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Tumour Review

Hormones of adipose tissue and their biologic role in lung cancer

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ABSTRACT

Introduction: Adipose tissue secretes numerous bioactive peptides, collectively termed "adipocytokines" or "adipokines". Adipokines act in a paracrine, autocrine, or endocrine manner and regulate several physiological and pathological processes. Increasing evidence indicates that adipokines are implicated also in several malignancies, including lung cancer as well.
Aim: The aim of this study is to summarize data concerning adipokines in lung cancer pathogenesis, prognosis and survival; the role of adipokines in lung cancer cachexia is also examined.
Materials and Methods: A systematic literature search was performed in the electronic database of Medline. Several studies and review articles met the inclusion criteria.
Results: Leptin and adiponectin are the best studied adipokines. The majority of the relevant studies has investigated the potential correlations mainly between leptin, adiponectin, and sometimes also resistin, and nutritional status, systemic inflammation of lung cancer or lung cancer cachexia and have also assessed their prognostic significance. Few other studies have studied genetic variations in leptin, leptin receptor and adiponectin genes and their association with lung cancer susceptibility and prognosis. The ongoing list of adipokines associated with lung cancer also includes resistin, chemerin, and visfatin.
Conclusions: Increasing evidence points to the involvement of certain adipocytokines in lung cancer development, progression and prognosis. No conclusive evidence exists so far with regards to the role of adipocytokines in lung cancer cachexia. Future, longitudinal studies are warranted in order to clarify the role of adipocytokines in lung cancer and also uncover adipocytokines as novel therapeutic targets.

Introduction

Adipose tissue is now recognized as a highly active endocrine and immune organ. It was the cloning of the ob gene product leptin in 1994 that shed light into the new physiological properties of the adipose tissue [1]. Until recently, it was only known that adipose tissue is specialized in lipid metabolism and glucose homeostasis and that it serves as energy storage depot in periods of nutritional abundance. However, it is now recognized that adipocytes secrete more than twenty hormones and signaling molecules, collectively termed "adipocytokines" or "adipokines", which exert their biological role in an autocrine, paracrine or systemic manner and influence several physiological processes concerning the vascular system, energy, glucose homeostasis, reproduction, bone metabolism and immunity [2]. Some adipocytokines are produced either almost exclusively by adipocytes or by macrophages and other immune cells that also reside in adipose tissue. The continually expanding family of adipokines also includes adiponectin, resistin, visfatin, chemerin, tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), interleukin-1 (IL-1), complement factors and palsminogen activator inhibitor-1 (PAI-1) [3,4]. The amount of adipose tissue determines to a great extent adipokines' serum values. Many studies have found an association between adipokines and the development of metabolic disturbances, like insulin resistance, observed in extreme body weight states such as obesity and cachexia, and also the development of common obesity-related diseases such as atherosclerosis, diabetes mellitus, and hypertension [5–8].

The epidemiological observation that the prevalence and mortality of certain cancers such as breast, endometrium, colon and prostate cancer, increase with obesity triggered further research on adipokines as a plausible link between obesity and cancer [9]. Multiple in vitro studies have demonstrated that certain adipokines are capable of promoting tumor growth and proliferation via their functional receptor signaling at different cancer cell lines. Furthermore, several clinical studies have investigated the role of adipokines in different tumor types and reported significant associations between adipokines and tumor susceptibility, pathogenesis and prognosis [10–12].

Lung cancer is not considered to be an obesity related cancer and in the past it was even suggested that lean subjects have an elevated risk for lung cancer [13–15]. Data also suggest that obesity decreases lung cancer mortality independently of smoking status and exerts a protective effect on lung cancer survival [16,17]. The rationale behind the investigation of adipokines in

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lung cancer lies in the emerging carcinogenic and immunomodulatory properties of adipokines, making them potential mediators of the complex and still unclear multistep lung carcinogenesis. Moreover, adipokines' inflammatory properties along with their role in appetite and energy homeostasis regulation, made their investigation in lung cancer cachexia almost demanding.

Materials and methods

Electronic databases of Medline (from 1950 to present) were searched to identify articles published in English and German that involved adipocytokines in lung cancer. The key words used were "adipokines" or "adipocytokines" and "lung cancer" and "leptin" and "adiponectin" and "resistin" and "visfatin" and "chemerin". Studies were included if they reported a group of adult patients (>18 years of age) with lung cancer and the adipokines described by the key words. Additional articles were extracted from the reference list of included articles.

Results

This study summarized data concerning adipokines and lung cancer pathogenesis, prognosis and lung cancer associated cachexia. The large body of data studied is about the primary adipokines leptin and adiponectin. Data concerning the less reported resistin, chemerin and visfatin has also been tracked.

Leptin

Leptin, general information

Leptin was discovered in 1994 as a product of the obese (ob) gene [1]. It is synthesized and secreted mainly by adipose tissue and its actions are mediated by leptin receptor (OB-R) that belongs to the cytokine class I receptors. OB-R has three classes of isoforms, the long (OB-Rb), the short (OB-Ra), and the soluble (sOB-R) isoform. OB-Rb is the major signaling isoform of leptin, located predominantly in the hypothalamus, but also with widely distributed at the periphery [1,18]. Serum leptin levels correlate with total fat mass and fat cell volume, and they are higher in women than men [19,20]. The production of leptin by adipose tissue is upregulated in obesity, with insulin stimulation, glucocorticoids, in acute infections and under the influence of cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-1 (IL-1), while fasting, cold exposure, testosterone and β-adrenergic agonists decrease leptin levels. Leptin plays a fundamental role in the control of food intake and energy expenditure by regulating appetite at hypothalamic appetite centers. Hyperleptinaemia as a result of increased fat mass induces satiety through anorexigenic (Propiomelanocortin) signals, whereas low leptin levels during fasting act as "starvation signal" through enhanced orexigenic Neuropeptide Y (NPY) activity. Obese individuals display high circulating levels of leptin in proportion to their increased adipose tissue mass but paradoxically their food intake is not restricted under the anorexigenic effect of leptin. This is referred in the literature as "leptin resistance" and the mechanism underlying this condition is still under investigation [21]. Leptin is involved in many physiological processes such as pregnancy, pubertal and normal sexual development, and bone metabolism. It also affects immunity and is considered an insulin-sensitizing hormone [22–30].

Leptin and lung cancer

Increasing evidence underlines leptin's angiogenic, mitogenic, and immunomodulatory properties and suggests that it is capable of mediating critical steps of carcinogenesis such as tumor invasion and migration. Several studies demonstrate that leptin is expressed and involved in many types of cancer, such as prostate, breast, gastrointestinal cancer and haematological malignancies [12,31–33].

With regards to lung cancer, human leptin receptor mRNA expression was identified in normal human lung tissue and in SQ-5 human clonal squamous lung cancer derived cell lines as well [34]. Furthermore, in the same study, in vitro stimulation of SQ-5 cell proliferation was demonstrated after the addition of recombinant human leptin, an effect mediated probably by MAP kinase pathway.

Thus, leptin seems to mediate and amplify a complex interplay between tumor and immunoinflammatory cells, resulting in the development and progression of lung cancer [35]. Besides obesity, certain genetic variations in leptin gene have also been associated with increased leptin expression [36]. Given the carcinogenic properties of leptin, Ribeiro et al. raised the question in 140 lung cancer patients in control with healthy individuals if genetic polymorphisms of leptin gene are associated with increased risk for lung cancer. It was demonstrated that AA genotype carriers of a functional polymorphism in the promoter region of the leptin gene (-2548G/A) had increased susceptibility for non-small cell lung cancer (NSCLC) (OR = 1.97, CI: 1.13–3.43) and showed significantly lower time to the onset of the disease ($p = 0.023$). The AA genotype was overrepresented only in non-metastatic disease (OR = 1.89, CI: 1.13–3.04). Logistic regression analysis demonstrated that the AA genotype variant of leptin gene is an independent risk factor after adjusting for age and gender (OR = 2.57, CI: 1.34–4.92) [37].

The effect of genetic polymorphisms in leptin receptor (LEPR) gene on lung cancer has been investigated in alarge Chinese study that recruited 744 Chinese patients with NSCLC versus 832 healthy controls [38]. Among the three studied polymorphisms of LEPR, the Arg/Arg genotype of the Gln223Arg polymorphism in LEPR gene was found significantly more prevalent in NSCLC subjects versus controls ($p < 0.05$) and the carriers of the Arg/Arg genotype carried a significantly higher risk for NSCLC compared with controls (OR = 3.12, 95% CI: 2.25–4.56, $p = 0.0023$ with Gln/Gln as reference). Kaplan–Mier curve showed that Arg/Arg carriers had a poor prognosis and shorter survival (Arg/Arg carriers: 17.6 ± 5.6 months, Gln/Arg: 23.4 ± 7.1 months, and Gln/Gln: 23.6 ± 5.2 months, $p < 0.001$).

Terzidis et al. evaluated circulating levels of leptin in a population of 66 advanced NSCLC patients in control with 132 healthy volunteers and demonstrated that elevated serum leptin levels represent, after controlling for body mass index (BMI) and weight loss, an independent risk factor for NSCLC (OR = 4.58, CI: 1.94–10.82, $p = 0.001$) [39]. There was also a trend for higher leptin levels in earlier disease states, without however reaching statistical significance. This study implies again, albeit without further investigating underlying mechanisms, that enhanced leptin secretion may mediate lung cancer growth and promotion. In line with these findings, another study also reported statistically significantly higher leptin levels among 32 patients with NSCLC versus 20 healthy controls [40]. The investigators suggested that leptin is involved in lung carcinogenesis and proposed serum leptin measurements for diagnostic and follow up purposes in NSCLC.

Leptin's mechanism in lung cancer

Leptin's signaling through OB-Rb is transmitted predominantly through Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway with the activation of STAT-3. Leptin binding also activates insulin targets such as mitogen activated protein (MAP) kinase, Akt, and phosphoinositide 3-kinase (PI3-K) pathway [21] Beside the effect on cell proliferation [34] leptin has been shown to stimulate the angiogenesis as well [41].

Additionally, leptin affects both innate and adaptive immunity, resulting in upregulation of inflammation, which is already evident in most lung cancer patients due to cigarette smoking. It is well