World Journal of
Clinical Oncology

Contents

Contents

World Journal of Clinical Oncology
Volume 8 Number 2 April 10, 2017

ABOUT COVER

Editorial Board Member of *World Journal of Clinical Oncology*, Hua-Feng Wei, MD, PhD, Research Associate, Cancer Center Lab, General Hospital of Chinese PLA, China and Second Military Medical University, International Joint Cancer Institute, Beijing 100853, China

AIM AND SCOPE

World Journal of Clinical Oncology (*World J Clin Oncol*, *WJCO*, online ISSN 2218-4333, DOI: 10.5306) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJCO covers a variety of clinical medical topics, including etiology, epidemiology, evidence-based medicine, informatics, diagnostic imaging, endoscopy, tumor recurrence and metastasis, tumor stem cells, radiotherapy, chemotherapy, interventional radiology, palliative therapy, clinical chemotherapy, biological therapy, minimally invasive therapy, physiotherapy, psycho-oncology, comprehensive therapy, and oncology-related nursing. Priority publication will be given to articles concerning diagnosis and treatment of oncology diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

We encourage authors to submit their manuscripts to *WJCO*. We will give priority to manuscripts that are supported by major national and international foundations and those that are of great clinical significance.

INDEXING/ABSTRACTING

World Journal of Clinical Oncology is now indexed in PubMed, PubMed Central and Scopus.

FLYLEAF

EDITORS FOR THIS ISSUE

FRONTIER

Leptin signaling and cancer chemoresistance: Perspectives

Pierre V Candelaria, Antonio Rampoldi, Adriana Harbuzariu, Ruben R Gonzalez-Perez

Pierre V Candelaria, Antonio Rampoldi, Adriana Harbuzariu, Ruben R Gonzalez-Perez, Department of Microbiology, Biochemistry and Immunology, Morehouse School of Medicine, Atlanta, GA 30310, United States

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 cancers 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; Cancer stem cells; Leptin; Chemoresistance; Breast cancer; Pancreatic cancer

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.

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, pancreas 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, and 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 cyto-plasmic 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. Phos-phorylated 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 for-mation[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 in the onset of puberty[30], regulates glucose homeostasis[31], hematopoiesis[32], and 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 a 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 transforming growth factor beta (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 in 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, but the role of leptin in this disease still needs further investigation as Ob-R mRNA was found in several immortalized EOC cell lines[50]. Limited data suggested also a link between 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 vascular endothelial growth factor (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: Interleukin (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 tumor necrosis factor (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 roles 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

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	4-Oct	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			

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. Rasheed *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 roles 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)

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	Ji *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

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 pancreatic ductal 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 PC. 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 (NFκB) 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 Doxorubicin. ABCG2 also called the breast cancer resistance protein or CDw338, allows cancer cell resistance to Mitoxantrone and Doxorubicin[146].

NFκB pathway

NFκB signaling pathway is a survival mechanism that

controls DNA transcription of several genes. In non-malignant cells NFκB 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 lipopoly-saccharide, IL-β and TNF-α. To drive oncogenesis, NFκB 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].

NFκB signaling is a critical mediator of chemoresistance in cancer. Glioblastoma multiforme's resistance to Gemcitabine involves NFκB, ALDH and ROS actions[148]. Anti-ovarian cancer effects of MK5108 compound relied on the inhibition of the Aurora-A kinase and NFκB signaling, which induced polyploidy and cell cycle arrest[149]. In breast cancer, targeting NFκB signaling increased apoptosis and reduced proliferation in drug resistant breast cancer cell lines[150]. In mesothelioma, the STAT3-NFκB signaling crosstalk is essential in ALDH-mediated chemoresistance[151]. Abnormal activation of NFκB 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 diminished apoptosis rate, and over activation of detoxification proteins and survival pathways as NFκB 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 antagonizes 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 Doxorubicin 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 NFκB signaling. It is known that NFκB 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 pro-oncogenic 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 d 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 vitro*[172]. D-ser, peptide inhibitor is an analogue of Allo-aca that at 1 nM 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. per 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 chemo-resistance[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.

REFERENCES
1   **Ng M**, Fleming T, Robinson M, Thomson B, Graetz N, Margono C, Mullany EC, Biryukov S, Abbafati C, Abera SF, Abraham JP, Abu-

Rmeileh NM, Achoki T, AlBuhairan FS, Alemu ZA, Alfonso R, Ali MK, Ali R, Guzman NA, Ammar W, Anwari P, Banerjee A, Barquera S, Basu S, Bennett DA, Bhutta Z, Blore J, Cabral N, Nonato IC, Chang JC, Chowdhury R, Courville KJ, Criqui MH, Cundiff DK, Dabhadkar KC, Dandona L, Davis A, Dayama A, Dharmaratne SD, Ding EL, Durrani AM, Esteghamati A, Farzadfar F, Fay DF, Feigin VL, Flaxman A, Forouzanfar MH, Goto A, Green MA, Gupta R, Hafezi-Nejad N, Hankey GJ, Harewood HC, Havmoeller R, Hay S, Hernandez L, Husseini A, Idrisov BT, Ikeda N, Islami F, Jahangir E, Jassal SK, Jee SH, Jeffreys M, Jonas JB, Kabagambe EK, Khalifa SE, Kengne AP, Khader YS, Khang YH, Kim D, Kimokoti RW, Kinge JM, Kokubo Y, Kosen S, Kwan G, Lai T, Leinsalu M, Li Y, Liang X, Liu S, Logroscino G, Lotufo PA, Lu Y, Ma J, Mainoo NK, Mensah GA, Merriman TR, Mokdad AH, Moschandreas J, Naghavi M, Naheed A, Nand D, Narayan KM, Nelson EL, Neuhouser ML, Nisar MI, Ohkubo T, Oti SO, Pedroza A, Prabhakaran D, Roy N, Sampson U, Seo H, Sepanlou SG, Shibuya K, Shiri R, Shiue I, Singh GM, Singh JA, Skirbekk V, Stapelberg NJ, Sturua L, Sykes BL, Tobias M, Tran BX, Trasande L, Toyoshima H, van de Vijver S, Vasankari TJ, Veerman JL, Velasquez-Melendez G, Vlassov VV, Vollset SE, Vos T, Wang C, Wang X, Weiderpass E, Werdecker A, Wright JL, Yang YC, Yatsuya H, Yoon J, Yoon SJ, Zhao Y, Zhou M, Zhu S, Lopez AD, Murray CJ, Gakidou E. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2014; **384**: 766-781 [PMID: 24880830 DOI: 10.1016/S0140-6736(14)60460-8]

2   **Baer HJ**, Tworoger SS, Hankinson SE, Willett WC. Body fatness at young ages and risk of breast cancer throughout life. *Am J Epidemiol* 2010; **171**: 1183-1194 [PMID: 20460303 DOI: 10.1093/aje/kwq045]

3   **Llewellyn A**, Simmonds M, Owen CG, Woolacott N. Childhood obesity as a predictor of morbidity in adulthood: a systematic review and meta-analysis. *Obes Rev* 2016; **17**: 56-67 [PMID: 26440472 DOI: 10.1111/obr.12316]

4   **Jarvis D**, Mitchell JS, Law PJ, Palin K, Tuupanen S, Gylfe A, Hänninen UA, Cajuso T, Tanskanen T, Kondelin J, Kaasinen E, Sarin AP, Kaprio J, Eriksson JG, Rissanen H, Knekt P, Pukkala E, Jousilahti P, Salomaa V, Ripatti S, Palotie A, Järvinen H, Renkonen-Sinisalo L, Lepistö A, Böhm J, Meklin JP, Al-Tassan NA, Palles C, Martin L, Barclay E, Farrington SM, Timofeeva MN, Meyer BF, Wakil SM, Campbell H, Smith CG, Idziaszczyk S, Maughan TS, Kaplan R, Kerr R, Kerr D, Buchanan DD, Win AK, Hopper JL, Jenkins MA, Lindor NM, Newcomb PA, Gallinger S, Conti D, Schumacher F, Casey G, Taipale J, Aaltonen LA, Cheadle JP, Dunlop MG, Tomlinson IP, Houlston RS. Mendelian randomisation analysis strongly implicates adiposity with risk of developing colorectal cancer. *Br J Cancer* 2016; **115**: 266-272 [PMID: 27336604 DOI: 10.1038/bjc.2016.188]

5   **Renehan AG**, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet* 2008; **371**: 569-578 [PMID: 18280327 DOI: 10.1016/S0140-6736(08)60269-X]

6   **Troy JD**, Hartge P, Weissfeld JL, Oken MM, Colditz GA, Mechanic LE, Morton LM. Associations between anthropometry, cigarette smoking, alcohol consumption, and non-Hodgkin lymphoma in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. *Am J Epidemiol* 2010; **171**: 1270-1281 [PMID: 20494998 DOI: 10.1093/aje/kwq085]

7   **Emaus MJ**, van Gils CH, Bakker MF, Bisschop CN, Monninkhof EM, Bueno-de-Mesquita HB, Travier N, Berentzen TL, Overvad K, Tjønneland A, Romieu I, Rinaldi S, Chajes V, Gunter MJ, Clavel-Chapelon F, Fagherazzi G, Mesrine S, Chang-Claude J, Kaaks R, Boeing H, Aleksandrova K, Trichopoulou A, Naska A, Orfanos P, Palli D, Agnoli C, Tumino R, Vineis P, Mattiello A, Braaten T, Borch KB, Lund E, Menéndez V, Sánchez MJ, Navarro C, Barricarte A, Amiano P, Sund M, Andersson A, Borgquist S, Olsson A, Khaw KT, Wareham N, Travis RC, Riboli E, Peeters PH, May AM. Weight change in middle adulthood and breast cancer risk in the EPIC-PANACEA study. *Int J Cancer* 2014; **135**: 2887-2899 [PMID: 24771551 DOI: 10.1002/ijc.28926]

8   **Rosner B**, Eliassen AH, Toriola AT, Hankinson SE, Willett WC, Natarajan L, Colditz GA. Short-term weight gain and breast cancer risk by hormone receptor classification among pre- and postmenopausal women. *Breast Cancer Res Treat* 2015; **150**: 643-653 [PMID: 25796612 DOI: 10.1007/s10549-015-3344-0]

9   **Vrieling A**, Buck K, Kaaks R, Chang-Claude J. Adult weight gain in relation to breast cancer risk by estrogen and progesterone receptor status: a meta-analysis. *Breast Cancer Res Treat* 2010; **123**: 641-649 [PMID: 20711809 DOI: 10.1007/s10549-010-1116-4]

10   **Chan DS**, Vieira AR, Aune D, Bandera EV, Greenwood DC, McTiernan A, Navarro Rosenblatt D, Thune I, Vieira R, Norat T. Body mass index and survival in women with breast cancer-systematic literature review and meta-analysis of 82 follow-up studies. *Ann Oncol* 2014; **25**: 1901-1914 [PMID: 24769692 DOI: 10.1093/annonc/mdu042]

11   **Casabiell X**, Piñeiro V, Tomé MA, Peinó R, Diéguez C, Casanueva FF. Presence of leptin in colostrum and/or breast milk from lactating mothers: a potential role in the regulation of neonatal food intake. *J Clin Endocrinol Metab* 1997; **82**: 4270-4273 [PMID: 9398752 DOI: 10.1210/jc.82.12.4270]

12   **Guo S**, Liu M, Wang G, Torroella-Kouri M, Gonzalez-Perez RR. Oncogenic role and therapeutic target of leptin signaling in breast cancer and cancer stem cells. *Biochim Biophys Acta* 2012; **1825**: 207-222 [PMID: 22289780 DOI: 10.1016/j.bbcan.2012.01.002. Oncogenic]

13   **Brennan AM**, Mantzoros CS. Drug Insight: the role of leptin in human physiology and pathophysiology--emerging clinical applications. *Nat Clin Pract Endocrinol Metab* 2006; **2**: 318-327 [PMID: 16932309 DOI: 10.1038/ncpendmet0196]

14   **Pan H**, Guo J, Su Z. Advances in understanding the interrelations between leptin resistance and obesity. *Physiol Behav* 2014; **130**: 157-169 [PMID: 24726399 DOI: 10.1016/j.physbeh.2014.04.003]

15   **Considine RV**, Sinha MK, Heiman ML, Kriauciunas A, Stephens TW, Nyce MR, Ohannesian JP, Marco CC, McKee LJ, Bauer TL. Serum immunoreactive-leptin concentrations in normal-weight and obese humans. *N Engl J Med* 1996; **334**: 292-295 [PMID: 8532024 DOI: 10.1056/NEJM199602013340503]

16   **Lipsey CC**, Harbuzariu A, Daley-Brown D, Gonzalez-Perez RR. Oncogenic role of leptin and Notch interleukin-1 leptin crosstalk outcome in cancer. *World J Methodol* 2016; **6**: 43-55 [PMID: 27019796 DOI: 10.5662/wjm.v6.i1.43]

17   **Margetic S**, Gazzola C, Pegg GG, Hill RA. Leptin: a review of its peripheral actions and interactions. *Int J Obes Relat Metab Disord* 2002; **26**: 1407-1433 [PMID: 12439643 DOI: 10.1038/sj.ijo.0802142]

18   **Emilsson V**, Liu YL, Cawthorne MA, Morton NM, Davenport M. Expression of the functional leptin receptor mRNA in pancreatic islets and direct inhibitory action of leptin on insulin secretion. *Diabetes* 1997; **46**: 313-316 [PMID: 9000710 DOI: 10.2337/diabetes.46.2.313]

19   **Laud K**, Gourdou I, Bélair L, Keisler DH, Djiane J. Detection and regulation of leptin receptor mRNA in ovine mammary epithelial cells during pregnancy and lactation. *FEBS Lett* 1999; **463**: 194-198 [PMID: 10601666 DOI: 10.1016/S0014-5793(99)01616-6]

20   **Tsiotra PC**, Pappa V, Raptis SA, Tsigos C. Expression of the long and short leptin receptor isoforms in peripheral blood mononuclear cells: implications for leptin's actions. *Metabolism* 2000; **49**: 1537-1541 [PMID: 11145113 DOI: 10.1053/meta.2000.18519]

21   **Mullen M**, Gonzalez-Perez RR. Leptin-Induced JAK/STAT Signaling and Cancer Growth. *Vaccines* (Basel) 2016; **4**: pii: E26 [PMID: 27472371 DOI: 10.3390/vaccines4030026]

22   **Ghilardi N**, Ziegler S, Wiestner A, Stoffel R, Heim MH, Skoda RC. Defective STAT signaling by the leptin receptor in diabetic mice. *Proc Natl Acad Sci USA* 1996; **93**: 6231-6235 [PMID: 8692797 DOI: 10.1073/pnas.93.13.6231]

23   **Huang L**, Li C. Leptin: a multifunctional hormone. *Cell Res* 2000; **10**: 81-92 [PMID: 10896170 DOI: 10.1038/sj.cr.7290038]

24   **Ducy P**, Amling M, Takeda S, Priemel M, Schilling AF, Beil FT, Shen J, Vinson C, Rueger JM, Karsenty G. Leptin inhibits bone formation through a hypothalamic relay: a central control of bone mass. *Cell* 2000; **100**: 197-207 [PMID: 10660043 DOI: 10.1016/S0092-8674(00)81558-5]

25   **Comninos AN**, Jayasena CN, Dhillo WS. The relationship between gut and adipose hormones, and reproduction. *Hum Reprod Update*

2014; **20**: 153-174 [PMID: 24173881 DOI: 10.1093/humupd/dmt033]

26   **Garonna E**, Botham KM, Birdsey GM, Randi AM, Gonzalez-Perez RR, Wheeler-Jones CP. Vascular endothelial growth factor receptor-2 couples cyclo-oxygenase-2 with pro-angiogenic actions of leptin on human endothelial cells. *PLoS One* 2011; **6**: e18823 [PMID: 21533119 DOI: 10.1371/journal.pone.0018823]

27   **González RR**, Caballero-Campo P, Jasper M, Mercader A, Devoto L, Pellicer A, Simon C. Leptin and leptin receptor are expressed in the human endometrium and endometrial leptin secretion is regulated by the human blastocyst. *J Clin Endocrinol Metab* 2000; **85**: 4883-4888 [PMID: 11134157 DOI: 10.1210/jcem.85.12.7060]

28   **Ramos MP**, Rueda BR, Leavis PC, Gonzalez RR. Leptin serves as an upstream activator of an obligatory signaling cascade in the embryo-implantation process. *Endocrinology* 2005; **146**: 694-701 [PMID: 15539553 DOI: 10.1210/en.2004-1186]

29   **Gonzalez RR**, Rueda BR, Ramos MP, Littell RD, Glasser S, Leavis PC. Leptin-induced increase in leukemia inhibitory factor and its receptor by human endometrium is partially mediated by interleukin 1 receptor signaling. *Endocrinology* 2004; **145**: 3850-3857 [PMID: 15142989 DOI: 10.1210/en.2004-0383]

30   **Sanchez-Garrido MA**, Tena-Sempere M. Metabolic control of puberty: roles of leptin and kisspeptins. *Horm Behav* 2013; **64**: 187-194 [PMID: 23998663 DOI: 10.1016/j.yhbeh.2013.01.014]

31   **Denroche HC**, Huynh FK, Kieffer TJ. The role of leptin in glucose homeostasis. *J Diabetes Investig* 2012; **3**: 115-129 [PMID: 24843554 DOI: 10.1111/j.2040-1124.2012.00203.x]

32   **Fantuzzi G**, Faggioni R. Leptin in the regulation of immunity, inflammation, and hematopoiesis. *J Leukoc Biol* 2000; **68**: 437-446 [PMID: 11037963]

33   **Taleb S**, Herbin O, Ait-Oufella H, Verreth W, Gourdy P, Barateau V, Merval R, Esposito B, Clément K, Holvoet P, Tedgui A, Mallat Z. Defective leptin/leptin receptor signaling improves regulatory T cell immune response and protects mice from atherosclerosis. *Arterioscler Thromb Vasc Biol* 2007; **27**: 2691-2698 [PMID: 17690315 DOI: 10.1161/ATVBAHA.107.149567]

34   **Newman G**, Gonzalez-Perez RR. Leptin-cytokine crosstalk in breast cancer. *Mol Cell Endocrinol* 2014; **382**: 570-582 [PMID: 23562747 DOI: 10.1016/j.mce.2013.03.025]

35   **Zhao L**, Shen ZX, Luo HS, Shen L. Possible involvement of leptin and leptin receptor in developing gastric adenocarcinoma. *World J Gastroenterol* 2005; **11**: 7666-7670 [PMID: 16437696 DOI: 10.3748/wjg.v11.i48.7666]

36   **Garofalo C**, Surmacz E. Leptin and cancer. *J Cell Physiol* 2006; **207**: 12-22 [PMID: 16110483 DOI: 10.1002/jcp.20472]

37   **Carino C**, Olawaiye AB, Cherfils S, Serikawa T, Lynch MP, Rueda BR, Gonzalez RR. Leptin regulation of proangiogenic molecules in benign and cancerous endometrial cells. *Int J Cancer* 2008; **123**: 2782-2790 [PMID: 18798554 DOI: 10.1002/ijc.23887]

38   **Gogas H**, Trakatelli M, Dessypris N, Terzidis A, Katsambas A, Chrousos GP, Petridou ET. Melanoma risk in association with serum leptin levels and lifestyle parameters: a case-control study. *Ann Oncol* 2008; **19**: 384-389 [PMID: 17925285 DOI: 10.1093/annonc/mdm464]

39   **Yeh WL**, Lu DY, Lee MJ, Fu WM. Leptin induces migration and invasion of glioma cells through MMP-13 production. *Glia* 2009; **57**: 454-464 [PMID: 18814267 DOI: 10.1002/glia.20773]

40   **Long E**, Beales IL. The role of obesity in oesophageal cancer development. *Therap Adv Gastroenterol* 2014; **7**: 247-268 [PMID: 25364384 DOI: 10.1177/1756283X14538689]

41   **Yang WH**, Chang AC, Wang SW, Wang SJ, Chang YS, Chang TM, Hsu SK, Fong YC, Tang CH. Leptin promotes VEGF-C production and induces lymphangiogenesis by suppressing miR-27b in human chondrosarcoma cells. *Sci Rep* 2016; **6**: 28647 [PMID: 27345723 DOI: 10.1038/srep28647]

42   **Akinci M**, Kosova F, Cetin B, Aslan S, Ari Z, Cetin A. Leptin levels in thyroid cancer. *Asian J Surg* 2009; **32**: 216-223 [PMID: 19892624 DOI: 10.1016/S1015-9584(09)60397-3]

43   **Chitturi S**, Farrell G, Frost L, Kriketos A, Lin R, Fung C, Liddle C, Samarasinghe D, George J. Serum leptin in NASH correlates with hepatic steatosis but not fibrosis: a manifestation of lipotoxicity? *Hepatology* 2002; **36**: 403-409 [PMID: 12143049 DOI: 10.1053/jhep.2002.34738]
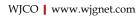
44   **Uddin S**, Bu R, Ahmed M, Hussain AR, Ajarim D, Al-Dayel F, Bavi P, Al-kuraya KS. Leptin receptor expression and its association with PI3K/AKT signaling pathway in diffuse large B-cell lymphoma. *Leuk Lymphoma* 2010; **51**: 1305-1314 [PMID: 20443680 DOI: 10.3109/10428191003802365]

45   **Attoub S**, Noe V, Pirola L, Bruyneel E, Chastre E, Mareel M, Wymann MP, Gespach C. Leptin promotes invasiveness of kidney and colonic epithelial cells via phosphoinositide 3-kinase-, rho-, and rac-dependent signaling pathways. *FASEB J* 2000; **14**: 2329-2338 [PMID: 11053255 DOI: 10.1096/fj.00-0162]

46   **Hardwick JC**, van den Brink GR, Offerhaus GJ, van Deventer SJ, Peppelenbosch MP. NF-kappaB, p38 MAPK and JNK are highly expressed and active in the stroma of human colonic adenomatous polyps. *Oncogene* 2001; **20**: 819-827 [PMID: 11314016 DOI: 10.1038/sj.onc.1204162]

47   **Song CH**, Liao J, Deng ZH, Zhang JY, Xue H, Li YM, Liang C, Han M, Zhang K, Yan GT. Is leptin a predictive factor in patients with lung cancer? *Clin Biochem* 2014; **47**: 230-232 [PMID: 24355691 DOI: 10.1016/j.clinbiochem.2013.12.003]

48   **Konopleva M**, Zhao S, Xie Z, Segall H, Younes A, Claxton DF, Estrov Z, Kornblau SM, Andreeff M. Apoptosis. Molecules and mechanisms. *Adv Exp Med Biol* 1999; **457**: 217-236 [PMID: 10500797]

49   **Somasundar P**, Frankenberry KA, Skinner H, Vedula G, McFadden DW, Riggs D, Jackson B, Vangilder R, Hileman SM, Vona-Davis LC. Prostate cancer cell proliferation is influenced by leptin. *J Surg Res* 2004; **118**: 71-82 [PMID: 15093720 DOI: 10.1016/j.jss.2004.01.017]

50   **Choi JH**, Park SH, Leung PC, Choi KC. Expression of leptin receptors and potential effects of leptin on the cell growth and activation of mitogen-activated protein kinases in ovarian cancer cells. *J Clin Endocrinol Metab* 2005; **90**: 207-210 [PMID: 15522945 DOI: 10.1210/jc.2004-0297]

51   **Glasow A**, Bornstein SR, Chrousos GP, Brown JW, Scherbaum WA. Detection of Ob-receptor in human adrenal neoplasms and effect of leptin on adrenal cell proliferation. *Horm Metab Res* 1999; **31**: 247-251 [PMID: 10333078 DOI: 10.1055/s-2007-978726]

52   **Gonzalez RR**, Cherfils S, Escobar M, Yoo JH, Carino C, Styer AK, Sullivan BT, Sakamoto H, Olawaiye A, Serikawa T, Lynch MP, Rueda BR. Leptin signaling promotes the growth of mammary tumors and increases the expression of vascular endothelial growth factor (VEGF) and its receptor type two (VEGF-R2). *J Biol Chem* 2006; **281**: 26320-26328 [PMID: 16825198]

53   **Gillespie C**, Quarshie A, Penichet M, Gonzalez-Perez RR. Potential Role of Leptin Signaling in DMBA induced Mammary Tumors by Non-Responsive C57BL/6J Mice Fed a High-Fat Diet. *J Carcinog Mutagen* 2012; **3**: 132 [DOI: 10.4172/2157-2518.1000132]

54   **Brown JE**, Dunmore SJ. Leptin decreases apoptosis and alters BCL-2 : Bax ratio in clonal rodent pancreatic beta-cells. *Diabetes Metab Res Rev* 2007; **23**: 497-502 [PMID: 17318810 DOI: 10.1002/dmrr.726]

55   **Gonzalez-Perez RR**, Xu Y, Guo S, Watters A, Zhou W, Leibovich SJ. Leptin upregulates VEGF in breast cancer via canonic and non-canonical signalling pathways and NFkappaB/HIF-1alpha activation. *Cell Signal* 2010; **22**: 1350-1362 [PMID: 20466060 DOI: 10.1016/j.cellsig.2010.05.003]

56   **Rene Gonzalez R**, Watters A, Xu Y, Singh UP, Mann DR, Rueda BR, Penichet ML. Leptin-signaling inhibition results in efficient anti-tumor activity in estrogen receptor positive or negative breast cancer. *Breast Cancer Res* 2009; **11**: R36 [PMID: 19531256 DOI: 10.1186/bcr2321]

57   **Bouloumié A**, Drexler HC, Lafontan M, Busse R. Leptin, the product of Ob gene, promotes angiogenesis. *Circ Res* 1998; **83**: 1059-1066 [PMID: 9815153 DOI: 10.1161/01.RES.83.10.1059]

58   **Lanier V**, Gillespie C, Leffers M, Daley-Brown D, Milner J, Lipsey C, Webb N, Anderson LM, Newman G, Waltenberger J, Gonzalez-Perez RR. Leptin-induced transphosphorylation of vascular endothelial growth factor receptor increases Notch and stimulates endothelial cell angiogenic transformation. *Int J Biochem Cell Biol* 2016; **79**: 139-150 [PMID: 27590851 DOI: 10.1016/j.biocel.2016.08.023]

59   **Zhou W**, Guo S, Gonzalez-Perez RR. Leptin pro-angiogenic signature in breast cancer is linked to IL-1 signalling. *Br J Cancer* 2011; **104**:

128-137 [PMID: 21139583 DOI: 10.1038/sj.bjc.6606013]

60   **Guo S**, Gonzalez-Perez RR. Notch, IL-1 and leptin crosstalk outcome (NILCO) is critical for leptin-induced proliferation, migration and VEGF/VEGFR-2 expression in breast cancer. *PLoS One* 2011; **6**: e21467 [PMID: 21731759 DOI: 10.1371/journal.pone.0021467]

61   **Gonzalez RR**, Devoto L, Campana A, Bischof P. Effects of leptin, interleukin-1alpha, interleukin-6, and transforming growth factor-beta on markers of trophoblast invasive phenotype: integrins and metalloproteinases. *Endocrine* 2001; **15**: 157-164 [PMID: 11720241 DOI: 10.1385/ENDO: 15: 2: 157]

62   **Park HY**, Kwon HM, Lim HJ, Hong BK, Lee JY, Park BE, Jang Y, Cho SY, Kim HS. Potential role of leptin in angiogenesis: leptin induces endothelial cell proliferation and expression of matrix metalloproteinases in vivo and in vitro. *Exp Mol Med* 2001; **33**: 95-102 [PMID: 11460888 DOI: 10.1038/emm.2001.17]

63   **Gonzalez RR**, Leavis PC. A peptide derived from the human leptin molecule is a potent inhibitor of the leptin receptor function in rabbit endometrial cells. *Endocrine* 2003; **21**: 185-195 [PMID: 12897384 DOI: 10.1385/ENDO: 21: 2: 185]

64   **Guo S**, Liu M, Gonzalez-Perez RR. Role of Notch and its oncogenic signaling crosstalk in breast cancer. *Biochim Biophys Acta* 2011; **1815**: 197-213 [PMID: 21193018 DOI: 10.1016/j.bbcan.2010.12.002]

65   **Zhou S**, Fujimuro M, Hsieh JJ, Chen L, Miyamoto A, Weinmaster G, Hayward SD. SKIP, a CBF1-associated protein, interacts with the ankyrin repeat domain of NotchIC To facilitate NotchIC function. *Mol Cell Biol* 2000; **20**: 2400-2410 [PMID: 10713164 DOI: 10.1128/MCB.20.7.2400-2410.2000]

66   **Hsieh JJ**, Zhou S, Chen L, Young DB, Hayward SD. CIR, a corepressor linking the DNA binding factor CBF1 to the histone deacetylase complex. *Proc Natl Acad Sci USA* 1999; **96**: 23-28 [PMID: 9874765 DOI: 10.1073/pnas.96.1.23]

67   **Kovall RA**. More complicated than it looks: assembly of Notch pathway transcription complexes. *Oncogene* 2008; **27**: 5099-5109 [PMID: 18758478 DOI: 10.1038/onc.2008.223]

68   **Dontu G**, Jackson KW, McNicholas E, Kawamura MJ, Abdallah WM, Wicha MS. Role of Notch signaling in cell-fate determination of human mammary stem/progenitor cells. *Breast Cancer Res* 2004; **6**: R605-R615 [PMID: 15535842 DOI: 10.1186/bcr920]

69   **Harrison H**, Farnie G, Howell SJ, Rock RE, Stylianou S, Brennan KR, Bundred NJ, Clarke RB. Regulation of breast cancer stem cell activity by signaling through the Notch4 receptor. *Cancer Res* 2010; **70**: 709-718 [PMID: 20068161 DOI: 10.1158/0008-5472. CAN-09-1681]

70   **Daley-Brown D**, Oprea-Ilies GM, Lee R, Pattillo R, Gonzalez-Perez RR. Molecular cues on obesity signals, tumor markers and endometrial cancer. *Horm Mol Biol Clin Investig* 2015; **21**: 89-106 [PMID: 25781554 DOI: 10.1515/hmbci-2014-0049]

71   **Giordano C**, Chemi F, Panza S, Barone I, Bonofiglio D, Lanzino M, Cordella A, Campana A, Hashim A, Rizza P, Leggio A, Győrffy B, Simões BM, Clarke RB, Weisz A, Catalano S, Andò S. Leptin as a mediator of tumor-stromal interactions promotes breast cancer stem cell activity. *Oncotarget* 2016; **7**: 1262-1275 [PMID: 26556856 DOI: 10.18632/oncotarget.6014]

72   **Battle M**, Gillespie C, Quarshie A, Lanier V, Harmon T, Wilson K, Torroella-Kouri M, Gonzalez-Perez RR. Obesity induced a leptin-Notch signaling axis in breast cancer. *Int J Cancer* 2014; **134**: 1605-1616 [PMID: 24114531 DOI: 10.1002/ijc.28496]

73   **Kulic I**, Robertson G, Chang L, Baker JH, Lockwood WW, Mok W, Fuller M, Fournier M, Wong N, Chou V, Robinson MD, Chun HJ, Gilks B, Kempkes B, Thomson TA, Hirst M, Minchinton AI, Lam WL, Jones S, Marra M, Karsan A. Loss of the Notch effector RBPJ promotes tumorigenesis. *J Exp Med* 2015; **212**: 37-52 [PMID: 25512468 DOI: 10.1084/jem.20121192]

74   **Rampoldi A**, Harbuzariu A, Harmon TL, Gonzalez-Perez RR. Abstract 1006: Novel adjuvants in triple negative breast cancer chemotherapy. *Cancer Res* 2016; 1006-1006 [DOI: 10.1158/1538-7445.AM 2016-1006]

75   **Smith-Kirwin SM**, O'Connor DM, De Johnston J, Lancey ED, Hassink SG, Funanage VL. Leptin expression in human mammary epithelial cells and breast milk. *J Clin Endocrinol Metab* 1998; **83**:

76   **Ishikawa M**, Kitayama J, Nagawa H. Enhanced expression of leptin and leptin receptor (OB-R) in human breast cancer. *Clin Cancer Res* 2004; **10**: 4325-4331 [PMID: 15240518 DOI: 10.1158/1078-0432. CCR-03-0749]

77   **Porter GA**, Inglis KM, Wood LA, Veugelers PJ. Effect of obesity on presentation of breast cancer. *Ann Surg Oncol* 2006; **13**: 327-332 [PMID: 16485153 DOI: 10.1245/ASO.2006.03.049]

78   **Frankenberry KA**, Skinner H, Somasundar P, McFadden DW, Vona-Davis LC. Leptin receptor expression and cell signaling in breast cancer. *Int J Oncol* 2006; **28**: 985-993 [PMID: 16525650]

79   **Yue W**, Yager JD, Wang JP, Jupe ER, Santen RJ. Estrogen receptor-dependent and independent mechanisms of breast cancer carcinogenesis. *Steroids* 2013; **78**: 161-170 [PMID: 23178278 DOI: 10.1016/j.steroids.2012.11.001]

80   **Catalano S**, Mauro L, Marsico S, Giordano C, Rizza P, Rago V, Montanaro D, Maggiolini M, Panno ML, Andó S. Leptin induces, via ERK1/ERK2 signal, functional activation of estrogen receptor alpha in MCF-7 cells. *J Biol Chem* 2004; **279**: 19908-19915 [PMID: 14985328 DOI: 10.1074/jbc.M313191200]

81   **MacDonald PC**, Edman CD, Hemsell DL, Porter JC, Siiteri PK. Effect of obesity on conversion of plasma androstenedione to estrone in postmenopausal women with and without endometrial cancer. *Am J Obstet Gynecol* 1978; **130**: 448-455 [PMID: 629289]

82   **Catalano PM**, Thomas A, Huston-Presley L, Amini SB. Increased fetal adiposity: a very sensitive marker of abnormal in utero development. *Am J Obstet Gynecol* 2003; **189**: 1698-1704 [PMID: 14710101 DOI: 10.1016/S0002-9378(03)00828-7]

83   **Garofalo C**, Sisci D, Surmacz E. Leptin interferes with the effects of the antiestrogen ICI 182,780 in MCF-7 breast cancer cells. *Clin Cancer Res* 2004; **10**: 6466-6475 [PMID: 15475434 DOI: 10.1158/1078-0432.CCR-04-0203]

84   **Chen HY**, Yang YM, Stevens BM, Noble M. Inhibition of redox/Fyn/c-Cbl pathway function by Cdc42 controls tumour initiation capacity and tamoxifen sensitivity in basal-like breast cancer cells. *EMBO Mol Med* 2013; **5**: 723-736 [PMID: 23606532 DOI: 10.1002/emmm.201202140]

85   **Eisenberg A**, Biener E, Charlier M, Krishnan RV, Djiane J, Herman B, Gertler A. Transactivation of erbB2 by short and long isoforms of leptin receptors. *FEBS Lett* 2004; **565**: 139-142 [PMID: 15135067 DOI: 10.1016/j.febslet.2004.03.089]

86   **McDermott SP**, Wicha MS. Targeting breast cancer stem cells. *Mol Oncol* 2010; **4**: 404-419 [PMID: 20599450 DOI: 10.1016/j.molonc. 2010.06.005]

87   **Kleffel S**, Schatton T. Tumor dormancy and cancer stem cells: two sides of the same coin? *Adv Exp Med Biol* 2013; **734**: 145-179 [PMID: 23143979 DOI: 10.1007/978-1-4614-1445-2_8]

88   **Pang LY**, Argyle DJ. Using naturally occurring tumours in dogs and cats to study telomerase and cancer stem cell biology. *Biochim Biophys Acta* 2009; **1792**: 380-391 [PMID: 19254761 DOI: 10.1016/j.bbadis.2009.02.010]

89   **Andò S**, Barone I, Giordano C, Bonofiglio D, Catalano S. The Multifaceted Mechanism of Leptin Signaling within Tumor Microenvironment in Driving Breast Cancer Growth and Progression. *Front Oncol* 2014; **4**: 340 [PMID: 25505738 DOI: 10.3389/fonc. 2014.00340]

90   **Korkaya H**, Paulson A, Iovino F, Wicha MS. HER2 regulates the mammary stem/progenitor cell population driving tumorigenesis and invasion. *Oncogene* 2008; **27**: 6120-6130 [PMID: 18591932 DOI: 10.1038/onc.2008.207]

91   **Feldman DE**, Chen C, Punj V, Tsukamoto H, Machida K. Pluripotency factor-mediated expression of the leptin receptor (OB-R) links obesity to oncogenesis through tumor-initiating stem cells. *Proc Natl Acad Sci USA* 2012; **109**: 829-834 [PMID: 22207628 DOI: 10.1073/pnas.1114438109]

92   **Zhou J**, Wulfkuhle J, Zhang H, Gu P, Yang Y, Deng J, Margolick JB, Liotta LA, Petricoin E, Zhang Y. Activation of the PTEN/mTOR/STAT3 pathway in breast cancer stem-like cells is required for viability and maintenance. *Proc Natl Acad Sci USA* 2007; **104**: 16158-16163 [PMID: 17911267 DOI: 10.1073/pnas.0702596104]

1810-1813 [PMID: 9589698 DOI: 10.1210/jc.83.5.1810]

93   **Pratt MA**, Tibbo E, Robertson SJ, Jansson D, Hurst K, Perez-Iratxeta C, Lau R, Niu MY. The canonical NF-kappaB pathway is required for formation of luminal mammary neoplasias and is activated in the mammary progenitor population. *Oncogene* 2009; **28**: 2710-2722 [PMID: 19483731 DOI: 10.1038/onc.2009.131]

94   **Kakarala M**, Wicha MS. Implications of the cancer stem-cell hypothesis for breast cancer prevention and therapy. *J Clin Oncol* 2008; **26**: 2813-2820 [PMID: 18539959 DOI: 10.1200/JCO.2008.16.3931]

95   **Chiotaki R**, Polioudaki H, Theodoropoulos PA. Cancer stem cells in solid and liquid tissues of breast cancer patients: characterization and therapeutic perspectives. *Curr Cancer Drug Targets* 2015; **15**: 256-269 [PMID: 25669721]

96   **Nigam A**. Breast cancer stem cells, pathways and therapeutic perspectives 2011. *Indian J Surg* 2013; **75**: 170-180 [PMID: 24426422 DOI: 10.1007/s12262-012-0616-3]

97   **Yeo SK**, Wen J, Chen S, Guan JL. Autophagy Differentially Regulates Distinct Breast Cancer Stem-like Cells in Murine Models via EGFR/Stat3 and Tgfβ/Smad Signaling. *Cancer Res* 2016; **76**: 3397-3410 [PMID: 27197172 DOI: 10.1158/0008-5472.CAN-15-2946]

98   **Zhang H**, Lu H, Xiang L, Bullen JW, Zhang C, Samanta D, Gilkes DM, He J, Semenza GL. HIF-1 regulates CD47 expression in breast cancer cells to promote evasion of phagocytosis and maintenance of cancer stem cells. *Proc Natl Acad Sci USA* 2015; **112**: E6215-E6223 [PMID: 26512116 DOI: 10.1073/pnas.1520032112]

99   **Stivarou T**, Stellas D, Vartzi G, Thomaidou D, Patsavoudi E. Targeting highly expressed extracellular HSP90 in breast cancer stem cells inhibits tumor growth in vitro and in vivo. *Cancer Biol Ther* 2016; **17**: 799-812 [PMID: 27259689 DOI: 10.1080/15384047.2016.1195041]

100   **Baccelli I**, Schneeweiss A, Riethdorf S, Stenzinger A, Schillert A, Vogel V, Klein C, Saini M, Bäuerle T, Wallwiener M, Holland-Letz T, Höfner T, Sprick M, Scharpff M, Marmé F, Sinn HP, Pantel K, Weichert W, Trumpp A. Identification of a population of blood circulating tumor cells from breast cancer patients that initiates metastasis in a xenograft assay. *Nat Biotechnol* 2013; **31**: 539-544 [PMID: 23609047 DOI: 10.1038/nbt.2576]

101   **Tume L**, Paco K, Ubidia-Incio R, Moya J. CD133 in breast cancer cells and in breast cancer stem cells as another target for immunotherapy. *Gac Mex Oncol* 2016; **15**: 22-30 [DOI: 10.1016/j.gamo.2016.01.003]

102   **Leccia F**, Del Vecchio L, Mariotti E, Di Noto R, Morel AP, Puisieux A, Salvatore F, Ansieau S. ABCG2, a novel antigen to sort luminal progenitors of BRCA1- breast cancer cells. *Mol Cancer* 2014; **13**: 213 [PMID: 25216750 DOI: 10.1186/1476-4598-13-213]

103   **Kim SH**, Singh SV. The role of polycomb group protein Bmi-1 and Notch4 in breast cancer stem cell inhibition by benzyl isothiocyanate. *Breast Cancer Res Treat* 2015; **149**: 681-692 [PMID: 25663545 DOI: 10.1007/s10549-015-3279-5]

104   **Fernandez-Zapico ME**. GLI1 finds a new role in cancer stem cell biology. *EMBO Mol Med* 2013; **5**: 483-485 [PMID: 23505092 DOI: 10.1002/emmm.201302505]

105   **McClements L**, Yakkundi A, Papaspyropoulos A, Harrison H, Ablett MP, Jithesh PV, McKeen HD, Bennett R, Donley C, Kissenpfennig A, McIntosh S, McCarthy HO, O'Neill E, Clarke RB, Robson T. Targeting treatment-resistant breast cancer stem cells with FKBPL and its peptide derivative, AD-01, via the CD44 pathway. *Clin Cancer Res* 2013; **19**: 3881-3893 [PMID: 23741069 DOI: 10.1158/1078-0432.CCR-13-0595]

106   **Li C**, Heidt DG, Dalerba P, Burant CF, Zhang L, Adsay V, Wicha M, Clarke MF, Simeone DM. Identification of pancreatic cancer stem cells. *Cancer Res* 2007; **67**: 1030-1037 [PMID: 17283135 DOI: 10.1158/0008-5472.CAN-06-2030]

107   **Hermann PC**, Huber SL, Herrler T, Aicher A, Ellwart JW, Guba M, Bruns CJ, Heeschen C. Distinct populations of cancer stem cells determine tumor growth and metastatic activity in human pancreatic cancer. *Cell Stem Cell* 2007; **1**: 313-323 [PMID: 18371365 DOI: 10.1016/j.stem.2007.06.002]

108   **Lee CJ**, Dosch J, Simeone DM. Pancreatic cancer stem cells. *J Clin Oncol* 2008; **26**: 2806-2812 [PMID: 18539958 DOI: 10.1200/JCO.2008.16.6702]

109   **Rasheed ZA**, Yang J, Wang Q, Kowalski J, Freed I, Murter C, Hong SM, Koorstra JB, Rajeshkumar NV, He X, Goggins M, Iacobuzio-Donahue C, Berman DM, Laheru D, Jimeno A, Hidalgo M, Maitra A, Matsui W. Prognostic significance of tumorigenic cells with mesenchymal features in pancreatic adenocarcinoma. *J Natl Cancer Inst* 2010; **102**: 340-351 [PMID: 20164446 DOI: 10.1093/jnci/djp535]

110   **Hage C**, Rausch V, Giese N, Giese T, Schönsiegel F, Labsch S, Nwaeburu C, Mattern J, Gladkich J, Herr I. The novel c-Met inhibitor cabozantinib overcomes gemcitabine resistance and stem cell signaling in pancreatic cancer. *Cell Death Dis* 2013; **4**: e627 [PMID: 23661005 DOI: 10.1038/cddis.2013.158]

111   **Van den Broeck A**, Vankelecom H, Van Delm W, Gremeaux L, Wouters J, Allemeersch J, Govaere O, Roskams T, Topal B. Human pancreatic cancer contains a side population expressing cancer stem cell-associated and prognostic genes. *PLoS One* 2013; **8**: e73968 [PMID: 24069258 DOI: 10.1371/journal.pone.0073968]

112   **Wang YH**, Li F, Luo B, Wang XH, Sun HC, Liu S, Cui YQ, Xu XX. A side population of cells from a human pancreatic carcinoma cell line harbors cancer stem cell characteristics. *Neoplasma* 2009; **56**: 371-378 [PMID: 19580337]

113   **Bailey JM**, Alsina J, Rasheed ZA, McAllister FM, Fu YY, Plentz R, Zhang H, Pasricha PJ, Bardeesy N, Matsui W, Maitra A, Leach SD. DCLK1 marks a morphologically distinct subpopulation of cells with stem cell properties in preinvasive pancreatic cancer. *Gastroenterology* 2014; **146**: 245-256 [PMID: 24096005 DOI: 10.1053/j.gastro.2013.09.050]

114   **Sancho P**, Alcala S, Usachov V, Hermann PC, Sainz B. The ever-changing landscape of pancreatic cancer stem cells. *Pancreatology* 2016; **16**: 489-496 [PMID: 27161173 DOI: 10.1016/j.pan.2016.04.004]

115   **Lu Y**, Zhu H, Shan H, Lu J, Chang X, Li X, Lu J, Fan X, Zhu S, Wang Y, Guo Q, Wang L, Huang Y, Zhu M, Wang Z. Knockdown of Oct4 and Nanog expression inhibits the stemness of pancreatic cancer cells. *Cancer Lett* 2013; **340**: 113-123 [PMID: 23872274 DOI: 10.1016/j.canlet.2013.07.009]

116   **Quint K**, Tonigold M, Di Fazio P, Montalbano R, Lingelbach S, Rückert F, Alinger B, Ocker M, Neureiter D. Pancreatic cancer cells surviving gemcitabine treatment express markers of stem cell differentiation and epithelial-mesenchymal transition. *Int J Oncol* 2012; **41**: 2093-2102 [PMID: 23026911 DOI: 10.3892/ijo.2012.1648]

117   **Herreros-Villanueva M**, Bujanda L, Billadeau DD, Zhang JS. Embryonic stem cell factors and pancreatic cancer. *World J Gastroenterol* 2014; **20**: 2247-2254 [PMID: 24605024 DOI: 10.3748/wjg.v20.i9.2247]

118   **Misra S**, Ghatak S, Toole BP. Regulation of MDR1 expression and drug resistance by a positive feedback loop involving hyaluronan, phosphoinositide 3-kinase, and ErbB2. *J Biol Chem* 2005; **280**: 20310-20315 [PMID: 15784621 DOI: 10.1074/jbc.M500737200]

119   **Hong SP**, Wen J, Bang S, Park S, Song SY. CD44-positive cells are responsible for gemcitabine resistance in pancreatic cancer cells. *Int J Cancer* 2009; **125**: 2323-2331 [PMID: 19598259 DOI: 10.1002/ijc.24573]

120   **Molejon MI**, Tellechea JI, Moutardier V, Gasmi M, Ouaissi M, Turrini O, Delpero JR, Dusetti N, Iovanna J. Targeting CD44 as a novel therapeutic approach for treating pancreatic cancer recurrence. *Oncoscience* 2015; **2**: 572-575 [PMID: 26244163 DOI: 10.18632/oncoscience.172]

121   **Chai X**, Chu H, Yang X, Meng Y, Shi P, Gou S. Metformin Increases Sensitivity of Pancreatic Cancer Cells to Gemcitabine by Reducing CD133+ Cell Populations and Suppressing ERK/P70S6K Signaling. *Sci Rep* 2015; **5**: 14404 [PMID: 26391180 DOI: 10.1038/srep14404]

122   **Moitra K**, Lou H, Dean M. Multidrug efflux pumps and cancer stem cells: insights into multidrug resistance and therapeutic development. *Clin Pharmacol Ther* 2011; **89**: 491-502 [PMID: 21368752 DOI: 10.1038/clpt.2011.14]

123   **Ji Q**, Hao X, Zhang M, Tang W, Yang M, Li L, Xiang D, Desano JT, Bommer GT, Fan D, Fearon ER, Lawrence TS, Xu L. MicroRNA miR-34 inhibits human pancreatic cancer tumor-initiating cells. *PLoS One* 2009; **4**: e6816 [PMID: 19714243 DOI: 10.1371/journal.pone.0006816]

124   **Evans AC**, Papachristou GI, Whitcomb DC. Obesity and the risk of severe acute pancreatitis. *Minerva Gastroenterol Dietol* 2010; **56**:

169-179 [PMID: 20485254]

125 **Pini M**, Rhodes DH, Castellanos KJ, Hall AR, Cabay RJ, Chennuri R, Grady EF, Fantuzzi G. Role of IL-6 in the resolution of pancreatitis in obese mice. *J Leukoc Biol* 2012; **91**: 957-966 [PMID: 22427681 DOI: 10.1189/jlb.1211627]

126 **Lazar M**, Sullivan J, Chipitsyna G, Aziz T, Salem AF, Gong Q, Witkiewicz A, Denhardt DT, Yeo CJ, Arafat HA. Induction of monocyte chemoattractant protein-1 by nicotine in pancreatic ductal adenocarcinoma cells: role of osteopontin. *Surgery* 2010; **148**: 298-309 [PMID: 20579680 DOI: 10.1016/j.surg.2010.05.002]

127 **Yako YY**, Kruger D, Smith M, Brand M. Cytokines as Biomarkers of Pancreatic Ductal Adenocarcinoma: A Systematic Review. *PLoS One* 2016; **11**: e0154016 [PMID: 27170998 DOI: 10.1371/journal.pone.0154016]

128 **Chen L**, Fan J, Chen H, Meng Z, Chen Z, Wang P, Liu L. The IL-8/CXCR1 axis is associated with cancer stem cell-like properties and correlates with clinical prognosis in human pancreatic cancer cases. *Sci Rep* 2014; **4**: 5911 [PMID: 25081383 DOI: 10.1038/srep05911]

129 **Fan Y**, Gan Y, Shen Y, Cai X, Song Y, Zhao F, Yao M, Gu J, Tu H. Leptin signaling enhances cell invasion and promotes the metastasis of human pancreatic cancer via increasing MMP-13 production. *Oncotarget* 2015; **6**: 16120-16134 [PMID: 25948792 DOI: 10.18632/oncotarget.3878]

130 **Hoshino Y**, Nishida J, Katsuno Y, Koinuma D, Aoki T, Kokudo N, Miyazono K, Ehata S. Smad4 Decreases the Population of Pancreatic Cancer-Initiating Cells through Transcriptional Repression of ALDH1A1. *Am J Pathol* 2015; **185**: 1457-1470 [PMID: 25769430 DOI: 10.1016/j.ajpath.2015.01.011]

131 **Gao C**, Li S, Zhao T, Chen J, Ren H, Zhang H, Wang X, Lang M, Liu J, Gao S, Zhao X, Sheng J, Yuan Z, Hao J. SCF, regulated by HIF-1α, promotes pancreatic ductal adenocarcinoma cell progression. *PLoS One* 2015; **10**: e0121338 [PMID: 25799412 DOI: 10.1371/journal.pone.0121338]

132 **Ren H**, Jia L, Zhao T, Zhang H, Chen J, Yang S, Liu J, Yu M, Hao J. Hypoxia inducible factor (HIF)-1α directly activates leptin receptor (Ob-R) in pancreatic cancer cells. *Cancer Lett* 2014; **354**: 172-180 [PMID: 25130171 DOI: 10.1016/j.canlet.2014.08.001]

133 **Bain GH**, Collie-Duguid E, Murray GI, Gilbert FJ, Denison A, McKiddie F, Ahearn T, Fleming I, Leeds J, Phull P, Park K, Nanthakumaran S, Grabsch HI, Tan P, Welch A, Schweiger L, Dahle-Smith A, Urquhart G, Finegan M, Matula KM, Petty RD. Tumour expression of leptin is associated with chemotherapy resistance and therapy-independent prognosis in gastro-oesophageal adenocarcinomas. *Br J Cancer* 2014; **110**: 1525-1534 [PMID: 24569475 DOI: 10.1038/bjc.2014.45]

134 **Ono H**, Basson MD, Ito H. P300 inhibition enhances gemcitabine-induced apoptosis of pancreatic cancer. *Oncotarget* 2016; **7**: 51301-51310 [PMID: 27322077 DOI: 10.18632/oncotarget.10117]

135 **Biglia N**, Peano E, Sgandurra P, Moggio G, Pecchio S, Maggiorotto F, Sismondi P. Body mass index (BMI) and breast cancer: impact on tumor histopathologic features, cancer subtypes and recurrence rate in pre and postmenopausal women. *Gynecol Endocrinol* 2013; **29**: 263-267 [PMID: 23174088 DOI: 10.3109/09513590.2012.736559]

136 **Sládek NE**, Kollander R, Sreerama L, Kiang DT. Cellular levels of aldehyde dehydrogenases (ALDH1A1 and ALDH3A1) as predictors of therapeutic responses to cyclophosphamide-based chemotherapy of breast cancer: a retrospective study. Rational individualization of oxazaphosphorine-based cancer chemotherapeutic regimens. *Cancer Chemother Pharmacol* 2002; **49**: 309-321 [PMID: 11914911 DOI: 10.1007/s00280-001-0412-4]

137 **Wilson WR**, Hay MP. Targeting hypoxia in cancer therapy. *Nat Rev Cancer* 2011; **11**: 393-410 [PMID: 21606941 DOI: 10.1038/nrc3064]

138 **Mani SA**, Guo W, Liao MJ, Eaton EN, Ayyanan A, Zhou AY, Brooks M, Reinhard F, Zhang CC, Shipitsin M, Campbell LL, Polyak K, Brisken C, Yang J, Weinberg RA. The epithelial-mesenchymal transition generates cells with properties of stem cells. *Cell* 2008; **133**: 704-715 [PMID: 18485877 DOI: 10.1016/j.cell.2008.03.027]

139 **O'Connor PM**, Jackman J, Bae I, Myers TG, Fan S, Mutoh M, Scudiero DA, Monks A, Sausville EA, Weinstein JN, Friend S, Fornace AJ, Kohn KW. Characterization of the p53 tumor suppressor pathway in cell lines of the National Cancer Institute anticancer drug screen and correlations with the growth-inhibitory potency of 123 anticancer agents. *Cancer Res* 1997; **57**: 4285-4300 [PMID: 9331090]

140 **Abdullah LN**, Chow EK. Mechanisms of chemoresistance in cancer stem cells. *Clin Transl Med* 2013; **2**: 3 [PMID: 23369605 DOI: 10.1186/2001-1326-2-3]

141 **Keitel U**, Scheel A, Thomale J, Halpape R, Kaulfuß S, Scheel C, Dobbelstein M. Bcl-xL mediates therapeutic resistance of a mesenchymal breast cancer cell subpopulation. *Oncotarget* 2014; **5**: 11778-11791 [PMID: 25473892 DOI: 10.18632/oncotarget.2634]

142 **Real PJ**, Sierra A, De Juan A, Segovia JC, Lopez-Vega JM, Fernandez-Luna JL. Resistance to chemotherapy via Stat3-dependent overexpression of Bcl-2 in metastatic breast cancer cells. *Oncogene* 2002; **21**: 7611-7618 [PMID: 12400004 DOI: 10.1038/sj.onc.1206004]

143 **Végran F**, Boidot R, Oudin C, Riedinger JM, Bonnetain F, Lizard-Nacol S. Overexpression of caspase-3s splice variant in locally advanced breast carcinoma is associated with poor response to neoadjuvant chemotherapy. *Clin Cancer Res* 2006; **12**: 5794-5800 [PMID: 17020986 DOI: 10.1158/1078-0432.CCR-06-0725]

144 **Douville J**, Beaulieu R, Balicki D. ALDH1 as a functional marker of cancer stem and progenitor cells. *Stem Cells Dev* 2009; **18**: 17-25 [PMID: 18573038 DOI: 10.1089/scd.2008.0055]

145 **Alamgeer M**, Ganju V, Kumar B, Fox J, Hart S, White M, Harris M, Stuckey J, Prodanovic Z, Schneider-Kolsky ME, Watkins DN. Changes in aldehyde dehydrogenase-1 expression during neoadjuvant chemotherapy predict outcome in locally advanced breast cancer. *Breast Cancer Res* 2014; **16**: R44 [PMID: 24762066 DOI: 10.1186/bcr3648]

146 **Klein I**, Sarkadi B, Váradi A. An inventory of the human ABC proteins. *Biochim Biophys Acta* 1999; **1461**: 237-262 [PMID: 10581359 DOI: 10.1016/S0005-2736(99)00161-3]

147 **Hoesel B**, Schmid JA. The complexity of NF-κB signaling in inflammation and cancer. *Mol Cancer* 2013; **12**: 86 [PMID: 23915189 DOI: 10.1186/1476-4598-12-86]

148 **Liu P**, Brown S, Goktug T, Channathodiyil P, Kannappan V, Hugnot JP, Guichet PO, Bian X, Armesilla AL, Darling JL, Wang W. Cytotoxic effect of disulfiram/copper on human glioblastoma cell lines and ALDH-positive cancer-stem-like cells. *Br J Cancer* 2012; **107**: 1488-1497 [PMID: 23033007 DOI: 10.1038/bjc.2012.442]

149 **Chefetz I**, Holmberg JC, Alvero AB, Visintin I, Mor G. Inhibition of Aurora-A kinase induces cell cycle arrest in epithelial ovarian cancer stem cells by affecting NFκB pathway. *Cell Cycle* 2011; **10**: 2206-2214 [PMID: 21623171 DOI: 10.4161/cc.10.13.16348]

150 **Antoon JW**, White MD, Slaughter EM, Driver JL, Khalili HS, Elliott S, Smith CD, Burow ME, Beckman BS. Targeting NFκB mediated breast cancer chemoresistance through selective inhibition of sphingosine kinase-2. *Cancer Biol Ther* 2011; **11**: 678-689 [PMID: 21307639]

151 **Canino C**, Luo Y, Marcato P, Blandino G, Pass HI, Cioce M. A STAT3-NFkB/DDIT3/CEBPβ axis modulates ALDH1A3 expression in chemoresistant cell subpopulations. *Oncotarget* 2015; **6**: 12637-12653 [PMID: 25868979 DOI: 10.18632/oncotarget.3703]

152 **Yip NC**, Fombon IS, Liu P, Brown S, Kannappan V, Armesilla AL, Xu B, Cassidy J, Darling JL, Wang W. Disulfiram modulated ROS-MAPK and NFκB pathways and targeted breast cancer cells with cancer stem cell-like properties. *Br J Cancer* 2011; **104**: 1564-1574 [PMID: 21487404 DOI: 10.1038/bjc.2011.126]

153 **Harris AL**. Hypoxia--a key regulatory factor in tumour growth. *Nat Rev Cancer* 2002; **2**: 38-47 [PMID: 11902584 DOI: 10.1038/nrc704]

154 **Samanta D**, Gilkes DM, Chaturvedi P, Xiang L, Semenza GL. Hypoxia-inducible factors are required for chemotherapy resistance of breast cancer stem cells. *Proc Natl Acad Sci USA* 2014; **111**: E5429-E5438 [PMID: 25453096 DOI: 10.1073/pnas.1421438111]

155 **Notte A**, Ninane N, Arnould T, Michiels C. Hypoxia counteracts taxol-induced apoptosis in MDA-MB-231 breast cancer cells: role of autophagy and JNK activation. *Cell Death Dis* 2013; **4**: e638 [PMID: 23681233 DOI: 10.1038/cddis.2013.167]

156 **Dalerba P**, Cho RW, Clarke MF. Cancer stem cells: models and concepts. *Annu Rev Med* 2007; **58**: 267-284 [PMID: 17002552 DOI:

10.1146/annurev.med.58.062105.204854]

157   **Bhola NE**, Balko JM, Dugger TC, Kuba MG, Sánchez V, Sanders M, Stanford J, Cook RS, Arteaga CL. TGF-β inhibition enhances chemotherapy action against triple-negative breast cancer. *J Clin Invest* 2013; **123**: 1348-1358 [PMID: 23391723 DOI: 10.1172/JCI65416]

158   **Visvader JE**, Lindeman GJ. Cancer stem cells in solid tumours: accumulating evidence and unresolved questions. *Nat Rev Cancer* 2008; **8**: 755-768 [PMID: 18784658 DOI: 10.1038/nrc2499]

159   **Koda M**, Sulkowska M, Kanczuga-Koda L, Jarzabek K, Sulkowski S. Expression of leptin and its receptor in female breast cancer in relation with selected apoptotic markers. *Folia Histochem Cytobiol* 2007; **45** Suppl 1: S187-S191 [PMID: 18292831]

160   **Singel SM**, Cornelius C, Zaganjor E, Batten K, Sarode VR, Buckley DL, Peng Y, John GB, Li HC, Sadeghi N, Wright WE, Lum L, Corson TW, Shay JW. KIF14 promotes AKT phosphorylation and contributes to chemoresistance in triple-negative breast cancer. *Neoplasia* 2014; **16**: 247-256, 256.e2 [PMID: 24784001 DOI: 10.1016/j.neo.2014.03.008]

161   **Hoda MR**, Keely SJ, Bertelsen LS, Junger WG, Dharmasena D, Barrett KE. Leptin acts as a mitogenic and antiapoptotic factor for colonic cancer cells. *Br J Surg* 2007; **94**: 346-354 [PMID: 17212381 DOI: 10.1002/bjs.5530]

162   **Saxena NK**, Sharma D, Ding X, Lin S, Marra F, Merlin D, Anania FA. Concomitant activation of the JAK/STAT, PI3K/AKT, and ERK signaling is involved in leptin-mediated promotion of invasion and migration of hepatocellular carcinoma cells. *Cancer Res* 2007; **67**: 2497-2507 [PMID: 17363567 DOI: 10.1158/0008-5472.CAN-06-3075]

163   **Sharma D**, Saxena NK, Vertino PM, Anania FA. Leptin promotes the proliferative response and invasiveness in human endometrial cancer cells by activating multiple signal-transduction pathways. *Endocr Relat Cancer* 2006; **13**: 629-640 [PMID: 16728588 DOI: 10.1677/erc.1.01169]

164   **Montales MT**, Melnyk SB, Liu SJ, Simmen FA, Liu YL, Simmen RC. Metabolic history impacts mammary tumor epithelial hierarchy and early drug response in mice. *Endocr Relat Cancer* 2016; **23**: 677-690 [PMID: 27402613 DOI: 10.1530/ERC-16-0136]

165   **Han G**, Wang L, Zhao W, Yue Z, Zhao R, Li Y, Zhou X, Hu X, Liu J. High expression of leptin receptor leads to temozolomide resistance with exhibiting stem/progenitor cell features in gliobalastoma. *Cell Cycle* 2013; **12**: 3833-3840 [PMID: 24131927 DOI: 10.4161/cc.26809]

166   **Koda M**, Lenczewski A, Sulkowska M, Kanczuga-Koda L, Wincewicz A, Tomaszewski J, Sulkowski S. The effect of chemotherapy on status of estrogen receptors in primary tumors and lymph node metastases of human ductal breast cancer. *Oncol Rep* 2007; **17**: 385-391 [PMID: 17203178]

167   **Koda M**, Sulkowska M, Wincewicz A, Kanczuga-Koda L, Musiatowicz B, Szymanska M, Sulkowski S. Expression of leptin, leptin receptor, and hypoxia-inducible factor 1 alpha in human endometrial cancer. *Ann N Y Acad Sci* 2007; **1095**: 90-98 [PMID: 17404022 DOI: 10.1196/annals.1397.013]

168   **Koda M**, Kanczuga-Koda L, Sulkowska M, Surmacz E, Sulkowski S. Relationships between hypoxia markers and the leptin system, estrogen receptors in human primary and metastatic breast cancer: effects of preoperative chemotherapy. *BMC Cancer* 2010; **10**: 320 [PMID: 20569445 DOI: 10.1186/1471-2407-10-320]

169   **Sarraf P**, Frederich RC, Turner EM, Ma G, Jaskowiak NT, Rivet DJ, Flier JS, Lowell BB, Fraker DL, Alexander HR. Multiple cytokines and acute inflammation raise mouse leptin levels: potential role in inflammatory anorexia. *J Exp Med* 1997; **185**: 171-175 [PMID: 8996253]

170   **Nadal-Serrano M**, Sastre-Serra J, Valle A, Roca P, Oliver J. Chronic-leptin attenuates Cisplatin cytotoxicity in MCF-7 breast cancer cell line. *Cell Physiol Biochem* 2015; **36**: 221-232 [PMID: 25967962 DOI: 10.1159/000374066]

171   **Shpilman M**, Niv-Spector L, Katz M, Varol C, Solomon G, Ayalon-Soffer M, Boder E, Halpern Z, Elinav E, Gertler A. Development and characterization of high affinity leptins and leptin antagonists. *J Biol Chem* 2011; **286**: 4429-4442 [PMID: 21119198 DOI: 10.1074/jbc.M110.196402]

172   **Otvos L**, Kovalszky I, Riolfi M, Ferla R, Olah J, Sztodola A, Nama K, Molino A, Piubello Q, Wade JD, Surmacz E. Efficacy of a leptin receptor antagonist peptide in a mouse model of triple-negative breast cancer. *Eur J Cancer* 2011; **47**: 1578-1584 [PMID: 21353530 DOI: 10.1016/j.ejca.2011.01.018]

173   **Beccari S**, Kovalszky I, Wade JD, Otvos L, Surmacz E. Designer peptide antagonist of the leptin receptor with peripheral antineoplastic activity. *Peptides* 2013; **44**: 127-134 [PMID: 23567149 DOI: 10.1016/j.peptides.2013.03.027]

174   **Catalano S**, Leggio A, Barone I, De Marco R, Gelsomino L, Campana A, Malivindi R, Panza S, Giordano C, Liguori A, Bonofiglio D, Liguori A, Andò S. A novel leptin antagonist peptide inhibits breast cancer growth in vitro and in vivo. *J Cell Mol Med* 2015; **19**: 1122-1132 [PMID: 25721149 DOI: 10.1111/jcmm.12517]

175   **Harmon T**, Gonzalez-Perez RR. Evaluation of Nanoparticle-Based Therapy for Triple-Negative Breast Cancer using Cellometer Vision CBA - Nexcelom Blog. Nexcelom 2014; Available from: URL: http://www.nexcelom.com/Nexcelom-Blog/evaluation-of-sanoparticle-based-therapy-for-triple-negative-breast-cancer-using- cellometer-vision-cba/

176   **Harmon T**, Harbuzariu A, Lanier V, Lipsey CC, Kirlin W, Yang L, Gonzalez-Perez RR. Nanoparticle-linked antagonist for leptin signaling inhibition in breast cancer. *World J Clin Oncol* 2017; **8**: 54-66 [DOI: 10.5306/wjco.v8.i1.54]

Published by **Baishideng Publishing Group Inc**