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Review Article

Obesity Related Adipokine Resistin Molecular Actions and Clinical Significance in Breast Cancer

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Abstract: Globally at present cancer and obesity are two greatest health concerns. Obesity and its metabolic complications have rapidly become major global health issues and are associated with increased risk for cancer, especially breast cancer in postmenopausal women.Adipose tissue is considered as a genuine endocrine organ secreting a variety of bioactive adipokines, such as resistin. Current evidence has shown that the constellation of obesity, insulin resistance and adipokines is connected with the risk and prognosis of postmenopausalbreast cancer.Current review Focus on improving understanding of the obesity related adipokine resistin molecular mechanisms and Clinical significance of underpinning major diseases such as breast cancer and obesity, in order to develop novel diagnostic and therapeutic strategies and thus contribute to lowering the global burden of disease significantly.
Keywords: Obesity, Breast Cancer, Adipokine, Resistin

INTRODUCTION

Cancer and obesity are two greatest health concerns worldwide at present; both of which are continuously rising in incidence and are associated with high morbidity and mortality. Understanding the aetiology and mechanisms of these diseases is critical for developing clear and effective strategies for improving global health [1]. As the second commonest cause of death in the developed world (after heart disease),According to GLOBOCAN 2012, an estimated 14.1 million new cancer cases and 8.2 million cancer-related deaths occurred in 2012, compared with 12.7 million and 7.6 million, respectively, in 2008. Prevalence estimates for 2012 show that there were 32.6 million people (over the age of 15 years) alive who had had a cancer diagnosed in the previous five years.Breast cancer is the commonest malignancy in women and the foremost cause of death in the developed world. Obesity is another major public health concern. The incidence of this disease spectrum is rising rapidly, and contributes significantly to global morbidity, mortality and socioeconomic problem. Although they are individual disease entities, associations between obesity and cancer are emerging.There were an estimated 1.67 million new breast cancer cases diagnosed in 2012 (25% of all cancers). It is the most common cancer in women both in more and less developed regions with slightly more cases in less developed (883,000 cases) than in more developed (794,000) regions. Incidence rates vary nearly four-fold across the world regions, with rates ranging from 27 per 100,000 in Middle Africa and Eastern Asia to 96 in Western Europe [2]. In particular the relationship between obesity and breast cancer in post-menopausal women is well established [3]. However the mechanism by which excess adiposity contributes to carcinogenesis remains poorly understood. Current review Focus on improving understanding of the Obesity Related Adipokine Resistin molecular mechanismsand Clinical significance of underpinning major diseases such as breast cancer and obesity, in order to develop novel diagnostic and therapeutic strategies and thus contribute to lowering the global burden of disease significantly.

ADIPOISTY AND BREAST CANCER LINK

There is considerable evidence to show that increases in adiposity increase breastcancer risk among postmenopausal women.Among pre-menopausal women therelationship between adiposity and breast cancer appears to be protective.This might be the reason weight gain appears more harmful in terms of breast cancer risk than body mass index (BMI, kg/m2). Women who were lean as young adults and heavier postmenopausally would have a greater risk of breast cancer in both time periods. In addition to its impact on weight change, physical activity has been shown to be an independent predictor of breast cancer risk.

Presently there are three core hypothesized molecular pathways between adiposity and breast cancer: increased insulin and insulin-like growth factor (IGF), increased estrogen, and autocrine, paracrine, and endocrine signaling from proteins secreted by adipocytes, they are all inextricably linked.

ESTROGEN

Biosynthesis of estrone and estradiol from adipose tissue is the main source of estrogen in postmenopausal women. Women who have high levels of circulating estrogen have a 2-3 times increase in breast cancer risk related to those with low estrogen levels [4]. Estradiol (the bioactive form of estrogen) is synthesized from the conversion of androgens and estrone by the enzymes aromatase and 17-β hydroxysteroid dehydrogenase (17-βHSD). In addition, adipokines such as leptin, TNF, and IL6 have been shown to upregulate aromatase and 17-βHSD or transcriptionally activate the estrogen receptor in the absence of estrogen. SNPs in the genes that produce these estrogen biosynthesis factors have been studied in relation to breast cancer risk, but results have identified very few associations [5].

INSULIN/IGFs

In obese folks increased levels of free fatty acids (FFA) are released from adiposetissue. These increases in FFA force the liver and other tissues to focus on storage and oxidation of fats, and as a result, they have a reduced capacity to absorb, store, and metabolize glucose. The outcome is insulin resistance and hyperinsulinemia. These increased levels of insulin in turn lead to reduced liver synthesis and blood levels of insulin-like growth factor binding proteins (IGFBP) 1 and 2. In the lack of the binding proteins there are excesses of free insulin-like growth factor-1. These increased levels of insulin and IGFs are hypothesized to lead to increased cell proliferation and, therefore carcinogenesis [6].

ADIPOKINES

Adipokines, secreted by the adipose tissue, are strong candidates for the link between obesity and risk of breast cancer. In addition to adipocytes, adipose tissue contains a connective tissue matrix, nerve tissue, stromovascular cells, and immune cells [7]. We know now that there are two types of adipocytes: white and brown. Brown adipocytes are commonly responsible for heat production [8]. White adipocytes are themain energy reservoir in humans and provide long term fuel for the body. Whiteadipocytes absorb fatty acids from food, as well as those derived from glucose in the liverand contribute to the expanding lipid droplet [9].The adipokine genes functional genetic variationsmay be involved directly and/or indirectly in the development of postmenopausal breast cancer.Animal studies,microarray analysis, and *in vitro* tumor studies provide evidence that adipose tissue and these adipokines can directly influence tumor growth [10,11].So many adipokines have now been discovered, while this review mainly focuses on one adipokine such as Rrsistin.

RESISTIN

The discovery of resistin (also known as FIZZ3 and adipocyte specific secretory factor; ADSF) was concurrent in two separate groups, the work of Holcomb and co-workers (2000) was published first and they named the new genes as Found in Inflammatory Zone (FIZZ) 1–3. After a nucleotide homology search, they identified two additional mouse genes (Fizz2 and Fizz3) and only two human genes (FIZZ2 and FIZZ3) though they stayed focused on Fizz1 known as resistin like alpha [12]. Shortly after the report of Holcomb *et al.*, Steppan and colleagues presented their findings. "The hormone resistin links obesity to diabetes" received more attention than Holcomb's studies and resistin became the basis of the official names of the gene family [13]. These findings made resistin a hot topic of obesity and diabetes research.

Resistin, a gene coding for human resistin, is located at chromosome position 19p13.3 [14]. *RETN* is composed of four exons of which three participate in the formation of the protein. The processed ribonucleic acid (RNA) product of *RETN* is 478 nucleotides in length [15]. The protein translation begins from the exon II and ends in the middle of the exon IV leading to a product consisting of 108 amino acids. Human resistin, estimated to be of 11.3 kDa size [16], has been claimed to hold the same structural properties as mouse resistin. Common features to all members of the RELM gene family are an N-terminal signal peptide, a variable middle region, and a C-terminal cysteine-rich sequence. Human resistin has also been detected to form oligomers. It exists in three forms: a trimer, a hexamerand a monomer, with the lower molecular weight form being themost active [16].

RESISTIN MOLECULAR ACTION

Various pathophysiological mechanisms linking obesity to cancer are not completely understood, but have been postulated. In contrast to mouse resistin, human resistin is synthesized in cells other than adipocytes, predominantly in macrophages and monocytes particularly in the visceral adipose tissue characterized by a high metabolic turnover. Elevated resistin levels caused by genetic or environmental factors such as obesity, inflammation and diet may play a vital role in the pathogenesis of insulin resistance,t2DM, gestational diabetes, atherosclerosis, hypertension, cardiovascular disease and several malignancies such as breast, gastric, colorectal and esophageal cancers [17].

Possible mechanisms associating resistin with breast cancer pathogenesis may involve: (1) Upregulation of proinflammatory cytokines *via* the NF-κB pathway, an important component of cancer-promoting machinery.

Resistin may also promote a pro-thrombotic state *via* mediating the lipoprotein metabolism and inducing inflammation in a hypercoagulable environment observed in breast cancer; (2) Activation of signaling pathways playing an important role in inflammation and tumorigenesis. Resistin phosphorylated both MAPKs, such as Erk or p38, and Akt, a downstream substrate of PI3K, in several cell lines [18]; (3) Induction of the proangiogenic protein: vascular endothelial growth (VEGF) and formation of endothelial cell tubes contributing to metastasis; and (4) Induction of the expression of MMPs and reduction of MMPs tissue inhibitors participating in tumor invasiveness and metastasis [19]. Further mechanistic, larger prospective and longitudinal studies are required to confirm these findings and determine whether resistin may play a role as a breast cancer tumor marker.

RESISTIN AND BREAST CANCER CLINICAL SIGNIFICANCE

To our knowledge very few genetic studies on human *RETN* have focussed on breast cancer. These studies have not provided strong support for the hypothesis that resistin would be an important factor in breast cancer. In Table 1, particular studies on the *RETN* and its connection to breast cancer have been summarised. The majority of epidemiologic studies studying the association of serum resistin with Breast Cancer have shown that hyperrestinemia*in vivo* is linked to the risk of Breast Cancer, particularly in postmenopausal women.

Resistin Gene Functional Polymorphism (−420 C/G) with Breast Cancer

The importance of the genetic component in the expression of resistin and its concentration in blood has not been widely studied. The genetic background seems to explain part of the variation in plasma resistin levels. Most of the genetic studies of resistin are based on SNPs but not in breast cancer. Several SNPs in *RETN* have been described in the literature, with most of them being in noncoding regions of the gene such as in the 5' promoter region and intron 3 [26-28], intron 1 [29], intron 2 [30,31], and in the 3'untranslated region (UTR) [32].With respect to the reported resistin variants, the mostly extensively studied has been the promoter variant SNP-420C>G. This promoter variant is located 420 nucleotides upwards from the translation starting point in exon 2. The promoter with the rarer G allele in SNP-420C>G has been reported to be more active in several studies [33, 34].

To our knowledge, no data have been published on the association of the RETN −420C>G polymorphism with the risk of Breast cancer. In our study, we aimed to investigate resistin gene variant −420 C>G (rs1862513), in RETN gene and their possible association with breast cancer susceptibility in obese women.The results of our study indicate that the−420 C/G genotype showed 2.6 folds increased risk of breast cancer (p = 0.05). Whereas individuals with joint genotypes (CG/GG) showed 1.79 folds increased risk of breast cancer. In our study, we have also clearly found significantly higher expression in breast cancer tissues in comparison with control tissues (P =0.002).our overall results suggest that, resistin gene −420 C/G polymorphism is significantly associated with risk of breast cancer obese women. However, there was a significant association between resistin expression levels and −420 C/G polymorphism in the patients. −420 C/G polymorphism may play a role in inducing breast cancer risk by altering the expression level of the resistin gene [35].

Table 1: Resistin and breast cancer studies and their Implications

	Author & Year	Significant
Resistin and Breast cancer	Dalamaga M *et al.* [20]	Resistin level correlated significantly with tumor markers and inflammatory parameters
	Dalamaga M *et al.* [21]	Resistin was significantly associated with tumor and inflammatory markers, cancer stage, tumor size, grade and lymph node invasion
	Rabab Aly *et al.* [22]	High resistin levels are likely to be associated with increased breast cancer risk
	Sun CA *et al*. [23]	Adipocytokineresistin may have an adiposity-independent role in breast carcinogenesis
	HOU Wei-kai *et al*. [24]	Increased serum resistin levels are risk factors of breast cancer
	Jee-Hyun Kang *et al.* [25]	High resistin levels are likely to be associated with increased breast cancer risk

CONCLUSION

Obesity, its metabolic complications and breast cancer have become major global health issues. Obesity increases the risk of breast cancer incidence and mortality. Recent data suggest that adipokines could be promising breast cancer biomarkers in conjunction with other tumor markers, that reflect advanced stage, adverse prognosis and inflammatory state. Moderating

adipokines might be a particularly attractive objective for breast cancer prevention, specifically in overweight/obese women. In summary, there is evidence for a strong link between obesity-driven chronic inflammation, insulin resistance, adipokines and breast cancer. Advances in adipokine research may hold promise for the use of adipokines as potential prognostic markers and therapeutic targets.

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