

Resistin and Cancer Risk: A Mini-Review

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Abstract

Obesity and cancer are two major epidemics of this century. Obesity is associated with greater risk of many types of cancer. However, the biological mechanism of the increased cancer risk among obese population is not fully understood. Studies on the role of adipose-derived factors in cancer development may provide insights into the mechanistic link between obesity and cancer risks. Resistin is an important hormone protein that is mainly produced by adipose tissue, and has been found to be actively involved in the regulation of inflammation and insulin resistance. This mini-review aimed to summarize findings from both experimental and epidemiological studies investigating the association between resistin levels and cancer risk and identify areas requiring further research.

Keywords: Cancer; Obesity; Resistin; Review

Introduction

The prevalence of obesity is growing to epidemic proportions worldwide. Obesity is associated with an increased risk of cancer [1]. Although the mechanisms by which obesity raises cancer risk remain to be determined, experimental and epidemiological studies suggest a potential role of various adipose-derived factors in the pathogenesis and progression of certain cancers. Adiponectin, leptin and resistin are major hormones synthesized and released by adipose tissue, and may provide novel insights into the mechanisms of cancer progression, regression and persistence. The role of adiponectin and leptin in various cancers were summarized in a number of recent review articles [2-4]. This mini-review will focus on the role of resistin in the cancer development.

Resistin biology

Resistin is a 12.5 kDa protein originally found to be secreted by mouse adipocytes [5]. Although adipocyte is a major source of resistin in rodents, resistin is mainly expressed by macrophages in humans [6]. Compared with other adipose depots, visceral adipose tissue may serve as a primary source of resistin production. The release of resistin is 2.5-fold greater by explants of human omental adipose than by explants of human subcutaneous abdominal adipose tissue [7]. Moreover, resistin released by adipocytes is negligible as compared to that by non-fat cells of human adipose tissue [7]. As an important adipose-derived hormone, resistin causes insulin resistance [8] and inflammation [9], and is involved in the pathogenesis of endothelial dysfunction and atherosclerosis.

Role of resistin in cancer: experimental studies: The association between resistin and cancer development has been studied in cultured cells and animal models. In MDA-MB-231 human breast cancer cell line, 5-10,000 ng/ml resistin-13-peptide, which contains 13 amino acids (22 to 34 amino acids in the human resistin molecule), decreased the activity of metalloproteinases (MMP)-2 and MMP-9 [10], active contributors to cancer progression [11]. Resistin also enhanced the protein expression of tissue inhibitors of metalloproteinases (TIMP)-1 and TIMP-2, and dose-dependently inhibited MDA-MB-231 cell growth and colony formation [10]. The effects were more profound at supraphysiological concentration (500 ng/ml, 5,000 ng/ml, and 10,000 ng/ml) [10]. Moreover, 2.5 mg/kg and 5 mg/kg resistin-13-peptide treatment repressed tumor growth in a dose-dependent manner in 5 to 6-week-old female athymic nude mice [10], although the serum concentration of resistin following treatment was not examined and reported. In contrast, in human choriocarcinoma cells (BeWo),

resistin (10–100 ng/ml) enhanced MMP-2 protein and mRNA expression, significantly reduced TIMP-1/TIMP-2 levels and increased trophoblast-like cell invasiveness [12]. Interestingly, in addition to adipose tissue, human prostate cancer cell lines PC-3 and DU-145 also express resistin [13]. Treatment of resistin mature peptide (10-200 ng/ml) or overexpression of full-length resistin genes stimulated prostate cancer cell proliferation through phosphoinositide kinase-3 (PI3K)/protein kinase B (Akt) signaling pathways [13]. Thus, the biological activity of resistin may be cell line-specific and dose-dependent; and truncated resistin and full-length resistin may exert distinct effects.

Resistin expression has been examined in different rodent models of obesity and diabetes. Stepan et al. [5] reported that serum resistin levels were elevated in both diet-induced and genetically obese mice (ob/ob and db/db) [5]. In contrast, Rajala et al. [14] suggested that serum levels of resistin in db/db mice were decreased [14]. Resistin expression was significantly lower in the white adipose tissue of several murine models of obesity, including the ob/ob, db/db, tub/tub, and KKAY mice [15]. The reason for the discrepancies in the measured resistin levels remains unclear; therefore, there might be limitation to use animal models of obesity to examine the role of resistin in tumor development.

Genetics of serum resistin has also drawn considerable research interests [16]. Mattevi et al. [17] found resistin gene polymorphism (-420°C>G) was associated with body mass index (BMI) and reported that women carrying G-allele had lower BMI compared to women carrying C/C homozygotes [17]. However, -420°C>G resistin polymorphism was not a potential genetic susceptibility factor in colorectal cancer patients [18]. Although patients with endometrial cancer showed significantly higher circulating levels of resistin compared to control subjects, no significant association between resistin levels and -420°C >G resistin polymorphism was found [19].

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Role of resistin in cancer: epidemiological studies

Human epidemiological studies on the relationship between resistin and obesity [20-21], as well as the relationship between resistin and cancers revealed inconsistent results [22].

Resistin and breast cancer: Central obesity measured by waist-to-hip circumference was linked to postmenopausal breast cancer [23] but the body fat distribution was not related to premenopausal breast cancer [24]. Up to now, four studies examining the link between circulating resistin levels and overall breast cancer risk demonstrated inconclusive results. Three case-control studies that were conducted separately in China [25], Korea [26] and Taiwan [27] found that high levels of resistin were associated with increases in breast cancer risk. In contrast, a nested case-control study, which includes 234 postmenopausal breast cancer patients and 234 controls in a subcohort of US women whose blood was collected in National Cancer Institute's Biological Markers Project since 1977, did not find statistically significant associations between circulating resistin levels and breast cancer risk after taking into account of BMI [28].

There are no studies longitudinally investigating the change of resistin levels during the period of menopause, although a cross-sectional study among healthy premenopausal and postmenopausal women did not find any association between serum resistin levels and menopausal status [29]. The results of resistin levels across menstrual period were inconsistent. Dafopoulos et al. [30] found serum resistin levels did not change significantly during normal menstrual cycle [30] and ovarian hormones were not associated with the regulation of resistin secretion [31]. However, Asimakopoulos et al. [32] found serum resistin levels were higher in luteal phase than in follicular phase and midcycle during the menstrual cycle [32].

A link between estrogen and postmenopausal breast cancer was reported by a reanalysis of nine prospective cohort studies [33]. Moreover, the European Prospective Investigation into Cancer and Nutrition (EPIC) study provided further evidence for this association in premenopausal women [34]. However, studies examining the association between resistin and estrogen levels revealed inconsistent results. Sun et al. [27] reported that women having excessive exposure to estrogens had higher resistin levels [27], but Gaudet et al. [28] did not find association between resistin and sex hormone estradiol levels [28].

Resistin and prostate cancer: Central adiposity has been reported to be associated with prostate cancer and high grade prostate cancer among diverse populations [35-37]. There were only two studies examining the difference of resistin levels between prostate cancer patients and control subjects [38-39]. An age-matched case-control study with 123 pairs found serum levels of resistin were underexpressed among prostate cancer patients [39]. However, another hospital-based study including 26 patients with benign prostate hyperplasia (BPH) and 42 patients with different stages of prostate cancer reported that resistin was expressed at a higher level in high-grade prostate cancer tissues than in low-grade prostate cancer and BPH tissues [38]. This study also found a decreased prostate-specific antigen (PSA) level among prostate cancer patients who had lower plasma resistin concentrations [38]. Moreover, among 26 recurrent or locally advanced prostate cancer patients with gonadotropin-releasing hormone (GnRH) agonist's therapy, there was no significant change in resistin level as well as waist-to hip ratio over the course of 12 months of treatment [40]. In addition, another study among 25 prostate cancer patients with leuprolide depot and bicalutamide treatment showed no significant change of resistin during a 12-week prospective study [41]. From these human studies,

the associations between resistin levels and prostate cancer risk remain inconsistent, but it appears that resistin levels showed no significant change during the period of prostate cancer treatment.

Resistin and colon cancer: The EPIC study found that central obesity measured by waist-to-hip ratio and waist circumference was associated with colon cancer in both men and women although this study as well as many other studies found body weight and BMI were positively related to colorectal cancer only in men [42]. Three hospital-based case-control studies found an association between resistin and colorectal cancer in different countries. A hospital-based case-control study including 29 colon cancer patients and 27 healthy volunteers in Romania found higher levels of resistin were associated with increased risk for colon cancer [43]. In addition, a hospital-based case-control study in Japan with 115 patients and 115 controls also found elevated resistin levels were associated with increased risk for colorectal cancer [44]. Furthermore, another hospital-based case-control study involving 248 patients and 256 controls in Sweden reported positive associations between resistin protein expression and colorectal cancer but the genetic distributions of -420°C > G resistin polymorphism were not significantly different between patients and controls [18].

3.2.4) Resistin and other cancers: The association between resistin and other cancers has not been extensively investigated. One study including 156 gastric cancer patients and controls in Japan found a positive association with blood resistin levels [45]. Another study on endometrial cancer among 37 pairs of matched patients and healthy controls in Czech Republic also showed positive association between resistin levels and endometrial cancer risk [19]. However, no association was found between blood resistin levels and childhood acute lymphoblastic leukaemia in a case-control study involving 54 patients and 51 controls in the United Kingdom [46]. There were no studies on the relationship between resistin and lung cancer, although a prospective study in Greece including 101 non-small cell lung cancer patients and 51 healthy control volunteers reported that serum resistin rather than adiponectin or leptin was associated with weight loss among these lung cancer patients [47]. The relationship between resistin levels and other unmentioned types of cancer needs to be further explored.

Perspectives

There is increasing evidence that resistin may have pathophysiological effects that extend beyond its traditional roles in energy homeostasis; in particular its role in cancer has received considerable experimental and epidemiological supports. However, as resistin expression in humans and mice appears to be regulated differently, it is critically important to determine whether results from rodents can be properly translated to humans [48]. It is also crucial to identify resistin receptor and delineate both receptor-dependent and independent effects induced by this important hormone. Furthermore, in addition to dissecting the distinct mechanisms of hormones in the regulation of cancer development, efforts are needed to examine the synergistic effects of various adipose-derived hormones that may orchestrate the influence of obesity on the development of these malignancies.

Although epidemiological studies generally support the linkage between resistin levels and cancer risk, there are no studies examining the correlations between resistin and molecular subtype of cancers. Moreover, most of the epidemiological studies are hospital-based case control studies. Ideally, the cases should be a random sample of all the cases in a source population. Recruiting hospital cases without randomization process in the study design may be affected by Berksonian bias due to selective factors that lead the hospital cases and

controls to be systematically different from each other. Therefore, the possibility of spurious associations cannot be ruled out. In addition, the studies with negative findings may not have enough power to detect the possible associations with limited sample size. Future case-control studies with adequate sampling procedure or longitudinal studies are necessary to better elucidate the associations.

Thus, we are just beginning to explore the complex biology and epidemiological characteristics of resistin. Further investigations are needed to provide novel insights into the potential role of resistin as a mediator of obesity in cancer development, which may enhance our understanding of tumor development and allow for the discovery of novel biomarkers or therapeutic targets for cancer treatments.

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