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Leptin, obesity and breast cancer: progress to understanding the molecular connections

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Obesity has a complicated connection to both breast cancer risk and the clinical behaviour of the established disease. The obese setting provides a unique adipose tissue microenvironment that, in association with systemic endocrine modifications, promotes tumor initiation, primary growth, invasion, and metastatic progression. This review presents an overview of the clinical and experimental evidences highlighting the adipokine leptin as the most important molecular mediator of obesity-breast cancer axis. The research of leptin network operating in this context could launch a new field not only in the knowledge of risk factors for breast cancer but also in the development of leptin targeting drugs as promising anticancer agents.

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Introduction

The prevalence of obesity has been increasing at an alarming rate in several developed and developing countries, reaching pandemic proportions over the last two decades. This growing incidence has deep clinical implications, since obesity is a key driver of serious health problems, such as type II diabetes, cardiovascular diseases, hypertension and cancer. Indeed, prospective epidemiological studies have shown that excessive adiposity strongly influences risk, prognosis and progression of multiple malignancies, including breast cancer [1,2]. Female breast cancer patients who are obese at the time of the diagnosis are more likely to have a worse prognosis and a higher risk of recurrence regardless of therapy than lean patients [3,4]. A meta-analysis of 43 studies, that enrolled women diagnosed with breast cancer over a long period: 1963–2005, also estimated a 33% increase in the rate of death among obese women [3]. Several hypotheses have been proposed to unravel the direct link between obesity and breast cancer and these include hyperinsulinemia, estrogen signalling, inflammation and adipokine expression [5,6]. Certainly, the revised concept of adipose tissues from an inert depot for body energy to endocrine and immunologically active organs placed particular emphasis on the potential role of adipokines in various biological processes. Acting through endocrine, paracrine and autocrine mechanisms, adipokines, that are not only produced by adipocytes but also by stromal cells (mainly fibroblasts), macrophages and cancer cells, impact the development and progression of obesity-related cancers [6]. Among adipokines, leptin, whose circulating levels increase in proportion to fat mass, has been recognized as a crucial mediator of molecular effects of obesity on breast cancer [7,8]. In this review, we will highlight the emerging knowledge and our recent findings showing the multifaceted oncogenic effects of leptin on breast carcinogenesis. We will also envision the potential therapeutical strategies targeting leptin actions in breast cancer patients, especially obese women.

Links between leptin and breast cancer

Leptin structure and function

Leptin, a 16 kDa product of the obese (Ob) gene, is a pleiotropic molecule that influences appetite control, energy balance, immune response, reproduction, haematopoiesis, bone development, angiogenesis and proliferation of different cell types including cells of the breast [7,8]. Biological activities of leptin are mediated through binding to the transmembrane receptor (ObR), a member of the class I cytokine receptor superfamily, that includes six isoforms different in the length of their intracellular tails. Leptin binding to the extracellular domain of the long isoform leptin receptor leads to the activation of a broad array of multiple intracellular downstream signal pathways, including Janus kinase 2-signal transducer and activator of transcription 3 (JAK2/STAT3), mitogen-activated protein kinase (MAPK), and phosphatidylinositol 3-kinase-protein kinase B (PI3K/Akt) pathways [9]. Several manuscripts reporting data from clinical and experimental studies strongly support the hypothesis that leptin activity is correlated with breast cancer occurrence and tumor behaviour.

Clinical evidences: epidemiological and ex vivo approaches

Most epidemiological studies have attempted to establish a relationship between leptinemia values and risk of breast cancer, but contradictory results have been reported (Table 1, [10–21]). To better clarify this issue, Niu *et al.* conducted a meta-analysis, from which they concluded that assessing leptin levels may become an important diagnostic tool in breast cancer [22••]. Indeed, findings from this study indicated that circulating leptin levels change among diverse population groups ranking from low to high as it follows: healthy people < patients with breast benign diseases < breast cancer patients < lymph node metastasis positive patients. A cross-sectional study, comparing a group of obese patients with a recent diagnosis of breast cancer with a control group of obese women of similar age without breast cancer, revealed that both serum leptin levels and leptin/BMI (Body Mass Index) ratio were significantly increased in patients with breast cancer [17]. Interestingly, weight loss induced by behavioural changes in diet and exercise in breast cancer survivors who were overweight or obese was accompanied by favourable effects on selected biologic factors linked to breast cancer recurrence and mortality, including a decrease of estrogen, insulin, and leptin concentrations and an increase of SHBG (Sex Hormone Binding Globulin) levels [23]. However, circulating levels of leptin do not necessarily reflect the local leptin concentrations within the mammary gland. Leptin and both short and long isoforms of the leptin receptor are over-expressed in breast cancer biopsies compared with healthy epithelium and benign lesions [24–28]. The expression of leptin and the leptin receptor were positively correlated, suggesting that leptin acts on mammary tumor cells via an autocrine pathway. Additionally, a strong correlation between tumor expression of leptin/leptin receptor and grade of the tumor, occurrence of metastasis and poor prognosis was observed [24–26,28,29]. Kaplan–Meier survival analysis indicated that leptin receptor expression was associated with reduced overall survival in breast carcinoma patients, especially in those with basal-like subtypes [30•]. Leptin receptor was recently positively associated with the expression of the oncogenic lipid kinase sphingosine kinase-1 and both these genes showed a significant increase in patients with higher BMI [31]. In addition, leptin and its receptor were expressed not only in breast cancer epithelial cells and adipocytes but also in a subpopulation of fibroblasts, known as cancer-associated fibroblasts (CAFs), within the breast tumor microenvironment [32].

Experimental evidences: 'in vivo' and 'in vitro' approaches

It has been extensively demonstrated using both '*in vivo*' and '*in vitro*' experimental models that the adipokine leptin modulates many aspects of breast cancer biology from initiation and primary tumor growth to metastatic progression. The obese Zucker rats, a genetic obesity model characterized by a mutation in the leptin receptor gene, developed significantly fewer mammary carcinomas (10% incidence, all papillary) than the lean controls after treatment with the chemical carcinogen methylnitro-

Table 1

Plasma/serum leptin concentrations and breast cancer risk

Number of cases (age of women)	Number of controls (age of women)	Findings
58 (52.03 ± 1.39)	58 (51.83 ± 1.15)	Serum leptin higher in breast cancer patients than in controls [10]
90 (45.9 ± 9.2)	103 (46.6 ± 9.6)	Serum leptin higher in breast cancer patients than in patients with benign breast disease or in healthy controls [11]
100 (49.9 ± 1.0)	100 (48.9 ± 1.6)	Serum leptin higher in breast cancer patients than in controls [12]
297 (49.6 ± 8.72)	593 (48.71 ± 8.51)	Plasma leptin higher in breast cancer patients than in controls [13]
159 (59.51 ± 1.0)	41 (49 ± 1.7)	Serum leptin higher in breast cancer patients than in controls [14]
180 -82 pre; 98 post; (44.1 ± 4.7 pre; 60.5 ± 7.5 post)	221 -105 pre; 116 post; (42.4 ± 8.7 pre; 58.7 ± 8.5 post)	Serum leptin higher in breast cancer patients than in controls, only in postmenopausal women [15]
144 (50,3 ± 12)	77 (50.75 ± 12)	Plasma leptin higher in breast cancer patients than in controls [16]
76 (53.2 ± 10.4)	76 (46.1 ± 10.2)	Serum leptin higher in breast cancer patients than in controls [17]
56 (46.4 ± 11.3)	53 (43.1 ± 7.5)	Serum leptin higher in breast cancer patients than in controls [18]
85 -55 non metastatic; 30 metastatic; (51.2 ± 11.1; 48.5 ± 13.5)	25 (44.5 ± 11.2)	No association [19]
149 59.8 (50.1–68.7)	258 60.1 (50.1–68.8)	No association [20]
45 (30 pre, 15 post) <40 (5); 40–60 (33); ≥60 (7)	45 (26 pre, 19 post) <40 (5); 40–60 (33); ≥60 (7)	No association [21]