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**Leptin signaling and cancer chemoresistance: Perspectives**

Candelaria P *et al*. Leptin and cancer chemoresistance

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**Abstract**

Obesity is a major health problem and currently is endemic around the world**.** Obesity is a risk factor for several different types of cancer, significantly promoting cancer incidence, progression, poor prognosis and resistance to anti-cancer therapies. The study of this resistance is critical as development of chemoresistance is a serious drawback for the successful and effective drug-based treatments of cancer. There is increasing evidence that augmented adiposity can impact on chemotherapeutic treatment of cancer and the development of resistance to these treatments, particularly through one of its signature mediators, the adipokine leptin. Leptin is a pro-inflammatory, pro-angiogenic and pro-tumorigenic adipokine that has been implicated in many cancer promoting processes such as angiogenesis, metastasis, tumorigenesis and survival/resistance to apoptosis. Several possible mechanisms that could potentially be developed by cancer cells to elicit drug resistance have been suggested in the literature. Here, we summarize and discuss the current state of the literature on the role of obesity and leptin on chemoresistance, particularly as it relates to breast and pancreatic cancers. We focus on the role of leptin and its significance in possibly driving these proposed chemoresistance mechanisms, and examine its effects on cancer cell survival signals and expansion of the cancer stem cell sub-populations.

**Key words:** obesity-related cancer; leptin; chemoresistance; cancer stem cells; breast cancer; pancreatic cancer

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**Core tip:** Obesity and its main mediator leptin, are implicated in many protumorigenic processes, with emerging evidence from both the literature and our work pointing to a significant role in the development of resistance to chemotherapies. Chemoresistance is a major concern in the field of cancer therapy as some cancers have no targeted therapies available. As obesity reaches epidemic proportions around the world, its impact on diseases like cancer and its treatment becomes more relevant. In this paper, we will discuss the current state of the literature regarding the influence of obesity and leptin on cancer treatment and the development of chemoresistance.

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**INTRODUCTION**

Obesity is the state of having excessive adipose tissue reserves, commonly defined as having a body mass index (BMI) of 30 or more. The global prevalence of obesity is high, with 37% of men and 38% of women being either overweight or obese[1]. There are significant health consequences for being overweight or obese. Obesity is closely associated to high rates of morbidity and mortality. It is considered responsible for an estimated 3.4 million deaths and 4% of years spent with a disability. There is a well-documented increased risk in obese and overweight people for numerous cancers, including thyroid, esophageal, kidney, colon, rectal, melanoma, leukemia, endometrial, gallbladder and breast cancer[2–6]. In addition, weight gain before 50 has been associated with greater risk of breast cancer, especially estrogen negative breast cancer[7-9]. A contributing factor could be complications related to therapy, as obesity is correlated with breast cancer recurrence, with increasing BMI being correlated with increased risk of breast cancer relapse. Obesity impacts on life expectancy, with premenopausal and postmenopausal obese women being 1.75 and 1.34 times respectively at increased risk of death from breast cancer[10].

A distinctive characteristic of obesity and overweight conditions is the high serum level of the main adipokine, leptin secreted by adipose tissue. Leptin, from the Greek work “leptos”, thin, is a 16 kDa protein, composed of 167 aminoacids, its gene, *Ob*, is in humans on chromosome 7q32. Ob gene is composed by three exons and 2 introns, spanning 20 kb. Leptin is the first discovered adipokine, a cytokine secreted by adipocytes, both from the white adipose tissue and brown adipose tissue. Placenta, ovaries, skeletal muscle, bone marrow, stomach pituitary gland, mammary epithelial cells have been shown to express leptin[11]. Several cancer cell types and tumor stroma also express leptin[12].

**Obesity, Leptin/Ob-R and Cancer**

The main role of leptin is to regulate energy balance by inhibiting hunger. Leptin levels correlate to adiposity. Under physiological conditions leptin binds and activates receptors in the arcuate nucleus of the hypothalamus, which regulate appetite[13]. In obese people a decreased sensitivity to leptin was observed resulting in a decreased capacity to feel satiety[14]. A result of this resistance is overeating that results in obesity and the concomitant high serum levels of leptin. In obese individuals serum leptin levels are 10 times higher (*i.e*., 40 ng/ml) than normal weight people (*i.e*., 4 ng/ml)[15]. The upregulation of leptin has an important role in carcinogenesis[16].

Leptin receptor (Ob-R) is predominantly found in the hypothalamus[17], but is expressed at lower level in the whole body, including pancreas[18] and mammary epithelial cells[19]. Remarkably, cancer cells overexpress Ob-R, which enable them to respond to leptin that is more prominent in obese individuals showing high levels of the adipokine. Ob-R belongs to Class I super-family cytokine receptors. It is a transmembrane protein composed by an extra-cellular domain, responsible for binding leptin, a transmembrane domain and a cytoplasmic domain for signaling[20]. Currently six different isoforms of the leptin receptor have been identified, Ob-Ra-f, generated by mRNA splicing or proteolytic processing, Ob-R isoforms are divided in three classes, short and long (which are bound to the cellular membrane) and secreted (a soluble protein that binds leptin in blood). The long isoform Ob-Rb (or l) is the predominant one, expressed at high levels in different cell types. Ob-Rb has full signaling capabilities in contrast to short Ob-R isoforms. It is generally accepted that leptin binding to Ob-R provokes the formation of a homodimer that is responsible for leptin-mediated signals. Leptin and Ob-R have absolute specificity for binding. Once leptin binds to Ob-Rb, it activates several signaling pathways. Because Class I cytokine receptors lack auto phosphorylation function they need auxiliary kinases to initiate signaling upon ligand binding. The first signaling event after leptin binding to Ob-Rb is the activation of janus kinase/signaling transducer and activation of transcription factor pathway (JAK/STAT)[21]. JAK2 recruitment to Ob-R intracytoplasmatic tail leads to the phosphorylation of the kinase, subsequent phosphorylation of Ob-R in several intracytoplasmatic sites and recruitment and phosphorylation of tyrosine residue on STATs. Phosphorylated STATs, then form hetero or homodimers and translocate to the nucleus to induce the transcription of specific genes[22].

Leptin plays roles in other physiological functions, as indicated by the presence of its receptor in different organs and tissues types besides the hypothalamus[23]. Leptin is involved in immunity, proliferation, differentiation, apoptosis, angiogenesis, inflammation, fertility and oncogenesis[12,16,22]. Leptin is known to inhibit bone formation[24]. It can also regulate the ovulatory cycle by stimulating GnRH from the hypothalamus[25,26] and is an important factor in embryo implantation[27-29]. Leptin is involved the onset of puberty[30], regulates glucose homeostasis[31], hematopoiesis[32], modulate immunity, like T cell activity in response to atherosclerosis[33]. Leptin has been speculated to be an inflammatory marker that responds specifically to adipose-derived inflammatory cytokines[34].

Obesity is significant risk factor for cancer incidence and mortality. The effects of obesity on cancer could be due in part to leptin’s elevated levels and Ob-R over expression in cancer cells, which enable leptin-deregulated pleiotropic signals in cancer. Leptin has been shown to have several pro-tumorigenic effects, such as increasing cancer cell proliferation, anti-apoptosis, angiogenesis, self-renewal and possibly resistance to chemotherapeutic treatment[12,16].

Several studies linked the effects of leptin on the proliferation of cancer both *in vivo* and *in vitro* experimental models, and from patient data. Leptin signaling has been consistently linked to the development of breast, endometrial, pancreatic, colon, prostatic, hepatic, skin, brain, oesophagus, stomach, thyroid gland, and ovarian cancers, and leukemia and chondrosarcoma[35–43].

Leptin induces breast cancer cell growth *in vitro* and *in vivo*. Several leptin-induced signaling pathways and factors have been linked to the proliferation of breast, endometrial and pancreatic cancer cells[12,16,36,37]. Leptin induced tumor cell growth and inhibited apoptosis in papillary thyroid cancer (PTC) cells. Serum levels of leptin were shown to be higher in patients with PTC than in negative controls[42]. An increase in the expression of leptin receptor Ob-R was observed in PTC specimens[44]. Leptin can induce the development of non-alcoholic fatty liver disease (NAFLD), one of the major cause of hepatocellular carcinoma, by promoting insulin resistance, steatosis and hepatic inflammation by increasing TGF-β expression[43]. Leptin is overexpressed in colon cancer, Ob-R mRNA was found in cancer cell lines and colon tumors[45] and Ob-R protein expression was confirmed by western blot[46]. Serum leptin levels were significantly high patients with lung cancer, compared to healthy individuals. Lung cancer tissues showed higher expression of leptin compared to normal lung tissue[47]. Leptin was shown to stimulate the proliferation of human myeloid leukemia cell lines[48], and it might play a role in the development of prostate cancer, it can increase growth and survival of prostate cancer cells and Ob-R mRNAs has been found in prostate cancer cells through RT-PCR[49]. Epithelial ovarian cancer (EOC) is one of the principal cause of death in gynecological malignancies, the role of leptin still needs further investigation, Ob-R mRNA was found in several immortalized EOC cell lines[50]. Limited data suggested also a link with leptin and adrenal cancer[51].

Leptin induced pleiotropic effects in cancer cells. Leptin increased breast cancer cell proliferation, which was linked to the up regulation of cyclin D[52] and increased expression of anti-apoptotic proteins like Bcl-2 in breast cancer[53]. Additionally, leptin can down regulate pro-apoptotic Bax[54]. Leptin induces tumor angiogenesis that has a pivotal role in solid tumor growth and metastasis. Leptin not only promotes the expression of angiogenic factors like VEGF[55], VEGFR-2[52,56], and fibroblast growth factor 2 (FGF-2), but also itself induces vascular endothelial cell proliferation *in vitro* with similar effects than VEGF[57]. Moreover, in the absence of VEGF, leptin induced Notch signaling pathway in endothelial cells that was linked to leptin-induced transphosphorylation of VEGFR-1 and VEGFR-2[58]. Leptin induces two angiogenic factors: IL-1[59] and Notch[60] that can increase VEGF expression. Moreover, leptin induces the secretion and synthesis of proteases and adhesion molecules needed for the development of angiogenesis. Leptin induces expression of metalloproteinases 2 and 9 (MMP-2 and MMP-9) that are involved in tissue remodeling, specifically the breakdown of extracellular matrix proteins[61,62]. Additionally, leptin induces the expression of avB3 integrin that is also involved in angiogenesis[37,63]. Leptin induces production of inflammatory cytokines like IL-1, IL-6 and TNF-α, which like leptin can induce the expression of metalloproteinases, promoting tumor invasion and metastasis. TNF-α acts on adipocytes increasing leptin expression[34].

**Leptin-induced Notch and RBP-Jk affect cancer progression**

Gonzalez-Perez’s lab earlier reported that leptin signaling crosstalk to Notch in breast cancer[60]. Notch signaling is an embryonic conserved pathway involved in proliferation, angiogenesis, cell fate and development. Notch system is composed by transmembrane proteins: receptors (Notch1-4) and ligands expressed in adjacent cells (Delta-like, Dll1-3, and Jagged-like, JAG1-2), and molecular targets hairy enhancer of split (Hes1–7), hairy/enhancer-of-split related with YRPW motif subfamilies (Hey1, Hey2, HeyL, HesL/HelT, Dec1/BHLHB2, Dec2/BHLHB3) and survivin. Notch receptors are all composed of an extracellular domain (NECD) where ligands bind, a transmembrane domain (TM) and an intracellular domain (NICD). Notch is activated upon binding to a ligand that triggers a proteolytic cascade producing activated NICD, which is transported to the nucleus where it binds to a tumor repressor, DNA-binding protein, recombination signal binding protein for immunoglobulin kappa J (RBP-Jk) or CBF1/Su(H)/Lag-1 (CSL) family of transcription factors[64].

RBP-Jk is a DNA binding factor, which mediate either transcriptional repression or transcriptional activation. RBP-Jk binds to the ubiquitous corepressor proteins (Co-R: silencing mediator of retinoid and thyroid hormone receptors, SMRT and Ski-interacting protein, SKIP)[65], histone deacetylases (HDACs), CBF1 interacting corepressors (CIR), and SAP30 (a linker between CBF1 and the HDAC complex)[66], which repress transcription of some genes. Thus, RBP-Jk is a transcription factor that acts as a repressor in complex with SMRT and SKIP when it is not associated with Notch. In contrast, activated NICD-RBP-Jk complex displaces co-repressors and recruits coactivator (Co-A). When RBP-Jk is associated with NICD it acts as a transcriptional activator in complex with mastermind-like proteins, MAML[67]. This process is required for Notch-induced canonical signals that increase the transcription of target genes such as Hes, Hey, nuclear factor-kappa B (NF-κB), cyclin D, c-Myc and others[64]. Additionally, Notch signaling is linked to expansion of cancer stem cell populations (CSC), which show self-renewal capabilities and can recapitulate tumor heterogeneity and are believed to be responsible for recurrence and drug resistance[68,69].

Notch signaling is deregulated in many cancers. Indeed, deregulation of Notch signaling is a hallmark of breast cancer[64]. In breast and pancreatic cancer cells leptin upregulates Notch receptors, ligands and targets[16,60]. Moreover, latest reports show a positive correlation between leptin, Ob-R and Notch components in endometrial cancer tissues from obese patients[70]. Leptin induces RBP-Jk and Notch that impacts on CSC and self-renewal[16,60,71]. Moreover, a novel crosstalk between Notch, IL-1 and leptin (NILCO) was found in breast cancer[53,60,72]. NILCO induces proliferation/migration and upregulation of VEGF/VEGFR-2, and could represent the integration of developmental, pro-inflammatory and pro-angiogenic signals critical for leptin effects in breast cancer[60]. Paradoxically, low expression of RBP-Jk has been reported in several solid tumors that was associated with increase aggressiveness[73]. Our preliminary data indicate that knockdown of RBP-Jk in breast cancer cells induces a dramatic increase of Notch 3 and Notch 4 expression, CSC population (CD24-/CD44+) and N-cadherin (epithelial-mesenchymal-transformation marker)[74]. These data may suggest that tumor repressor activities of RBP-Jk could overcome the oncogenic actions of NICD-RBP-Jk complex upon activation of Notch, thus, cancer cells downregulate RBP-Jk expression in order to proliferate and develop tumors. However, this topic deserves follow up and more deep mechanistic investigation.

**Leptin signaling induces breast cancer progression**

Leptin and Ob-R are low expressed in human mammary glands, yet they play a role in the normal development[75]. In contrast, leptin and Ob-R expression is upregulated in breast cancer[76]. Obese patients with breast cancer show tumoral leptin overexpression that correlated to larger and more advanced tumors[77]. The molecular mechanisms involved in obesity-related breast carcinogenesis are not very clear. The binding of leptin to its receptor on breast cancer cells induces the activation of multiple oncogenic pathways, including Jak/STAT3, ERK1/2, and phosphoinositide 3-kinase (PI-3K) pathways, cyclin D1 expression and retinoblastoma protein hyperphosphorylation[78]. Triple negative breast cancer (TNBC) showed high level of molecules correlated with metastasis and lower survival of patients of leptin (*i.e*., IL-1, Notch and VEGF/VEGFR2). Notch, IL-1 and leptin crosstalk outcome (NILCO) seems to play essential role s in the regulation of leptin-mediated induction of proliferation/migration and expression of pro-angiogenic molecules in breast cancer[64].

Breast adipose tissue is a source of estrogen, which is involved in tumorigenesis. Estrogens promote cell proliferation by inhibiting apoptosis and inducing angiogenesis[79]. Therefore, these molecules are breast cancer markers and therapeutic targets. A functional crosstalk between estrogen and leptin exists and may act to promote tumorigenesis[80]. The aromatization of androstenedione in adipose tissue is the main source of estrogen[81], a reaction catalysed by the enzyme aromatase, whose expression is increased by leptin in ER positive breast cancer cells[82]. Leptin has been shown to induce resistance in ER positive cancer cells to Faslodex[83] and Tamoxifen[84]. Leptin binding to ObR was also shown to transactivate HER2/neu[85], which is an important oncogenic protein involved in breast cancer growth. All these data indicate that leptin is involved in the development of breast cancer. Therefore, the use of leptin-signaling targeting drugs could be a novel strategy in breast cancer management.

**Leptin signaling promotes the expansion of cancer stem cells**

***Breast cancer stem cells***

The cancer stem cell (CSC) theory postulates the existence of a sub-population of cancer cells with the ability to undergo self-renewal and also tumor differentiation[86]. The presence of these cells is a risk factor for carcinogenesis. CSC can recreate the bulk of the tumor, and are believed to be responsible for tumor initiation, cancer recurrence and metastatic progression[87]. CSC in breast cancer (BCSC) initiate and drive carcinogenesis and tumor differentiation[88]. BCSC can be identified by several molecular phenotypic markers. Networks of cytokines and growth factors, including leptin, have been implicated in BCSC interaction with the tumor micro-environment[89]. BCSC exhibit a high sensitized responses to leptin. It was reported that leptin mediates microenvironment effects on BCSC activity that establishes a self-reinforcing signaling circuit. Leptin upregulates several factors considered BCSC markers in several breast cancer cell lines like, including CD44, ALDH1[60], HER2[90], Oct-4 and Sox2[91]. Leptin is also involved in activation of transcriptional factors associated with BCSC, like STAT3[92] and NF-κB[93].BCSC markers are shown in Table 1[60,90,91,94-105]

**Pancreatic cancer stem cells**

***Characterization of pancreatic cancer stem cells***

Pancreatic cancer stem cells (PCSC) are characterized by the expression of cell markers, including CD24+CD44+, CD133+, CD24+CD44+ and epithelial specific antigen (ESA+ or EpCAM+) and aldehyde dehydrogenase (ALDH+)[106-108]. PCSC represent a rare cell population of 0.5%-1% of total PC cells (Table 2). Remarkably, when isolated and inoculated into nude mice PCSC generate tumors, whereas implantation of PC cells negative for these markers could not. Hermann *et al*[109]showed that a subpopulation of PCSC, CD133+CXCR4+ was found in patients with PC metastatic disease. Additionally, PC ALDH+ cells showed enhanced clonogenic growth, migratory potential and affected negatively the overall survival of PC patients. In 2011, Li *et al*[106] described a new population of PCSC c-Met+ involved in PC growth and metastasis. Recent preclinical data suggest PC c-Met+ cells are involved in drug resistance. Indeed, the use of a c-Met inhibitor (Cabozantinib) in PC patient overcomes Gemcitabine resistance[110]. PCSC could also be identified by flow cytometry using Hoechst 33342 dye. PC side population that can exclude Hoechst 33342 dye correlated with chemoresistance and poor survival[111]. Wang *et al*[112] described a similar PC side population (Hoechst 33342 negative) showing high expression for CD133+, ABCG2+ and Notch1+, which were more chemoresistant compared to non-side population cells. A PCSC population marked by the expression of Doublecortin and Ca/Calmodulin- Dependent Kinase-Like 1(Dclk1) was described by Bailey *et al*[113]in 2014. PCSC Dclk1+ were found in PanIN (pancreatic intraepithelial neoplasia) lesions, as well as in invasive stages of PC. These findings suggest that PCSC populations can be identified at the early stages of pancreatic tumorigenesis and may serve as a biomarker for early detection of this deadly disease.

PCSC show self-renewal and multipotency, and can initiate and propagate the parental tumor while serial passage into immunocompromised mice[114]. CSC including PCSC have retained the expression of at least three of the transcription factors that are characteristic to embryonic stem cells (ESC) (Oct-4, Sox-2 and Nanog). Increased levels of Oct-4 and Nanog are correlated with early stages of carcinogenesis and worse prognosis. Oct-4 and Nanog play important rolse in embryonic development, and also in maintaining the stemness of PCSC. In contrast, PCSC double knockdown of Oct-4 and Nanog show reduced proliferation, migration, invasion and tumorigenesis[115]. Additionally, Oct-4 contributes to metastasis and cancer multidrug resistance[116]. De novo Sox2 expression alone in PC is sufficient to promote self-renewal, differentiation and stemness. Although ESC and PCSC share the property of self-renewal, ESC favors differentiation, while PCSC act more toward proliferation and inhibition of apoptosis. Targeting PCSC may be a viable therapeutic strategy against PC. A better understanding of Oct-4, Sox-2 and Nanog regulation could facilitate the design of individualized therapies for PC patients[117].

Current studies demonstrate that PCSC determine tumor relapse and metastasis following chemotherapy[118]. From a clinical perspective, targeting PCSC populations would ensure tumor eradication. However, PCSC possess escape mechanisms shared with normal stem cells, such as over-expression of multi-drug transporters. These transporters increase the efflux of anticancer drugs, thereby reducing their accumulation inside the cancer cells[118]. ABCB1 protein was significantly augmented in CD44+ cells during acquisition of PC cells resistance to Gemcitabine. CD44 expression in PC was correlated with histologic grade and poor prognosis. These data indicate that cancer stem cells were expanded during the acquisition of Gemcitabine chemoresistance[119]. In line with these findings, the administration of anti-CD44 monoclonal antibody to a human PC xenograft mouse model increased Gemcitabine sensitivity[120]. Additionally, Metformin enhanced the capacity of Gemcitabine to inhibit the proliferation of PC cells by inhibiting the proliferation of CD133+ cells[121]. Side population PCSC identified by Van der Broeck in 2012[111] are resistant to Gemcitabine. Side population PC cells isolated from Panc-1 cell line have been found to express both ABCB1 and ABCG2, which contribute to chemoresistance[122]. Identification of enhanced stem cell populations within PC tumors might be used as biomarkers for personalized therapy.

***Pancreatic cancer stem cell regulators***

Several factors could affect PCSC. Accumulated evidence suggested that microRNAs are involved in the regulation of PCSC. Specifically, miRNA34 affects the maintenance and survival of PCSC[123]. Obesity is associated with increased severity of acute pancreatitis[124] and decreased survival of PC patients. In obese mice, IL-6 contributes to prolonging inflammation and altering resolution from pancreatic damage, possibly contributing to a microenvironment favorable to tumorigenesis[125]. Cigarette smoking and nicotine, a major risk factor in PC, increase monocyte chemoattractant protein 1 (MCP-1) expression in PC cells. MCP-1 was found in 60% of invasive PC lesions, of whom 66% were smokers[126]. The concentration of six cytokines (IL-1β; IL-6, IL-8, VEGF, TGF, IL-10) were consistently reported to be increased in pancreaticductal adenocarcinoma (PDAC) patients. These molecules were associated with the severity of PDAC (*i.e*., metastasis, tumor size, and advanced stage) that suggest these cytokines have prognostic biomarker for PC[127]. Additionally, IL-8/CXCR1 axis was associated with cancer stem cell properties in PC[128]. CXCR1 expression in PC patients correlates with lymph node metastasis and poor survival. MMP-13 has been shown to help mediate the effect of leptin on invasiveness and metastasis of pancreatic cancer. In addition, there was a positive correlation between the expression of PCSC markers CD133 and CD44, and CXCR1[129].

P300 is a tumor suppressor gene. However, this factor is also upregulated in various cancer types and associated with worse prognosis. In PC, P300 is associated with chemoresistance from apoptosis upon Gemcitabine-induced DNA damage[130]. TGF-β negatively regulates ALDH1 expression (a PCSC marker) in a SMAD dependent manner in PC cells. This regulatory mechanism might be disrupted by SMAD4 mutations and deletions in PC cells[131]. The binding of stem cell factor (SCF, a protein involved in PC progression) to its receptor, c-kit, determines an increase in HIF-1α synthesis that affects cancerous transformation, chemoradiotherapy resistance, and tumor progression[132].

Additionally, high levels of leptin receptor, Ob-R, are associated with PC stage and lymph node metastasis and overall shorter survival. Ob-R and HIF-1α expression was highly associated in PC tissues. HIF-1α regulated the expression of Ob-R in PC[133]. Leptin binding to Ob-R was earlier found to induce HIF-1α in breast cancer cells. Leptin-induced HIF-1α was involved in the upregulation of VEGFR2 in these cells[55]. Therefore, it is possible that a leptin-induced HIF-1α feedback regulating Ob-R is present in PC. Moreover, robust expression of Ob-R is a characteristic of tumor initiating stem cells and pluripotent stem cells that was mediated directly by Oct-4 and Sox2[91]. Furthermore, the expression of leptin in gastro-esophageal adenocarcinomas was associated with chemoresistance. The use of leptin receptor antagonist SHLA increased the sensitivity to Cisplatin in the resistant gastric cancer cell line, AGS Cis5, and the oesophageal adenocarcinoma cell line, OE33[134].

***Chemoresistance and cancer stem cells***

In the absence of targeted therapeutic options, chemotherapy, along with surgery and radiotherapy are usually the last and only options for cancer treatment. Thus, resistance to chemotherapy is a vital area of research. Investigations on the mechanisms involved in chemoresistance are essential to overcome this issue. There are several mechanisms related to chemoresistance that have been identified in cancer cells, which include reduction or inhibition of drug-induced apoptosis, overexpression of detoxification and efflux proteins, increased expression of survival factor and pathways as nuclear factor kappa-light-chain-enhancer of activated B cells (NFĸB) and PI-3K/Akt, hypoxia and hypoxia inducible factor HIF, and expansion of chemoresistant CSC among others[135-138].

***Inhibition of apoptosis***

Numerous chemotherapies target the increased DNA synthesis that cancer cells undergo. Classes of chemotherapeutics such as platinum agents (Cisplatin), alkylating agents (Cytoxane) and anthracyclines (Adriamycin or Doxorubicin) inhibit DNA synthesis. A consequence of the action of these agents is increased apoptosis due to DNA damage. The p53 pathway plays an important role in cancer cell avoidance of apoptosis, with mutations in the p53 gene associated with increased drug resistance in cancer cell lines and poor survival in cancer patients[135,139]. In addition, cancer cells have been known to competitively inhibit Caspase 3, a central molecule in the apoptosis pathway. These cells show increased expression of B cell lymphoma 2 (BCL-2) and B cell lymphoma extra-large (BCL-xL) anti apoptotic proteins[140-143].

***Detoxification and efflux proteins***

Aldehyde dehydrogenases (ALDH) are a class of enzymes that oxidise aldehydes. ALDH isoforms have been implicated in CSC and resistance to chemotherapeutics. ALDH1 is a marker of CSC and progenitor cells[144], whose expression correlated with poor response to Docetaxel therapy in advanced breast cancer[145]. Increased expression of ALDH1A1 and ALDH3A1 lead to greater inactivation of Cyclophosphamide in breast cancer[136].

ATP binding cassette (ABC) transporters are a family of transmembrane proteins involved in the efflux of drugs from cancer cells. ABC (ABCB1, ABCC1 and ABCG2) family of proteins are mainly found on CSC side-population (SP, Hoechst negative). ABCB1, also known as p-glycoprotein, CD243 or MDR1, is an efflux pump protein with broad substrate specificity. It is known to pump out chemotherapeutics such as Doxorubicin and Paclitaxel. ABCC1 is known to give cancer cell resistance to anthracyclines such as Doxurubicin. ABCG2 also called the breast cancer resistance protein or CDw338, allows cancer cell resistance to Mitoxantrone and Doxurubicin[146].

***NFĸB pathway***

NFĸB signaling pathway is a survival mechanism that controls DNA transcription of several genes. In non-malignant cells NFĸB signaling plays a central role in immune response to infection. It is responsible for cellular responses to a wide range of stimuli which include reactive oxygen species, ionising radiation, bacterial lipopolysaccharide, and IL-β and TNF-α. To drive oncogenesis, NFƙB signaling cooperates or crosstalks with signaling pathways, oncogenic or cancer-related proteins such as STAT3, p53, ALDH1, glycogen synthase kinase (GSK-3β), PI-3K, MAPK, PKC, and others[147].

NFƙB signaling is a critical mediator of chemoresistance in cancer. Glioblastoma multiforme's resistance to Gemcitabine involves NFkB, ALDH and ROS actions[148]. Anti-ovarian cancer effects of MK5108 compound relied on the inhibition of the Aurora-A kinase and NFkB signaling, which induced poliploidy and cell cycle arrest[149]. In breast cancer, targeting NFkB signaling increased apoptosis and reduced proliferation in drug resistant breast cancer cell lines[150]. In mesothelioma, the STAT3- NFĸB signaling crosstalk is essential in ALDH-mediated chemoresistance[151]. Abnormal activation of NFĸB signaling is also implicated in cancer resistance to Paclitaxel therapy[152].

***HIF and tumor hypoxia***

Hypoxia is a term which describes deficient oxygen supply to tissues due to poor vasculature, as it is in the case of obesity and cancer. Proliferation and expansion of adipose tissue induce tissue hypoxia and the expression of HIF. Hypoxia in cancer is associated with poor outcomes and chemoresistance[137,153]. In TNBC, chemotherapeutic treatment with Paclitaxel and Gemcitabine results in expression of HIF, and enrichment of CSC through IL-6 and IL-8 actions. Chemical inhibition of HIF results in the depletion of CSC and tumour abrogation *in vitro* and *in vivo*[154].

In addition, hypoxia promotes survival of TNBC MDA-MB231 from Paclitaxel-induced apoptosis via mTOR/JNK pathway[155].

***CSC resistance to chemotherapy***

The presence of CSC within tumors make them resistant to chemotherapy. CSC are commonly more resistant to chemotherapeutics which target the bulk of the tumour that allow the proliferation of CSC[156]. The CSC stemness phenotype and chemoresistance involve TGF-β signaling, which plays a prominent role in stem biology, facilitating epithelial to mesenchymal transition in mammary cancer cells, which is a property of CSC[138]. TNBC cell lines treated with Paclitaxel showed an enrichment of cancer cells with stem like properties and increased TGF-β signaling both *in vitro* and *in vivo*. Chemical inhibition of TGF-β signaling abrogates tumor formation[157]. CSC show higher expression of ABC family of proteins that increase their capability to efflux chemotherapeutics from cells. CSC also show dismished apoptosis rate, and over activation of detoxification proteins and survival pathways as NFB and PI-3K[158].

**Obesity, leptin and drug resistance**

Obesity and leptin signaling have been implicated in enhance capabilities of cancer cells to avoid apoptosis. Leptin expression was associated with higher expression of BCL-2 and BCL-xL expression in breast cancer cells[159]. Furthermore, leptin signaling has been reported to activate the PI-3K/Akt pathway that antogonizes apoptosis in various cancers such as colon cancer, liver cancers, endometrial cancers and lymphomas[44,160-163]. Additionally, obesity has been shown to influence breast cancer response to Doxurubicin therapy. Indeed, obese mice treated with Doxorubicin showed more proliferative tumors that also had more CSC as compared with non-obese mice[164]. Leptin increases the expression of ABC protein transporters in glioblastoma[165]. Our preliminary data further show that leptin increases the expression of ABCB1 in breast and pancreatic cancer cells.

Another mechanism involved in obesity-induced chemoresistant is NFƙB signaling. It is known that NFƙB is activated by leptin signaling and that can increase survival of cancer cells under chemotherapeutic treatment[55]. An additional link between obesity (via leptin signaling) and cancer chemoresistance is HIF, which correlates with activation of leptin signaling in several cancers including endometrial, pancreatic, breast and colon cancers[133,166-168]. A potential mechanism involved in obesity-mediated drug resistant is TGF- β signaling. Leptin and TGF-β are commonly co-expressed in breast cancer[34]. It is known that TGF-β signaling induces leptin expression. However, the connection between leptin and TGF-β signaling in breast cancer is still unclear[169].

Leptin increased proliferation and survival of breast cancer estrogen receptor positive cells, MCF-7 cells treated with Cisplatin. These data further assessed that leptin is a survival factor that induces drug resistant in breast cancer[170]. Moreover, leptin was found able to induce CSC expansion in breast[60] and pancreatic cancer[16]. Furthermore, our preliminary data suggest that leptin induces the expression of Oct-4 and Nanog in breast cancer cells. These factors are essential for the upregulation of Ob-R in cancer cells[91]. Thus, leptin can induce a feedback mechanism through Oct-4/Nanog to sustain Ob-R expression and its prooncogenic signals in breast cancer.

**Leptin antagonists and cancer progression**

Leptin signaling has numerous protumorigenic effects, including the increase chemoresistance found in several tumors. Therefore, leptin antagonism could be a new strategy to overcome drug resistance in cancer. Several molecules have been described as potential new agents to target leptin-induced cancer growth and drug resistance. Majority of the leptin antagonists reported are mutated or truncated versions of leptin molecule: leptin muteins, Allo-aca and D-ser, LDFI, and leptin peptide receptor antagonists ***(***LPrA).

***SMLA and SHLA***

Leptin muteins or mutant proteins, were generated using random mutagenesis of the leptin sequence and screened for high affinity variants using a yeast surface display. This resulted in the creation and identification of high affinity muteins. Two mutein antagonists named superactive mouse leptin antagonist (SMLA) and superactive human leptin antagonist (SHLA) were made by the introduction of an Asp23 mutation. These antagonists showing 4 aminoacid residue mutations (D23L/L39A/D40A/F41A) were reported to have 60-fold increased affinity for Ob-R and 14 fold greater antagonistic activity as compared with the original leptin antagonist showing 3 mutations (L39A/D40A/F41A)[171]. These muteins were pegylated at the N terminus to increase bioavailability and stability. However, the pegylated muteins increased BW in mice. Pegylated SMLA induced higher BW gain as compared with the pegylated SHLA[171]. No effects of muteins on leptin-induced chemoresistance in cancer have been reported to date.

***Allo-aca and D-ser***

Allo-aca is a non-toxic, 9-residue peptide leptin antagonist based on the C terminal Ob-R binding leptin site III. Allo-aca was reported to increase survival of CD1 nude mouse hosting TNBC. The effective dose of the peptide was found after 9 to 13 days of treatment by injecting intraperiotoneally between 0.1 and 1 mg Allo-Aca /kg body weight (BW)/day. Allo-aca was nontoxic in C57Bl/6 and CD1 nude mice, but showed hepatotoxicity at 0.2 mg/kg BW/day in SCID mice[172]. Additionally, it induced weight gain of 6% to 10% of BW[172]. Treatment of TNBC MDAMB231 cell line with Allo-aca 50 pM inhibited leptin-induced proliferation in *in vitro*[172]. D-ser, peptide inhibitor is an analogue of Allo-aca that at 1nM concentration inhibited leptin-induced proliferation in Ob-R positive breast and colon cancer cells *in vitro* without exhibiting agonist activity[173]. However, no data on the effects of these antagonists on leptin-induced drug resistance and CSC are available.

***LDFI***

LDFI is a leptin peptide antagonist composed by amino acid 39 to 42 on the leptin binding site I (Leu-Asp-Phe-Ile). LDFI was reported to inhibit leptin-induced growth of breast cancer cells *in vitro* and *in vivo*[174]. This peptide antagonist inhibited proliferation, colony formation on soft agar and Boyden chamber transmigration of estrogen receptor positive as well as estrogen receptor negative breast cancer cells. LDFI effects correlated with reduced expression of key downstream leptin effectors such as JAK2, STAT3, AKT and MAPK. *In vivo*, the pegylated peptide (LDFI-PEG) was shown to inhibit tumour growth in a murine mammary xenograft model. LDFI-PEG showed no toxicity or effects on BW of mice[174]. No reports on potential effects of LDFI on drug resistance in breast or other cancer types are available.

***LPrAs***

LPrA1 and LPrA2 were earlier designed and tested *in vitro* and *in vivo* in mouse models[52,53,56,72,175,176]. LPrAs are composed by aminoacid sections of the binding site I (LPrA1) and III (LPrA2) of the leptin molecule[63]. LPrA2 was conjugate to polyethylene glycol 20 kDa (PEG-LPrA2) or to iron-oxide nanoparticles (IONP-LPrA2) to increase its bioavaibility and effectiveness to block leptin signaling in cancer cells. Unconjugated and conjugated LPrA2 effectively inhibited leptin-induced protumorigenic actions in breast and pancreatic cancer cells[52,53,56,72,175,176]. LPrA2 showed potent effects for the reduction of leptin-induced growth of tumors and expression of inflammatory (IL-1/IL-1R tI), proliferation (Ki67, PCNA), angiogenic factors (VEGF/VEGFR2) and Notch in tumors and endothelial cells[53,56,58,72]. The antagonist effects of LPrA2 on tumor growth and angiogenesis were more evident in obese than in lean mice[53,72]. However, unconjugated or conjugated LPrA2 showed no toxicity and did not affect energy balance (BW or food intake) or general health when it was applied (0.1 mM/i.v./twice weekly) to many lean and obese mice for two months. Remarkably, LPrA2 negatively impact on leptin-induced expansion of CSC and Notch expression in breast and pancreatic cancer cells, derived tumorspheres and xenografts[16,74]. Moreover, LPrA2 significantly reduced the leptin-induced effects on drug resistance (Cisplatin, Sunitinib, Paclitaxel, Doxorubicin) in breast cancer cells[16,176].

**Conclusion**

Combination of poor dietary habits and low physical activity, which are reinforced by accessibility of low-cost high caloric and fat foods have led to the obesity pandemic. Accumulated evidence supports a negative role of obesity on cancer risk, progression and management. Despite many efforts and social programs to tackle obesity, its effects on morbidity and mortality and its influences on cancer incidence and treatment are in crescendo[1-5]. It is known that obesity and leptin signaling not only affect cancer cells, but also tumor stroma. Moreover, leptin and paracrine factors secreted from cancer and stroma cells (adipocytes, fibroblasts, endothelial cells and inflammatory cells) could affect tumor progression, CSC and chemoresistance[16,176]. In this regards, the use of nontoxic leptin antagonists that do not affect energy balance could be a novel adjuvant therapy for cancer drugs. These compounds can increase chemotherapeutic effectiveness and allow reducing their dosage and undesired side effects in cancer patients.

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**Table 1 Breast cancer stem cells markers**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Markers** | **Localization** | **Ref.** | **Markers** | **Localization** | **Ref.** |
| CD44 | Cell surface | Guo *et al*[60]*,* 2011 | MET | Cell surface | Baccelli *et al*[100]*,* 2013 |
| CD24 | Cell surface | Kakarala *et al* [94], 2008 | CD133 | Cell surface | Tume *et al*[101]*,* 2016 |
| Epcam | Cell surface | Chiotaki *et al*[95]*,* 2015 | CD338 | Cell surface | Leccia *et al*[102]*,* 2014 |
| CD49f | Cell surface | Chiotaki *et al*[95]*,* 2015 | ALDH1 | Cytoplasm | Guo *et al*[60]*,* 2011 |
| MUC1 | Cell surface | Nigam[96], 2013 | Bmi I | Cytoplasm | Kim *et al*[103], 2015 |
| CD29 | Cell surface | Yeo *et al*[97]*,* 2016 | GLI I | Cytoplasm | Fernandez-Zapico[104], 2013 |
| CD61 | Cell surface | Yeo *et al*[97]*,* 2016 | Sox2 | Cytoplasm | Feldman *et al*[91]*,* 2012 |
| CD47 | Cell surface | Zhang *et al*[98]*,* 2015 | Oct-4 | Cytoplasm | Feldman *et al*[91]*,* 2012 |
| HER2 | Cell surface | Korkaya *et al*[90]*,* 2008 | NANOG | Cytoplasm | McClements *et al*[105]*,* 2013 |
| eHSP90 | Cell surface | Stivarou *et al*[99]*,* 2016 |  |  |  |

**Table 2 Pancreatic cancer stem cells markers**

|  |  |  |
| --- | --- | --- |
| **Stem cell population** | **Localization** | **Ref.** |
| CD24+CD44+ | Extracellular | Li *et al*[106]*,* 2007 |
| CD24+CD44+ESA+ | Extracellular | Li *et al*[106]*,* 2007 |
| CD133+CXCR4+ | Extracellular | Hermann *et al*[107]*,* 2007 |
| CD133+CD44+ | Extracellular | Moitra *et al*[123]*,* 2011 |
| C-Met | Extracellular | Li *et al*[106]*,* 2007 |
| DCLK1 | Intracellular | Bailey *et al*[113]*,* 2014 |
| ABCB1 | Extracellular | Van den broeck *et al*[111]*,* 2013 |
| Sox2 | Intracellular | Herreros-Villanueva *et al*[117]*,* 2014 |