

Functions of Obesity-related Hormones in Breast Cancer: A Review

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ABSTRACT

Obesity is a health problem defined as abnormal or excessive fat accumulation in adipose tissue. Adipokines such as adiponectin, visfatin and resistin are bioactive polypeptides with pro- and anti-inflammatory properties that are secreted by the adipose tissue that are involved in the pathogenesis and prognosis of diseases such as type 2 diabetes, metabolic syndrome and cancer. This survey aimed to review the role of these hormones in the pathogenesis and prognosis of breast cancer in obese postmenopausal women. In obese individuals, increased level of leptin leads to tumorigenesis and progression of breast cancer through JAK/STAT3 pathway. These individuals have decreased level of adiponectin, which has a protective effect against carcinogenesis via AMPK pathway. Obese individuals also have increased level of visfatin, which induces the secretion of proinflammatory cytokines such as TNF α and triggers growth of cancer cells. Similarly, elevated resistin levels increases cell proliferation through PI3K and MAPK pathways. Obesity is associated with the dysregulated secretion of adipokines such as leptin, adiponectin, visfatin and resistin, which could be utilized for early diagnosis of breast cancer.

Keywords: Obesity, Breast Cancer, Adiponectin, Leptin, Visfatin, Resistin.

INTRODUCTION

Obesity is a health problem defined as abnormal or excessive fat accumulation in adipose tissue due to increased energy intake and decreased physical activity. It may cause medical disorders such as type 2 diabetes, metabolic syndrome, and cancer. Adipose tissue secretes various proteins or cytokines (called adipokines) (1-4). Dysregulated secretion of these adipokines can contribute to pathogenesis of obesity-linked complications because of adipose tissue dysfunction (5).

Breast cancer is the leading cause of cancer death in women. Obesity increases the risk of breast cancer in postmenopausal women by about 50%. Compared to lean patients, the mortality rate of breast cancer is higher for women who are overweight and obese at the time of diagnosis. Studies have highlighted the role of sex hormones alteration, insulin resistance and altered adipokines levels in the incidence of breast cancer in obese women. Recent studies on pathogenesis of breast cancer show that the alteration of adipokines results in proliferation, angiogenesis and consequently tumor invasion (6-10). Therefore, the purpose of the present survey was to review the role of leptin, adiponectin, visfatin and resistin in the outbreak, pathogenesis and prognosis of breast cancer in obese and postmenopausal women.

Leptin

General Information

Leptin is the product of the obese (*ob*) gene, and one of the first adipokines identified. This non-glycosylated 16 kDa-protein is coded by the *LEP* gene. Human leptin and mouse leptin share 84% sequence homology. Leptin is secreted from the adipose tissue into the blood, and is known as a satiety hormone. Leptin regulates body fat mass by affecting the arcuate nucleus of the hypothalamus. In low leptin conditions, leptin plays an important role in satiety, appetite and food intake. It has been suggested that loss of leptin efficacy in human obesity is due to the development of central leptin resistance or tolerance as well as increased circulating leptin levels upon and before development of obesity (11-16). Leptin acts via transmembrane receptors, presenting structural similarity to the class I cytokine receptor family (17). These receptors lack intrinsic kinase activity and need other kinases in order to become phosphorylated and activated. Leptin receptor (OB-R) has a short

(Ob-Ra) and long (Ob-Rb) isoform. Ob-Rb is the major signaling isoform of leptin, located predominantly in the hypothalamus, and widely distributed at the periphery (15-16). Leptin is involved in numerous physiological processes such as pregnancy, pubertal and normal sexual development, bone metabolism, immunity and insulin and glucose metabolism. Women have higher serum leptin levels compared to men with identical body fat mass. This could be due to the different effects of estrogens and androgens on leptin production (11, 18).

Leptin and breast cancer

The level of serum leptin in breast cancer patients is higher than in healthy subjects. It is also correlated with the body mass index (BMI), which implies that preventing obesity could help prevent breast cancer (19). Reports on the expression of leptin and Ob-R in primary breast cancer suggest that leptin affects breast cancer cells via an autocrine pathway, and Ob-R expression is positively correlated with tumor size. This may indicate the potential role of leptin and Ob-R as a growth factor and a new prognostic factor, respectively (20-21).

Studies also show that Ob-R expression is associated with reduced survival in breast carcinoma patients, especially in those with basal-like breast cancer (22). Leptin and its two main receptor isoforms are co-expressed in almost all breast cancer cells, suggesting that the human epithelial breast cancer cells respond to leptin acting via an autocrine pathway (20-21). Leptin affects mitogenesis, angiogenesis and immunity, and is involved in cancer invasion. It also acts as a proliferative factor in breast cancer, highlighting the relationship between obesity and cancer (23). The autocrine and paracrine effects of leptin in breast cancer cells induce production of inflammatory cytokines from cancer cells and these cytokines and leptin act synergistically in breast cancer cells (20). Leptin and Ob-R expression in primary breast carcinoma is positively correlated with estrogen receptor expression and tumor size. Co-expression of Ob-R and estrogen receptors may indicate a possible interaction between leptin and estrogen that promotes breast carcinogenesis (21, 24-25).

Visfatin and breast cancer

Increased expression of visfatin has been reported in a number of cancers such as colorectal cancer, gastric cancer, pancreatic cancer and breast cancer (38-41). Circulating Nampt levels are increased in obese women, and visfatin is expressed in human breast cancer tissue. Its serum levels are significantly elevated in postmenopausal breast cancer women compared to benign breast conditions and healthy individuals (39-42). The high expression of visfatin in breast cancer tissues is thought to be associated with more malignant cancer behavior as well as adverse prognosis (42). FK866/APO866 and CHS828/GMX1777 are two known inhibitors of Nampt/PBEF/visfatin and have been evaluated as anticancer agents in the clinic (43). A study has shown that curcumin down-regulates visfatin gene expression in human breast cancer cells by a mechanism that is partially nuclear factor $\kappa\beta$ (NF- $\kappa\beta$)-dependent. The mentioned study linked obesity to breast cancer development and progression, and suggested that visfatin may contribute to breast cancer cell invasion (44).

Resistin

General information

Adipocytes secrete a unique signaling molecule named resistin (for resistance to insulin). Resistin is a 12.5-kDa cysteine-rich adipose tissue-specific secretory factor (ADSF/resistin) and a novel secreted protein rich in serine and cysteine residues (76, 77). It has been shown that serum resistin levels and resistin gene expression in mice are induced during adipocyte differentiation because of developed obesity and insulin resistance through a high-fat diet. In humans, the primary sources of resistin in the blood are mononuclear cells, macrophages and bone marrow (11, 45-46). Therefore, serum level of resistin is increased during inflammation (47-48). Many studies have suggested a correlation between increased serum resistin level and obesity that leads to insulin resistance (49-51). Resistin also downregulates GLUT1 expression through suppression of PPAR γ (45).

Adenylyl cyclase-associated protein 1 is a functional receptor for human resistin and clarifies its intracellular signaling pathway to modulate inflammatory action of monocytes. Human resistin directly binds to Adenylyl cyclase-associated protein 1 in monocytes and

upregulates cyclic AMP concentrations and protein kinase A activity (52-53).

Resistin and breast cancer

Resistin has been proposed as the link between inflammatory processes triggered by obesity and development of cancer (54). Serum resistin is significantly higher in postmenopausal breast cancer patients compared to benign breast conditions and healthy individuals. It also has a significant correlation with tumor and inflammatory markers, cancer stage, tumor size, grade and lymph node invasion. Therefore, high resistin levels are likely to be associated with increased risk for breast cancer, and overexpression of resistin in breast cancer tissue is associated with a more malignant clinicopathological status as well as poor patient survival (53, 55-56). There is a direct relationship between serum resistin levels and CA15-3, carcinoembryonic antigen tumor markers and symptoms of inflammatory IL6, TNF α and CRP. This is directly indicative of poor prognosis in breast cancer patients (55). Thus, resistin might represent a new link between obesity and increased prevalence of malignancies (53). It can also act as a molecular mediator in the obesity-inflammation-eicosanoid axis and as a diagnostic and prognostic biomarker (47-49).

MECHANISMS OF ADIPOKINES ACTION IN BREAST CANCER

Studies show that adipokines act in breast cancer mainly through three mechanisms: cell proliferation, apoptosis, and angiogenesis.

Leptin

The proliferative effects of leptin in cancer cells are exerted through different mechanisms. In vitro studies have shown that leptin stimulates growth and survival of breast cells primarily by activating the Janus-activated kinase (JAK)/signal transducers, activators of transcription (STAT) signaling pathway, and phosphoinositol-3-kinase/Akt and mitogen-activated protein kinase (MAPK) pathways (17, 57-58). Leptin induces cell cycle progression by upregulating cyclin D1 expression and cyclin-dependent kinase 2 activity (17). Leptin may contribute to increased rates of cell cycle progression by increasing PKC- α , peroxisome proliferator-activated receptor (PPAR) γ and PPAR α levels (20). PPARs are three novel members of the

xenopus nuclear hormone receptor superfamily. Agents that induce peroxisome proliferation and carcinogenesis regulate the transcriptional activity of PPARs (59). Leptin stimulates the growth of tumor cells through downregulation of apoptosis or upregulation of anti-apoptotic genes (17-20). Leptin increases angiogenesis by overexpression of vascular endothelial growth factor (VEGF) and its receptor (VEGF-R2) in breast tumor cells (17, 24).

Leptin increases mitochondrial respiration and ATP production, which seems to be associated to invasive behavior of cancer cells. It has been shown that leptin promotes migration of cancer cells, and its effect on increased mitochondrial activity could aid cell motility (20). According to previous studies, leptin is essential in promoting S-phase cell cycle progression in breast cancer. Leptin-induced Notch and IL-1 are involved in the regulation of breast cancer cells survival and proliferation. It can crosstalk with many oncogenic signals and induce secretion of chemotaxis factors for macrophages in the mammary gland, eliciting pro-inflammatory changes that lead to malignant transformation of cells (17, 24). Moreover, leptin indirectly increases production of TNF α and other cytokines in monocytes. It induces the expression of inflammatory cytokines such as IL-1 in tumor cells and non-tumor cells of the tumor stroma. It is thought that leptin has anti-apoptotic effects on tumor cells by upregulation of NF κ B and STAT3 anti-apoptotic transcription factors (21). NF- κ B is a transcription factor that induces the expression of many pro-inflammatory adipokines (48).

Adiponectin

The main adiponectin signaling pathway is AMP-activated protein kinase (AMPK) in the cell. The anti-proliferative and pro-apoptotic effects of adiponectin are both mediated via AMPK activation (28-29, 31, 60). Thus, adiponectin is able to block the Akt pathway and increase activity of AMPK alpha and protein kinase A, and ultimately increase apoptosis and decrease cell proliferation. The activation of the extracellular signal-regulated kinase (ERK) and Akt pathways is essential for proliferation and apoptosis, and adiponectin decreases ERK (-50%) and Akt (-40%) activation in cells (28, 60). AMPK has been reported to inhibit fatty acid synthase (FAS), a key lipogenic enzyme, which has

been associated with various cancers including breast cancer (27). AMPK phosphorylates tuberous sclerosis protein 2 at multiple sites including serine 1387, which negatively regulates protein synthesis and cell proliferation inhibiting the promotion of carcinogenesis by repression of mammalian target of rapamycin. Adiponectin induces cell cycle arrest through downregulation of c-myc, cyclin D, and Bcl-2. It also induces apoptosis by increasing the expression of p53, p21 and Bax. In MDA-MB-231 breast cancer cells, adiponectin inhibits the phosphorylation of GSK3b and induces degradation of b-catenin, leading to reduced cyclin D1 expression and cell cycle arrest (28-29, 31, 60-61). Adiponectin modulates C-Jun N-terminal kinase as well as Rho kinase/interferon-inducible protein 10/matrix metalloproteinase 9 signaling, inhibiting tumor progression (60). Adiponectin is a regulator of pro-inflammatory cytokines such as IL-6 and TNF- α and a mediator of the anti-inflammatory cytokine IL-10. Adiponectin reduces the expression of cytokine signaling, interferon γ and NF- κ B. Low adiponectin levels increases the expression of pro-inflammatory cytokines, resulting in chronic inflammation and inflammation-associated cancers (28). Adiponectin potently inhibits endothelial cell proliferation and migration by activation of caspase-mediated endothelial cell apoptosis. It also induces caspase activation cascade such as caspase3, which leads to cell death (31). Moreover, it causes G0-G1 phase cell cycle arrest and reduces the number of cells entering the S phase (28).

Visfatin

Visfatin may contribute to breast cancer by increasing the cell proliferation rate through stimulation of cell cycle progression and increasing the expression of genes involved in metastasis and angiogenesis. Visfatin activates G1-S phase cell cycle progression by upregulation of cyclin D1 and CDK2 expression. Increased expression of matrix metalloproteinases 2, 9, and VEGF genes by visfatin indicates its involvement in metastasis and angiogenesis in breast cancer (37, 42, 62). Visfatin induces activation of ERK1/2 in endothelial cells and endothelial FGF-2 upregulation, which indicates the role of FGF-2 in mediating visfatin-induced angiogenesis (42, 63). The upregulation of IL-6-mediated visfatin-induced migration and upregulation of

MMP-2 (42) and IL-6 can increase proliferation, invasion and angiogenesis of carcinoma cells (64). Visfatin can activate several signals related to migration such as ERK1/2, p38-MAPK, PI3K/Akt, and NF- κ B. A recent study also suggested that visfatin could increase the expression of several potent angiogenic factors including FGF-2 and VEGF (42). Moreover, it increases the expression of pro-inflammatory cytokines such as TNF- α and IL-1 β (65).

Resistin

Similar to leptin, resistin can enhance cancer progression by stimulating cell proliferation through activation of PI3K and MAPK pathways (49, 55, and 56). Resistin may also act indirectly by regulating inflammatory responses via the NF- κ B pathway. It links inflammation to cancer through the activation of transcription factors such as NF- κ B that leads to the activation of pro-inflammatory genes directly involved in the initiation, promotion, and progression of carcinogenesis. NF- κ B induces the transcription of pro-inflammatory cytokine genes such as *IL-1*, *IL-6* and *TNF α* . Another study suggests that the PI3K/Akt-Sp1 pathway is involved in resistin-induced VEGF expression in cancer cells. Resistin also significantly upregulates mRNA expression of VEGF receptors and matrix metalloproteinases at both mRNA and protein levels (55, 66). In addition, resistin reduces the synthesis of tissue inhibitors of metalloproteinases, facilitating tumor cell invasion. Furthermore, resistin can directly affect cancer cells by stimulating specific signaling pathways that are important components of the cancer-promoting machinery such as stimulation of toll-like receptor 4 (56).

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CONCLUSION

Obesity is a health problem defined as abnormal or excessive fat accumulation in adipose tissue. Adipokines are bioactive polypeptides secreted by the adipose tissue that are involved in the pathogenesis and prognosis of diseases such as type 2 diabetes, metabolic syndrome and cancer. Studies suggest that dysregulated secretion of adipokines such as leptin, adiponectin, visfatin and resistin is associated with the prognosis and pathogenesis of breast cancer in obese postmenopausal women. Increased level of serum leptin in these patients has a positive correlation with the prognosis and pathogenesis of breast cancer. Both resistin and visfatin have direct effects on the carcinogenesis of breast cancer in obese patients since they stimulate cell proliferation, angiogenesis and metastasis. Therefore, adipokines can be utilized for early diagnosis of breast cancer. More studies are required to further elucidate the therapeutic potential of these adipokines or their antagonists in treatment of breast cancer.

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CONFLICT OF INTEREST

All contributing authors declare no conflicts of interest.

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