

Oncogenic role of leptin and Notch interleukin-1 leptin crosstalk outcome in cancer

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Abstract

Obesity is a global pandemic characterized by high levels of body fat (adiposity) and derived-cytokines (*i.e.*, leptin). Research shows that adiposity and leptin provide insight on the link between obesity and cancer progression. Leptin's main function is to regulate energy balance. However, obese individuals routinely develop leptin resistance, which is the consequence of the breakdown in the signaling mechanism controlling satiety resulting in the accumulation of leptin. Therefore, leptin levels are often chronically elevated in human obesity. Elevated leptin levels are related to higher incidence, increased progression and poor prognosis of several human cancers. In addition to adipose tissue, cancer cells can also secrete leptin and overexpress leptin receptors. Leptin is known to act as a mitogen, inflammatory and pro-angiogenic factor that induces cancer cell proliferation and tumor angiogenesis. Moreover, leptin signaling induces cancer stem cells, which are involved in cancer recurrence and drug resistance. A novel and complex signaling crosstalk between leptin, Notch and interleukin-1 (IL-1) [Notch, IL-1 and leptin crosstalk outcome (NILCO)] seems to be an important driver of leptin-induced oncogenic actions. Leptin and NILCO signaling mediate the activation of cancer stem cells that can affect drug resistance. Thus, leptin and NILCO signaling are key links between obesity and cancer progression. This review presents updated data suggesting that adiposity affects cancer incidence, progression, and response to treatment. Here we show data supporting the oncogenic role of leptin in breast, endometrial, and pancreatic cancers.

Key words: Obesity; Leptin; Breast cancer; Endometrial cancer; Pancreatic cancer; Notch, interleukin-1 and leptin crosstalk outcome

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Core tip: Obesity is a global pandemic and a risk factor for a number of cancers. Obesity is characterized by high levels of body fat (adiposity) and leptin. Research shows that leptin and its oncogenic crosstalk Notch, interleukin-1 and leptin crosstalk outcome (NILCO) provide insight on the link between obesity and cancer progression. Thus, leptin and NILCO can act as mitogenic, inflammatory, and angiogenic cues promoting the progression of cancer, cancer stem cells, and drug resistance. This review shows updated information on leptin and NILCO's oncogenic roles in breast, endometrial, and pancreatic cancers.

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INTRODUCTION

Obesity is a global pandemic. As of 2014, there were at least 600 million obese adults across the globe^[1]. The Centers for Disease Control and Prevention reports that 1/3 of the United States adult population, or 78.6 million, is obese^[2]. The negative impact on the public health burden continues to increase with the number of overweight and obese individuals^[3]. A quantitative meta-analysis of 33 United States studies lists the direct medical cost of obesity as \$1723 per-person^[4]. Annual medical costs incurred by the overweight and obese are still increasing throughout the United States. Many healthcare costs occur because obesity is a risk factor for several chronic diseases: Cardiovascular disease^[5], type two diabetes mellitus^[6], and several different types of cancer^[7].

Clinical measures for obesity include having a body mass index (BMI) that is ≥ 30 ; clinical obesity can also be characterized by excessive accumulation of body fat^[8]. BMI measures body fat using an individual's height to weight ratio^[9]. Physicians, clinicians, nutritionists, and other scientists often assess an individual's BMI to determine obesity related health outcomes^[10]. While BMI continues to be a common variable for overall assessment of obesity, it has become evident that BMI is not the only crucial factor when investigating how obesity works to drive the development or progression of other diseases^[11]. Clinicians and researchers are now correlating body fat and waist circumference to increased risks for cardiovascular disease, type-two diabetes, and cancer^[12-14]. The connection between obesity and cancer is complex and still unclear. However, research shows that adiposity is providing insight on the link between obesity and cancer progression^[11].

Leptin and adiponectin are two key cytokines secreted from adipose tissue. Leptin levels are often chronically elevated in human obesity^[15]. Chronically high levels of leptin in the overweight and obese can lead to a mechanism known as "leptin resistance"^[16]. Leptin resistance can lead to loss of appetite control, increased food intake and accumulation of fat in adipose tissue^[17]. These issues could be crucial during cancer development as leptin mediates several signaling pathways that are essential to angiogenesis, cell proliferation, migration, and survival^[18].

Leptin has been shown to play a role in several types of cancers. The expression of leptin and its receptor (OB-R) has been reported in many cancer types including: Gliomas, Carcinomas, Adenocarcinomas, and Melanomas^[18]. Obesity signals (leptin) have been linked to the progression of several cancers. The connection between obesity signals (leptin and/or OB-R) and cancer progression has been detected in bladder, brain, breast, colon, endometriod, esophageal, kidney, liver, lung, ovarian, prostate, skin, and thyroid cancers^[18].

This review shows updated information on leptin's oncogenic role in breast, endometrial, and pancreatic cancers. We present experimental data obtained by using different research methodologies [including: Cell culture, animal trials, flow cytometry, immunological methods, polymerase chain reaction (PCR), *etc.*] suggesting that adiposity affects cancer progression. The effect of adiposity on cancer progression, leptin signaling mediated activation of cancer stem cells, and the link between leptin and drug resistance is discussed.

LEPTIN STRUCTURE, SOURCE, AND FUNCTION

Discovered in 1994^[19], leptin is a 16 kDa protein hormone that is composed of 167 amino acids and is coded by the *LEP* gene (also known as the *OB* gene)^[18]. This small protein binds to the leptin receptor (OB-R) leading to control of leptin ligand/receptor mediated pathways. Leptin binding to OB-R is highly specific. Indeed, leptin only binds OB-R, and this receptor can only binds leptin. OB-R belongs to the class I cytokine receptor superfamily composed by six different isoforms produced *via* alternative mRNA splicing. The long form OB-RI or OB-Rb, with full signaling capabilities, carries out primary biological functions of leptin, while short OB-R isoforms induce secondary signaling pathways^[18,20].

Through canonical leptin signaling, the secreted protein enacts its hormonal potential to control appetite, energy balance, and glucose homeostasis *via* negative feedback^[21]. When energy levels are high, meaning the body has high triglyceride (fat) stores, the hypothalamus sends signals received by receptors of adipocytes^[16]. Adipocytes produce and secrete leptin and the protein then circulates to the brain *via* endocrine signaling^[21]. Leptin then binds the extracellular domain of the long form OB-R that activates an associated

JAK2 protein^[18,22,23]. JAK2 phosphorylates three tyrosine residues (Tyr985, Tyr1077 and Tyr1138) on the intracellular portion of the OB-R^[18,23,24]. Phosphorylation and activation of these three residues in hypothalamic cells initiates the downstream signaling that ultimately regulates the negative feedback responsible for establishing satiety, maintaining energy/glucose balance, and regulation of reproduction^[24]. However, these mechanisms become dysfunctional during obesity as leptin continue to rise until the body no longer responds to endogenous leptin signaling pathways^[25]. This phenomenon is known as leptin resistance. Obese individuals are often leptin resistant. During leptin resistance circulating leptin levels increase in the body, however, there is a breakdown in the mechanism that signals satiety resulting in the accumulation of excess leptin. High leptin levels can induce cancer cell proliferation and, therefore, could be a key link between obesity and cancer progression^[26].

LEPTIN AND OB-R EXPRESSION IN BREAST CANCER

Understanding the role of leptin in normal breast development is important when describing how leptin and OB-R could affect breast cancer progression. Human breast are primarily composed of adipose tissue, thus this organ is a major site of leptin production and secretion. It has been demonstrated that leptin signaling plays a role in the development of mammary glands^[27]. The importance of leptin and OB-R expression has been tested in murine models. In one study, it was demonstrated that mutant mice with deficient leptin signaling (either lacking leptin *ob/ob*, or lacking functional OB-R *db/db*) show abnormal mammary glands^[27]. Additionally, *ob/ob* and *db/db* mice show very low incidence of mammary tumors^[27]. However, it is important to note that normal human mammary gland tissue show low OB-R expression. Conversely, cancerous cells found in the mammary gland overexpress OB-R and respond to leptin stimulus by increasing production of angiogenic factors [vascular endothelial growth factor (VEGF), VEGF receptor 2 (VEGFR-2)], increasing proliferation, and survival^[26,28,29]. These findings suggest that leptin signaling mediates proliferative pathways in normal and malignant breast cells.

Leptin oncogenic effects on breast cancer

Leptin has been shown to increase proliferation of estrogen responsive (ER⁺) and unresponsive (ER⁻) breast cancer cells *in vitro*^[30]. Moreover, inhibition of leptin signaling has been shown to abrogate ER⁺ and ER⁻ breast cancer growth^[31]. Recently, immunohistochemical analysis of breast cancer tissue samples obtained from Chinese patients ($n = 67$) confirmed a strong correlation between leptin expression and breast cancer progression, as 61% of the samples were positive for leptin and OB-R^[26,32,33]. Studies continue to be published

highlighting leptin's effects on proliferative pathways in breast cancer.

Leptin mediated induction of Cyclin D1 and Cdk2 has been shown in breast cancer cells *in vitro*^[30,34]. This was further assessed by Zheng *et al.*^[35] who have confirmed that Cyclin D1 expression is regulated by active leptin signaling in the MMTV-Wnt-1 transgenic mouse^[35]. We recently showed that inhibition of leptin signaling in triple negative breast cancer cells (TNBC) [using an innovative leptin antagonist bound to nanoparticles (IONP-LPrA2)] abrogated leptin-induced S phase progression of the cell cycle^[36]. These data suggest that leptin is essential in promoting S-phase cell cycle progression in breast cancer.

The effects of leptin signaling on proliferative pathways have also been linked to telomerase activity. Leptin has been shown to induce telomerase activity in MCF-7 breast cancer cells in a dose-dependent manner. Moreover, leptin signaling may be a key promoter of senescence evasion in human breast cancer cells *via* up regulation of telomerase activation^[37]. These authors also found that leptin activates the transcription of hTERT (the enzyme responsible for reverse transcriptase of telomerase). Taken together those findings suggest that leptin signaling increases cell proliferation *via* telomerase activation in breast cancer.

Leptin can also increase survival of breast cancer cells *via* additional mechanisms. Apoptosis evasion mechanisms in human breast cancer allows for the growth of solid tumors. Increase survival of TNBC *via* leptin signaling was demonstrated by Ray *et al.*^[38]. These authors found an inverse relationship between the expression of apoptotic protein in TNBC treated with leptin^[38]. Leptin induced Bcl-xL and Bcl-2 protein levels and increased survival of TNBC^[38]. These survival mechanisms are punctuated by apoptosis evasion *via* leptin's ability to regulate Bcl-2 proteins in human breast cancer cells^[38].

The expression of VEGF and its receptor, VEGFR-2, is instrumental for the formation and function of vasculature in tissues. VEGF binding to VEGFR-2 leads to signaling cascades that result in neovascularization^[39]. Additionally, VEGF/VEGFR-2 autocrine and paracrine actions in breast cancer have been shown to play an important role in cancer cell survival^[28].

Leptin is a non-classical pro-angiogenic factor that has an essential role in tumor angiogenesis^[40]. We have previously shown that leptin induces breast cancer growth and significantly increases production of both VEGF and VEGFR-2 supporting tumor angiogenesis^[28,29,31]. The IL-1 system has also been linked to angiogenesis *via* leptin's ability to upregulate VEGF/VEGFR-2 in breast cancer^[41]. Direct leptin induction of IL-1 can indirectly upregulate VEGF/VEGFR-2^[41].

Novel molecular links between inflammatory and angiogenic responses of leptin-stimulated human endothelial cells (hECs) were previously demonstrated. hECs were also shown to be a target of leptin signaling through the transactivation of VEGFR-2's intracytoplas-

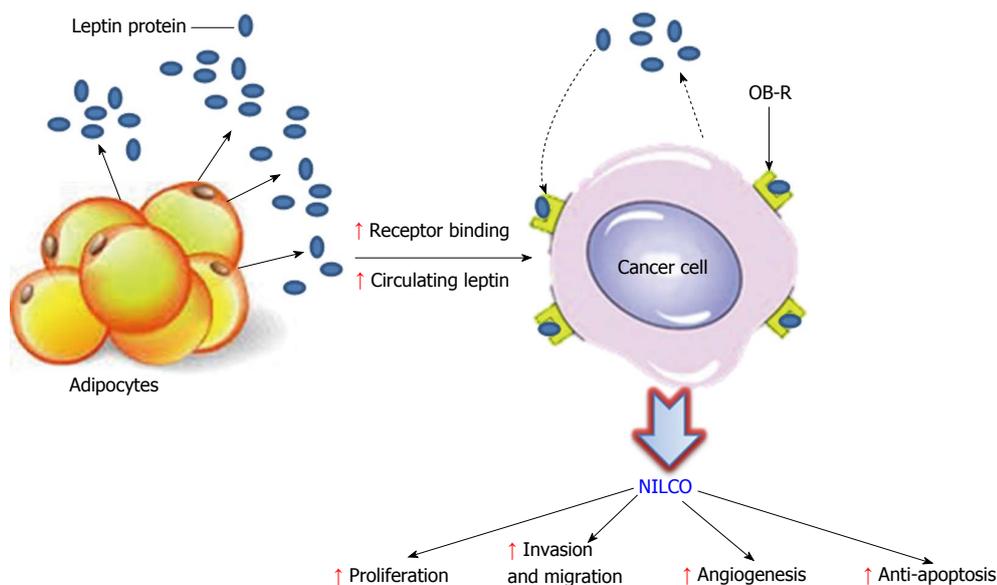


Figure 1 Obesity, leptin, Notch, interleukin-1 and leptin crosstalk outcome, and cancer progression. The complex relationship between obesity, leptin and Notch, IL-1 and leptin crosstalk outcome (NILCO) that occurs in cancer cells is illustrated here. Leptin secreted by adipocytes or cancer cells binds to its receptor, OB-R, on cancer cells. Leptin signaling crosstalks with Notch and IL-1 systems to induce survival, proliferation, invasion, migration, angiogenesis and anti-apoptosis of cancer cells. These leptin actions have also been shown to lead to the progression of breast, endometrial and pancreatic cancer^[29,71,85,89]. OB-R: Leptin receptor; IL-1: Interleukin-1.

matic tail and upregulation of enzymes involved in inflammatory pathways. In cultured human umbilical vein endothelial cells (HUVEC) leptin stimulated rapid phosphorylation of VEGFR-2 on Tyr (1175) and increased cyclo-oxygenase-2 (COX-2) expression *via* p38 mitogen-activated protein kinase (p38 MAPK) and Akt. Moreover, inhibition of these leptin-induced pathways and leptin/OB-R signaling (*via* the peptide LPrA2, a leptin antagonist produced by us) abrogated leptin-induced capillary-like tube formation by HUVEC on Matrigel. A functional endothelial p38(MAPK)/Akt/COX-2 signaling axis triggered by leptin/OB-R-induced VEGFR-2 transactivation is required for leptin's pro-angiogenic actions in hECs^[42]. More recently we have shown that leptin also induced phosphorylation of VEGFR-2 at sites Y951, Y996, Y1059 and Y1175 in porcine aortic ECs overexpressing VEGFR-2. Protein expression of Notch4 and Jagged1 was also induced by leptin treatment in fibroblast cells (NIH/3t3). Therefore, leptin secreted by fibroblast cells and/or adipose tissue may contribute to tumor angiogenesis by acting directly on stromal cells and inducing a VEGFR-2/Notch crosstalk^[43].

Proliferation and acquisition of malignant features in breast cancer cells has illustrated the important role of leptin signaling and crosstalk between several cellular pathways^[44]. A leptin-induced complex crosstalk between several factors [Notch, IL-1 and leptin crosstalk outcome (NILCO)] was detected in breast cancer cells and has been shown to drive cell survival and tumorigenesis^[44] (Figure 1). NILCO is an advanced model that provides evidence, and works to explain, the crosstalk outcomes that occur as a result of leptin signaling between Notch family proteins and IL-1 inflammatory systems. NILCO could represent the integration of developmental, pro-

inflammatory and pro-angiogenic signals critical for leptin-induced cell proliferation/migration and regulation of VEGF/VEGFR-2 in breast cancer^[44].

Notch is a hallmark of breast cancer^[44]. Notch is a family of transmembrane proteins that act as receptors of specific ligands expressed in the membrane of adjacent cells. Notch signaling activation is mediated by binding to those ligands followed by a series of proteolytic events of Notch intracytoplasmic tail *via* ADAM protease and γ -secretase, which have been shown to regulate cell differentiation^[45]. Notably, our group has recently shown that leptin induces Notch activation in estrogen responsive and TNBC cells *in vitro* and *in vivo*^[46]. Moreover, we have shown that leptin induced cell proliferation and migration are Notch dependent^[46]. To investigate whether obesity induces a leptin-Notch signaling axis in breast cancer, Notch was determined in human MCF-7 and MDA-MB231, and mouse E0771 cells and in E0771-tumors hosted by syngeneic lean and diet-induced obesity C57BL/6J female mice. Notch loss-of-function [*via* inhibition of γ -secretase with DAPT and transfection of dominant negative (R218H) RBP-Jk (CSL/CBF1)] showed that a functional leptin-Notch signaling axis was involved in the proliferation and migration of E0771 cells. These data suggest that leptin induced Notch could be involved in the reported higher incidence, aggressiveness, and poor prognosis of breast cancer in obese patients^[44,46].

NILCO biomarkers were found differentially expressed in ER⁺, ER⁻ and TNBC tissues obtained from Chinese women. TNBC showed differential localization patterns of NILCO. TNBC showed fewer nuclei and cytoplasm positive for Notch4 and JAG1, but more cytoplasm positive for leptin. Additionally, fewer

TNBC stromas were positive for Notch1 and Notch4, but 100% of TNBC stromas were positive for VEGFR-2. Moreover, TNBC had lower DLL4 and IL-1R tI expression. Remarkably, analysis of NILCO and targets using Pathway Studio9 software (Ariadine Genomics) showed multiple molecular relationships that suggest NILCO has potential prognostic biomarker value in breast cancer^[32].

Our lab has also shown that leptin-induced Notch and IL-1 inflammatory systems are involved in the regulation of breast cancer cell survival and proliferation. Concurrent activation of NILCO leptin signaling has been shown to be instrumental in the proliferation of breast cancer cells during spontaneous mammary tumor formation in obese mice that are resistant DMBA [7, 12-dimethylbenz(a)anthracene]-induced cancer^[47].

Taken together these mechanisms work to increase angiogenesis, cell proliferation, and survival in breast cancer that could be of utmost relevance for obese patients (Figure 1). Targeting NILCO may help to design new pharmacological strategies aimed at controlling breast cancer growth and angiogenesis^[18].

Leptin, epithelial to mesenchymal transition and tumor stroma

Leptin signaling induces adhesion, increases migration, and invasion in breast cancer cells *in vitro*^[44]. Cancer cells that gain an increased ability to migrate and invade surround tissues have undergone an epithelial to mesenchymal transition (EMT). It was found earlier that leptin inhibition decreased EMT and migration of hECs *via* signal transducer and activator of transcription 3 (STAT3) and Snail/vascular endothelial cadherin-independent mechanism. Moreover, leptin signaling in ECs was related to Akt signaling pathway, $\alpha v \beta 3$ integrin receptor and matrix metalloprotease 2, suggesting that leptin induces adhesion and migration processes^[48]. Furthermore, leptin was shown to stimulate phosphorylation of glycogen synthase kinase 3 β (GSK3 β) *via* Akt activation that decreased GSK3 β -LKB1-Axin complex formation and induced β -catenin, Wnt1 and MTA1 expression. Moreover, leptin-treated breast tumors hosted by mice showed increased expression of Wnt1, pGSK3 β , β -catenin and vimentin, but reduced E-cadherin expression. A novel crosstalk between leptin and MTA1/Wnt signaling was found in breast cancer cell-EMT^[49].

Research associated with obesity, leptin, and breast cancer progression continues to become more complex. Studies that focus on the tumor microenvironment are currently providing a framework for the overlap between several leptin mediated pathways. Increasing amounts of research show that several cell components of the breast cancer stroma (*i.e.*, cancer associated fibroblasts, macrophages, adipocytes, and cancer stem cells) are influenced by leptin signaling^[44,50]. Moreover, emerging data also show that tumor stroma cells secrete molecules that bolster survival for breast cancer cells. During this process, adipocytes secrete many factors, including leptin and the inflammatory cytokine IL-6, activating

paracrine signaling that leads to action of the JAK2/STAT3 pathway^[51]. The end result is an activation of pathways that confer stem-cell-like properties (OCT-4⁺/SOX2⁺) to the breast cancer cells^[51]. Our group has identified numerous other cytokines and inflammatory factors (Notch1-4, IL-1, VEGF and VEGFR-2) that are now shown to bolster breast cancer progression *via* the tumor microenvironment^[41,44]. We, and others, have also found that leptin can crosstalk with many oncogenic signals and induce secretion of chemotaxis factors for macrophages in the mammary gland environment eliciting pro-inflammatory changes that lead to malignant transformation of cells^[18,52,53].

It was proposed that obesity impacts breast cancer not only systemically but also at the local level in the breast. Paracrine factors resulting from the crosstalk among adipocytes, tumor cells and macrophages in the breast tumor microenvironment might contribute to tumor progression *via* additional mechanisms. Indeed, breast adipose tissue enables the crosstalk between adipocytes and breast tumor cells contributing to tumor macrophage recruitment. *In vivo* experiments demonstrated that mammary tumors from obese mice are larger, and that their associated adipose tissue contained higher numbers of activated macrophages and hypertrophic and more inflamed adipocytes. Then, breast adipose tissue could play an additional role in breast cancer development in obesity by recruiting and activating macrophages^[52].

Leptin, obesity, and breast cancer therapies

The Food and Drug Administration authorized the use of Tamoxifen (TAM), a selective estrogen receptor modulator, for treatment of breast cancer in 1998. TAM is widely used as the first line drug for chemoprevention of pre-menopausal/post-menopausal women at high risk of breast cancer. TAM targets ER⁺ and/or progesterone responsive (PR⁺) breast cancers^[54]. Additionally, TAM is indicated for reduction of contra lateral BC risk^[55]. Therefore, the National Cancer Institute recommends long-term TAM chemoprevention. To date more than 7 million patients a year use TAM^[56].

Traditional therapeutic breast cancer treatments can often become taxing on patients due to several adverse side effects (fatigue, pain, loss of appetite, nausea, vomiting). Additionally, cancer cell populations often become resistant to therapies^[39,57]. Breast cancer patients treated with TAM often show drug resistance, causes for this are not completely known. However, it could be linked to obesity signals (*i.e.*, leptin). TAM induces an increase in leptin expression^[58]. In turn, leptin can transactivate ER, and increase aromatase activity, which leads to the induction of estrogen synthesis^[59]. Reciprocally, estrogen signaling can induce leptin and OB-R expression, increase the development of vascular thrombosis^[60] and impair TAM effects^[58].

It was shown that leptin counters the chemotherapeutic actions of TAM in breast cancer cells *in*

vitro^[61]. Moreover, TAM-resistant breast cancer cells were less proliferative *in vitro* when OB-R was knocked-down^[57]. Consequently, leptin signaling has become a target for the development of new inhibitors that can be used as adjuvants during chemotherapeutic treatments^[33,62].

A recent finding has reported the role the synergistic relationship between leptin and STAT3 phosphorylation as a mediator of TAM resistance in breast cancer cells^[63]. When treated *in vitro* with 2 $\mu\text{mol/L}$ of TAM for 72 h, ER positive MCF-7 and MCF-7/HER2 cell lines showed a statistically significant decrease in cell viability as measured by MTT assay^[63]. However, 72 h combination treatment of MCF-7 and MCF-7/HER2 cell lines with 2 $\mu\text{mol/L}$ TAM + 200 ng/mL leptin had a restorative effect on cell viability^[63]. The study used Western blot analysis of p-STAT3, OB-R, HER2, and ER to investigate leptin's role in STAT3 phosphorylation in the presence of TAM. STAT3 phosphorylation (activation) increased in MCF-7 cells treated with TAM alone and TAM plus leptin^[63]. In contrast, MCF-7/HER2 cells treated with TAM alone had decreased expression of phosphorylated STAT3^[63]. More interestingly, leptin restored phosphorylated STAT3 to levels that were comparable to untreated cells in the presence of TAM at 24 h and 7 d time points^[63]. This research provided insight on two key mechanistic pathways that could be critical for decreasing TAM resistance in obese breast cancer patients.

However, recent studies investigating the effects of TAM treatment in obese and non-obese ER⁺ breast cancer patients are showing that TAM may continue to be an effective treatment for obese patients suffering from the disease. Analysis of the data acquired after the National Surgical Adjuvant Breast and Bowel Project protocol B-14, shows that overall mortality rates were reduced in both obese and non-obese women who were treated with TAM when compared to women with similar BMI who received a placebo^[64]. Obese patients ($n = 687$) had higher TAM/placebo hazard ratios for breast cancer recurrence, contralateral breast cancer, total mortality, and mortality after breast cancer events compared to underweight ($n = 83$), normal weight ($n = 1593$), and overweight ($n = 1022$) patients^[64]. However, TAM effectively reduced breast cancer recurrence and mortality rates across all BMIs, and there was no statistically significant increase in mortality for obese women^[64].

A published secondary analysis of the double blind Arimidex, Tamoxifen Alone or in Combination clinical trial shows that overall recurrence rates were equal in ER⁺ breast cancer patients who were treated with TAM^[65]. Similarly, the Austrian Breast and Colorectal Cancer Study Group trial 6 reports that there was no difference in outcomes (disease-free survival, distant recurrence-free survival, and overall survival) between obese and non-obese women who received TAM treatment^[66]. However, obese women who received TAM in combination with an aromatase inhibitor had worse outcomes than non-obese

counterparts receiving the same treatment^[66]. These studies show that there may be strong associations between body weight and TAM efficacy. Azrad *et al.*^[67] have presented additional background on this subject including studies that compare the efficacy of TAM and aromatase inhibitors. A major section of Azrad's review provides data from four clinical studies and each suggests that aromatase inhibitors are less effective than TAM when treating women with hormone-receptor positive breast cancers^[67].

Links between leptin levels and chemotherapeutic resistance mechanisms have also been identified in the MCF-7 breast cancer cell line *in vitro*^[68]. MCF-7 cells were treated with 100 ng/mL of leptin for 10 d, on the 9th day cells were treated with 10 $\mu\text{mol/L}$ concentration of cisplatin (CIS)^[68]. The effect of chronic leptin exposure on cell proliferation during CIS treatment was measured using Crystal Violet assays^[68]. The data included in the study showed that chronically high leptin concentrations counteracted CIS-induced cytotoxicity in MCF-7 breast cancer cell line *in vitro*, which supports the notion that leptin works as a survival factor that confers chemotherapeutic resistance in breast cancer^[68].

TNBC are refractory to hormonal therapies, do not have a targeted therapy and are mainly treated with chemotherapeutic drugs. TNBC patients often develop drug resistance. The mechanisms leading to chemotherapy resistance in TNBC patients are still unclear. Data show that obesity may lead to chemo-resistance in breast cancer. Increasing BMI of TNBC patients was associated with significantly more advanced disease and higher incidence and lower response rates to chemotherapeutics^[69].

Breast cancer stem cells (BCSC), population of drug-refractory cancer cells with self-renewal capabilities, have been linked to the development of drug resistance and are present in TNBC cell lines and derived tumors^[70]. Importantly, leptin activates several molecules critically associated with BCSC, (*i.e.*, Notch, Akt, STAT3, nuclear factor- κB)^[71-73]. Our preliminary data further suggest that leptin induced stemness and drug resistance in breast cancer cells. Leptin increased the levels of several genes and molecules associated with BCSC maintenance, and cellular markers CD44 and ALDH1. Notably, OB-R expression and STAT3 phosphorylation (leptin's main downstream effector) are characteristic features of tumor and embryonic stemness, which are mediated by a feedback mechanism involving the pluripotency-associated transcription factors, OCT4, SOX2 and NANOG^[72]. We further tested the effects of leptin in human ER⁺ (MCF-7) and TNBC cell lines (HCC1806) exposed to various concentrations of CIS^[74], sunitinib, paclitaxel, and doxorubicin^[36]. Leptin induced a significant increase in cell survival that was abrogated by the use of a leptin peptide receptor antagonist-conjugated to iron oxide nanoparticles (IONP-LPrA2)^[36]. Therefore, the inhibition of leptin signaling could help to the reduction of drug resistance and increase effectiveness of chemo-

therapeutic drugs used for BC, especially in obese contexts.

ENDOMETRIAL CANCER

Endometrial cancer (EmCa) is the most frequent gynecological malignancy of the female reproductive tract, and is the fourth most commonly diagnosed new cancer among women in the United States following breast, lung/bronchus, and colorectal cancers^[75,76]. The 2015 Surveillance, Epidemiology, and End Results Program report from the National Cancer Institute (NCI) estimates that 54870 women will be diagnosed with EmCa in the United States, and roughly 10170 women will succumb to the disease. The 5-year survival rate is favorable at 96% when diagnosed at a local stage and decreases to 16% when it is diagnosed at distant sites^[77].

EmCa can be classified as type I and type II^[75]. Type I EmCa accounts for 85% of all EmCa cases, and is thought to be caused by un-opposed estrogen stimulation, and is considered low grade with a favorable prognosis^[75]. Indeed, type I EmCa is less aggressive and less likely to spread to distant sites^[75,78]. Type II makes up approximately 10% of EmCa, but its etiology is still unclear, and seems to be independent from estrogen stimulation. Type II EmCa shows high grade, low differentiation, and poor prognosis^[75]. Moreover, type II EmCa is more likely to metastasize to distant sites^[75,78]. Type II EmCa includes several subtypes (*i.e.*, papillary serous carcinoma and clear-cell carcinoma)^[75]. Less frequent EmCa types, malignant mixed müllerian tumors or carcinosarcomas, are considered Type II tumors that represent approximately 4% of uterine cancers^[78].

The incidence of EmCa is highest in Caucasian women (24.8/100000) when compared to African American women (21.8/100000), and other ethnic groups^[77]. However, African American women are more likely to die from EmCa when compared to Caucasian women. Mortality rates in African American women (7.3/100000) are higher than in Caucasian women (3.9/100000)^[77]. The basis for this health disparity is ambiguous, but could be due to factors which include but are not limited to socioeconomic status, lack of access to healthcare, type of healthcare provided, culture, lifestyle, and/or biological differences between patients belonging to diverse ethnic groups^[77].

Obesity and EmCa incidence strongly correlate^[7]. Approximately 40% of EmCa cases are related to obesity^[75]. EmCa is more than three times as common in obese women when compared to normal healthy weight women^[75]. The relationship between obesity and EmCa incidence and progression is characterized by elevated levels of estrogens (unopposed estrogen stimulus), insulin growth factor-1, adipokines (leptin; resistin), and cytokines^[75]. Clinical data have been published showing links between obesity, EmCa type, and race. The study showed that 55.3% ($n = 871$) of the women diagnosed

with type I EmCa were obese, while 36% ($n = 64$) were obese and more likely to belong to a non-white race^[79]. Although this study did not clearly define the relationship between obesity and type II, the data suggest that obesity and health disparities play a role in EmCa.

Leptin signaling was correlated with the expression of several pro-angiogenic factors in EmCa cell lines^[75]. In An3Ca, Ishikawa, and SK-UT2 (malignant endometrial epithelial) cell lines leptin regulates VEGF, IL-1 β , LIF and their respective receptors. However, IL-1 β was only increased by leptin in benign primary endometrial cells. IL-6, resistin, and tumor necrosis factor α are additional factors involved in leptin oncogenic crosstalk in EmCa^[18]. The short OB-R isoforms are expressed higher than the long OB-R isoform in EmCa^[75,80].

As previously described in this review, NILCO, a complex crosstalk between leptin and pro-angiogenic, inflammatory and mitogenic factors occurs in breast cancer^[44]. Additionally, NILCO could also be present in EmCa^[75]. Our preliminary data suggest that leptin signaling and NILCO may be associated with the more aggressive type II EmCa, which affects more postmenopausal and African-American women. Studies using type II EmCa tissue microarrays from Chinese and African American patients assessed this notion^[75].

We have previously reported an interesting observation showing that NILCO components are differentially expressed in type I and type II EmCa^[75]. Table 1 shows the expression levels of NILCO components in type I and type II EmCa from obese African American women and lean Chinese women. Immunohistochemical staining, Western Blot and Real-time PCR analyses confirm that NILCO was expressed higher in type II EmCa. These data suggested that the more aggressive and non-hormonal type II form of EmCa may be dependent on Notch signaling. The results may also suggest that an active crosstalk between obesity related leptin signals and Notch occurs in EmCa. Therefore, NILCO expression in EmCa may serve as a new tumor marker.

Androgens, estrogens and leptin in the menstrual cycle

Estrogens are the main regulators of the menstrual cycle. Estrogens are mainly produced by the ovaries and regulated by neuroendocrine hormone signaling^[81]. However, estrogens are also synthesized by adipose tissue^[82]. In fact, estradiol levels varied throughout the menstrual cycle between women with different body fat content^[83]. Women with both very low and very high body fat had significantly lower estradiol levels during the follicular phase and midcycle during their menstrual cycle^[83].

Androgens are produced and accumulated in adipose tissue. They can be converted into estrogen *via* the actions of aromatase. Excessive size of adipose tissue can convert androgens into estradiol and estrone *via* aromatase providing an important estrogenic surge in obese patients^[75]. Therefore, these molecules could alter female reproductive function and hormonal equilibrium especially after menopause in obese women^[84]. Andro-

Table 1 Expression of Notch, interleukin-1 and leptin crosstalk outcome components in African American and Chinese women suffering from endometrial cancer

	Endometrial cancer						
	African American women			Chinese women			
	Type I (n = 12)	Type II (n = 17)	P value	Type I (n = 97)	Type II (n = 23)	H SCORE	P value
NILCO IHC	H SCORE	H SCORE	P value	H SCORE	H SCORE		P value
Notch1	1.19	1.80	< 0.01	1.00	1.78		< 0.01
Notch2	1.10	1.30	0.05	1.00	1.15		> 0.05
Notch3	1.15	1.45	> 0.05	1.10	1.20		> 0.05
Notch4	1.50	1.96	< 0.01	1.10	1.58		< 0.05
JAG1	1.36	2.20	< 0.01	1.30	1.87		< 0.01
DLL4	1.80	2.49	< 0.01	1.31	1.80		< 0.01
Survivin	1.20	1.96	< 0.01	1.17	1.60		< 0.01
OB-R	1.60	1.73	< 0.01	1.10	1.50		< 0.05
IL-1R t I	1.28	2.00	< 0.01	1.40	1.73		< 0.05
Hey2	1.14	1.45	< 0.01	1.07	1.30		< 0.05
WB	Protein expression	Protein expression	P value				
Notch1	48	58	< 0.05				
Notch2	38	36	> 0.05				
Notch3	48	44	> 0.05				
Notch4	44	98	< 0.01				
JAG1	140	172	< 0.05				
DLL4	40	115	< 0.01				
Survivin	131	230	< 0.05				
OB-R	25	70	< 0.01				
IL-1R t I	59	109	< 0.05				
Hey2	46	100	< 0.01				
qPCR	mRNA expression	mRNA expression	P value				
Notch1	1.00	1.30	< 0.01				
Notch3	0.45	0.80	< 0.05				
Notch4	0.80	1.40	< 0.01				
JAG1	0.05	0.52	< 0.01				
DLL4	1.10	1.50	< 0.01				
Survivin	0.48	0.51	< 0.05				
OB-R	0.45	0.65	> 0.05				
IL-1R t I	0.82	1.56	< 0.01				
Hey2	0.03	0.62	< 0.01				

NILCO: Notch, interleukin-1 and leptin crosstalk outcome; IHC: immunohistochemistry; H SCORE^[32]: Semi-quantitative value calculated for each antigen as determined by the following equation $H\ SCORE = \sum pi(i + 1)$; WB: Western blot; qPCR: Real-time polymerase chain reaction; Notch1-4: Transmembrane receptors; JAG1: Jagged 1; DLL4: Delta like-4 protein, and Notch ligand; Survivin: An anti-apoptotic factor and Notch target; OB-R: Leptin receptor; IL-1R t I : Interleukin 1 receptor type I ; Hey2: Hes-related family BHLH transcription factor with YRPW motif 2 and Notch ligand.

gens and estrogens influence the menstrual cycle. In normal weight women, testosterone fluctuates throughout the menstrual cycle and peaks during the ovulation phase^[84]. Conversely, androstenedione and dehydroepiandrosterone showed no significant variations throughout the menstrual cycle^[84]. Androstenedione levels were found to peak at ovulation^[85]. Yet, epidemiological studies have shown increased EmCa risk among pre- and postmenopausal women who have elevated plasma androstenedione and testosterone, and among postmenopausal women who have increased levels of estrone and estradiol. Interestingly, free testosterone levels were significantly higher in obese women when compared to non-obese women and slight variations of testosterone were observed during each phase of the menstrual cycle^[86].

Also, the menstrual cycle may be influenced by the levels of serum leptin^[87]. In obese women, the highest serum leptin levels are observed during the luteal phase. Similarly, an increase in estradiol levels coincided

with the increase in serum leptin levels^[87]. However, serum leptin levels were unchanged throughout the menstrual cycle of women with normal weight^[87].

PANCREATIC CANCER

Pancreatic cancer (PC), including pancreatic adenocarcinoma, has been the fourth leading cause of cancer related death in the past few decades. The risk factors associated with PC are chronic pancreatitis, diabetes, smoking and high BMI (> 30). Obesity, pandemic in the United States, has been linked to PC: Increased BMI was associated with more advanced stage at diagnosis; 72.5% of obese patients presenting metastatic disease compared to 59.4% of the normal weight patients^[88]. A positive significant association between waist circumference and PC was determined in a combined meta-analysis of cohort studies for the Asia-Pacific region^[89].

There are few reports on the role of leptin in PC. It was shown that high levels of leptin were associated

Table 2 Leptin signaling impacts on pancreatic cancer progression

Treatments	Human pancreatic cancer cell lines										
	BxPC-3 less aggressive			MiaPaCa-2 more aggressive			Panc-1 more aggressive				
	Control	Leptin	Leptin + CT	Control	Leptin	Leptin + CT + LI	Control	Leptin	CT	Leptin + CT	Leptin + CT + LI
Proliferation (%)	100	212 ²		100	120 ²		100	130 ²			
Survival ¹ (%)	100	100	63 ²	100	100	55 ²	100	100	35 ²	41 ²	36 ²
PCSC (%)	100	130-140		100	120-130		100				
Notch1	100	170 ²		100	NC		100				
Notch2	100	147 ²		100	75		100				
Notch3 (%)	100	NC		100	NC		100				
Notch4	100	71		100	146 ²		100				
Tumorsphere formation (%)	100	197 ²		100	184 ²		100	221 ²			

¹Cell survival was determined by flow cytometry and MTT assays in media containing 10% fetal bovine serum (BxPC-3) or serum free medium containing leptin (Panc-1); ²Statistically significant ($P < 0.05$) vs control. CT: Chemotherapy, LI: Leptin inhibitor 90; PCSC: Pancreatic cancer stem cell markers; NC: No change.

with PC development. In a pooled analysis from PC patients, it was found that an association between leptin levels and elevated OB-R expression in PC correlated to the stem cell marker OCT-4^[90]. Overexpression of leptin was shown to significantly promote the growth of human PC xenografts and lymph node metastasis in mice^[91]. We have found that leptin significantly increased Notch1 and Notch2 expression in BxPC-3 cells, and Notch4 in MiaPaCa-2 cells. Therefore, Notch induced by leptin could be involved in PC progression, and could be a link between obesity and PC.

There are some reports^[92,93], showing that leptin inhibited proliferation of PC cells *in vitro*. However, in our recent studies using PC lines that showed different degrees of aggressiveness: BxPC-3 (less aggressive) and MiaPaCa-2 and Panc-1 (more aggressive), we found that leptin signaling increases PC cell progression *in vitro* (Table 2)^[94]. Leptin-induced cell proliferation was determined by MTT and cell cycle assays. PC cells treated with leptin increased proliferation, survival, and expression of stem cell markers [PC stem cell (PCSC)], and the ability to produce tumorspheres *in vitro*, which are features that characterize enhanced tumorigenesis (Table 2)^[88].

Present data further support the notion that leptin can accelerate PC growth. The reason for these discordant data is unknown.

Leptin signaling has also been suggested to influence PCSC populations. Increased expression of CD24⁺/CD44⁺ markers in PC correlated to higher tumorsphere formation. Moreover, triple positive PC cells (CD24⁺/CD44⁺/ESA) were identified as PCSC^[95]. Our preliminary data show that leptin significantly increased PCSC (CD24⁺/CD44⁺/ESA) and tumorigenesis (formation of tumorspheres) *in vitro* in both BxPC-3 and MiaPaCa-2 cells. PCSC are believed to play a role in drug resistance. Indeed, leptin-induced survival of PC cells treated with chemotherapeutics was abrogated by the addition of IONP-LPrA2, a specific leptin signaling inhibitor coupled to iron oxide nanoparticles. Therefore, the inhibition of leptin signaling via IONP-LPrA2 might be used as an adjuvant therapy with current chemotherapeutic drugs, and could lead to a new way for prolonging survival of obese PC patients.

EFFECTS OF WEIGHT LOSS ON LEPTIN LEVELS IN CANCER

Despite the recognized role of overweight and obesity on cancer incidence, the majority of the clinical trials addressing BMI reduction are relegated to breast cancer. Few reports are available for endometrial and pancreatic cancers. A retrospective study suggests bariatric surgery may improve quality of life for morbidly obese women suffering from low risk type I endometrial cancer^[96]. Clinical insights on the effects of weight loss in endometrial cancer patients include a retrospective study with findings that suggest weight loss after diagnosis and treatment may lead to poor prognosis^[97]. Similar findings on the deleterious effects of weight reduction in pancreatic cancer patients show that significant weight loss during or following treatment correlates to poor post-treatment outcomes^[98,99].

It is believed that obesity may promote the progression of ER⁺ breast cancer in post-menopausal obese women via increased production of the estrogens by adipocytes^[100]. In contrast to endometrial and pancreatic cancer data, long-term survival prognosis after treatment is poorer in overweight or obese who suffer from pre or post-menopausal

breast cancer^[101]. Several clinical studies show trends between weight loss and lower leptin levels in patients with breast cancer. One recent study, randomized patients into low fat ($n = 73$) or low carbohydrate ($n = 66$) diet intervention groups to determine how weight loss affects plasma leptin and adiponectin levels in overweight or obese postmenopausal breast cancer survivors^[102]. Following the 6 mo diet intervention the women in both groups, exhibited significant reductions in body weight and fat mass. Results from this trial show that the mean leptin level of the patients prior to intervention was 36 ng/mL, more than a 3 fold increase to concentration associated with normal weight (5-10 ng/mL)^[102]. Interestingly, 50% of the patients had circulating adiponectin levels that are the same as normal weight women^[102]. Moreover, the diet interventions decreased leptin levels by 92% of the patients; yet only 32% of the patients showed a decrease in adiponectin levels during intervention. However, this study did not address the impact of weight loss and adipokine reduction on breast cancer recurrence. Knowing how reduction of body weight and leptin levels affects breast cancer progression would be instrumental for the design of new chemotherapeutics. Obtaining clinical information on the mechanisms linking body weight loss, cancer progression, and recurrence could be also be key for developing preventative strategies that target leptin mediated breast cancer progression in obese women.

CONCLUSION

To date, several clinical trials have aimed to reduce body weight in cancer patients and have successfully implemented intervention strategies that have led to sustained weight loss in patients who have been treated for different types of cancer^[96,102,103]. Consequently, many of these clinical studies predict that weight loss may be a major mediator of cancer progression, and majority of such studies focus on breast cancer^[101-104]. Disparagingly, there currently are not many trials that report overall survival and/or cancer recurrence rates in obese patients who have successfully sustained weight loss after cancer treatment. Thus, data reporting how weight loss may improve outcomes in cancer patients have not been well documented. One reason explaining the lack of clinical data in this area may be that funding for large scale trials is not readily available^[104]. An additional factor may be that the number of patients who are motivated and willing to participate in such studies is insufficient.

Leptin levels correlated to adiposity, and are elevated in obese individuals. Then, body weight loss decreases leptin levels. Leptin signaling is a key player in the progression of several types of cancer. Increasing evidences continues to implicate the role of leptin signaling and its associated crosstalk NILCO pathways in breast, endometrial, and pancreatic cancers. Leptin and OB-R signaling is linked to increased proliferation, angiogenesis, invasion and migration, and survival of cancer

cells. Recent data continues to emerge highlighting the NILCO system components as a key driver of leptin-oncogenic actions in breast, endometrial and pancreatic cancer, specifically in cancer cells that show low or not responsiveness to steroid hormonal cues. High levels of leptin found in obese patients could potentially exacerbate NILCO impact on cancer progression and could also modify the tumor microenvironment. NILCO could be the integration of leptin-induced proliferation, angiogenic and inflammatory actions affecting several cancer types.

In the last 5 years, leptin signaling crosstalk has also become a focus in the area of cancer stem cell development and chemotherapy resistance. However, little data exist detailing these mechanisms in breast, pancreatic and endometrial cancer. The stemness effect of leptin signaling could play an important role in cancer recurrence and drug resistant, and therefore, warrants more intense research. This review highlights how the direct association between obesity, high levels of leptin, and NILCO signaling could induce the progression of cancer. Inhibition of leptin and NILCO signaling could lead to the development of new adjuvant therapies to reduce or eliminate the impact of obesity on cancer.

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