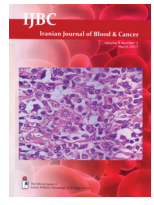
IJBC 2017; 9(1): 1-4

Iranian Journal of Blood & Cancer

Journal Home Page: www.ijbc.ir



Review Article

Leptin in Breast Cancer: Its Relationship with Insulin, Estrogens and Oxidative Stress

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ARTICLE INFO

Article History:
Received: 15.12.2016
Accepted: 28.01.2017

Keywords:
Leptin
Breast cancer
Estrogens
Insulin
Oxidative stress

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ABSTRACT

Breast cancer is the most common cancer in women. Several risk factors such as age, family history of breast cancer, marital status, early menarche and late menopause are related to breast cancer. Obesity is also a main health problem associated with breast cancer incidence and subsequent mortality. Association between obesity and expansion of breast cancer may be due to excessive sex steroid hormone production, particularly estrogen. Moreover, adipose tissue is not only a source of estrogen secretion, but also a producer of certain "adipocytokines" including leptin. Leptin is a neuroendocrine hormone with 167 amino acid produced predominantly by white adipose tissue. Leptin after binding to receptor activate JAK/STAT/MAP. Leptin also increased expression of cyclin D1 and cdk2 and induces proliferation. It may also develop mammary tumor growth via multiple mechanisms like pro-inflammatory, oxidative, and anti-apoptotic proangiogenic effects. Leptin can increase aromatase activity in MCF-7 cell line which may increase estrogen production and subsequently induce tumor cell growth. Hyperinsulinism through enhanced leptin production by adipose tissue can affect poor breast cancer prognosis.

Please cite this article as: Sheikhpour R. Leptin in Breast Cancer: Its Relationship with Insulin, Estrogens and Oxidative Stress. IJBC 2017; 9(1): 1-4.

Introduction

Breast cancer (BC) is the most common cancer in women.[1,2] It affects one of every 8 women in the United States. Also, it is one of the most frequent malignancies among Iranian women.[3] Several risk factors such as age, family history of breast cancer, marital status, early menarche and late menopause are related to development of breast cancer.[4] Obesity, as a main health problem, is associated with increased breast cancer incidence and subsequent mortality.[5] However, the mechanism of how obesity relates to the development of breast cancer remains unknown.[4] Studies have shown that the association between obesity and breast cancer may be due to excessive sex steroid hormone production, particularly estrogens.[6] A group of studies showed that obese individuals have high level of serum leptin that is linked to breast cancer development. In fact, obesity is characterized as a leptin resistant process.[7] Moreover, adipose tissue is not only a source of estrogen secretion, but also a producer of certain ''adipocytokines" including leptins.[8] Adipokines, particularly leptin, may have a major role in breast cancer biology.[5] It is suggested that leptin could stimulate mammary glands' growth via multiple mechanisms.[4]

Leptin

After identification of the obese (*OB)* gene, "leptin" was discovered and it is now considered as a member of adipokines. It is a 16 KDa neuroendocrine hormone that acts as a multifunctional protein with 167 amino acids, produced predominantly by white adipose tissue.[8,9] Leptin is secreted into the blood, where it circulates in both bound and free forms.[10] Stomach, placenta, ovary, liver, pituitary and skeletal muscles are among tissues

that expression of leptin mRNA have been reported. Leptin gene expression can be regulated by epigenetic mechanisms. Also there is a reverse relationship between DNA methylation and leptin expression. This relationship was associated with lower methylation density in visceral adipocyte fraction compared to the stromal vascular fraction of white adipose tissue and liver.[7] The principal role of leptin is the regulation of energy homeostasis via controlling energy intake and expenditure, by its function on the arcuate nucleus of the hypothalamus.[9] Obesity is associated with high levels of leptin. In fact, obesity is associated with leptin resistance.[7] However, it is difficult to separate the independent effects of BMI and leptin because of their close biological association.[11] There is minimal leptin production in normal conditions which increases in certain pathological processes such as inflammation and malignant transformation.[12]

Leptin has also contributions to the endocrine and immune systems including reproduction, glucose homeostasis, bone formation, tissue remodelling, inflammation, and angiogenesis.[4] Leptin may also play a main role in the growth of mammary tumors via modulation of the extracellular environment, down-regulation of apoptosis and/or up-regulation of anti-apoptotic genes.[4] It also promotes proliferation and angiogenic differentiation of endothelial cells in vitro and in vivo.[7] It is recognized that leptin is expressed in the vicinity of breast cancer cells and leptin receptors are expressed on the cells of ductal and lobular breast carcinomas.[6] Breast cancer cell lines MCF-7, T47D and MDA-MB-231 and non-malignant cell line MCF10A also express leptin. It can stimulate the proliferative activity of breast cancer cell lines via the presence of a leptin receptor detected on these cell lines by different signaling pathways.[13] Researchers have reported that leptin and its receptors (a member of the cytokine receptor family with two cytokine domains and a single transmembrane domain) are overexpressed in breast tumors.[14] In obese mice, the incidence of mammary tumors is correlated with high level of leptin and leptin receptors. Moreover, leptin may exert its capability in breast cancer development via cell proliferation or tumor progression.[11]

Leptin, Insulin and Breast Cancer

A variety of metabolically active factors such as insulin and glucocorticoids can influence circulating level of leptin.[9] Insulin stimulates leptin secretion following meals and leptin is decreased during insulin deficiency.[9] Leptin also decreases insulin secretion through direct action on pancreatic beta cells. This finding compared with the fact that insulin is able to increase leptin expression, reveals a negative feedback loop between insulin and leptin.[9] A number of studies have shown that there is positive correlation between leptin, obesity and insulin resistance, but other studies could not support this.[10] Insulin as a mitogenic agent stimulates the secretion of leptin and hyperinsulinism through enhanced leptin production by adipose tissue can affect poor prognosis of breast cancer patients.[9] It is hypothesized that the potential interaction between insulin and metastatic cascade is mediated through leptin.[9]

Leptin, Estrogen and Breast Cancer

Numerous studies demonstrated that leptin (OB-R) and estrogen receptors are co-expressed in breast cancers. It seems that interaction between leptin and estrogen promotes breast carcinogenesis.[7] Therefore, estrogen as well as other hormones and growth factors can act as intermediates or biological effectors for leptin's mitogenic activity and stimulates breast cancer.[9] Chezet and colleagues reported that leptin can promote breast cancer development in obese women via enhancing estradiol production in situ, not only via adipose tissue but also via epithelial breast cells.[6] Another study also reported that estrogen production can be promoted by leptin or follicular estradiol secretion may be limited by it. Leptin can increase aromatase activity in MCF-7 cell line which may increase estrogen production and subsequently induce tumor cell growth. Moreover, leptin receptors expressed in T47D breast cancer cell line induced proliferation of T47D cells by leptin.[11] When leptin binds to its receptor Ob-R1 (Obesity receptor), tyrosine phosphorylation and transactivation of signal transducer and activator of transcription 3(STAT 3) were enhanced at the same time with expression of estrogen receptor (ER).[15] On the other hand, leptin-induced STAT3 activation acts as a key event in ER α dependent development of malignant diseases and estrogen receptor alpha expression increases the activity of leptin-induced STAT3 in breast cancer cells.[15]

Impact of Leptin in Angiogenesis

Leptin acts as a positive regulator of vascular endothelial growth factor (VEGF) in breast cancer and blockage of leptin signaling, decreases VEGF expression and tumor growth in mouse xenografts.[16] Another study reported that leptin signaling plays a major role in the growth of both ER positive and ER negative breast cancer that is associated with regulation of pro-angiogenic factors (VEGF/VEGF-R2) as a biomarker of poor prognosis in invasive breast cancer and pro- proliferative molecules.[9] The data supported potential use of leptin-signaling inhibition as a novel treatment for Breast Cancer.[7]

Leptin, Oxidative Stress and Breast Cancer

Leptin may play a main role in "reactive oxygen species" (ROS) production. It is interesting that leptin decreases production of mitochondrial ROS; therefore, it can have protective role for cells, but in many cases it increases the oxidative damage in the cells. This mechanism is not clearly understood, but there is some evidence of modulation of the NADPH oxidase enzymes which cause production of several compounds directly involved in cell survival or cycle disruption.[13]

Impact of Leptin in Apoptosis

Leptin can regulate apoptosis via exerting anti-apoptotic effects. Therefore, it decreases apoptosis through expression of apoptosis inhibitor like survivin and Bcl2 in MCF-7 cells and by inhibiting of pro-apoptotic caspase

9 activity.[13] Therefore, leptin via pro-inflammatory, oxidative and anti-apoptotic proangiogenic effects can have a main role in the pathogenesis of breast cancer.[13]

PPAR Ligand and Leptin Signaling in Breast Cancer

Peroxisome proliferator-activated receptor (PPAR) is a member of the nuclear receptor family of ligand dependent transcription factor.[17] Leptin after binding to receptor activates JAK/STAT/MAPK. It increases GR phosphorylation (pGR) and nuclear translocation. pGR transactivates leptin promoter by binding to GRE motif and activates breast tumor growth. Rosiglitazone (BRL) acts as a new class of antidiabetic drugs and reduces hyperglycemia and hyperinsulinemia in insulin-resistant states. In the presence of BRL, PPAR binds to GRE and as a result GR/PPAR complex is formed, which finally reduce breast tumor growth.[17]

It has been shown that PPAR ligands suppress ObR mRNA and its promoter activity and block signaling of leptin.[18-20] They also reported that PPAR-ligands may show pharmacologic properties and be employed as new therapeutic adjuvant strategies for breast cancer treatment.[17]

Other Leptin Signaling Pathways in Breast Cancer

Another study demonstrated that leptin increases cell proliferation via progression of cell cycle in MCF-7 human breast cancer cells, with up-regulation of "protein kinase C", PPARc, and PPARa, but others reported that leptin through activation of the mitogen-activated protein kinase (MAP kinase) pathway stimulates proliferation of MCF-7 cell line[6] and T47D cell line.[20] The effect of leptin on cell proliferation was decreased through inhibition of MAPK pathways, AKT and PI3K activated by leptin.[21-26]

Conclusion

According to the literature, leptin promotes mammary tumor growth via multiple mechanisms such as pro-inflammatory, oxidative, anti-apoptotic and pro-angiogenic effects. Enhanced leptin production by adipose tissue through hyperinsulinemia can affect poor breast cancer prognosis.

Conflict of Interest: None declared.

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