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# Adipokines – Toward the Molecular Dissection of Interactions Between Stromal Adipocytes and Breast Cancer Cells

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## 1. Introduction

After more than a half century of efforts, cancer remains the leading cause of death globally, second only to cardiovascular diseases. The World Health Organization estimates that 84 million people will die from cancer in the next ten years if no action is taken (<http://www.who.int/cancer>). Obesity appears to play important roles not only in cardiovascular and metabolic diseases, but also in cancer etiology (Bray 2004). For example, overweight and obesity account for 25% of the patients with breast cancer, the most frequent cancer and the second leading cause of cancer death among women (Calle et al. 2003; McTiernan 2003). Excess adiposity over the pre- and post-menopausal years is an independent risk factor for breast cancer and its relapse (Alokail et al. 2009; Katoh et al. 1994; McTiernan 2005; Saxe et al. 1999), and is associated with late-stage disease and poor prognosis (Lorincz and Sukumar 2006). On the other hand, information is limited on why excess body fat increases cancer risks and how obesity affects the prognosis and therapy of cancer.

Dysfunctional adipose tissue, characterized by aberrant production of adipokines, is believed to be a key player in obesity-related mammary carcinogenesis. Adipokines are a family of molecules selectively secreted by fat tissue (Deng and Scherer 2010). In obese subjects, the production of adipokines is dysregulated, which in turn contributes to medical conditions associated with obesity (Galic et al. 2010). Evidence from clinical, epidemiological and experimental studies suggest that adipokines are key pathological mediators in obesity-related cancer diseases, although the underlying mechanisms remain to be uncovered and may vary from site to site (Prieto-Hontoria et al. 2010; van Kruijsdijk et al. 2009). The present review is to provide a systemic update on how adipokines affect breast cancer cell function and mammary tumor initiation and development. Specifically, the detailed roles of three adipokines [adiponectin, lipocalin-2 and leptin] in mammary carcinogenesis will be discussed by integrating the information derived from cellular, animal and clinical studies.

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The mechanistic links for each adipokine will be assembled to model the process of breast cancer development under obesity conditions.

## 2. Stromal adipocytes in obesity-associated mammary carcinogenesis

Mammary gland comprises of epithelial and stromal cells. Stromal tissue regulates the development and differentiation of breast epithelial cells (Creydt et al. 2010; Polyak and Kalluri 2010). Adipocyte is one of the predominant stromal cell types in the microenvironment of mammary tissue. Proper function of adipose tissue plays an important role in mammary gland development and lactation process (Couldrey et al. 2002; Wiseman and Werb 2002). The differentiation/redifferentiation of fat cells apparently regulates epithelial cell cycles and contributes to the maintenance of the mammary epithelial “niche” (Arendt et al. 2010; Hovey and Aimo 2010). The close relationship between adipose tissue and mammary tumor growth has been demonstrated by many *in vitro* and *in vivo* experimental studies (Elliott et al. 1992; Miller et al. 1981; Sheffield and Welsch 1988). Mature adipocytes can promote the growth of breast carcinoma cells in a collagen gel matrix culture (Manabe et al. 2003). Co-transplantation of tumor cells with adipocytes into mice results in increased tumor growth and metastasis (Iyengar et al. 2005). On the other hand, factors derived from mammary tumor cells stimulate the reversion of mammary adipose phenotype and promote the differentiation of adipose stem cells into carcinoma-associated fibroblast (Guerrero et al. 2010; Jotzu et al. 2010). Conditioned media from breast cancer cells facilitates the accumulation of pre-adipocyte cells in the cancer tissue (Meng et al. 2001).

Multiple mechanisms are implicated in linking abnormal adipose tissue with breast cancer development (Figure 1). First, adipocyte is the predominant stromal cell type in mammary tissue responsible for local estrogen production, thus contributing to the development of estrogen-dependent breast cancer in postmenopausal women (Sinicrope and Dannenberg 2011). Obese women are at increased risk of developing estrogen receptor (ER)-positive breast cancer (Cleary and Grossmann 2009). Under obese condition, adipose tissue becomes “inflamed” to produce inflammatory mediators, such as tumor necrosis factor alpha (TNF $\alpha$ ) and interleukin (IL)-1 $\beta$ , which promote the expression of cytochrome P450 aromatase, an enzyme responsible for the synthesis of estrogen from androgen, in adipocytes (Subbaramaiah et al. 2011). Second, increased fat mass in obese condition is associated with altered energy metabolism (McTiernan 2005). The concept of a relationship between dysregulated metabolism and carcinogenesis was first enunciated by Otto Warburg more than 80 years ago (Davison and Schafer 2010). There is now a large body of evidence supporting a link between obesity, metabolic syndrome, insulin resistance with increased risk of cancers (Vona-Davis et al. 2007; Wysocki and Wierusz-Wysocka 2010). Type 2 diabetes and high level of circulating blood glucose have been shown to be positively correlated with increased breast cancer mortality (Bjorge et al. 2010; Wolf et al. 2005). Recent studies show that the use of metformin, an oral antidiabetic drug that has been used for many years, is associated with decreased cancer risk (Dowling et al. 2011). Additionally, the increased fat mass is associated with aberrant insulin signaling (insulin resistance) and increased insulin levels, which directly stimulate mammary carcinogenesis (Vona-Davis et al. 2007). During breast cancer progression, the composition of the extracellular matrix is dynamically altered and adipose tissue is critically participated in this process (Erler et al. 2006; Fata et al. 2004). Adipocyte-derived collagen VI could activate the pro-survival and

proliferation pathways to promote tumor growth and development (Iyengar et al. 2003). More recently, fat tissue has been recognized as an important secretory organ that can produce various hormones, cytokines and growth factors, collectively called adipokines (Galic et al. 2010). Dys-regulated expression and function of these adipokines play significant roles in the pathogenesis of obesity-related breast cancer diseases (Deng and Scherer 2010; Paz-Filho et al. 2011; Schaffler et al. 2007) (Figure 2). A number of them, including leptin and lipocalin-2, promote breast cancer cell survival, proliferation and tumor development, whereas adiponectin, the anti-inflammatory adipokine, has opposite effects (Jarde et al. 2011; Leng et al. 2011; Wang et al. 2007b; Yang and Moses 2009). Obese women with reduced serum adiponectin levels and low serum adiponectin levels are associated with an increased risk for breast cancer development and mortality (Duggan et al. 2011; Mantzoros et al. 2004). Women with higher adiponectin levels have a reduced risk of breast cancer (Korner et al. 2007; Miyoshi et al. 2003). Moreover, tumors in women with low serum adiponectin levels are more likely to show a biologically aggressive phenotype with poor prognosis (Miyoshi et al. 2003). The level of leptin increases in serum with increasing adiposity. In women diagnosed with breast cancer, the balance of adiponectin and leptin has been indicated to correlate with the disease development (Grossmann et al. 2008b). Serum leptin to adiponectin ratio is increased significantly in breast cancer patients and positively correlated with tumor size (Chen et al. 2006). Adiponectin levels are negatively correlated with leptin, and patients with higher levels of leptin are at increased risk for late stage tumors (Cust et al. 2009). The reduced levels of adiponectin and elevated leptin are associated with lymph node metastasis (Hou et al. 2007). Another adipokine, lipocalin-2, is found to be associated with aggressive types of breast cancers and poor prognosis (Leng et al. 2011).

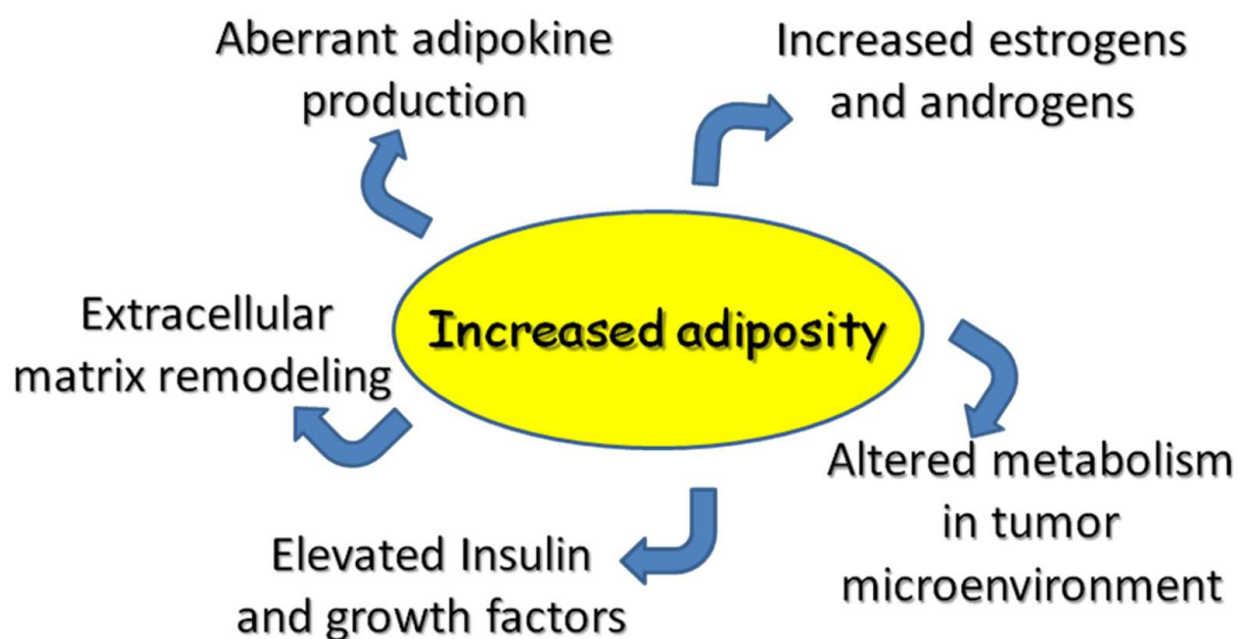


Fig. 1. Multiple mechanisms are implicated in linking increased adiposity with breast cancer development.

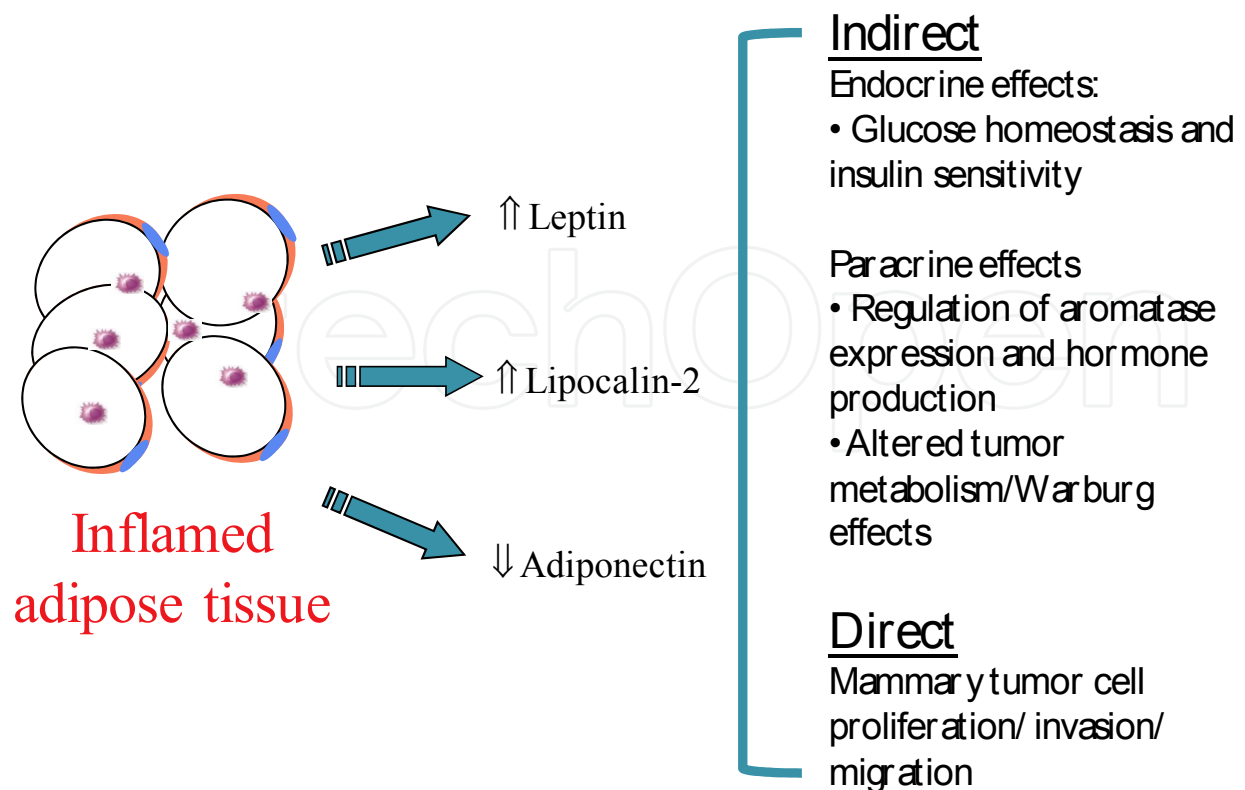


Fig. 2. Dysregulated production of adipokines, such as leptin, lipocalin-2 and adiponectin, from inflamed adipose tissue, contributes to mammary tumor development through both indirect and direct mechanisms.

Taken together, the above experimental and epidemiological evidences suggest that adipose tissue play an important role in breast cancer development and adipokines are key mediators linking obesity with breast cancer disease. The following sections of this chapter will elucidate the detailed role of adipokines, with special focus on the three adipokines, adiponectin, leptin and lipocalin-2, in mediating the stromal-epithelial interactions, in turn influencing the growth and proliferation of breast cancer cells.

### 3. Adipokines as key stromal factors in regulating mammary carcinogenesis

#### 3.1 Adiponectin

Adiponectin is a 30-kDa glycoprotein exclusively secreted from adipocytes (Scherer et al. 1995). Human adiponectin gene is located on chromosome 3q27 and encodes a 244 amino acids polypeptide (Wang et al. 2008). Circulating concentrations of adiponectin range from 3-30  $\mu\text{g}/\text{mL}$ , accounting for  $\sim 0.05\%$  of total human blood proteins (Ryan et al. 2003). Unlike many other adipokines that are up-regulated in obesity, circulating levels of adiponectin are inversely associated with obesity-related disorders (Cnop et al. 2003; Pajvani and Scherer 2003; Wang et al. 2009).

Endogenous adiponectin is predominantly present as several characteristic oligomeric complexes (Wang et al. 2008). The basic building block of the adiponectin complex is a trimer or low molecular weight (LMW) oligomer, which is formed via hydrophobic interactions within its globular domain. Two trimers self-associate to form a disulfide-linked hexamer or middle molecular weight (MMW) oligomer, which further assembles into a

bouquet-like high molecular weight (HMW) multimeric complex that consists of 12-18 monomers (Radjainia et al. 2008). Post-translational modifications, including disulfide bond formation at a conserved cysteine residue and glycosylations occurred on several hydroxylated lysine residues within the collagenous domain, are involved in the assembly and stabilization of the oligomeric structures (Wang et al. 2006b; Wang et al. 2005a; Wang et al. 2002). Different oligomeric complexes of adiponectin activate distinct signalling pathways and possess different biological functions.

Two putative adiponectin receptors, termed AdipoR1 and AdipoR2, have been identified. Both receptors are integral membrane proteins containing seven transmembrane spanning domains (Yamauchi et al. 2003). They show unique distributions in various tissues and different affinities for the distinctive forms of circulating adiponectin. T-cadherin, which is highly expressed in endothelium and smooth muscle, has been identified as an adiponectin co-receptor with preference for hexameric and HMW adiponectin multimers (Hug et al. 2004).

Unlike most of the adipokines that are causally linked to obesity-related diseases, adiponectin has potent insulin-sensitizing, anti-inflammatory, anti-atherogenic and anti-tumorigenic activities (Kadowaki et al. 2006; Wang et al. 2007b; Wang et al. 2008; Wang et al. 2009). Notably, adiponectin potently inhibits the proliferation of various types of cells, including aortic smooth muscle cells, myelomonocytic cells, hepatic stellate cells and several types of cancer cells (Arita et al. 2002; Ding et al. 2005; Wang et al. 2005b; Yokota et al. 2000). It selectively binds to various carcinogenic growth factor and prevent the interactions of these growth factors to their respective receptors (Wang et al. 2005a). In addition, adiponectin inhibits the growth and migration of vascular endothelial cells, prevents new blood vessel formation, and attenuates the growth of transplanted fibrosarcoma cell tumors in mice (Brakenhielm et al. 2004).

The stromal effects of adiponectin have been nicely presented in mouse models with spontaneous mammary tumor development. Study by Lam et al demonstrates that insufficient production of adiponectin in adipocyte *per se* promotes tumor onset and development in MMTV-polyomavirus middle T antigen (MMTV-PyVT) transgenic mice (Lam et al. 2009; Landskroner-Eiger et al. 2009). A distinctive basal-like subtype of tumors, characterized by high proliferative activity and unfavorable prognosis, is derived from adiponectin haplodeficient MMTV-PyVT mice (Lam et al. 2009). Histological analysis demonstrated typical morphologic features including markedly elevated geographic tumor necrosis, ribbon-like architecture associated with central necrosis, pushing margin of invasion, and stromal lymphocytic response in tumors (Livasy et al. 2007). In contrast, the original MMTV-PyVT mice showed a well-structured and organized morphology. In more advanced malignant stages, mice lacking adiponectin give rise to a larger tumor burden, an increase in the mobilization of circulating endothelial progenitor cells, and a gene expression fingerprint indicative of more aggressive tumor cells. The potent angio-mimetic properties of adiponectin modulate tumor vascularization and deficiency of this hormone creates a chronically hypoxic microenvironment (Landskroner-Eiger et al. 2009). Breast cancer consists of a heterogeneous group of tumors classified into five types, in which the HER2/neu positive and the basal type (most are ER and HER2 negative) have the worst clinical prognosis. Tumors derived from adiponectin haplodeficient MMTV-PyVT mice show a triple-negative genotype (Lam et al. 2009), which may be aroused from a different origin or subgroups of stem cells that develop tumor more aggressively. The origin of this

subtype tumor is unclear, but suggested to be the basal/myoepithelial cells, derived from epithelial-to-mesenchymal transition as a result of dedifferentiation, or from stem cells (Livasy et al. 2007).

In human mammary tumor tissue, adiponectin mRNA expression was observed only in the adipose tissues. On the other hand, AdipoR1 and AdipoR2 mRNA expression was observed in breast cancer cells, adipose tissues and normal breast epithelial cells (Takahata et al. 2007). In breast cancer specimen, a strong positive correlation between insulin as well as IGF1 receptor and AdipoR1 expression, but not AdipoR2 expression, could be observed. AdipoR1 is significantly higher in invasive breast cancer compared to preinvasive DCIS and inversely correlated with tumor size (Pfeiler et al. 2011). AdipoR2 expression is significantly correlated with vascular and lymphovascular invasion of breast cancer (Pfeiler et al. 2009). These results suggest a possibility that adiponectin might modulate the growth of normal breast epithelial cells and breast cancer cells directly through AdipoR1 and AdipoR2 receptors, and that the association of low serum adiponectin levels with a high breast cancer risk might be explained, at least in part, by the direct effect of adiponectin on the breast epithelial cells. The altered expression of AdipoR1 in invasive breast cancer also suggests that adiponectin might exert inhibitory effects on the transformation of preinvasive to invasive breast cancer. Further studies are warranted to investigate the prospective association between the mammary adiponectin levels and the risk of obesity-related breast cancers in humans.

### 3.2 Leptin

Leptin is a 16-kDa protein hormone abundantly expressed in white adipose tissue (Jarde et al. 2011). The circulating level of leptin is in the range of 5-50 ng/ml (Garofalo and Surmacz 2006). Obese individuals show a much higher plasma level (over 100 ng/ml) (Oksanen et al. 1997). Leptin was originally discovered by positional cloning of the obese (*ob*) gene, which is mutated in the massively obese *ob/ob* mice (Zhang et al. 1994). Leptin acts in the brain to regulate food intake and energy expenditure (Kelesidis et al. 2011). Treatment with leptin significantly reduces the body weight and food intake of the *ob/ob* mice. The leptin receptor mutant *db/db* mice, which are phenotypically similar to *ob/ob* mice, do not respond to leptin treatment (Campfield et al. 1995). The biological activity of leptin is mediated through the transmembrane leptin receptor ObR, which is expressed as at least six different subtypes in numerous tissues and cell types. Primarily the long isoform (ObRb) is responsible for activating leptin signaling pathways (Ahima and Osei 2004).

In general, higher body weight and/or obesity has been associated with shortened mammary tumor latency and increased incidence for development of spontaneous and carcinogen-induced tumors in animals (Dogan et al. 2007). In two sequential studies, MMTV-transforming growth factor (TGF)- $\alpha$  mice were crossed to genetically obese *ob/ob* and *db/db* mice. Surprisingly, neither type of these mice developed mammary tumors, suggesting that an intact leptin axis is essential for mammary tumorigenesis (Cleary et al. 2004). On the other hand, obesity induced by high fat diet significantly increases the number of tumors and reduces the tumor latency in MMTV-TGF- $\alpha$  mice (Cleary et al. 2010). The involvement of leptin signaling in mammary tumorigenesis was further confirmed by a study using obese Zucker rats, a rat model of genetic leptin receptor deficiency. Administration of chemical carcinogen methylnitrosourea could only induce a smaller number of Zucker rats to develop mammary tumor compared to lean controls (Lee et al.

2001). These findings demonstrate that leptin is a growth factor to support breast cancer development.

Both normal and malignant mammary tissues have been shown to produce leptin and express leptin receptors (Sheffield 2008). Leptin and its receptor are overexpressed in human breast tumor tissues (Garofalo et al. 2006). Expression of ErbB2 promotes high level expression of long-form leptin receptor and response to leptin. In general, the leptin/ObR correlates with higher tumor grade and worse prognosis (Surmacz 2007). Ishikawa et al observed that overexpression of both leptin and leptin receptors in breast cancer tissue are associated with distant metastasis (Ishikawa et al. 2004). The expression of leptin receptor showed a significant positive correlation with the level of leptin expression, suggesting an autocrine regulation of leptin expression in mammary tumor cells (Fiorio et al. 2008; Ishikawa et al. 2004; Revillion et al. 2006). The mRNA levels of leptin and leptin receptor are correlated positively with estrogen (ER) and progesterone receptors (PR), suggesting a possible interaction between leptin and oestrogen systems to promote breast carcinogenesis (Jarde et al. 2008b; Revillion et al. 2006). Analysis of human breast tumor tissues has also suggested an inverse relationship between leptin and adiponectin in breast cancer development (Jarde et al. 2008b). While leptin was expressed in a similar manner in invasive ductal carcinoma and *in situ* lesions, no tissue from *in situ* ductal carcinoma exhibited adiponectin expression. Moreover, myoepithelial cells of normal tissue adjacent to breast cancer exhibited 65% positivity for adiponectin while no cells in this group were positive for leptin expression, suggesting a possible leptin-adiponectin interaction on myoepithelial cells (Jarde et al. 2008b).

### 3.3 Lipocalin-2

Lipocalin-2, a 25-kDa secretory glycoprotein originally purified from human neutrophils, is constitutively expressed in adipose tissue (Esteve et al. 2009; Law et al. 2010). This protein structurally belongs to the lipocalin superfamily that shares the highly conserved structure of an 8-stranded antiparallel beta-barrel (Goetz et al. 2002). Circulating level of lipocalin-2 is elevated in obese animals and humans (Auguet et al. 2011; Hoo et al. 2008; Wang et al. 2007a; Yan et al. 2007; Zhang et al. 2008). Clinical, animal and cellular studies demonstrate the causal involvement of lipocalin-2 in obesity-associated medical complications (Auguet et al. 2011; Catalan et al. 2009; Esteve et al. 2009; Jin et al. 2010; Kanaka-Gantenbein et al. 2008; Law et al. 2010; Moreno-Navarrete et al. 2010; Sommer et al. 2009; van Dam and Hu 2007; Yan et al. 2007; Zhang et al. 2008). In humans, the serum concentration of lipocalin-2 is associated closely with obesity-related anthropometric and biochemical variables, and represents an independent risk factor for metabolic and cardiovascular disorders (Catalan et al. 2009; Choi et al. 2008; Ding et al. 2010; Esteve et al. 2009; Hemdahl et al. 2006; Lee et al. 2010; Wang et al. 2007a; Yndestad et al. 2009). Role of lipocalin-2 in regulation of cell proliferation, differentiation and apoptosis has been demonstrated (Devireddy et al. 2001). Lipocalin-2 may sequester the intracellular iron causing cell death.

Lipocalins function to transport and present ligands to cell surface receptors and to form macromolecular complexes (Flower 1995). The first identified ligand of lipocalin-2 was bacterial catecholate-type ferric siderophores, such as enterobactin (Goetz et al. 2002). Thus this protein was originally considered as a potent bacteriostatic agent (Berger et al. 2006). A number of studies have reported that lipocalin-2 weakly binds to the tripeptide N-formyl-



Met-Leu-Phe (fMLF), a potent neutrophil chemoattractant, and possibly other lipophilic mediators of inflammation, including platelet activating factor and leukotriene B<sub>4</sub> (Strong et al. 1998). Recently, chemical screens combined with crystallography and fluorescence detection reveal a complex of lipocalin-2 that binds iron together with a small metabolic product called catechol (Bao et al. 2010). The formation of the complex blocks the reactivity of iron, permits its transport in the circulation and facilitates recycling in endosomes. The lipocalin-2-catechol-Fe(III) complex represents an unforeseen endogenous siderophore for iron traffic in aseptic tissues. This mammalian siderophore plays a critical role in both cytoplasmic and mitochondrial iron homeostasis. Lacking this siderophore results in the accumulation of abnormally high amounts of cytoplasmic iron and elevated levels of reactive oxygen species (Devireddy et al. 2010).

The promoting effects of lipocalin-2 on mammary tumor development have been signified by two independent studies using MMTV-ErbB2 (V664E) and MMTV-PyVT mouse models (Berger et al. 2010; Leng et al. 2009). Leng et al found that the initiation time of the mammary tumor in MMTV-ErbB2 (V664E) mice complete lacking lipocalin-2 expression was dramatically delayed by ~100 days compared to the mice with two copies of lipocalin-2 alleles (Leng et al. 2009). Furthermore, the tumor burden, the number of tumors per mouse as well as the lung metastasis were dramatically reduced. Another study also showed reduced tumor weight and number of tumors per mouse in MMTV-PyVT mice lacking lipocalin-2 expression (Berger et al. 2010). However, there was no difference observed during early mammary tumorigenesis between the wild type and lipocalin-2 knockout group. Based on this, they concluded that lipocalin-2 played a more important role in the later stage of tumor development in MMTV-PyVT model, which shows a more aggressive phenotype with much shorter tumor latency (Berger et al. 2010).

Positive correlations between the circulating level of lipocalin-2 and the invasive and metastatic status of breast cancer have been reported (Yang and Moses 2009). The expression patterns of lipocalin-2 in mammary tumor samples have been analyzed by a number of studies (Bauer et al. 2008; Stoesz et al. 1998; Yang et al. 2009). Lipocalin-2 positive cells can be identified in the infiltrating carcinomas but not in normal mammary tissues (Bauer et al. 2008). High expression of lipocalin-2 correlates with low ER and PR expression, high-histologic grade, lymph nodes metastasis, high-proliferation index and poor disease-free survival (Leng et al. 2011). The induced expression of lipocalin-2 staining in either the tumor or the stroma area is correlated with the advanced stages and the metastatic status. Orthotopic studies demonstrated that lipocalin-2-expressing breast tumors displayed a poorly differentiated phenotype and showed increased local tumor invasion and lymph node metastasis (Yang et al. 2009).

In summary, animal models have provided unique tools to dissect the roles of individual adipokine in mammary tumor development and to elucidate the multiple pathways responsible for the dialogue between adipocytes and breast cancer cells. The information obtained from the mammary tumor models with deficient adipokine expressions demonstrate that in general, adipokines elicit their activities on tumor progression through regulating a) cancer cell transformation, proliferation and migration; b) local and systemic inflammation; and c) pathological angiogenesis. In addition, the role of adipokines to regulate systematic energy metabolism also impacts the behaviors of breast cancer cells and tumor development.

#### **4. Signaling mechanisms responsible for the regulation of breast cancer cell function by adiponectin, leptin and lipocalin-2**

Although adipokines are the key players in obesity-related mammary carcinogenesis, the underlying mechanisms remain largely uncharacterized. Individual adipokines affect mammary tumor development in different manners through distinctive signalling pathways, with concomitant influences on proliferative, inflammatory, and metastatic properties of the tumor cells (Schaffler et al. 2007; Vona-Davis and Rose 2007). Moreover, the mechanistic networks of adipokines in mammary tumor development are usually intertwined with their role in regulating inflammation and angiogenesis (Lorincz and Sukumar 2006; Wang et al. 2007b). Here, the specific signaling mechanisms that are directly involved in regulating the breast cancer cell functions will be discussed and linked with animal and clinical presentations.

##### **4.1 Diversified signaling mechanisms of adiponectin: cross-talking with Wnt/ $\beta$ -catenin pathway**

Adiponectin acts as an inhibitory factor for the proliferation of human breast carcinoma cells and mammary tumor development (Arditi et al. 2007; Dieudonne et al. 2006; Grossmann et al. 2008a; Hebbard et al. 2008; Jarde et al. 2008a; Kang et al. 2005; Nakayama et al. 2008; Pfeiler et al. 2008; Wang et al. 2006a). *In vitro* treatment with adiponectin at physiological concentrations attenuates the growth of an ER-negative human breast carcinoma MDA-MB-231 cells by inhibiting cell proliferation and inducing apoptosis (Kang et al. 2005; Wang et al. 2006a). It also inhibits insulin- and growth factors-stimulated proliferation in ER-positive human breast cancer cells (Li et al. 2011; Wang et al. 2006a). These *in vitro* data are supported by animal study demonstrating that adiponectin supplement therapy suppresses the MDA-MB-231 breast tumor development in nude mice (Wang et al. 2006a).

Cell-type dependent signalling mechanisms have been suggested to mediate the growth inhibitory effects of adiponectin (Grossmann et al. 2008a) (Figure 3). In MCF-7 cells, adiponectin induces AMP-activated protein kinase (AMPK) phosphorylation and inactivates p42/p44 MAPkinase (ERK1/2) (Dieudonne et al. 2006). By contrast, the inhibitory effects of adiponectin on T47D cell growth are associated with inactivation of ERK1/2 but not AMPK or p38 MAPK (Korner et al. 2007; Wang et al. 2006a). In MDA-MB-231 cells with ectopic ER over-expression, globular adiponectin inhibits cell proliferation by blocking JNK2 signaling (Grossmann et al. 2008a). A cross-talk between adiponectin and ER signaling exists in breast cancer cells and that adiponectin effects on the growth and apoptosis of breast cancer cells *in vitro* are partly dependent on the presence of 17-beta estradiol (Pfeiler et al. 2008). In ER-negative MDA-MB-231 cells, adiponectin could modulate the glycogen synthase kinase-3beta (GSK3 $\beta$ )/ $\beta$ -catenin signaling pathway (Wang et al. 2006a). Prolonged treatment with adiponectin markedly reduces serum-induced phosphorylation of Akt and GSK3 $\beta$ , decreases intracellular accumulation and nuclear translocation of  $\beta$ -catenin, and suppresses cyclin D1 expression (Wang et al. 2006a). An increase of protein phosphatase 2A activity has been implicated in the dephosphorylation of Akt by adiponectin treatment in MDA-MB-231 cells (Kim et al. 2009). Although the effects of adiponectin on tumor metastasis are not conclusive, it is suggested that LKB1 is required for adiponectin-mediated inhibition of adhesion, migration and invasion of breast cancer cells (Taliaferro-Smith et al. 2009).

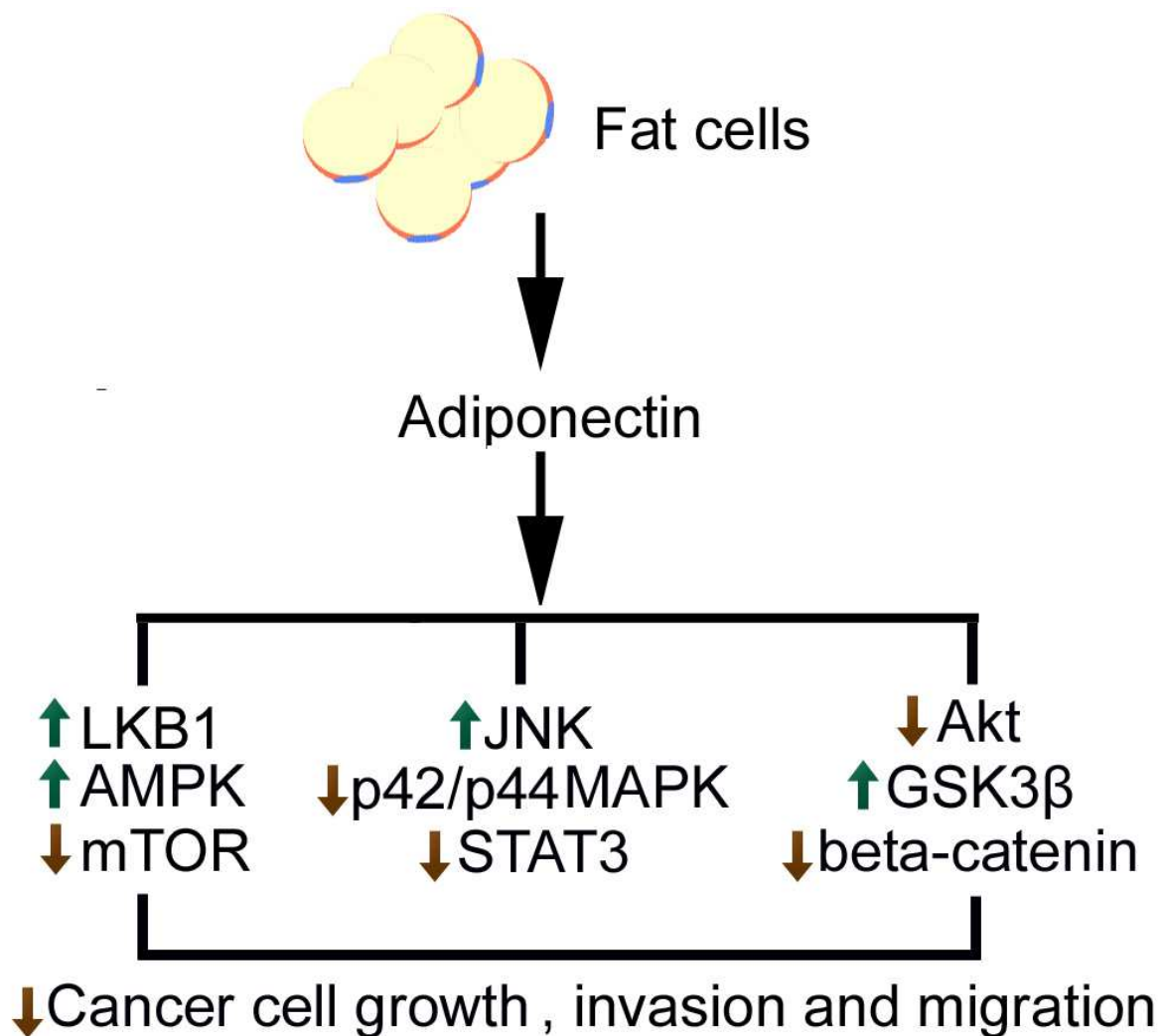


Fig. 3. Signaling pathways that mediate the anti-tumor activities of adiponectin.

Hyperactivation of the canonical Wnt/ $\beta$ -catenin pathway is one of the most frequent signal abnormalities in many types of cancers (Brown 2001; Howe and Brown 2004; Prosperi and Goss 2010). The central event in this pathway is the stabilization and nuclear translocation of  $\beta$ -catenin, where it binds to the transcription factor TCF/LEF and consequently activates a cluster of genes that ultimately establish the oncogenic phenotype (Jin et al. 2008). Stabilization of  $\beta$ -catenin protein and over-expression of cyclin D1 have been observed in over 50% of human breast tumors and increased  $\beta$ -catenin activity was found to be significantly correlated with the poor prognosis of breast cancer patients (Brown 2001). Given the close proximity between mammary gland cells and adipocytes, decreased adiponectin production might be causally linked to increased  $\beta$ -catenin accumulation and cyclin D1 overexpression observed in breast cancer patients. This possibility is supported by animal studies. The isolated mammary tumor cells from adiponectin haplodeficient MMTV-PyVT mice are presented with hyperactivated phosphatidylinositol-3-kinase (PI3K)/Akt/ $\beta$ -catenin signaling, which at least partly attributes to the decreased phosphatase and tensin homolog (PTEN) activities (Lam et al. 2009). PTEN is one of the most frequently mutated tumor suppressors that can prevent the activation of the cell survival PI3K/Akt signaling pathway (Carnero et al. 2008). In MMTV-PyVT animals with reduced production of

adiponectin, PTEN is inactivated by a redox-regulated mechanism involving thioredoxin and thioredoxin reductase. Specificity protein 1, a redox-regulated transcription factor, is involved in mediating the effects of adiponectin to stimulate the expression of Wnt inhibitory factor-1, a Wnt antagonist frequently silenced in human breast tumors (Liu et al. 2008). In summary, these findings have not only suggested a cross-talk between adiponectin and Wnt signaling pathway, but also provided a novel mechanistic insight to explain how metabolic alterations in adiponectin haplodeficient tumor may gain a survival advantage.

#### **4.2 Leptin-mediated signaling in breast cancer cells: in relation to other mitogenic receptors**

Leptin acts as a mitogen and survival factor for human breast cancer cells (Markowska et al. 2004). Leptin receptors are expressed in various human breast cancer cell lines and in human primary breast carcinoma (Frankenberry et al. 2006; Garofalo et al. 2006; Hu et al. 2002; Laud et al. 2002; Sheffield 2008). Leptin acts through multifaceted signaling pathways, including Jak2/STAT3 (Janus kinase 2/signal transducer and activator of transcription 3), PI3K/Akt, ERK1/2 and SOCS3 (Fusco et al. 2010; Palianopoulou et al. 2011; Saxena et al. 2007; Yin et al. 2004). Different sensitivities to recombinant leptin treatment have been found in distinctive breast carcinoma cell lines. For example, in MCF 7 cells, leptin induces a strong phosphorylation of STAT3 and ERK1/2, leading to an increased cell viability and proliferation (Fusco et al. 2010). This response is not present in MDA-MB 231 cells, in which leptin potentiates the anti-proliferative action of cAMP elevating agents by concurring to cell cycle arrest at G1 phase and inducing apoptosis (Naviglio et al. 2009).

Leptin induces the expression of vascular endothelial growth factor (VEGF) in both human and mouse mammary tumor cells, and promotes angiogenesis, which is related to the worse prognosis of breast cancer (Zhou et al. 2011). HIF-1 $\alpha$  and NF $\kappa$ B are implicated in leptin-regulated VEGF expression through both canonic (MAPK, PI-3K) and non-canonic (PKC, JNK and p38 MAP) signalling pathways (Gonzalez-Perez et al. 2010). Leptin contributes to the elevated circulating estrogen levels in obese women. It stimulates aromatase activity in adipose stromal cells at high concentrations (Magoffin et al. 1999). The action of leptin to enhance the promoter activity of aromatase is mediated by AP-1 in MCF-7 cells (Catalano et al. 2003). These evidence suggest that elevated leptin concentrations may cause locally augmented VEGF and estrogen in the breast and thereby promote tumor formation.

Leptin exerts its activity not only through its own receptors, but also through crosstalks with other signaling systems implicated in tumorigenesis (Ozbay and Nahta 2008). Co-treatment of leptin and insulin-like growth factor (IGF)-I significantly increases proliferation as well as invasion and migration of breast cancer cells (Saxena et al. 2008). A bidirectional crosstalk between leptin and IGF-I signaling exists to synergistically activate the downstream effectors, Akt and ERK1/2. Moreover, leptin and IGF-I treatment transactivates epidermal growth factor receptor (EGFR) to induce invasion and migration of breast cancer cells. In breast cancer cell lines, HER2 and ObR are coexpressed and physically interacted (Fiorio et al. 2008; Ray et al. 2007). Leptin treatment increases HER2 phosphorylation on Tyr 1248 (Fiorio et al. 2008). Coexpression of HER2 and the leptin/ObR system might contribute to enhanced HER2 activity and reduced sensitivity to anti-HER2 treatments. These data suggest indicate the possibility of using EGFR inhibitors to counter the pro-cancerous effects of leptin and IGF-I in breast cancers. Exogenous leptin induces tyrosine phosphorylation of HER2 in SKBR3 cells, which showed marked overexpression of HER2. Leptin-induced HER2 phosphorylation was partially reduced by an EGFR inhibitor, AG1478, or a Jak

inhibitor, AG490. Moreover, leptin-induced phosphorylation of ERK1/2 could be abrogated by a HER2 tyrosine kinase inhibitor, AG825 (Soma et al. 2008). In fact, the influence of leptin on breast cancer development not only relates to the presence or absence of HER2 but also depends on ER status (Ray et al. 2007). Knocking down of ERalpha attenuates leptin-induced activation of STAT3, whereas the enhancement of leptin-mediated STAT3 activity is independent of ERalpha ligands. ERalpha binding to STAT3 and Jak2 might lead to an increased ERalpha-dependent cell viability (Binai et al. 2010). Leptin plays important role in enhancing in situ estradiol production and promoting estrogen-dependent breast cancer progression. The ability of leptin to transactivate ERalpha and mimic the classic features of ERalpha signaling has been observed in MCF-7 breast cancer cell line. MAPK pathway is found to be involved in this process. Moreover, estradiol-induced activation of ERalpha can be potentiated by leptin exposure (Catalano et al. 2004).

Taken together, these findings suggest that the leptin system plays an important role in breast cancer pathogenesis and progression, and that it represents a novel target for therapeutic intervention in breast cancer disease (Cirillo et al. 2008).

#### **4.3 Lipocalin-2: Controversies and role in epithelial to mesenchymal transition**

Lipocalin-2 is a putative *in vivo* estrogen target gene and paracrine factor that mediates the growth regulatory effects of estrogen in normal breast epithelium (Seth et al. 2002). It contains an ER response element in its promoter. On the other hand, in T47D breast cancer cells, hormone treatment decreases the mRNA expression of lipocalin-2 (Mrusek et al. 2005), suggesting that normal and cancerous estrogen receptor-positive cells are distinct at the molecular level. Elevated lipocalin-2 may influence the steroid status of the mammary epithelial cells. When ectopically introducing lipocalin-2 into MCF-7 cells, their ER-dependent tumor growth in the xenografted mice is lost and the tumor cells become ER-negative (Yang et al. 2009). These data imply that modulation of lipocalin-2 expression may enable the breast cancer cells to become sensitive to ER therapy, a result that might be translated into clinical usage for ER-targeted therapy.

Both human and mouse mammary tumor cell lines have been used to examine the importance of lipocalin-2 in mammary tumor formation. Overexpression of lipocalin-2 in mouse 4T1 and human MDA-MB-468 cells greatly promoted their ability in cell migration and invasion (Leng et al. 2009; Shi et al. 2008). Moreover, implantation of 4T1 or MDA-MB-468 cells ectopically expressing lipocalin-2 generated a significant more number of lung metastatic nodules compared to those implanted with the unmodified cells. The lung metastasis could be blocked by injection of a polyclonal antibody against lipocalin-2 (Leng et al. 2009). In HER2-positive human breast cancer cell line SKBR3, knocking down lipocalin-2 expression reduced the migration and in ER-positive MCF-7 cells, These findings are consistent with the study by Fougere et al suggesting that the anti-migration activity of NFAT3 is through inhibition of lipocalin-2 gene expression (Fougere et al. 2010). In human tissue and urine samples, lipocalin-2 levels are consistently associated with invasive breast cancer (Yang et al. 2009).

Lipocalin-2 has been shown to induce the epithelial to mesenchymal transition (EMT) in breast cancer cells (Leng et al. 2011). Cells undergone EMT show increased motility and invasiveness as well as elevated lipocalin-2 expression. When ectopically expressed in MCF-7 cells, lipocalin-2 induces a typical EMT change of the cell morphology, accompanied by a loss of epithelial marker (E-cadherin) and an increased expression of the mesenchymal markers (vimentin and fibronectin) (Yang et al. 2009). Lipocalin-2 silencing in aggressive

breast cancer cells inhibits cell migration and the mesenchymal phenotype. Increased secretion of lipocalin-2 from the tumor cells might directly affect MMP-9 activity to promote cell motility or the transition to a more mesenchymal/aggressive phenotype (Leng et al. 2011). Much higher blood gelatinase activities are found in the tumor-bearing MMTV-ErbB mice with normal lipocalin-2 expression than those deficient of lipocalin-2 expression (Leng et al. 2009). ER $\alpha$  is also suggested to participate in lipocalin-2-induced EMT. By contrast, in 4T1 cells lipocalin-2 appears to reverse the EMT process induced by Ras expression (Hanai et al. 2005). Different phases or sites of lipocalin-2 treatment have been suggested for these controversial findings. During EMT, the initial increased lipocalin-2 stimulates epithelial migration and the elevated exogenous lipocalin-2 may facilitate the recovery (Mori et al. 2005; Yang et al. 2002).

In summary, although lipocalin-2 regulates EMT, one of the key processes involved in tumor progression and metastasis, the underlying mechanisms remain to be further elucidated.

## 5. Concluding remarks

The prevalence of obesity and its associated diseases has posed a huge healthcare impact on our society. During the past two decades, a panel of adipokines critically involved in pathological processes of obesity-associated breast cancer diseases has been discovered. Their contributions to the development of breast cancer and the underlying mechanisms are divergent. For example, adiponectin deficiency is associated with an accelerated mammary tumor development and altered Wnt/ $\beta$ -catenin signaling. On the other hand, the tumors of mice without lipocalin-2 are less metastatic and show slower rate of growth. Clearly, individual adipokines are able to modulate specific oncogenic and metabolic pathways, which synergistically promote or antagonize the development of breast cancer disease under obese conditions. The three adipokines discussed in this chapter not only represent potential therapeutic targets for breast cancer, but can also serve as biomarkers for early diagnosis and disease prevention. Compounds related to leptin that may have therapeutic use are currently being investigated in pre-clinical studies (Gonzalez et al. 2006; Ray and Cleary 2010; Rene Gonzalez et al. 2009; Surmacz 2007). Continued research will undoubtedly provide more insights into the relationship between adipose tissue-derived factors and breast cancer development, as well as the ways to intervene these interactions.

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## 7. References

- Ahima RS, Osei SY (2004) Leptin signaling. *Physiol Behav* 81:223-41
- Alokail MS, Al-Daghri NM, Al-Attas OS, Hussain T (2009) Combined effects of obesity and type 2 diabetes contribute to increased breast cancer risk in premenopausal women. *Cardiovasc Diabetol* 8:33

- Arditi JD, Venihaki M, Karalis KP, Chrousos GP (2007) Antiproliferative effect of adiponectin on MCF7 breast cancer cells: a potential hormonal link between obesity and cancer. *Horm Metab Res* 39:9-13
- Arendt LM, Rudnick JA, Keller PJ, Kuperwasser C (2010) Stroma in breast development and disease. *Semin Cell Dev Biol* 21:11-8
- Arita Y, Kihara S, Ouchi N, Maeda K, Kuriyama H, Okamoto Y, Kumada M, Hotta K, Nishida M, Takahashi M, Nakamura T, Shimomura I, Muraguchi M, Ohmoto Y, Funahashi T, Matsuzawa Y (2002) Adipocyte-derived plasma protein adiponectin acts as a platelet-derived growth factor-BB-binding protein and regulates growth factor-induced common postreceptor signal in vascular smooth muscle cell. *Circulation* 105:2893-8
- Auguet T, Quintero Y, Terra X, Martinez S, Lucas A, Pellitero S, Aguilar C, Hernandez M, Del Castillo D, Richart C (2011) Upregulation of lipocalin 2 in adipose tissues of severely obese women: positive relationship with proinflammatory cytokines. *Obesity (Silver Spring)*
- Bao G, Clifton M, Hoette TM, Mori K, Deng SX, Qiu A, Viltard M, Williams D, Paragas N, Leete T, Kulkarni R, Li X, Lee B, Kalandadze A, Ratner AJ, Pizarro JC, Schmidt-Ott KM, Landry DW, Raymond KN, Strong RK, Barasch J (2010) Iron traffics in circulation bound to a siderocalin (Ngal)-catechol complex. *Nat Chem Biol* 6:602-9
- Bauer M, Eickhoff JC, Gould MN, Mundhenke C, Maass N, Friedl A (2008) Neutrophil gelatinase-associated lipocalin (NGAL) is a predictor of poor prognosis in human primary breast cancer. *Breast Cancer Res Treat* 108:389-97
- Berger T, Cheung CC, Elia AJ, Mak TW (2010) Disruption of the *Lcn2* gene in mice suppresses primary mammary tumor formation but does not decrease lung metastasis. *Proc Natl Acad Sci U S A* 107:2995-3000
- Berger T, Togawa A, Duncan GS, Elia AJ, You-Ten A, Wakeham A, Fong HE, Cheung CC, Mak TW (2006) Lipocalin 2-deficient mice exhibit increased sensitivity to *Escherichia coli* infection but not to ischemia-reperfusion injury. *Proc Natl Acad Sci U S A* 103:1834-9
- Binai NA, Damert A, Carra G, Steckelbroeck S, Lower J, Lower R, Wessler S (2010) Expression of estrogen receptor alpha increases leptin-induced STAT3 activity in breast cancer cells. *Int J Cancer* 127:55-66
- Bjorge T, Lukanova A, Jonsson H, Tretli S, Ulmer H, Manjer J, Stocks T, Selmer R, Nagel G, Almquist M, Concin H, Hallmans G, Haggstrom C, Stattin P, Engeland A (2010) Metabolic syndrome and breast cancer in the me-can (metabolic syndrome and cancer) project. *Cancer Epidemiol Biomarkers Prev* 19:1737-45
- Brakenhielm E, Veitonmaki N, Cao R, Kihara S, Matsuzawa Y, Zhiotovskiy B, Funahashi T, Cao Y (2004) Adiponectin-induced antiangiogenesis and antitumor activity involve caspase-mediated endothelial cell apoptosis. *Proc Natl Acad Sci U S A* 101:2476-81
- Bray GA (2004) Medical consequences of obesity. *J Clin Endocrinol Metab* 89:2583-9
- Brown AM (2001) Wnt signaling in breast cancer: have we come full circle? *Breast Cancer Res* 3:351-5
- Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ (2003) Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. *N Engl J Med* 348:1625-38

- Campfield LA, Smith FJ, Guisez Y, Devos R, Burn P (1995) Recombinant mouse OB protein: evidence for a peripheral signal linking adiposity and central neural networks. *Science* 269:546-9
- Carnero A, Blanco-Aparicio C, Renner O, Link W, Leal JF (2008) The PTEN/PI3K/AKT signalling pathway in cancer, therapeutic implications. *Curr Cancer Drug Targets* 8:187-98
- Catalan V, Gomez-Ambrosi J, Rodriguez A, Ramirez B, Silva C, Rotellar F, Gil MJ, Cienfuegos JA, Salvador J, Fruhbeck G (2009) Increased adipose tissue expression of lipocalin-2 in obesity is related to inflammation and matrix metalloproteinase-2 and metalloproteinase-9 activities in humans. *J Mol Med* 87:803-13
- Catalano S, Marsico S, Giordano C, Mauro L, Rizza P, Panno ML, Ando S (2003) Leptin enhances, via AP-1, expression of aromatase in the MCF-7 cell line. *J Biol Chem* 278:28668-76
- Catalano S, Mauro L, Marsico S, Giordano C, Rizza P, Rago V, Montanaro D, Maggiolini M, Panno ML, Ando S (2004) Leptin induces, via ERK1/ERK2 signal, functional activation of estrogen receptor alpha in MCF-7 cells. *J Biol Chem* 279:19908-15
- Chen DC, Chung YF, Yeh YT, Chaung HC, Kuo FC, Fu OY, Chen HY, Hou MF, Yuan SS (2006) Serum adiponectin and leptin levels in Taiwanese breast cancer patients. *Cancer Lett* 237:109-14
- Choi KM, Lee JS, Kim EJ, Baik SH, Seo HS, Choi DS, Oh DJ, Park CG (2008) Implication of lipocalin-2 and visfatin levels in patients with coronary heart disease. *Eur J Endocrinol* 158:203-7
- Cirillo D, Rachiglio AM, la Montagna R, Giordano A, Normanno N (2008) Leptin signaling in breast cancer: an overview. *J Cell Biochem* 105:956-64
- Cleary MP, Grossmann ME (2009) Minireview: Obesity and breast cancer: the estrogen connection. *Endocrinology* 150:2537-42
- Cleary MP, Grossmann ME, Ray A (2010) Effect of obesity on breast cancer development. *Veterinary pathology* 47:202-13
- Cleary MP, Juneja SC, Phillips FC, Hu X, Grande JP, Maible NJ (2004) Leptin receptor-deficient MMTV-TGF-alpha/Lepr(db)Lepr(db) female mice do not develop oncogene-induced mammary tumors. *Exp Biol Med (Maywood)* 229:182-93
- Cnop M, Havel PJ, Utzschneider KM, Carr DB, Sinha MK, Boyko EJ, Retzlaff BM, Knopp RH, Brunzell JD, Kahn SE (2003) Relationship of adiponectin to body fat distribution, insulin sensitivity and plasma lipoproteins: evidence for independent roles of age and sex. *Diabetologia* 46:459-69
- Couldrey C, Moitra J, Vinson C, Anver M, Nagashima K, Green J (2002) Adipose tissue: a vital in vivo role in mammary gland development but not differentiation. *Dev Dyn* 223:459-68
- Creydt VP, Sacca PA, Tesone AJ, Vidal L, Calvo JC (2010) Adipocyte differentiation influences the proliferation and migration of normal and tumoral breast epithelial cells. *Mol Med Report* 3:433-9
- Cust AE, Stocks T, Lukanova A, Lundin E, Hallmans G, Kaaks R, Jonsson H, Stattin P (2009) The influence of overweight and insulin resistance on breast cancer risk and tumour stage at diagnosis: a prospective study. *Breast Cancer Res Treat* 113:567-76
- Davison CA, Schafer ZT (2010) Keeping a breast of recent developments in cancer metabolism. *Curr Drug Targets* 11:1112-20



- Deng Y, Scherer PE (2010) Adipokines as novel biomarkers and regulators of the metabolic syndrome. *Annals of the New York Academy of Sciences* 1212:E1-E19
- Devireddy LR, Hart DO, Goetz DH, Green MR (2010) A mammalian siderophore synthesized by an enzyme with a bacterial homolog involved in enterobactin production. *Cell* 141:1006-17
- Devireddy LR, Teodoro JG, Richard FA, Green MR (2001) Induction of apoptosis by a secreted lipocalin that is transcriptionally regulated by IL-3 deprivation. *Science* 293:829-34
- Dieudonne MN, Bussiere M, Dos Santos E, Leneuve MC, Giudicelli Y, Pecquery R (2006) Adiponectin mediates antiproliferative and apoptotic responses in human MCF7 breast cancer cells. *Biochem Biophys Res Commun* 345:271-9
- Ding L, Hanawa H, Ota Y, Hasegawa G, Hao K, Asami F, Watanabe R, Yoshida T, Toba K, Yoshida K, Ogura M, Kodama M, Aizawa Y (2010) Lipocalin-2/neutrophil gelatinase-B associated lipocalin is strongly induced in hearts of rats with autoimmune myocarditis and in human myocarditis. *Circ J* 74:523-30
- Ding X, Saxena NK, Lin S, Xu A, Srinivasan S, Anania FA (2005) The roles of leptin and adiponectin: a novel paradigm in adipocytokine regulation of liver fibrosis and stellate cell biology. *Am J Pathol* 166:1655-69
- Dogan S, Hu X, Zhang Y, Maihle NJ, Grande JP, Cleary MP (2007) Effects of high-fat diet and/or body weight on mammary tumor leptin and apoptosis signaling pathways in MMTV-TGF-alpha mice. *Breast cancer research : BCR* 9:R91
- Dowling RJ, Goodwin PJ, Stambolic V (2011) Understanding the benefit of metformin use in cancer treatment. *BMC medicine* 9:33
- Duggan C, Irwin ML, Xiao L, Henderson KD, Smith AW, Baumgartner RN, Baumgartner KB, Bernstein L, Ballard-Barbash R, McTiernan A (2011) Associations of insulin resistance and adiponectin with mortality in women with breast cancer. *J Clin Oncol* 29:32-9
- Elliott BE, Tam SP, Dexter D, Chen ZQ (1992) Capacity of adipose tissue to promote growth and metastasis of a murine mammary carcinoma: effect of estrogen and progesterone. *Int J Cancer* 51:416-24
- Erler JT, Bennewith KL, Nicolau M, Dornhofer N, Kong C, Le QT, Chi JT, Jeffrey SS, Giaccia AJ (2006) Lysyl oxidase is essential for hypoxia-induced metastasis. *Nature* 440:1222-6
- Esteve E, Ricart W, Fernandez-Real JM (2009) Adipocytokines and insulin resistance: the possible role of lipocalin-2, retinol binding protein-4, and adiponectin. *Diabetes Care* 32 Suppl 2:S362-7
- Fata JE, Werb Z, Bissell MJ (2004) Regulation of mammary gland branching morphogenesis by the extracellular matrix and its remodeling enzymes. *Breast Cancer Res* 6:1-11
- Fiorio E, Mercanti A, Terrasi M, Micciolo R, Remo A, Auriemma A, Molino A, Parolin V, Di Stefano B, Bonetti F, Giordano A, Cetto GL, Surmacz E (2008) Leptin/HER2 crosstalk in breast cancer: in vitro study and preliminary in vivo analysis. *BMC Cancer* 8:305
- Flower DR (1995) Multiple molecular recognition properties of the lipocalin protein family. *J Mol Recognit* 8:185-95

- Fougere M, Gaudineau B, Barbier J, Guaddachi F, Feugeas JP, Auboeuf D, Jauliac S (2010) NFAT3 transcription factor inhibits breast cancer cell motility by targeting the Lipocalin 2 gene. *Oncogene* 29:2292-301
- Frankenberry KA, Skinner H, Somasundar P, McFadden DW, Vona-Davis LC (2006) Leptin receptor expression and cell signaling in breast cancer. *Int J Oncol* 28:985-93
- Fusco R, Galgani M, Procaccini C, Franco R, Pirozzi G, Fucci L, Laccetti P, Matarese G (2010) Cellular and molecular crosstalk between leptin receptor and estrogen receptor- $\alpha$  in breast cancer: molecular basis for a novel therapeutic setting. *Endocr Relat Cancer* 17:373-82
- Galic S, Oakhill JS, Steinberg GR (2010) Adipose tissue as an endocrine organ. *Mol Cell Endocrinol* 316:129-39
- Garofalo C, Koda M, Cascio S, Sulkowska M, Kanczuga-Koda L, Golaszewska J, Russo A, Sulkowski S, Surmacz E (2006) Increased expression of leptin and the leptin receptor as a marker of breast cancer progression: possible role of obesity-related stimuli. *Clin Cancer Res* 12:1447-53
- Garofalo C, Surmacz E (2006) Leptin and cancer. *J Cell Physiol* 207:12-22
- Goetz DH, Holmes MA, Borregaard N, Bluhm ME, Raymond KN, Strong RK (2002) The neutrophil lipocalin NGAL is a bacteriostatic agent that interferes with siderophore-mediated iron acquisition. *Mol Cell* 10:1033-43
- Gonzalez-Perez RR, Xu Y, Guo S, Watters A, Zhou W, Leibovich SJ (2010) Leptin upregulates VEGF in breast cancer via canonic and non-canonical signalling pathways and NF $\kappa$ B/HIF-1 $\alpha$  activation. *Cell Signal* 22:1350-62
- Gonzalez RR, Cherfils S, Escobar M, Yoo JH, Carino C, Styer AK, Sullivan BT, Sakamoto H, Olawaiye A, Serikawa T, Lynch MP, Rueda BR (2006) 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* 281:26320-8
- Grossmann ME, Nkhata KJ, Mizuno NK, Ray A, Cleary MP (2008a) Effects of adiponectin on breast cancer cell growth and signaling. *Br J Cancer* 98:370-9
- Grossmann ME, Ray A, Dogan S, Mizuno NK, Cleary MP (2008b) Balance of adiponectin and leptin modulates breast cancer cell growth. *Cell Res* 18:1154-6
- Guerrero J, Tobar N, Caceres M, Espinoza L, Escobar P, Dotor J, Smith PC, Martinez J (2010) Soluble factors derived from tumor mammary cell lines induce a stromal mammary adipose reversion in human and mice adipose cells. Possible role of TGF- $\beta$ 1 and TNF- $\alpha$ . *Breast Cancer Res Treat* 119:497-508
- Hanai J, Mammoto T, Seth P, Mori K, Karumanchi SA, Barasch J, Sukhatme VP (2005) Lipocalin 2 diminishes invasiveness and metastasis of Ras-transformed cells. *J Biol Chem* 280:13641-7
- Hebbard LW, Garlatti M, Young LJ, Cardiff RD, Oshima RG, Ranscht B (2008) T-cadherin supports angiogenesis and adiponectin association with the vasculature in a mouse mammary tumor model. *Cancer Res* 68:1407-16
- Hemdahl AL, Gabrielsen A, Zhu C, Eriksson P, Hedin U, Kastrup J, Thoren P, Hansson GK (2006) Expression of neutrophil gelatinase-associated lipocalin in atherosclerosis and myocardial infarction. *Arterioscler Thromb Vasc Biol* 26:136-42

- Hoo RC, Yeung CY, Lam KS, Xu A (2008) Inflammatory biomarkers associated with obesity and insulin resistance: a focus on lipocalin-2 and adipocyte fatty acid-binding protein. *Expert Rev. Endocrinol. Metab.* 3:29-41
- Hou WK, Xu YX, Yu T, Zhang L, Zhang WW, Fu CL, Sun Y, Wu Q, Chen L (2007) Adipocytokines and breast cancer risk. *Chin Med J (Engl)* 120:1592-6
- Hovey RC, Aimo L (2010) Diverse and active roles for adipocytes during mammary gland growth and function. *J Mammary Gland Biol Neoplasia* 15:279-90
- Howe LR, Brown AM (2004) Wnt signaling and breast cancer. *Cancer Biol Ther* 3:36-41
- Hu X, Juneja SC, Maihle NJ, Cleary MP (2002) Leptin--a growth factor in normal and malignant breast cells and for normal mammary gland development. *J Natl Cancer Inst* 94:1704-11
- Hug C, Wang J, Ahmad NS, Bogan JS, Tsao TS, Lodish HF (2004) T-cadherin is a receptor for hexameric and high-molecular-weight forms of Acrp30/adiponectin. *Proc Natl Acad Sci U S A* 101:10308-13
- Ishikawa M, Kitayama J, Nagawa H (2004) Enhanced expression of leptin and leptin receptor (OB-R) in human breast cancer. *Clin Cancer Res* 10:4325-31
- Iyengar P, Combs TP, Shah SJ, Gouon-Evans V, Pollard JW, Albanese C, Flanagan L, Tenniswood MP, Guha C, Lisanti MP, Pestell RG, Scherer PE (2003) Adipocyte-secreted factors synergistically promote mammary tumorigenesis through induction of anti-apoptotic transcriptional programs and proto-oncogene stabilization. *Oncogene* 22:6408-23
- Iyengar P, Espina V, Williams TW, Lin Y, Berry D, Jelicks LA, Lee H, Temple K, Graves R, Pollard J, Chopra N, Russell RG, Sasisekharan R, Trock BJ, Lippman M, Calvert VS, Petricoin EF, 3rd, Liotta L, Dadachova E, Pestell RG, Lisanti MP, Bonaldo P, Scherer PE (2005) Adipocyte-derived collagen VI affects early mammary tumor progression in vivo, demonstrating a critical interaction in the tumor/stroma microenvironment. *The Journal of clinical investigation* 115:1163-76
- Jarde T, Caldefie-Chezet F, Damez M, Mishellany F, Buechler C, Bernard-Gallon D, Penault-Llorca F, Guillot J, Vasson MP (2008a) Antagonistic proliferative activities of adiponectin and leptin in breast cancer: study on MCF7 cells. *Proc Nutr Soc* 67:E184
- Jarde T, Caldefie-Chezet F, Damez M, Mishellany F, Penault-Llorca F, Guillot J, Vasson MP (2008b) Leptin and leptin receptor involvement in cancer development: a study on human primary breast carcinoma. *Oncol Rep* 19:905-11
- Jarde T, Perrier S, Vasson MP, Caldefie-Chezet F (2011) Molecular mechanisms of leptin and adiponectin in breast cancer. *Eur J Cancer* 47:33-43
- Jin D, Guo H, Bu SY, Zhang Y, Hannaford J, Mashek DG, Chen X (2010) Lipocalin 2 is a selective modulator of peroxisome proliferator-activated receptor-gamma activation and function in lipid homeostasis and energy expenditure. *FASEB J* 25:754-64
- Jin T, George Fantus I, Sun J (2008) Wnt and beyond Wnt: multiple mechanisms control the transcriptional property of beta-catenin. *Cell Signal* 20:1697-704
- Jotzu C, Alt E, Welte G, Li J, Hennessy BT, Devarajan E, Krishnappa S, Pinilla S, Droll L, Song YH (2010) Adipose tissue-derived stem cells differentiate into carcinoma-associated fibroblast-like cells under the influence of tumor-derived factors. *Anal Cell Pathol (Amst)* 33:61-79

- Kadowaki T, Yamauchi T, Kubota N, Hara K, Ueki K, Tobe K (2006) Adiponectin and adiponectin receptors in insulin resistance, diabetes, and the metabolic syndrome. *The Journal of clinical investigation* 116:1784-92
- Kanaka-Gantenbein C, Margeli A, Pervanidou P, Sakka S, Mastorakos G, Chrousos GP, Papassotiropoulos I (2008) Retinol-binding protein 4 and lipocalin-2 in childhood and adolescent obesity: when children are not just "small adults". *Clin Chem* 54:1176-82
- Kang JH, Lee YY, Yu BY, Yang BS, Cho KH, Yoon do K, Roh YK (2005) Adiponectin induces growth arrest and apoptosis of MDA-MB-231 breast cancer cell. *Arch Pharm Res* 28:1263-9
- Katoh A, Watzlaf VJ, D'Amico F (1994) An examination of obesity and breast cancer survival in post-menopausal women. *Br J Cancer* 70:928-33
- Kelesidis T, Kelesidis I, Chou S, Mantzoros CS (2011) Narrative review: the role of leptin in human physiology: emerging clinical applications. *Ann Intern Med* 152:93-100
- Kim KY, Baek A, Hwang JE, Choi YA, Jeong J, Lee MS, Cho DH, Lim JS, Kim KI, Yang Y (2009) Adiponectin-activated AMPK stimulates dephosphorylation of AKT through protein phosphatase 2A activation. *Cancer Res* 69:4018-26
- Korner A, Pazaitou-Panayiotou K, Kelesidis T, Kelesidis I, Williams CJ, Kaprara A, Bullen J, Neuwirth A, Tseleni S, Mitsiades N, Kiess W, Mantzoros CS (2007) Total and high-molecular-weight adiponectin in breast cancer: in vitro and in vivo studies. *J Clin Endocrinol Metab* 92:1041-8
- Lam JB, Chow KH, Xu A, Lam KS, Liu J, Wong NS, Moon RT, Shepherd PR, Cooper GJ, Wang Y (2009) Adiponectin haploinsufficiency promotes mammary tumor development in MMTV-PyVT mice by modulation of phosphatase and tensin homolog activities. *PLoS One* 4:e4968
- Landskroner-Eiger S, Qian B, Muise ES, Nawrocki AR, Berger JP, Fine EJ, Koba W, Deng Y, Pollard JW, Scherer PE (2009) Proangiogenic contribution of adiponectin toward mammary tumor growth in vivo. *Clin Cancer Res* 15:3265-76
- Laud K, Gourdou I, Pessemesse L, Peyrat JP, Djiane J (2002) Identification of leptin receptors in human breast cancer: functional activity in the T47-D breast cancer cell line. *Mol Cell Endocrinol* 188:219-26
- Law IK, Xu A, Lam KS, Berger T, Mak TW, Vanhoutte PM, Liu JT, Sweeney G, Zhou M, Yang B, Wang Y (2010) Lipocalin-2 deficiency attenuates insulin resistance associated with aging and obesity. *Diabetes* 59:872-82
- Lee WM, Lu S, Medline A, Archer MC (2001) Susceptibility of lean and obese Zucker rats to tumorigenesis induced by N-methyl-N-nitrosourea. *Cancer Lett* 162:155-60
- Lee YH, Lee SH, Jung ES, Kim JS, Shim CY, Ko YG, Choi D, Jang Y, Chung N, Ha JW (2010) Visceral adiposity and the severity of coronary artery disease in middle-aged subjects with normal waist circumference and its relation with lipocalin-2 and MCP-1. *Atherosclerosis* 213:592-7
- Leng X, Ding T, Lin H, Wang Y, Hu L, Hu J, Feig B, Zhang W, Pusztai L, Symmans WF, Wu Y, Arlinghaus RB (2009) Inhibition of lipocalin 2 impairs breast tumorigenesis and metastasis. *Cancer research* 69:8579-84
- Leng X, Wu Y, Arlinghaus RB (2011) Relationships of lipocalin 2 with breast tumorigenesis and metastasis. *J Cell Physiol* 226:309-14

- Li G, Cong L, Gasser J, Zhao J, Chen K, Li F (2011) Mechanisms underlying the anti-proliferative actions of adiponectin in human breast cancer cells, MCF7-dependency on the cAMP/protein kinase-A pathway. *Nutr Cancer* 63:80-8
- Liu J, Lam JB, Chow KH, Xu A, Lam KS, Moon RT, Wang Y (2008) Adiponectin stimulates Wnt inhibitory factor-1 expression through epigenetic regulations involving the transcription factor specificity protein 1. *Carcinogenesis*
- Livasy CA, Perou CM, Karaca G, Cowan DW, Maia D, Jackson S, Tse CK, Nyante S, Millikan RC (2007) Identification of a basal-like subtype of breast ductal carcinoma in situ. *Hum Pathol* 38:197-204
- Lorincz AM, Sukumar S (2006) Molecular links between obesity and breast cancer. *Endocr Relat Cancer* 13:279-92
- Magoffin DA, Weitsman SR, Agarwal SK, Jakimiuk AJ (1999) Leptin regulation of aromatase activity in adipose stromal cells from regularly cycling women. *Ginekol Pol* 70:1-7
- Manabe Y, Toda S, Miyazaki K, Sugihara H (2003) Mature adipocytes, but not preadipocytes, promote the growth of breast carcinoma cells in collagen gel matrix culture through cancer-stromal cell interactions. *J Pathol* 201:221-8
- Mantzoros C, Petridou E, Dessypris N, Chavelas C, Dalamaga M, Alexe DM, Papadiamantis Y, Markopoulos C, Spanos E, Chrousos G, Trichopoulos D (2004) Adiponectin and breast cancer risk. *J Clin Endocrinol Metab* 89:1102-7
- Markowska A, Malendowicz K, Drews K (2004) The role of leptin in breast cancer. *Eur J Gynaecol Oncol* 25:192-4
- McTiernan A (2003) Behavioral risk factors in breast cancer: can risk be modified? *Oncologist* 8:326-34
- McTiernan A (2005) Obesity and cancer: the risks, science, and potential management strategies. *Oncology (Williston Park)* 19:871-81; discussion 881-2, 885-6
- Meng L, Zhou J, Sasano H, Suzuki T, Zeitoun KM, Bulun SE (2001) Tumor necrosis factor alpha and interleukin 11 secreted by malignant breast epithelial cells inhibit adipocyte differentiation by selectively down-regulating CCAAT/enhancer binding protein alpha and peroxisome proliferator-activated receptor gamma: mechanism of desmoplastic reaction. *Cancer research* 61:2250-5
- Miller FR, Medina D, Heppner GH (1981) Preferential growth of mammary tumors in intact mammary fatpads. *Cancer Res* 41:3863-7
- Miyoshi Y, Funahashi T, Kihara S, Taguchi T, Tamaki Y, Matsuzawa Y, Noguchi S (2003) Association of serum adiponectin levels with breast cancer risk. *Clin Cancer Res* 9:5699-704
- Moreno-Navarrete JM, Manco M, Ibanez J, Garcia-Fuentes E, Ortega F, Gorostiaga E, Vendrell J, Izquierdo M, Martinez C, Nolfi G, Ricart W, Mingrone G, Tinahones F, Fernandez-Real JM (2010) Metabolic endotoxemia and saturated fat contribute to circulating NGAL concentrations in subjects with insulin resistance. *Int J Obes (Lond)* 34:240-9
- Mori K, Lee HT, Rapoport D, Drexler IR, Foster K, Yang J, Schmidt-Ott KM, Chen X, Li JY, Weiss S, Mishra J, Cheema FH, Markowitz G, Suganami T, Sawai K, Mukoyama M, Kunis C, D'Agati V, Devarajan P, Barasch J (2005) Endocytic delivery of lipocalin-siderophore-iron complex rescues the kidney from ischemia-reperfusion injury. *J Clin Invest* 115:610-21

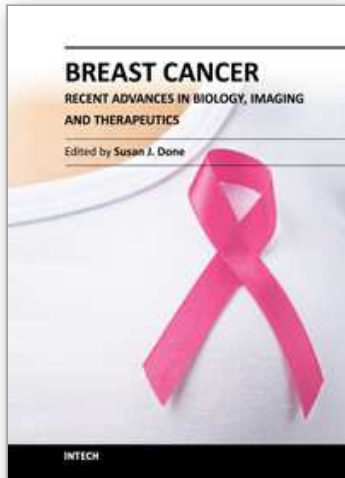
- Mrusek S, Classen-Linke I, Vloet A, Beier HM, Krusche CA (2005) Estradiol and medroxyprogesterone acetate regulated genes in T47D breast cancer cells. *Mol Cell Endocrinol* 235:39-50
- Nakayama S, Miyoshi Y, Ishihara H, Noguchi S (2008) Growth-inhibitory effect of adiponectin via adiponectin receptor 1 on human breast cancer cells through inhibition of S-phase entry without inducing apoptosis. *Breast Cancer Res Treat* 112:405-10
- Naviglio S, Di Gesto D, Romano M, Sorrentino A, Illiano F, Sorvillo L, Abbruzzese A, Marra M, Caraglia M, Chiosi E, Spina A, Illiano G (2009) Leptin enhances growth inhibition by cAMP elevating agents through apoptosis of MDA-MB-231 breast cancer cells. *Cancer Biol Ther* 8:1183-90
- Oksanen L, Ohman M, Heiman M, Kainulainen K, Kaprio J, Mustajoki P, Koivisto V, Koskenvuo M, Janne OA, Peltonen L, Kontula K (1997) Markers for the gene ob and serum leptin levels in human morbid obesity. *Hum Genet* 99:559-64
- Ozbay T, Nahta R (2008) A novel unidirectional cross-talk from the insulin-like growth factor-I receptor to leptin receptor in human breast cancer cells. *Mol Cancer Res* 6:1052-8
- Pajvani UB, Scherer PE (2003) Adiponectin: systemic contributor to insulin sensitivity. *Curr Diab Rep* 3:207-13
- Palianopoulou M, Papanikolaou V, Stefanou N, Tsezou A (2011) The activation of leptin-mediated survivin is limited by the inducible suppressor SOCS-3 in MCF-7 cells. *Exp Biol Med (Maywood)* 236:70-6
- Paz-Filho G, Lim EL, Wong ML, Licinio J (2011) Associations between adipokines and obesity-related cancer. *Front Biosci* 16:1634-50
- Pfeiler G, Hudelist G, Wulfing P, Mattsson B, Konigsberg R, Kubista E, Singer CF (2011) Impact of AdipoR1 expression on breast cancer development. *Gynecol Oncol* 117:134-8
- Pfeiler G, Treeck O, Wenzel G, Goerse R, Hartmann A, Schmitz G, Ortmann O (2009) Influence of insulin resistance on adiponectin receptor expression in breast cancer. *Maturitas* 63:253-6
- Pfeiler GH, Buechler C, Neumeier M, Schaffler A, Schmitz G, Ortmann O, Treeck O (2008) Adiponectin effects on human breast cancer cells are dependent on 17-beta estradiol. *Oncol Rep* 19:787-93
- Polyak K, Kalluri R (2010) The role of the microenvironment in mammary gland development and cancer. *Cold Spring Harb Perspect Biol* 2:a003244
- Prieto-Hontoria PL, Perez-Matute P, Fernandez-Galilea M, Bustos M, Martinez JA, Moreno-Aliaga MJ (2010) Role of obesity-associated dysfunctional adipose tissue in cancer: A molecular nutrition approach. *Biochim Biophys Acta*
- Prosperi JR, Goss KH (2010) A Wnt-ow of opportunity: targeting the Wnt/beta-catenin pathway in breast cancer. *Curr Drug Targets* 11:1074-88
- Radjainia M, Wang Y, Mitra AK (2008) Structural polymorphism of oligomeric adiponectin visualized by electron microscopy. *J Mol Biol* 381:419-30
- Ray A, Cleary MP (2010) Leptin as a potential therapeutic target for breast cancer prevention and treatment. *Expert Opin Ther Targets* 14:443-51
- Ray A, Nkhata KJ, Cleary MP (2007) Effects of leptin on human breast cancer cell lines in relationship to estrogen receptor and HER2 status. *Int J Oncol* 30:1499-509

- Rene Gonzalez R, Watters A, Xu Y, Singh UP, Mann DR, Rueda BR, Penichet ML (2009) Leptin-signaling inhibition results in efficient anti-tumor activity in estrogen receptor positive or negative breast cancer. *Breast Cancer Res* 11:R36
- Revillion F, Charlier M, Lhotellier V, Hornez L, Giard S, Baranzelli MC, Djiane J, Peyrat JP (2006) Messenger RNA expression of leptin and leptin receptors and their prognostic value in 322 human primary breast cancers. *Clin Cancer Res* 12:2088-94
- Ryan AS, Berman DM, Nicklas BJ, Sinha M, Gingerich RL, Meneilly GS, Egan JM, Elahi D (2003) Plasma adiponectin and leptin levels, body composition, and glucose utilization in adult women with wide ranges of age and obesity. *Diabetes Care* 26:2383-8
- Saxe GA, Rock CL, Wicha MS, Schottenfeld D (1999) Diet and risk for breast cancer recurrence and survival. *Breast Cancer Res Treat* 53:241-53
- Saxena NK, Taliaferro-Smith L, Knight BB, Merlin D, Anania FA, O'Regan RM, Sharma D (2008) Bidirectional crosstalk between leptin and insulin-like growth factor-I signaling promotes invasion and migration of breast cancer cells via transactivation of epidermal growth factor receptor. *Cancer Res* 68:9712-22
- Saxena NK, Vertino PM, Anania FA, Sharma D (2007) leptin-induced growth stimulation of breast cancer cells involves recruitment of histone acetyltransferases and mediator complex to CYCLIN D1 promoter via activation of Stat3. *J Biol Chem* 282:13316-25
- Schaffler A, Scholmerich J, Buechler C (2007) Mechanisms of disease: adipokines and breast cancer - endocrine and paracrine mechanisms that connect adiposity and breast cancer. *Nature clinical practice. Endocrinology & metabolism* 3:345-54
- Scherer PE, Williams S, Fogliano M, Baldini G, Lodish HF (1995) A novel serum protein similar to C1q, produced exclusively in adipocytes. *J Biol Chem* 270:26746-9
- Seth P, Porter D, Lahti-Domenici J, Geng Y, Richardson A, Polyak K (2002) Cellular and molecular targets of estrogen in normal human breast tissue. *Cancer Res* 62:4540-4
- Sheffield L (2008) Malignant transformation of mammary epithelial cells increases expression of leptin and leptin receptor. *Endocr Res* 33:111-8
- Sheffield LG, Welsch CW (1988) Transplantation of human breast epithelia to mammary-gland-free fat-pads of athymic nude mice: influence of mammatrophic hormones on growth of breast epithelia. *Int J Cancer* 41:713-9
- Shi H, Gu Y, Yang J, Xu L, Mi W, Yu W (2008) Lipocalin 2 promotes lung metastasis of murine breast cancer cells. *J Exp Clin Cancer Res* 27:83
- Sinicrope FA, Dannenberg AJ (2011) Obesity and breast cancer prognosis: weight of the evidence. *J Clin Oncol* 29:4-7
- Soma D, Kitayama J, Yamashita H, Miyato H, Ishikawa M, Nagawa H (2008) Leptin augments proliferation of breast cancer cells via transactivation of HER2. *J Surg Res* 149:9-14
- Sommer G, Weise S, Kralisch S, Lossner U, Bluher M, Stumvoll M, Fasshauer M (2009) Lipocalin-2 is induced by interleukin-1beta in murine adipocytes in vitro. *J Cell Biochem* 106:103-8
- Stoesz SP, Friedl A, Haag JD, Lindstrom MJ, Clark GM, Gould MN (1998) Heterogeneous expression of the lipocalin NGAL in primary breast cancers. *International journal of cancer. Journal international du cancer* 79:565-72
- Strong RK, Bratt T, Cowland JB, Borregaard N, Wiberg FC, Ewald AJ (1998) Expression, purification, crystallization and crystallographic characterization of dimeric and

- monomeric human neutrophil gelatinase associated lipocalin (NGAL). *Acta Crystallogr D Biol Crystallogr* 54:93-5
- Subbaramaiah K, Howe LR, Bhardwaj P, Du B, Gravaghi C, Yantiss RK, Zhou XK, Blaho VA, Hla T, Yang P, Kopelovich L, Hudis CA, Dannenberg AJ (2011) Obesity is associated with inflammation and elevated aromatase expression in the mouse mammary gland. *Cancer Prev Res (Phila)* 4:329-46
- Surmacz E (2007) Obesity hormone leptin: a new target in breast cancer? *Breast Cancer Res* 9:301
- Takahata C, Miyoshi Y, Irahara N, Taguchi T, Tamaki Y, Noguchi S (2007) Demonstration of adiponectin receptors 1 and 2 mRNA expression in human breast cancer cells. *Cancer Lett* 250:229-36
- Taliaferro-Smith L, Nagalingam A, Zhong D, Zhou W, Saxena NK, Sharma D (2009) LKB1 is required for adiponectin-mediated modulation of AMPK-S6K axis and inhibition of migration and invasion of breast cancer cells. *Oncogene* 28:2621-33
- van Dam RM, Hu FB (2007) Lipocalins and insulin resistance: etiological role of retinol-binding protein 4 and lipocalin-2? *Clin Chem* 53:5-7
- van Kruijsdijk RC, van der Wall E, Visseren FL (2009) Obesity and cancer: the role of dysfunctional adipose tissue. *Cancer Epidemiol Biomarkers Prev* 18:2569-78
- Vona-Davis L, Howard-McNatt M, Rose DP (2007) Adiposity, type 2 diabetes and the metabolic syndrome in breast cancer. *Obes Rev* 8:395-408
- Vona-Davis L, Rose DP (2007) Adipokines as endocrine, paracrine, and autocrine factors in breast cancer risk and progression. *Endocrine-related cancer* 14:189-206
- Wang Y, Lam JB, Lam KS, Liu J, Lam MC, Hoo RL, Wu D, Cooper GJ, Xu A (2006a) Adiponectin modulates the glycogen synthase kinase-3 $\beta$ /beta-catenin signaling pathway and attenuates mammary tumorigenesis of MDA-MB-231 cells in nude mice. *Cancer Res* 66:11462-70
- Wang Y, Lam KS, Chan L, Chan KW, Lam JB, Lam MC, Hoo RC, Mak WW, Cooper GJ, Xu A (2006b) Posttranslational modifications on the four conserved lysine residues within the collagenous domain of adiponectin are required for the formation of its high-molecular-weight oligomeric complex. *J Biol Chem*
- Wang Y, Lam KS, Kraegen EW, Sweeney G, Zhang J, Tso AW, Chow WS, Wat NM, Xu JY, Hoo RL, Xu A (2007a) Lipocalin-2 is an inflammatory marker closely associated with obesity, insulin resistance, and hyperglycemia in humans. *Clin Chem* 53:34-41
- Wang Y, Lam KS, Xu A (2007b) Adiponectin as a negative regulator in obesity-related mammary carcinogenesis. *Cell Res* 17:280-2
- Wang Y, Lam KS, Xu JY, Lu G, Xu LY, Cooper GJ, Xu A (2005a) Adiponectin inhibits cell proliferation by interacting with several growth factors in an oligomerization-dependent manner. *The Journal of biological chemistry* 280:18341-7
- Wang Y, Lam KS, Xu JY, Lu G, Xu LY, Cooper GJ, Xu A (2005b) Adiponectin inhibits cell proliferation by interacting with several growth factors in an oligomerization-dependent manner. *J Biol Chem* 280:18341-7
- Wang Y, Lam KS, Yau MH, Xu A (2008) Post-translational modifications of adiponectin: mechanisms and functional implications. *Biochem J* 409:623-33
- Wang Y, Xu A, Knight C, Xu LY, Cooper GJ (2002) Hydroxylation and glycosylation of the four conserved lysine residues in the collagenous domain of adiponectin. Potential role in the modulation of its insulin-sensitizing activity. *J Biol Chem* 277:19521-9



- Wang Y, Zhou M, Lam KS, Xu A (2009) Protective roles of adiponectin in obesity-related fatty liver diseases: mechanisms and therapeutic implications. *Arq Bras Endocrinol Metabol* 53:201-12
- Wiseman BS, Werb Z (2002) Stromal effects on mammary gland development and breast cancer. *Science* 296:1046-9
- Wolf I, Sadetzki S, Catane R, Karasik A, Kaufman B (2005) Diabetes mellitus and breast cancer. *Lancet Oncol* 6:103-11
- Wysocki PJ, Wierusz-Wysocka B (2010) Obesity, hyperinsulinemia and breast cancer: novel targets and a novel role for metformin. *Expert Rev Mol Diagn* 10:509-19
- Yamauchi T, Kamon J, Ito Y, Tsuchida A, Yokomizo T, Kita S, Sugiyama T, Miyagishi M, Hara K, Tsunoda M, Murakami K, Ohteki T, Uchida S, Takekawa S, Waki H, Tsuno NH, Shibata Y, Terauchi Y, Froguel P, Tobe K, Koyasu S, Taira K, Kitamura T, Shimizu T, Nagai R, Kadowaki T (2003) Cloning of adiponectin receptors that mediate antidiabetic metabolic effects. *Nature* 423:762-9
- Yan QW, Yang Q, Mody N, Graham TE, Hsu CH, Xu Z, Houstis NE, Kahn BB, Rosen ED (2007) The adipokine lipocalin 2 is regulated by obesity and promotes insulin resistance. *Diabetes* 56:2533-40
- Yang J, Bielenberg DR, Rodig SJ, Doiron R, Clifton MC, Kung AL, Strong RK, Zurakowski D, Moses MA (2009) Lipocalin 2 promotes breast cancer progression. *Proceedings of the National Academy of Sciences of the United States of America* 106:3913-8
- Yang J, Goetz D, Li JY, Wang W, Mori K, Setlik D, Du T, Erdjument-Bromage H, Tempst P, Strong R, Barasch J (2002) An iron delivery pathway mediated by a lipocalin. *Mol Cell* 10:1045-56
- Yang J, Moses MA (2009) Lipocalin 2: a multifaceted modulator of human cancer. *Cell Cycle* 8:2347-52
- Yin N, Wang D, Zhang H, Yi X, Sun X, Shi B, Wu H, Wu G, Wang X, Shang Y (2004) Molecular mechanisms involved in the growth stimulation of breast cancer cells by leptin. *Cancer Res* 64:5870-5
- Yndestad A, Landro L, Ueland T, Dahl CP, Flo TH, Vinge LE, Espevik T, Froland SS, Husberg C, Christensen G, Dickstein K, Kjekshus J, Oie E, Gullestad L, Aukrust P (2009) Increased systemic and myocardial expression of neutrophil gelatinase-associated lipocalin in clinical and experimental heart failure. *Eur Heart J* 30:1229-36
- Yokota T, Oritani K, Takahashi I, Ishikawa J, Matsuyama A, Ouchi N, Kihara S, Funahashi T, Tenner AJ, Tomiyama Y, Matsuzawa Y (2000) Adiponectin, a new member of the family of soluble defense collagens, negatively regulates the growth of myelomonocytic progenitors and the functions of macrophages. *Blood* 96:1723-32
- Zhang J, Wu Y, Zhang Y, Leroith D, Bernlohr DA, Chen X (2008) The role of lipocalin 2 in the regulation of inflammation in adipocytes and macrophages. *Mol Endocrinol* 22:1416-26
- Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, Friedman JM (1994) Positional cloning of the mouse obese gene and its human homologue. *Nature* 372:425-32
- Zhou W, Guo S, Gonzalez-Perez RR (2011) Leptin pro-angiogenic signature in breast cancer is linked to IL-1 signalling. *Br J Cancer* 104:128-37



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In recent years it has become clear that breast cancer is not a single disease but rather that the term encompasses a number of molecularly distinct tumors arising from the epithelial cells of the breast. There is an urgent need to better understand these distinct subtypes and develop tailored diagnostic approaches and treatments appropriate to each. This book considers breast cancer from many novel and exciting perspectives. New insights into the basic biology of breast cancer are discussed together with high throughput approaches to molecular profiling. Innovative strategies for diagnosis and imaging are presented as well as emerging perspectives on breast cancer treatment. Each of the topics in this volume is addressed by respected experts in their fields and it is hoped that readers will be stimulated and challenged by the contents.

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