Mini-review
DOI 10.1007/s12038-012-9191-9

Adipokine leptin in obesity-related pathology of breast cancer

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1. Introduction

Breast cancer is one of the most common cancers and a leading cause of cancer death in women worldwide. Incidences of breast cancer are substantially higher among postmenopausal than premenopausal women. Obesity is a common risk factor for postmenopausal breast cancer. For the development of postmenopausal breast cancer, several phenomena may function in relation with obesity. It is well known that adipose tissue is the major source of oestrogens in postmenopausal women, and oestrogens are associated with the pathological process of breast cancer. The enzyme aromatase (CYP19), present in the adipose tissue, catalyses the conversion of oestrone from androstenedione, which is mainly produced in the adrenal gland under the influence of adrenocorticotropic hormone. As the rate of oestrogen production is related to the amount of the adipose tissue, the quantity of body fat could be a significant source of oestrogens. Furthermore, there is an inverse association between obesity and circulating levels of sex hormone-binding globulin (SHBG), the principal carrier protein for oestrogen. Lower levels of SHBG increase the free or unbound form of oestrogen in blood, and unbound oestrogens may elevate the risk of breast cancer. Interestingly, a conflicting relationship exists between obesity and breast cancer prognosis. It has been documented that obesity is involved with the pathogenesis of oestrogen receptor-positive (ER+) breast cancer, which usually has a better prognosis than ER− breast cancer. On the other hand, obese women with breast cancer have been found to have a poor prognosis. Consequently some important factors other than the oestrogens may be crucial in the mechanisms by which obesity influences the prognosis of breast cancer. Evidence about the importance of insulin, insulin-like growth factors (IGFs) and leptin is accumulating in this complicated pathological phenomenon (Stephenson and Rose 2003; McTiernan 2005; Goodwin *et al*. 2012).

Systemic low-grade inflammation and insulin resistance are two related mechanisms that have been hypothesized to play a role in the obesity–disease associations. In insulin resistance, serum levels of insulin and IGFs are elevated and the insulin/IGF-I signalling is altered (Probst-Hensch 2010). Furthermore, adipose tissue can act like an endocrine organ, releasing several hormone-like cytokines (adipokines) such as leptin, resistin and adiponectin. The majority of these adipokines, including leptin, participates in the pro-inflammatory processes in obesity and perpetuates the state of insulin resistance. A recent report on breast cancer observed higher expression of leptin and its receptors (Ob-R) at the lesion site in patients with insulin resistance (Carroll *et al*. 2011). On the other hand, adiponectin is an anti-inflammatory adipokine, and a growing body of evidence suggests its anti-cancer effects (Grossmann *et al*. 2008a; Cleary *et al*. 2010) (table 1). This review briefly discusses relevant current findings on leptin biology and breast cancer as well as approaches to modulate the deleterious effects of this adipokine.

2. Leptin and breast cancer: Selected clinical and *in vivo* studies

Findings of several studies indicate that leptin is involved with different aspects of tumour pathology such as cell growth, angiogenesis and metastasis (Ray *et al*. 2007a; McMurtry *et al*. 2009; Rene Gonzalez *et al*. 2009). A study of Italian subjects documented that blood leptin levels in postmenopausal patients with ER+ breast cancer significantly correlated with pathological staging (Macciò *et al*. 2010). Similarly, a number of investigators observed higher blood leptin concentrations in breast cancer patients than in controls (Wu *et al*. 2009; Hancke *et al*. 2010). Interestingly, Miyoshi *et al*. (2006) demonstrated that higher intra-tumoral

Keywords. Adipokine; adiponectin; breast cancer; leptin; obesity

Published online: 3 April 2012

Table 1. Biological characteristics of leptin and adiponectin – a brief description

	Leptin	Adiponectin
Sources and general features	Leptin was one of the first adipokines identified. It is a 16 kDa protein, encoded by the *ob* gene on chromosome 7 (human). Leptin levels are pulsatile and follow a circadian rhythm. It is synthesized mainly from adipocytes; also secreted from the mucosa of gastric fundus, mammary epithelial cells, skeletal muscle cells, ovaries, bone marrow, lymphoid tissues and placenta. Lack of leptin due to a mutation in its gene or disturbance in its signalling system results in obesity.	A 30 kDa protein, gene is located on chromosome 3, mainly secreted by the adipose tissue. It belongs to complement protein C1q and has a close structural homology with tumour necrosis factor-α. It exists in multimeric forms such as low-molecular-weight trimer (LMW) by combining 3 monomers, middle-molecular-weight hexameric form (MMW) and high-molecular-weight form (HMW) constituted by several monomers. Full-length adiponectin may be cleaved to form a smaller globular fragment.
Receptors	Leptin acts via transmembrane receptors (Ob-R), which belong to the class I cytokine receptor family that includes the receptors of interleukin-2 (IL-2), IL-6, granulocyte colony-stimulating factor (G-CSF), etc. Ob-R has at least 6 alternatively spliced isoforms: 4 forms with short cytoplasmic domains (Ob-Ra, Ob-Rc, Ob-Rd and Ob-Rf), the long form Ob-Rb, and a secretory or soluble form Ob-Re, also known as sOb-R. Ob-Rb appears to be important for leptin's weight regulating effects and pro-inflammatory role.	So far, two different receptor isoforms AdipoR1 and AdipoR2 have been well characterized. AdipoR1 is ubiquitously expressed, a high-affinity receptor for globular adiponectin and a low-affinity receptor for full-length adiponectin. AdipoR2 is predominantly expressed in the liver and has intermediate affinity for both forms of adiponectin. Both are 7-transmembrane domain proteins; and unlike G-protein-coupled receptors, these receptors have internal N-terminal region and extracellular C-terminal end.
Intracellular signalling	Like other class I cytokine signalling, leptin predominantly functions through the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) signal transduction pathway (particularly with the activation of JAK2/STAT3), finally leading to nuclear translocation and stimulation of transcription. Also, leptin is associated with other signalling molecules like phosphatidylinositol 3-kinase (PI3K) and mitogen-activated protein kinases (MAPK) particularly extracellular signal-regulated kinase 1 and 2 (ERK1/2). There may be crosstalk between the leptin and insulin signalling pathways via PI3K.	Adiponectin via its receptors mediates increased activities of 5'- adenosine monophosphate-activated protein kinase (AMPK), peroxisome proliferator-activated receptor-α (PPARα) and p38 MAP kinase. AMPK is a serine/threonine kinase and considered to have an important function in regulating glucose and lipid metabolism including fatty acid oxidation and pathways involved in cellular energy status. Also, adiponectin activates other intracellular signalling pathways, e.g. mammalian target of rapamycin (mTOR), nuclear transcription factor-κB (NF-κB), STAT3, and c-jun amino-terminal kinase (JNK).
Functions	Leptin maintains the energy homeostasis by influencing anorexigenic pathway (through a central feedback mechanism). Also, it regulates neuroendocrine, reproductive, immune, and metabolic functions. Leptin has peripheral effects on different tissues and involvement with several endocrine activities such as ghrelin release, oestrogenic response and insulin sensitivity. Moreover, leptin probably influences various gastrointestinal functions including absorption of nutrients.	Adiponectin levels are decreased in obesity particularly in visceral fat accumulation. It appears to have insulin-sensitizing effects; and its levels are inversely proportional to insulin resistance and type 2 diabetes. Also, it has been shown to have effects on lipid metabolism including hepatic fatty acid catabolism, and anti-inflammatory effects. In addition to its peripheral actions, adiponectin may act centrally to modulate food intake and energy expenditure.

mRNA levels of both long and short Ob-R isoforms were significantly associated with a poor prognosis for patients who also had high serum leptin or high intra-tumoral leptin mRNA levels. In a study conducted by Ishikawa *et al*. (2004), 92% and 83% cases showed overexpression of leptin and Ob-R respectively in breast tumour tissues. In the same manner, Garofalo *et al.* (2006) reported significant overexpression of leptin and Ob-R in primary and metastatic breast cancer relative to non-cancer tissues. They also observed that leptin positively correlated with Ob-R in primary tumours and that the expression of both proteins was more abundant in high-grade tumours. In another study, Jardé *et al*. (2008) detected 85% and 75% overexpression of leptin and Ob-R respectively in primary breast cancer cases, with the expression of leptin significantly correlated with that of Ob-R. In addition, Ob-R expression in cancer tissue was positively correlated with ER status and tumour size. Likewise, Koda *et al*. (2010) revealed that both leptin and Ob-R overexpressions were positively correlated with hypoxia-inducible factor-1α, which is associated with angiogenesis. Perhaps, the results of

these clinical studies indicate a significant role of leptin in the development of breast cancer.

To understand the precise role of leptin in the pathogenesis of breast cancer, tumours were developed from ER+ MCF-7 and ER− MDA-MB-231 human breast cancer cells in athymic female mice fed a high-fat diet to generate obesity (Ray *et al*. 2007b). Aggressive MDA-MB-231 tumours from mice fed the high-fat diet expressed elevated levels of long isoform of Ob-R (Ob-Rb) in comparison with tumours from low-fat group and non-aggressive MCF-7 tumours. On the other hand, mammary tumours developed from ER+ T47-D human breast cancer cells in ovariectomized CD-1 nude mice, which were made obese chemically by goldthioglucose, exhibited 100% tumour development without oestrogen supplementation (Nkhata *et al*. 2009a). However, 50% of these tumours overexpressed leptin without expressing Ob-R, whereas tumours from the corresponding non-obese group showed 75% and 50% overexpression of leptin and Ob-R, respectively. Similarly, in another study of CD-1 nude mice where MCF-7 cells were inoculated and a high-fat diet was provided to induce obesity, Ob-R was detected in 21% tumours from the high-fat diet group, while leptin was not expressed in any tumour tissue from this group. In the low-fat group, however, 75% and 100% tumours overexpressed Ob-R and leptin, respectively (Grossmann *et al*. 2010). Lower expression rates of leptin and Ob-R in mammary tumour tissue of this mouse model maintained on high-fat diets are possibly associated with leptin resistance (i.e. decline of leptin receptors and leptin signalling). In a study conducted by Yu *et al*. (2010), leptin was injected around tumours originating from MCF-7 cells in nude mice, whereas the controls received normal saline. They observed significantly higher levels of both mRNA and protein for ERα, but lower expression of ERβ mRNA and protein in the tumour tissue when the leptin group was compared with controls. In the management of breast cancer, ER is a therapeutic target, and thus leptin can influence the outcome.

3. Pathophysiological mechanisms of leptin

Leptin has pleiotropic effects and functions through different signalling pathways. It is known that leptin acts mainly via Ob-Rb, which activates the Janus kinase/signal transducer and activator of transcription (JAK/STAT) signalling pathways; induction of JAK stimulates phosphatidylinositol 3-kinase (PI3K) that can increase cell migration and invasion, and stimulate the major growth and survival Akt pathway (Jeong *et al*. 2011; Ray and Cleary 2012). However, JAK/STAT3 signalling is a critical regulatory component of tumorigenesis in obesity-related breast cancer (McCormack *et al*. 2011). On the other hand, leptin activates the mitogen-activated protein kinase (MAPK) pathway by inducing extracellular signal-regulated kinase 1 (ERK1) and ERK2 phosphorylation, and leptin-induced proliferation is associated with enhanced expression of c-myc and cyclin D1 (Jardé *et al*. 2011). Interestingly, Frankenberry *et al*. (2006) observed that higher levels of circulating leptin contributed to breast cancer proliferation by the activation of the MAPK and PI3K signalling pathways, although in this study the mitogenic effects of leptin were not a consequence of altered Ob-R expression. It may be noteworthy that the suppressor of cytokine signalling 3 (SOCS-3) is a leptin-inducible inhibitor of leptin signalling. Expression of SOCS-3 blocks Ob-R-mediated signal transduction in mammalian cell lines, demonstrating it functions as a negative feedback loop for leptin signalling (Cirillo *et al*. 2008).

Leptin may influence breast cancer development in relation to ER status and aromatase activity, suggesting functional crosstalk between leptin and oestrogen signalling (Artac and Altundag 2011). Similarly, leptin may transactivate HER2 through both epidermal growth factor receptor and JAK2 activation, which can cause the growth of breast cancer cells with HER2 overexpression (Soma *et al*. 2008). In addition, leptin has been shown to up-regulate the transcriptional expression of vascular endothelial growth factor (VEGF) and VEGF receptor type 2 (VEGFR2) (Rene Gonzalez *et al*. 2009). It is known that VEGF plays an important role in tumour angiogenesis, thereby promoting tumour growth and metastases. In this connection, a recent report has suggested that Notch, interleukin-1 (IL-1) and leptin crosstalk could be crucial in the regulation of leptin-mediated induction of proliferation/migration and expression of pro-angiogenic molecules in breast cancer (Guo and Gonzalez-Perez 2011).

Obesity-related pathological processes may involve altered immune functioning (McTiernan 2005). Leptin, through its induction of pro-inflammatory cytokines and stimulation of macrophage function, has pro-inflammatory effects on T cell populations and shifts the T helper (TH) balance towards a TH1 phenotype. Additionally, treatment with leptin enhances the production of pro-inflammatory cytokines like tumour necrosis factor-α (TNFα) and IL-6 by macrophages (Babaei *et al*. 2011). Elevated circulating levels of leptin in obese persons appear to contribute to low-grade inflammation, which makes obese individuals more susceptible to developing cancer and other obesity-related diseases (Iikuni *et al*. 2008). An important component of obesity-related pathology is increased macrophage infiltration into body fat deposits including breast adipose tissue; macrophage-derived pro-inflammatory mediators have been shown to induce aromatase and oestrogen-dependent gene expressions, which may influence breast cancer risk and prognosis (Doyle *et al*. 2012; Subbaramaiah *et al*. 2011).

4. Leptin–adiponectin ratio in disease processes

Overweight/obesity in adults is associated with elevated circulating levels of leptin and decreased levels of adiponectin in comparison with lean persons. Interestingly, Chen *et al*. (2006) reported that low adiponectin and high leptin levels in the blood were associated with an increased risk for breast cancer. In addition, it was observed that a high ratio of adiponectin to leptin reduced the proliferation of breast cancer cells, while a low ratio of adiponectin to leptin did not (Grossmann *et al*. 2008b). Therefore, the ratio of these two adipokines may be more important than either adipokine alone in regulating the development of breast cancer (Cleary *et al*. 2009; Nkhata *et al*. 2009b). A homeostatic balance between leptin and adiponectin may provide a proper cellular microenvironment for normal mammary epithelial cell division and growth (Nkhata *et al*. 2009b). In recent times, a number of reports have emphasized the significance of leptin–adiponectin ratio (Friedenreich *et al*. 2011; Jardé *et al*. 2011; Rogozina *et al*. 2011). Fascinatingly, a growing body of evidence suggests that leptin and/or adiponectin levels may be modulated by dietary factors and lifestyle

Table 2. Recent pharmaceutical approaches for modulation of the effects of leptin

Therapeutic agents	Biological characteristics and experimental/clinical aspects
Metreleptin (recombinant methionyl human leptin) (Tam *et al*. 2011)	It is an analog of human leptin, used for leptin replacement therapy. Clinical indication: Patients with congenital leptin deficiency (a rare autosomal recessive disease caused by mutations in the leptin gene), lipodystrophy and hypothalamic amenorrhea. The drug is administered subcutaneously, and it helps in improvement of hyperphagia secondary to leptin deficiency, fatty acid oxidation, and insulin-dependent glucose metabolism.
Metreleptin-pramlintide combination (leptin-amylin combination therapy) (Tam *et al*. 2011)	Pramlintide acetate is a synthetic analog of amylin (a peptide that is secreted from pancreatic β-cells along with insulin). Leptin-amylin combination treatment has shown obvious synergistic effects and elicited sustained reductions in food intake and body weight.
P85-leptin (a leptin agonist modified by the addition of pluronic block copolymers) (Banks *et al*. 2011)	The incorporation of drugs into pluronic/poloxamer micelles results in increased solubility and stability of drugs. P85-leptin retains biological activity and is capable of crossing the blood–brain barrier (BBB) by a mechanism that is not dependent on the leptin transporter. In obesity, the transport of leptin across the BBB is impaired and it is difficult to treat obesity with leptin or its analogs that depend on the leptin transporter for access to the central nervous system.
Leptin mutants replacing residue Asp-23 with a non-negatively charged amino acid (Shpilman *et al*. 2011)	Superactive human leptin antagonist (SHLA): Mutagenesis of Asp-23 allowed construction of novel compounds that induce potent and reversible central and peripheral leptin deficiency. These antagonists may have potentialities for future therapeutic use in disease pathologies involving leptin.
Ob-R antagonist peptide Allo-aca (Otvos and Surmacz 2011)	It is a nine-amino acid-long peptide analog of Ob-R binding site III of leptin. Treatment with this Ob-R antagonist has shown efficacy in the experimental model of triple-negative breast cancer (i.e., tumour tissue that does not express ER, progesterone receptor and HER2/neu).
S120A/T121A leptin antagonist (Babaei *et al*. 2011)	A S120A/T121A binding site III leptin mutant binds to Ob-R but is unable to activate it (competitive inhibition of Ob-R signalling), and could be useful for prevention and treatment of immunity-related disorders.
Ob-R agonist glycopeptide derivative (Kovalszky *et al*. 2010)	This glycopeptide has been comprised of two additional non-proteinogenic amino acids. The 12-residue glycosylated leptin-based peptidomimetic E1/6-amino-hexanoic acid (E1/Aca) was designed to target a principal leptin/Ob-R binding interface. It has been shown in the experimental models that E1/Aca induced leptin effects in Ob-R(+) cells and readily crossed the BBB. Also, the peptide reduced weight gain in mice fed with high-fat diet in a dose-dependent manner.
Pegylated leptin peptide receptor antagonist 2 (PEG-LPrA2) (Rene Gonzalez *et al*. 2009)	Pegylation is a process, which can change the properties of a drug such as immunogenicity, molecular size and water solubility, by attachment with polyethylene glycol polymer chains. In experimental models, PEG-LPrA2 reduced the expression of pro-angiogenic VEGF, VEGFR2, Ob-R, IL-1 receptor type I, and pro-proliferative molecules proliferating cell nuclear antigen (PCNA) and cyclin D1 in ER+ breast tumours. It also reduced the overall growth of ER+ tumours.

changes, which may favorably alter the ratio of these two adipokines (Murthy *et al*. 2009; Friedenreich *et al*. 2011; Rogozina *et al*. 2011). Another strategy to reduce the body's leptin concentrations, thereby helping to balance the levels of leptin and adiponectin, could be using a suitable leptin antagonist. Such studies are currently in the experimental stage (Ray and Cleary 2010) (table 2). Nevertheless, lifestyle changes, including dietary habits, may be effective as a preventative measure for both obesity and cancer (Ray 2005; Ray *et al*. 2010).

5. Conclusions

Obesity has emerged as an important public health problem worldwide; its clinical manifestations often start from disorders like insulin resistance and metabolic syndrome, which, in turn, promote various pathological processes, including type 2 diabetes, cardiovascular diseases and tumour development. Leptin may play a significant role in these diseases. Although leptin acts like an anti-obesity hormone (anorexigenic) physiologically, its behaviour changes in obese conditions probably due to disturbances in leptin signalling or leptin resistance. Appropriate knowledge about the molecular mechanisms of this complex protein is imperative to formulate effective strategies for primary prevention, laboratory diagnosis and the development of pharmaceutical agents.

Acknowledgements

I am grateful to Dr Margot P Cleary (Professor, University of Minnesota) for providing an opportunity to work on obesity-related cancer problems. Also I would like to thank my colleague Dr Este Armstrong for useful discussions and critical reading of the manuscript.

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MS received 13 September 2011; accepted 02 February 2012

Corresponding editor: Sorab Dalal