considered to be metabolically active organ with the ability to secrete a wide range of biologically active adipokines. Multiple studies have evaluated the potential mechanisms correlating obesity to increased risk of breast cancer. Altered circulating levels of adipokines or changed adipokine signaling pathways are now increasingly recognized to be associated with breast cancer development and progression. Leptin and adiponectin were the main adipokines that have been investigated in the context of breast cancer in both preclinical and epidemiological studies. Obesity is also believed to promote inflammatory response and induce activity of key enzymes like aromatase, leading to higher risk of breast cancer development. The goal of this review is to provide recent insights into the potential molecular mechanisms linking adipokines to the etiopathogenesis of breast cancer including recently identified adipokines and trying to correlate these molecular mechanisms to more established metabolic and hormonal dysregulations of obesity. A better understanding of the interplay between adipokines and other deregulated mechanisms in obesity is important for the development of preventive strategies with therapeutic potential against breast cancer in obese patients.

Keywords: Adipokines, Obesity, Leptin, Adiponectin, Visfatin, Inflammation.

INTRODUCTION

Breast cancer remains the leading cause of cancer deaths reported in women between 20 to 59 years of age [1]. In United States, breast cancer alone is expected to account for 29% of all new cancers among women in 2014 [1]. Despite progress in breast cancer detection and treatment, incidence rates of the disease remained relatively unchanged since the year 2003 [1]. Breast cancer is a heterogeneous disease with various pathological and molecular subtypes [2, 3]. Approximately 60–70% of breast cancers express estrogen receptors (ER) and/or progesterone receptors (PR). About 20–30% of breast cancers have amplified levels of human epidermal growth factor receptor 2 (HER2). However, in approximately 15–20% of patients with breast cancer, the tumors do not express ER or PR and do not have amplification of HER2, these tumors commonly known as triple negative breast cancers [4]. Several factors can influence the development, treatment, and survival of patients with breast cancer [5, 6]. It is well-established that tumor stage, grade, age at diagnosis, hormone receptor status, genomic factors, race, and comorbidities can influence outcome in patients with breast cancer [7]. In addition, multiple modifiable lifestyle factors have been proposed to correlate with risk of development as well as outcomes in breast cancer patients [7, 8]. Obesity is a global health problem. It is characterized as an excess of adipose tissue and defined by a body mass index (BMI) greater than 30 in most reports [3, 9-11]. At present, obesity is an established risk factor for epithelial cancers [12]. Recent epidemiological and clinical data confirmed that obesity is associated with increased breast cancer risk, development of more aggressive breast tumors, and resistance to certain anti-breast cancer treatments [13-16]. Additionally, many studies have established that obesity is correlated with poor survival and high chance of recurrence [6, 11, 15-22].

Multiple epidemiological studies have evaluated the impact of obesity on breast cancer patients. However, epidemiological findings of the effect of obesity on breast cancer risk and characteristics were inconsistent. High BMI was significantly associated with larger tumor size in both pre- and postmenopausal women [23]. In addition, a high BMI was significantly correlated with nodal stage, axillary lymph node ratio, ER positivity, PR positivity, and menopausal status at diagnosis [24-26]. Higher BMI was associated with worse pathological complete response to neoadjuvant chemotherapy in postmenopausal patients with breast cancer [27]. Although the effect of obesity is less clear for premenopausal women, obesity was associated

*Address correspondence to this author at the Department of Clinical Pharmacy, Faculty of Pharmacy, Jordan University of Science and Technology, Irbid 22110, Jordan; Tel: +962-2-7201000, Ext. 23809; Fax: +962-2-7201075; E-mail: nmayoub@just.edu.jo

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with ER and PR negative tumors and poor overall survival in premenopausal women with breast cancer [28]. Obese premenopausal women showed worse histopathologic features compared to under/normal weight group [23, 29]. Alternatively, a meta-analysis by Cheraghi and colleagues showed no significant effect of BMI on the incidence of breast cancer during premenopausal period [30]. The value of anthropometric measures in correlation with risk of breast cancer was evaluated in multiple studies in the literature. Waist circumference, waist-to-hip ratio, and hip circumference were evaluated for correlations with circulating levels of estradiol, testosterone, and sex hormone-binding globulin. All anthropometric measures were positively associated with estrogens and free testosterone, and negatively with sex hormone-binding globulin independently of BMI [31]. Further analysis showed that among postmenopausal women, the risk of ER-positive/PR-positive breast cancer increased with increasing weight, BMI, and both hip and waist circumference, however no association was seen with ER-negative/PR-negative breast cancers [32]. Further evaluation of anthropometric measures and hormone receptor status showed BMI, waist circumference, and waist-to-hip ratio may not be good predictors of steroid receptor status in breast malignancies in either pre- or postmenopausal women [33]. Recent evidence shows that adipose tissue is metabolically active [16, 34, 35]. Adipose tissue secretes adipokines, cytokines, growth factors, and inflammatory mediators. There is a growing interest in the possibility that humoral factors released by adipose tissue, or fat, might promote epithelial cancers [34, 36]. Although it is fairly well-established that obesity is an important risk factor for breast cancer, the exact molecular mechanisms of such association are recently the topic of discussion in medical literature.

The goal of the current review is to summarize recent findings regarding the molecular and cellular mechanisms correlating obesity to increased risk or aggressiveness of breast cancer altogether with related epidemiological findings. In particular, this review will focus on the role of adipokines, insulin, insulin-like growth factor, aromatase, and inflammation in an attempt to find potential crosstalk between these

Table 1: Adipokines in Breast Cancer

Adipokine	Description	Obesity-induced alteration in circulating levels	Downstream signaling	Association with breast cancer
Leptin	A 16 kDa protein. Leptin is a peptide containing 146 amino-acids was discovered in 1994. It is mostly secreted from adipose tissue and involved in regulation of body weight and body fat mass.	Elevated/unchanged	JAK/STAT, MAPK, PI3K	Leptin correlates with higher tumor grade and worse prognosis.
Adiponectin	It comprises 244 amino acids that represent a full 30 kDa-long protein. Adiponectin is encoded on human chromosome 3q27.	Decreased	AMPK, PI3K, STAT, mTOR, NF-κB	Hypoadiponectinemia is associated with increased risk of breast cancers of aggressive phenotype, large primary tumor size, and high histologic grade.
Visfatin	Visfatin is a protein of 471 amino acids and 52 kDa. It was originally discovered in liver, bone marrow, and muscle. A specific receptor for visfatin has not been identified yet.	Elevated	Cyclin D1, cdk2, Notch1, MMP-2, VEGF	Visfatin is associated with aggressive pathological and molecular features, such as ER negativity, HER2-enriched, and basal-like phenotypes.
Resistin	Resistin was discovered in 2001. It is considered a pro-inflammatory factor responsible for resistance to insulin.	Elevated	PI3K, MAPK, NF-κB, MMP-2	High resistin expression in breast cancer tissues correlated with tumor stage, tumor size, lymph node metastasis and ER status.
Hepatocyte Growth Factor (HGF)	Mature active HGF is a heterodimer composed of α-chain and β-chain linked by a disulfide bond. α-chain subunit contains an N-terminal hairpin domain and four kringle domains. β-chain subunit is a serine-protease-like domain lacking catalytic activity.	Elevated	MAPK, PI3K, Akt, MMP, NF-κB	Overexpression of HGF and its receptor correlates with triple-negative and basal type tumors, and are strong predictors of decreased survival in breast cancer.

Abbreviations: JAK, janus kinase; STAT, signal transducer and activator of transcription; MAPK, mitogen-activated protein kinase, PI3K, phosphatidylinositol 3-kinase; AMPK, 5′ adenosine monophosphate-activated protein kinase; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; VEGF, vascular endothelial growth factor; MMP, matrix metalloproteinase; cdk2, cyclin-dependent kinase 2; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2.

pathways in order to explain the role of obesity in breast cancer development and progression. In addition, the review will identify potential therapeutic targets to decrease the risk of development of breast cancer in obese female population.

1. ADIPOKINES

Adipokines refer to proteins secreted from adipocytes [37]. Adipokines exert activity through binding to their receptors in target organs [37]. Obesity can influence levels and function of a variety of adipokines. The following part will review adipokines known to correlate with breast cancer, focusing on relevant molecular and cellular mechanisms, epidemiological findings, and potential for therapeutic targeting in obese breast cancer patients. Table **1** summarizes adipokines mostly evaluated in the context of obesity-mediated breast carcinoma.

1.1. Leptin

One of the mechanisms by which obesity is now thought to contribute to breast cancer is through the increased levels of leptin [3, 5, 20]. Leptin is a 16 kDa protein which has a critical role on regulation of body weight and fat mass [38]. Leptin is an adipose-tissue derived signaling molecule and is overexpressed in breast cancer, particularly in high-grade tumors [5, 39]. Leptin levels in humans correlate with adiposity [14]. Leptin action is mediated through the transmembrane leptin receptor, ObR [5, 14, 20]. Leptin receptor is a member of the class I cytokine receptor super-family [40]. The major pathways activated by ObR are the classic cytokine Janus kinase (JAK)/signal transducer and activator of transcription (STAT) signal transduction pathway, mitogen-activated protein kinase (MAPK) signaling cascade, and the phosphatidylinositol 3-kinase (PI3K) pathway [5, 14, 20]. These pathways are often associated with tumor formation due to their involvement in cell proliferation and apoptosis [5, 14, 20]. In addition, leptin is a positive regulator of the vascular endothelial growth factor (VEGF) [41]. The role of leptin in breast cancer has been substantiated by the fact that breast tumors, but not normal mammary epithelium, overexpress both leptin and ObR, and the leptin/ObR system correlates with higher tumor grade and worse prognosis [14]. Several studies have examined the molecular mechanisms mediating leptin effects on breast cancer cell growth. Data from *in vitro* studies showed that leptin induced expression of tissue factor in a dose-dependent manner in MCF-7 human mammary cancer cells [42]. Tissue factor is implicated in cancer progression. This effect of leptin was mediated through its receptor, ObR [42]. Further investigations showed that leptin enhanced tolemerase activity in MCF-7 breast cancer cells in a dose-dependent fashion [43]. Recently, Khanal and colleagues showed that leptin induced CYP1B1 protein, mRNA expression, and promoter activity in ERα-positive MCF-7 cells but not in ERα-negative MDA-MB-231 breast cancer cells [44]. In the same study, exposure to leptin increased 4-hydroxyoestradiol levels in MCF-7 cells suggesting that leptin can promote growth of ER-positive breast cancer cells [44]. In addition to promoting growth of ER-positive breast cancer cells, *in vitro* studies indicated that leptin interferes with the action of tamoxifen in MCF-7 cells, at least partly, through inducing increased nuclear expression of ERα [45]. Exposure to leptin induced overexpression of leptin, ObR, ER, and aromatase mRNA in ER-positive MCF-7 and T47D breast cancer cells *in vitro* [46]. In a murine model of breast cancer, estrogen exposure increased leptin secretion [47]. Interestingly, recent evidence showed that leptin may exert its activity not only through ObR, but also through crosstalk with other signaling systems including ER, HER2, VEGF receptor, Notch signaling axis, and Wnt/β-catenin pathways [14, 48, 49].

Common genetic variations in leptin and leptin receptor genes have been considered to be implicated in the development of breast cancer [50, 51]. The leptin promoter polymorphism Lep-2548G/A can be associated with increased leptin secretion by adipocytes and elevated cancer risk [52]. In addition, the occurrence of Lep-2548G/A can enhance leptin expression in breast cancer cells and possibly contribute to intratumoral leptin overexpression [52]. Recently, the effect of ObR Q223R polymorphism on breast cancer susceptibly in a sample of Iranian subjects was evaluated [40]. The genotypes QQ, QR, and RR distributions were 25, 56, and 19% in breast cancer cases and 54, 40, and 6% in controls, respectively. Findings showed a significant association between Q223R genotypes and increased breast cancer risk as well as tumor grade in a sample of Iranian breast cancer patients as compared to controls [40]. Clinical attempts to relate the levels of leptin in serum or plasma to breast cancer risk produced conflicting results [53-55]. While some studies have shown leptin to be increased in women with breast cancer, others have found leptin to be decreased or unchanged [56]. More research is needed to elucidate the potential value of circulating leptin levels in

correlation to breast cancer risk and development. Circulating levels of leptin alone may have low prognositic value. It might be more informative to consider the circulating value of leptin together with other important adipokines in circulation instead of leptin alone.

Considering its potential implication in breast cancer risk and progression, targeting leptin has been recently evaluated in multiple studies. In ER-positive MCF-7 cells, the antidiabetic thiazolidinediones inhibited leptin gene expression through ligand activation of the peroxisome proliferator-activated receptor-γ (PPARγ), and exerted antiproliferative and apoptotic effects on breast carcinoma [57]. Activation of PPARγ prevented the development of leptin-induced MCF-7 tumor xenografts *in vivo*. In addition, PPARγ ligands inhibited leptin signaling mediated by MAPK/STAT3/Akt phosphorylation and counteracted leptin stimulatory effect on estrogen signaling in breast cancer cells [58]. Alternatively, others have reported that treatment of MDA-MB-231 and MCF-7 breast cancer cells with ciglitazone and GW1929, PPARγ agonists, has rather elevated the expression of leptin and increased cell viability and migration [41]. Leptin enhanced the expression of a chaperone protein Hsp90 resulting in increased HER2 protein levels. Silencing of Hsp90 gene expression by RNA interference abrogated leptin-mediated HER2 up-regulation. Leptin effects were dependent on JAK2/STAT3 activation [57]. Thus, the effect of PPARγ agonists on leptin signaling needs further examination in cell culture and animal models before strong conclusions of potential therapeutic activity can be made. Leptin, ObR, and their downstream substrates represent attractive targets in management of obese breast cancer patients.

1.2. Adiponectin

Obesity leads to decreased production of the peptide adiponectin [14]. Adiponectin comprises 244 amino acids composing a 30 kDa-long protein [59]. Adiponectin circulates in the plasma at concentrations that correlate inversely with BMI [35, 53, 60]. Full-length adiponectin exists in three forms in human serum as low molecular weight trimer, middle molecular weight hexamer, and high molecular weight multimer [59]. Three adiponectin receptors are currently identified. AdipoR1 and AdipoR2 have distinct affinities for the various circulating forms of adiponectin and consist of seven transmembrane regions. The third known receptor capable of binding adiponectin is T-cadherin which is located on the cellular surfaces of endothelial, epithelial, and smooth muscle cells [59]. Numerous signaling pathways are utilized by adiponectin in physiological responses. Adiponectin exerts its effects *via* 5′ adenosine monophosphate-activated protein kinase (AMPK), mammalian target of rapamycin (mTOR), PI3K/Akt, MAPK, STAT, nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), and the sphingolipid metabolic pathway [59]. *In vitro* assays studying the effect of adiponectin on cell proliferation have found an inhibitory role of adiponectin in mammary tumor growth [16]. Adiponectin may act directly on breast cancer cells by inhibiting proliferation and angiogenesis or by stimulating apoptosis [35]. Exposure to physiological concentrations of adiponectin was significantly associated with suppression of MDA-MB-231 breast cancer cell proliferation, while prolonged adiponectin treatment caused apoptosis of these cells [61, 62]. Adiponectin increases expression of tumor suppressor LKB1 in MCF-7 and T47D cells [63]. LKB1 is a serine/threonine protein kinase which has recently been identified as a critical upstream kinase for AMPK regulating its activity [63]. Further studies showed that apoptotic activity of adiponectin was mediated by enhanced expression of pro-apoptotic genes Bax and p53 [64]. Additional experiments *in vivo* suggested that the reduced mammary tumorigenesis of MDA-MB-231 cells in female nude mice by adiponectin was attributed to inhibition of the glycogen synthase kinase-3β/β-catenin signaling pathway [62]. Further *in vivo* studies in transgenic mice models showed that reduced or complete loss of adiponectin expression promotes mammary tumor development [65].

In normal breast tissue, plasma estradiol negatively correlated with local extracellular adiponectin levels and positively correlated with leptin and leptin:adiponectin ratio [47]. In postmenopausal women, tamoxifen treatment for six weeks increased adiponectin and decreased leptin and the leptin:adiponectin ratio [47]. In patients with breast cancer, extracellular leptin was higher and adiponectin was lower in tumors than in normal adjacent breast tissue [47]. In addition, multiple epidemiological studies showed that hypoadiponectinemia is associated with increased risk of development of breast cancers characterized by an aggressive phenotype, large primary tumor size, high histologic grade, and an increased propensity for metastasis to the regional lymph nodes [66-69]. Adiponectin plasma levels were also positively correlated with antioxidant levels in breast cancer patients, however such correlation had no effect on either the metastatic behavior or disease

outcome [70]. Alternatively, Cubukcu and colleagues showed lack of correlation between expression levels of adiponectin detected by immunohistochemical staining and prognostic significance in patients with triple-negative breast cancer [71].

Pharmacogenetic studies showed that polymorphisms of the adiponectin pathway are associated with breast cancer risk. Multiple variants were associated with breast cancer risk in Caucasian, African American, and Hispanic populations [72]. Thus, interpretation of the relationship between circulating adiponectin levels and risk or prognosis of breast cancer needs confirmation and amplification with larger patient groups to permit classification based on molecular subtypes of breast cancer and consideration of patient ethnicity.

Pharmacological modulation of adiponectin might prove clinically beneficial, especially for the prevention or treatment of breast cancer in obese patients [35, 60]. ADP 355 is a peptidomimetic lead compound for pharmaceutical development to replace low adiponectin levels in cancer and other malignancies [60]. In several adiponectin receptor-positive cancer cell lines, ADP 355 restricted proliferation in a dose-dependent manner and modulated the key signaling pathways AMPK, Akt, STAT3, and ERK1/2 in an adiponectin-like manner *in vitro*. In addition, administration of ADP 355 suppressed the growth of orthotopic human breast cancer xenografts [60]. Investigations in the fields of cardiovascular and metabolic disorders revealed that multiple pharmacologic agents such as PPARγ agonists, α-agonists, some statins, renin-angiotensin-aldosterone system blockers, some calcium channel blockers, mineralocorticoid receptor blockers, and new β-blockers can increase adiponectin levels and suppress or prevent disease initiation or progression [73]. Therefore, the potential for pharmacological interventions to modulate adiponectin in favor for management of obesity and decreased breast cancer risk in women is growing and requires further investigations.

1.3. Visfatin

Visfatin, also known as nicotinamide phosphoribosyltransferase, has recently been established as a novel adipokine that is highly enriched in visceral fat. Visfatin is a protein of approximately 471 amino acids and 52 kDa [74]. Visfatin exerts pleiotropic effects acting as a cytokine, a growth factor, and an enzyme found in visceral fat [75]. It plays an important role in variety of metabolic and stress responses as well as in the cellular energy metabolism [75, 76]. Data from *in vitro* and *in vivo* experiments indicated that higher visfatin levels are associated with aggressive pathological and molecular features, such as ER negativity, HER2-enriched, and basal-like phenotypes [77]. Visfatin exhibits proliferative, anti-apoptotic, pro-inflammatory and pro-angiogenic properties. Overexpression of visfatin in mammary epithelial cells induced epithelial-to-mesenchymal transition (EMT), a morphological and functional switch leading to increased metastatic potential of cancer cells [77]. In addition, visfatin induced Notch1 expression in MDA-MB-231 breast cancer cell line as well as in non-transformed MCF10A mammary epithelial cells [78]. Visfatin depletion reduced Notch1 mRNA and protein levels and attenuated breast cancer cell growth both *in vitro* and *in vivo* [78]. Exogenous administration of recombinant visfatin increased cell proliferation and DNA synthesis rate in MCF-7 cells. Exposure to visfatin activated G1-S phase cell cycle progression by upregulation of cyclin D1 and cyclin-dependent kinase 2 (cdk2) expression. In addition, visfatin increased the expression of matrix metalloproteinases-2 and VEGF genes, suggesting potential impact in metastasis and angiogenesis of breast cancer [75].

Circulating visfatin levels are increased in obese women [79]. Also, visfatin levels are significantly elevated in postmenopausal breast cancer patients than in healthy controls independently from known risk factors of breast cancer [80]. Further data from clinical studies showed that high visfatin expression in breast cancer tissues was significantly correlated with tumor size, ER negativity, and PR negativity [76].

Pharmacologic agents that neutralize visfatin biochemically or medications that decrease its levels or suppress signaling pathways downstream of visfatin may demonstrate to be useful anti-cancer agents [81]. In this context, curcumin treatment resulted in reduced mRNA and protein levels of visfatin in MDA-MB-231, MDA-MB-468, and MCF-7 breast cancer cell lines associated with decreased activity of constitutive NF-κB [82]. The combination of a visfatin small molecule inhibitor, FK866, with olaparib, a poly(ADP-ribose) polymerase (PARP) inhibitor, suppressed triple-negative breast tumor growth *in vivo* to a greater extent than either single agent alone providing new insights to targeting triple-negative breast cancer [83].

1.4. Resistin

Adipokine resistin is a member of the newly discovered family of cysteine-rich protein [84]. It is a

peptide and is also known as adipose tissue-specific secretory factor or C/EBP-epsilon-regulated myeloid-specific secreted cysteine-rich protein (XCP1) [85]. In circulation, resistin exists in two states, the high-molecular-mass hexamer that has a higher concentration and the low-molecular-mass complex which is more bioactive [86]. Resistin is linked to obesity, insulin resistance, and breast cancer [87]. Lee and colleagues reported high resistin expression was predominantly observed in breast cancer tissues but not the adjacent normal breast tissues [88]. High resistin expression in breast cancer tissues was correlated significantly with tumor stage, tumor size, lymph node metastasis and ER status [88]. *In vitro* findings to explain the potential mechanisms of procarcinogenic activity in breast cancer models are very limited. However, studies on other models of epithelial tumors indicated that resistin can increase matrix metalloproteinase-2 expression [89], activate MAPK and NF-κB pathways [90], and stimulate PI3K/Akt phosphorylation [91]. Multiple epidemiological studies indicated that breast cancer patients have elevated resistin concentrations as compared with control subjects [84, 87, 92, 93]. Resistin was expressed more than four times higher in breast tumors of African American patients compared to tumors from Caucasian Americans [87]. Amplified resistin expression was reported to correlate with insulin-resistant and obesity in African American breast cancer patients [87]. In addition, postmenopausal breast cancer patients showed significantly higher serum resistin levels than in control participants [92]. In these patients, resistin levels correlated significantly with tumor markers and inflammatory parameters, but not with metabolic and anthropometric variables [92]. Hou and colleagues evaluated blood levels of a panel of adipokines in newly diagnosed breast cancer patients [66]. Results indicated that decreased serum adiponectin levels and increased serum resistin and leptin levels are risk factors of breast cancer [66]. Similarly, low serum adiponectin levels and high resistin levels have been linked with increased breast cancer risk in a cohort of Korean women [94]. Thus, further evaluation of resistin pro-carcinogenic mechanisms in breast cancer and its potential correlation to other circulating adipokines is needed.

1.5. Hepatocyte Growth Factor (HGF)

Hepatocyte growth factor (HGF), also known as scatter factor, is a multifunctional growth factor known to act as a mitogen and morphogen for a variety of cells [95]. HGF belongs to the plasminogen-related growth factor family and comprises a 69 kDa α-chain and a 34 kDa β-chain [96, 97]. Met receptor tyrosine kinase is a high affinity receptor for HGF encoded by Met proto-oncogene [95, 98]. HGF is widely expressed in different tissues and mainly produced by mesenchymal and stromal cells [99]. HGF is secreted by adipocytes and adipose stromal cells qualifies it as an adipokine [100, 101]. Supporting evidence showed that circulating HGF levels has been found to be elevated in obese individuals than in those of normal body size [102, 103]. Deregulated HGF/Met signaling axis is associated with increased angiogenesis, tumorigenesis, invasiveness, and metastasis in numerous solid human tumors, including the breast [98, 104]. The biological functions of HGF/Met axis are mediated through a variety of downstream effectors including RAS-MAPK and PI3K/Akt/NF-κB [105, 106]. Met signaling also promotes breast cancer cell migration and invasion through upregulation of matrix metalloproteinases [106]. Overexpression of HGF and/or Met in breast carcinoma correlates with triple-negative and basal type tumors, and are strong independent predictors of decreased survival [98]. Sundaram and colleagues showed that obesity was associated with increased secretion of HGF in a murine model of basal-like breast cancer [107]. Further studies showed that weight loss significantly blunted the obesity-induced HGF/Met pathway and improved several metabolic risk factors associated with basal breast cancer in obese animal model [108, 109]. Thus, understanding correlation between obesity and HGF/Met signaling pathway may improve the understanding of driving factors for this invasive type of breast cancer and provide potential for prevention of obesity-driven tumor progression.

2. INSULIN

Obesity is associated with high levels of circulating insulin. Insulin has been shown to stimulate cell proliferation in human breast cancer cell lines and to enhance breast tumor growth in animal models [5, 20]. Insulin stimulates proliferation by mechanisms that utilize the PI3K or MAPK/Akt signaling pathways; in addition, it increases cell survival and invasive capacity [55]. In MCF-7 breast cancer cells, insulin increased proliferation through activation of JNK and ERK [110]. Interestingly, *in vitro* studies using MDA-MB-231 cells showed that insulin stimulated leptin mRNA and protein expression, which was associated with increased activation of the leptin gene promoter [111]. Inhibition of ERK1/2 and PI3K pathways decreased insulin-dependent leptin mRNA and protein expression in

MDA-MB-231 cells [111]. Further *in vitro* studies showed that ObR mRNA was induced by insulin in MCF-7 and MDA-MB-231 cancer cells [112].

Obesity and the Metabolic Syndrome are associated with multiple factors that may cause an increased risk for cancer and cancer-related mortality including hyperinsulinemia, hyperglycemia, and hyperlipidemia [113-115]. Insulin resistance is associated with alterations in the levels of pro-inflammatory cytokines, chemokines, and adipokines that may contribute to breast cancer risk [113]. Several previous studies examined the relationship between metabolic syndrome and insulin resistance and prognostic factors of breast cancer in breast cancer patients. In postmenopausal patients, Can and colleagues found no significant difference in the prognostic values of breast cancer between patients with and without metabolic syndrome [116]. Alternatively, a study of a cohort of Italian women indicated that in ER-positive/PR-positive patients, high blood glucose and high BMI are independently associated with increased risk of breast cancer death [117]. High insulin levels were associated with low circulating adiponectin levels, which were associated with obesity and increased mortality in breast cancer patients [118]. In addition, high fasting serum glucose levels have been associated with an increased breast cancer risk in both premenopausal and postmenopausal women [119]. The use of antidiabetic drugs may offer a new therapeutic approach for breast carcinoma that develops in the context of adiposity [120]. Metformin, a commonly used diabetes drug, appears to have potential effect on tumor cells which are mediated by activation of AMPK with downstream inhibition of mTOR [121]. Metformin suppressed obesity-induced secretion of adipokines as well as adipocyte-induced breast cancer proliferation *in vitro* [19]. In highlight for the role of insulin and hyperinsulinemia in progression and risk of breast cancer, further experiments are warranted to verify therapeutic potential for metformin and other antidiabetic treatments in obese patients with risk of breast cancer.

3. INSULIN-LIKE GROWTH FACTOR (IGF)

Another obesity-related signaling pathway which may contribute to breast cancer is insulin-like growth factor (IGF), especially IGF-1. IGF signaling system is involved in breast cancer initiation and progression [122]. Obesity is known to increase circulating IGF-1 which has been linked to tumor cell growth and survival [5, 20]. Recent evidence showed obesity enhanced tumor promotion during epithelial carcinogenesis, in part, due to altered IGF-1 receptor/epidermal growth factor (EGF) receptor crosstalk and downstream signaling to effectors such as Akt/mTOR leading to altered levels of cell-cycle proteins that favored enhanced epidermal proliferation during tumor promotion [12]. Moreover, *in vitro* studies showed that adipocytes from obese individuals displayed about twofold higher IGF-1 release than lean individuals. MCF-7 breast cancer cell growth was potentiated in a co-culture system of cancer cells and adipocytes [102]. In addition, IGF-1 induced migration of MCF-7 and MDA-MB-231 breast cancer cells *in vitro* [123]. Immunohistochemical analysis of breast tissue in patients diagnosed with invasive breast cancer showed that the expression of IGF-1 receptor and IGF-binding protein (IGFBP) to be associated with ER status [122]. ER-positive tumors were more likely to express IGFBP2, but less likely to express IGF-1 receptor and IGFBP3 [122]. In addition, IGFBP3 was positively correlated with BMI and premenopausal status [122]. A cooperative crosstalk between estrogens and insulin/IGF-1 signaling pathways plays a critical role in breast carcinogenesis, tumor cell proliferation, differentiation and survival [124]. A strong positive correlation between insulin as well as IGF-1 receptor and AdipoR1, but not AdipoR2, expression was observed in breast cancer tissue [125]. Remarkably, the insulin analogs glargine, detemir and lispro insulin showed proliferative effects that resemble IGF-1 action in multiple cancer cell lines, including the breast [126]. Glargine and detemir displayed an IGF-1-like anti-apoptotic activity. Glargine insulin induced phosphorylation of insulin receptor, IGF-1 receptor, ERK, and Akt [126]. Taken together, these findings support the need to evaluate multiple metabolic parameters for better assessment of the risk of development of breast cancer. Large-scale studies are recommended to analyze the interaction between hyperinsulinemia, hyperglycemia, high IGF-1 levels, and use of exogenous insulin products in obese diabetic patients as potential risk factors for breast cancer.

4. AROMATASE

Aromatase, a member of the cytochrome P450 superfamily, is the enzyme responsible for key steps in the synthesis of estrogens [127]. Aromatase is expressed in several tissues including adipose fibroblasts and breast tumors [127]. Obesity has been associated with abnormally high expression of the enzyme aromatase in the breast [127, 128]. After the

menopause, the major mechanism for the association with disease risk is elevated estrogen production by adipose tissue due to high levels of aromatase activity [55]. Inflammatory mediators regulate aromatase expression in the human breast as one mechanism whereby they increase the risk of breast cancer, especially in women who are obese [127, 129-131]. Recent epidemiological studies showed that aromatase inhibitors are less efficient at suppressing estradiol serum levels in obese compared with non-obese breast cancer patients [132]. In addition, serum leptin levels and waist-hip ratio may serve as potential prognostic markers in metastatic breast cancer patients treated with aromatase inhibitors [133]. Metformin is known to increase the activity of AMPK and was therefore hypothesized to inhibit aromatase expression in primary human breast adipose stromal cells suggesting that metformin would reduce the local production of estrogens within the breast of obese women [134].

5. INFLAMMATORY MEDIATORS

Obesity is now recognized to be an inflammatory condition [131, 135-137]. Cytokines, including interleukin-6 (IL-6), IL-10, lipocalin 2 were significantly higher in control obese and breast cancer group than their relevant lean controls [136]. Infiltrating macrophages support the growth of breast epithelial cells and vascular endothelial cells by producing a milieu of cytokines and growth factors including IL-6, IL-1β, TNFα, and cyclooxygenase-2 [130, 131]. This creates a microenvironment favorable to breast cancer growth and invasion [131]. In part, inflammation induces an increase in free radicals promoting oxidative stress and tumor development in obese persons. Therefore, obesity-related oxidative stress could be a direct trigger of neoplastic transformation in breast cancer cells [138]. In this regard, Subbaramaiah and colleagues suggested an obesity/inflammation/ aromatase axis in the mammary gland and visceral fat associated with increased risk of hormone receptor-positive breast cancer in obese postmenopausal women [139].

Figure **1** summarizes major factors altered by obesity and associated with increased risk of mammary tumor development and progression.

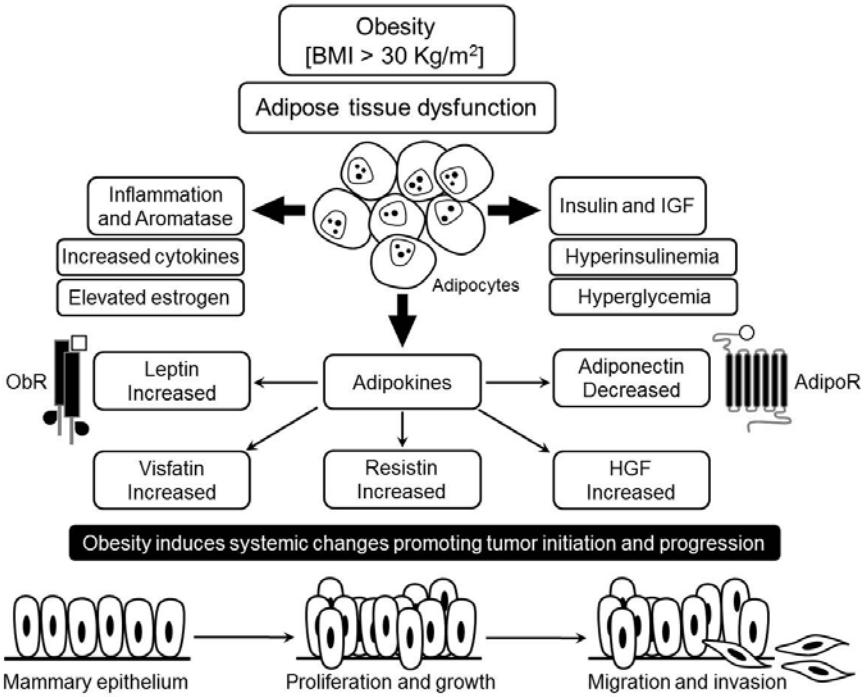

Figure 1: Obesity leads to altered function of adipocytes. Adipose tissue secretes increased amounts of inflammatory mediators and provides a source for aromatase leading to increased synthesis and circulating levels of estrogen. Additional systemic changes associated with obesity include hyperinsulinemia and increased levels of insulin-like growth factor (IGF). Obesity leads to altered adipokines profile secreted by adipocytes. Obesity causes elevated levels of circulating leptin, resistin, visfatin, and hepatocyte growth factor (HGF). Alternatively, obesity causes decreased levels of adiponectin. Altered adipokines profile is a well-established mechanism for the initiation and promotion for breast cancer. Obesity may also be associated with changes to leptin and adiponectin receptors, ObR, and AdipoR, respectively. These alterations mediated by obesity promote proliferation and growth of mammary epithelial tumors and causes increased risk of breast cancer development. Abbreviations: BMI, body mass index; IGF, insulin-like growth factor; HGF, hepatocyte growth factor; ObR, leptin receptor; AdipoR, adiponectin receptor.

CONCLUSIONS AND REMARKS

Although several potential mechanisms linking obesity and breast cancer have been proposed, the detailed molecular mechanism of obesity-mediated breast tumorigenesis has not yet been critically evaluated. Adipokines are receiving great attention for their potential correlation with breast cancer development and progression. Strong evidence from epidemiological studies indicated that obesity places female patients at higher risk of breast tumors regardless of menopausal status. Leptin correlated significantly with poor prognosis and resistance to breast cancer treatments. Alternatively, lower levels of adiponectin were associated with greater risk of breast cancer according to clinical findings in multiple patient populations. However, taking into consideration the endocrine nature of adipose tissue, deregulations in leptin and adiponectin may not occur in separation of other adipokines that are potentially secreted by adipocytes. A comprehensive evaluation of a panel of adipokines might be more informative to understand and predict the average risk of a female to develop breast cancer based on BMI. Attention should be also directed to examine the effect of newly identified adipokines and their interactions with the more understood leptin and adiponectin. Alterations to adipokines and their signaling pathways can also be potentiated by other hormones and growth factors well-known to increase breast cancer risk. A strong link exists between obesity and inflammation. Inflammatory settings can modulate release and effect of adipokines in favor for breast cancer progression and development. Although it is well-understood that inflammatory mediators can promote aromatase activity and risk of hormone-dependent breast tumors, the interplay between adipokines and inflammatory mediators requires further evaluation. In this regard, measures to decrease body weight, chronic inflammation, and hyperinsulinemia might be promising to decrease breast cancer risk and progression.

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