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MINIREVIEW

Adipocytokines and Cancer

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Summary

Adipose tissue-produced hormones significantly affect the metabolism of lipids and carbohydrates as well as numerous other processes in human body. It is generally accepted that endocrine dysfunction of adipose tissue may represent one of the causal links between obesity and insulin resistance/diabetes. Epidemiological studies underlined that obesity represents a significant risk factor for the development of cancer, although the exact mechanism of this relationship remains to be determined. Multiple recent studies have indicated that some of adipose tissue-derived hormones may significantly influence the growth and proliferation of tumorous stroma and malignant cells within. Here we review current knowledge about possible relationship of leptin and adiponectin to the etiopathogenesis of different malignant tumors. Most of the studies indicated that while leptin may potentiate the growth of cancer cells *in vitro*, adiponectin appears to have an opposite effect. Further studies are necessary to decide whether obesity-induced endocrine dysfunction of adipose tissue can directly influence carcinogenesis in different tissues and organs.

Key words

Obesity • Adipocytokine • Leptin • Adiponectin • Cancer • Adipose tissue

Introduction

Adipocytokines are a group of adipose tissue-derived hormones that have been discovered since early nineties when the first member of the family – leptin – was described. Before that adipose tissue was recognized only as an energy storage depot and mechanical barrier thus having only a passive function in the body. Therefore, scientific research was focused mainly on biochemical composition of lipids and eventually on the role of brown adipose tissue in thermogenesis (Ricquier 2005). The abrupt change occured as late as 1994 when the Friedman´s group (Zhang et al. 1994) discovered leptin. After this discovery, the adipose tissue came into the spotlight of extensive research and around 20 members of the adipocytokine family have been identified so far.

The adipocytokines can be classified into three different groups:

1. Hormones produced primarily in other tissues or organs with simultaneous adipose tissue

production (e.g. TNF-α).

2. Hormones produced mainly in the white adipose tissue. Nevertheless, adipocytes are not the only source of production and other cells residing in fat, e.g. immunocompetent cells, may also participate (resistin).
3. Hormones produced predominantly or exclusively by adipocytes of white adipose tissue (leptin and adiponectin).

Another classification of adipocytokines reflects their putative physiological role. According to this classification, adipocytokines may be divided into two groups: "insulin resistance-inducing factors" such as resistin, TNF-α and interleukin 6, and "insulin-sensitizing factors" such as leptin, adiponectin and the recently described visfatin (Fukuhara *et al.* 2005).

Since the relationship of obesity to some forms of cancer has been known for a long time (Bray 2002), it is not suprising that researchers were trying to discover the possible role of adipocytokines in the regulation of carcinogenesis as another link between obesity and cancer (Garofalo and Surmacz 2006). The aim of this review is to describe the relationship of two adipocytokines produced predominantly (leptin) or exclusively (adiponectin) by white adipose tissue adipocytes to the regulation of cell growth and proliferation with special focus on their possible role in the etiopatogenesis of malignant tumors. Physiology and pathophysiology of both hormones have been described in detail elsewhere (Haluzík *et al.* 2004, Janečková 2001); therefore it will be only shortly summarized here.

Leptin

Leptin (from Greek λεπτοσ – thin) was discovered by positional cloning of *ob* gene in 1994 (Zhang *et al.* 1994). Leptin is a proteohormone produced predominantly by white adipocytes with molecular weight 16 kDa. The protein belongs to the family of cytokines with long four-helice motifs in the structure. The circulating leptin concentration is usually proportional to the total adipose tissue mass, i.e. increased in obese and decreased in lean subjects (Rohner-Jeanrenaud and Jeanrenaud 1996). Serum leptin levels are 2-3 times higher in women than in men even when adjusted for age and BMI (Ostlund *et al.* 1996).

Leptin exerts its function through specific receptors (Tartaglia *et al.* 1995). There are four splice variants of the leptin receptor in man, long isoform (OB-Rb/Ob-Rl) and shorter isoforms huB219.1, huB219.2 and huB219.3 in literature collectively referred to as OB-Ra/Ob-Rt. Among leptin receptor isoforms only the long OB-R contains an intact intracellular domain and has the ability to activate the intracellular JAK-STAT pathway with the activation of STAT3 and ERK1/2 (extracellular regulating kinase). The second longest isoform huB219.1 is a potent activator of ERK1/2 but not of STAT3. Leptin also activates c-Jun NH-2 terminal kinase (JNK) activation pathway.

The main effect of leptin in human body lies in the regulation of energy homeostasis especially under the conditions of restricted energy availability. Circulating leptin is actively transported through the blood-brain barrier and acts on the hypothalamic satiety center level to decrease food intake. Numerous peripheral effects of leptin suggesting its involvement in glucose and lipid metabolism, angiogenesis, blood pressure regulation, bone mass formation etc. have been described. However, its importance in the regulation of the above mentioned processes under physiological circumstances in humans remains questionable.

Adiponectin

Adiponectin was first identified as a protein expressed in 3T3-L1 mouse adipocyte cell line. Human adiponectin was described one year later and named APM1 (AdiPose Most abundant gene transcript 1) (Scherer *et al.* 1995, Hu *et al.* 1996, Maeda *et al.* 1996, Nakano *et al.* 1996).

Adiponectin is a protein of molecular weight 30 kDa produced exclusively in white adipocytes, although some reports describe its expression also in brown adipose tissue in the T37i cell line (Viengchareun *et al.* 2002). The molecule of human adiponectin consists of 244 amino acid residues; at the N-terminus there is an 18 amino acid long signal peptide followed by short hypervariable region without homology to any known sequences and collagen domain with 22 repeated motifs. C-terminal contains globular domain homologous to C1q molecule of complement cascade. There is a striking sequential homology with type VII and X collagens, C1q portion of complement, precerebellin and hibernation-regulated proteins 20, 25 and 27. C-terminal globular domain also shows homology with TNF-α trimeric cytokines family. The structure of adiponectin receptors was revealed recently and two isoforms were identified

(Yamauchi *et al.* 2003). AdipoR1 is expressed mainly in striated muscles while AdipoR2 is expressed mainly in the liver. Both AdipoR1 and AdipoR2 contain – similarly to G-protein coupled receptors – seven transmembrane domains.

The most important functions of adiponectin identified so far are anti-atherogenic, anti-inflammatory and insulin-sensitizing effects. It remains to be determined whether adiponectin´s deficiency is a primary cause or rather a marker of atherosclerosis and insulin resistance (Beltowski 2003, Palomer *et al.* 2005).

Adipocytokines and cancer

In addition to the relationship between adipocytokines and obesity or diabetes numerous other functions of these hormones in human body have been identified, including its potential role in the regulation of angiogenesis and tumor growth. Disturbances in the production of adipocyte-derived hormones thus may represent a new link explaining the well-known relationship between obesity and increased prevalence of malignancies.

Leptin and male urogenital tract cancer

Leptin and prostate cancer: in vitro studies

Several *in vitro* studies explored the effects of leptin administration on the growth of cancer cell cultures and carcinogenesis pathways. Somasundar *et al.* (2003b, 2004) showed that leptin induced *in vitro* proliferation and inhibited apoptosis of DU145 and PC3 cell lines. Simultaneously, the activation of PI3 and MAPK pathway were shown to be involved in the process of leptin-induced proliferation. Response to leptin was mediated through activation of a short form of leptin receptor. Another report of this group showed the effect of leptin on cell migration and VEGF levels that may elucidate the relationship of obesity and higher leptin serum levels on prostate cancer progression (Frankenberry *et al.* 2004). Osawa *et al.* (2002) found that leptin mediated the growth effect only in androgen-independent tumor cell lines DU145 and PC-3 but not in androgen-dependent LNCaP-FCG cells. The effect was transmitted *via* c-Jun NH2-terminal kinase (JNK).

Several studies focused on the relationship between leptin/leptin receptor gene-polymorphisms and development of prostate cancer at earlier age. Kote-Jarai *et al.* (2003) showed no relationship of Lys109Arg and Gln223Arg polymorphisms in coding region of leptin receptor gene. On the contrary, Ribeiro *et al.* (2004) found an association of single nucleotide polymorphism G/A in region – 2548 bp of leptin gene with the risk of prostate cancer development and more advanced stage in already developed cancer.

Leptin and prostate cancer: clinical studies

The results of the studies focusing on the relationship between obesity and prostate cancer rate yielded inconsistent results (Koistinen *et al.* 1997, Schuurman *et al.* 2000, Jonsson *et al.* 2003, Hubbard *et al.* 2004, Rohrmann *et al.* 2004, Aziz *et al.* 2005) and indicated that both diet composition and body mass index (BMI) or waist-to-hip ratio (WHR) may be the important factors. Numerous clinical studies focused on comparison of serum leptin levels in benign prostatic hyperplasia, prostate cancer and control healthy subjects. Lagiou *et al.* (1998) hypothesized that benign prostatic hyperplasia (BPH) and prostate cancer were associated with dysregulation of circulating levels of leptin, but there were no statistically significant differences in leptin levels between elderly men with BPH and/or cancer in comparison to healthy control subjects. Chang *et al.* (2001) found a positive association of plasma leptin levels with large volume (>0.5 ml) of prostate cancer and/or extraprostatic/metastatic disease at the time of diagnosis. Leptin´s effect was independent of testosterone levels. Hsing *et al.* (2001) showed the association of prostate cancer development with WHR higher than 0.87. This finding suggests that leptin may interact with markers related to abdominal obesity such as sex hormones or IGF-1, to increase the risk of prostate cancer. Stattin *et al.* (2001) showed the association of moderately elevated leptin levels with prostate cancer risk. However, another report from this group failed to confirm previous results (Stattin *et al.* 2003).

Leptin and urinary bladder cancer

In the work of Yuan *et al.* (2004a) leptin and long form of leptin receptor was not detected in either normal or cancerous bladder tissue, while a decreased expression of short form of leptin receptor was observed in most urinary bladder cancer in both male and female patients. Overexpression of short form of leptin receptor in T24 bladder cancer cell line led to the suppressed S-phase entry. As most cases in the study were high grade, authors were not able to correlate the expression of short form of leptin receptor with tumor differentiation status.

Table 1. Effects of leptin on cancer cells *in vitro* (modified from Garofalo and Surmacz 2006)

Type of cancer	Effects of leptin	Cell model
Breast cancer	Increased cell proliferation	Human breast cancer cell lines; T47D, MCF-7, ZR75-1
	Increased cell transformation (anchorage-independent growth)	T47D human breast cancer cells
	Activation of the ERK1/2, STAT3, Akt/GSK3 and PKC-α pathways	Human breast cancer cell lines; T-47D, MCF-7
	Increased AP-1 activation, upregulation of cdk2, cyclinD1, hyperphosphorylation of pRb	MCF-7, T47-D breast cancer cells
	Increased aromatase expression *via* AP-1-dependent mechanism	MCF-7 breast cancer cells
	Induced expression of *c-myc*	MCF-7 breast cancer cells
	Stabilization of ER α expression	MCF-7 cells treated with antiestrogen ICI 182, 780
Esophageal cancer	Increased cell proliferation	BIC-1 and SEG-1 esophageal adenocarcinoma cell lines
Gastric cancer	Increased cell proliferation *via* ERK-2 and STAT3 phosphorylation	MKN-28 human gastric cancer cell line
Colorectal cancer	Increased cell invasion *via* PI-3K, Rho- and Rac-dependent pathway	Premalignant familial adenomatous colonic cells PC/AA/C1 and human adenocarcinoma colonic cells LoVo and HCT-8/S11
	Increased cell growth *via* ERK1/2 pathway	Human colon adenocarcinoma HT29 cell line
	Reduced cell apoptosis, stimulation of NF-κB signaling	Human colon cancer HT29 cells treated with sodium butyrate
Prostate cancer	Increased cell proliferation and suppression of apoptosis	DU145, PC3 human prostate cancer cells
Pancreatic cancer	Decreased cell proliferation	Mia-PaCa and PANC-1 human pancreatic cancer cells
	Stimulation of STAT3 and STAT5b phosphorylation	BRIN-BD11 rat insulinoma cell line
Ovarian cancer	Increased proliferation *via* the ERK1/2 pathway	BG-1 ovarian carcinoma cell line
Lung cancer	Stimulation of cell proliferation the ERK1/2 pathway	SQ-5 human lung squamous cell cancer
Liver cancer	No effect	SMMC-7721 liver cancer cell line
	Decreased apolipoprotein M expression	HepG2 liver carcinoma cell line
Myeloid leukemia	Increased cell proliferation	OCI/AML2 and MO7E myeloid leukemia cell line
Pituitary adenoma	Decreased cell proliferation, stimulation of apoptosis and SOC-3 expression and phosphorylation	HP75 non-functioning pituitary adenoma cell line
Squamous cell skin cancer	Growth inhibition and promotion of differentiation	DJM-1 squamous cell carcinoma of the skin cell line

Adipocytokines and breast cancer

Leptin and breast cancer

A strong relationship between breast cancer and adiposity has been recognized for many years. Interestingly, there is a substantial difference in the impact of obesity on carcinogenesis in premenopausal and postmenopausal women (Asseryanis *et al.* 2004, Rose *et al.* 2004). While in premenopausal women increased body weight seems to be inversely related to breast cancer risk, in postmenopausal women obesity represents a significant risk factor for breast cancer development. In postmenopausal obese women adipose tissue is the only place of estrogen production by aromatization of C19 steroid androstendione. As there is increased aromatase activity and androstendione production in obesity, the total pool of estrogens is higher in obese women. The adipose tissue-derived hormone estrone is readily prepared for peripheral conversion to more biologically potent estradiol. Obesity also affects the binding of plasma estradiol to the sex-hormone binding globulin (SHBG). Even more interestingly, fat tissue distribution rather than obesity itself carries the risk of breast cancer development. Women with predominant central obesity had higher circulating free estradiol concentration than subjects with lower waist-to-hip ratio. The biological effect of leptin on breast cancer cancerogenesis and its progression came from the observations of leptin-induced proliferation of breast cancer cell lines, increase of the expression of proteolytic enzymes that are essential in metastatic process and stimulatory effect on angiogenesis. Leptin itself can also enhance aromatase activity. Leptin exerts its growth effect on estrogen receptor-positive human breast cancer cell lines through activation of MAP kinase pathway. However, it has to be stressed that other important players in addition to leptin directly linking obesity and breast cancer, such as insulin and IGF-1, exist. Insulin directly stimulates proliferation of breast cancer cell lines and lowers the levels of SHBG thus increasing the free estradiol availability. Some authors also found relationship between elevated IGF-1 levels and the risk of breast cancer development in premenopausal women.

Expression of leptin was found in normal mammary tissue, breast cancer tissue as well as in breast cancer cell lines (O'Brien *et al.* 1999, Chilliard *et al.* 2001). The effect of leptin on breast carcinogenesis is probably mediated by the stimulation of aromatase activity (Magoffin *et al.* 1999), proteolytic cleavage of intercellular matrix promoting cancer cell invasion (Castellucci *et al.* 2000) and angiogenic activity (Sierra-Honigmann *et al.* 1998, Cao *et al.* 2001, Park *et al.* 2001, Ribatti *et al.* 2001, Rose *et al.* 2002). Antiestrogenic and aromatase inhibitor therapy are modalities available for current breast cancer treatment. It is of interest that tamoxifene and toremifene, two anti-estrogen drugs available on the market, elevate serum leptin levels in postmenopausal breast cancer patients (Ozet *et al.* 2001, Marttunen *et al.* 2000).

Numerous studies explored serum leptin levels in women with breast cancer. Mantzoros *et al.* (1999) found no difference between premenopausal patients with carcinoma *in situ* and healthy controls. An Italian case-control study observed elevated plasma leptin levels in breast cancer patients and increase in adipose tissue leptin mRNA levels (Tessitore *et al.* 2000, 2004). A study of invasive breast cancer from Greece reported significantly lower serum leptin levels in premenopausal breast cancer patients (Petridou *et al.* 2000).

Leptin receptor expression in the breast tissue was also described (Laud *et al.* 2002, Hug and Lodish 2005). In our study of invasive ductal carcinoma we found strong leptin receptor positivity in the cytoplasm of tumor cells but only focal and weaker positivity in epithelial duct cells and interstitial fibroblast-like elements (Housa, unpublished data). Both normal and transformed breast cancer cell lines express the long form of the leptin receptor. Leptin can activate STAT3, ERK and AP-1 pathways in these cells thus resulting in increased cell proliferation. Anchorage-independent cell growth is enhanced only in T47D cell line after leptin treatment. High levels of leptin were found to promote ERK phospohorylation but did not increase VEGF production in breast cell lines.

Adiponectin and breast cancer

Mantzoros *et al.* (2004) found an inverse relationship of circulating adiponectin levels and breast cancer risk in postmenopausal women independently of possible effects of IGF-1, leptin, BMI and other parameters. No such association was found in premenopausal women. Miyoshi *et al.* (2003) described an association of low serum adiponectin levels with increased risk of breast cancer in both postmenopausal and premenopausal women in comparison with high serum adiponectin levels patients. Also, the higher frequency of large tumors with higher histological grade was observed in patients with low serum adiponectin

levels when compared with intermediate and high levels.

Adipocytokines and female genital tract cancer

Leptin and endometrial, vulvar and ovarian cancer

Interest in the influence of adipocytokines on endometrial cancer came from the observations of a close association of obesity and endometrial cancer risk. Previous reports showed that both short and long forms of leptin receptor mRNA and proteins, but not leptin itself, were expressed in the endometrium (Kitawaki *et al.* 2000). The expression peaked in early secretory phase with a long form of leptin receptor predominating over other splice variants and declined during the mid- and late secretory phases towards menstruation. First report on the impact of serum leptin levels came from the study of Petridou *et al.* (2002) who showed a positive association between high leptin levels and endometrial cancer. Yuan *et al.* (2004a,b) described elevated leptin levels in endometrial cancer patients. Nevertheless, after normalization for body mass index no significant difference relative to healthy controls was found. Therefore, the elevated leptin levels in endometrial carcinogenesis may reflect rather the obesity itself than the direct role of leptin in endometrial cancer development. Also, lower expression of short leptin receptor isoform was observed in most endometrial cancers, especially in the poorly differentiated ones. Overexpression of short form of leptin receptor in RI-95.2 endometrial cancer cell line prevented cells from entering to S phase.

Lebrecht and coworkers measured leptin levels in patients with invasive squamous cell vulvar cancer (Lebrecht *et al.* 2001) and cervical intraepithelial dysplasia and cancer (Lebrecht *et al.* 2002). No relationship between leptin levels and tumor stage, lymph node involvement, histological grade or with disease-free interval and survival was found.

In ovarian cancer cell lines IOSE-80PC, BG-1, OVCAR-3 and SKOV-3 both short and long isoforms of leptin receptor are expressed (Choi *et al.* 2005). While a short isoform is expressed in all ovarian cell lines studied so far (SVOG-4o, IOSE-120, IOSE-80, IOSE-80PC, BG-1, CaOV-3, OVCAR-3 and SKOV-3), the long form is absent in SVOG-4o, IOSE-120, IOSE-80 and CaOV-3 cell lines. Leptin treatment resulted in growth stimulation of BG-1 cells, activation of ERK1/2 and inhibition of constitutive phosphorylation of p38 MAPK. No stimulatory effect of leptin on the cell growth was observed in IOSE-80PC and SKOV-3 cells that exclusively express a long isoform of leptin receptor. This means that different ovarian cancer cell lines differ in their responsiveness to leptin stimulation.

Adiponectin and endometrial cancer

Petridou *et al*. (2003) showed an inverse significant association of endometrial cancer in women younger than 65 years of age. Obesity and adiponectin had independent roles in promoting endometrial cancer. The results were confirmed in another study published by Dal Maso *et al.* (2004).

Adipocytokines and gastrointestinal cancer

Leptin and esophageal, gastric and colon cancer

Somasundar *et al.* (2003a) showed that leptin stimulated the proliferation of esophageal adenocarcinoma cell line BIC-1 and SEG-1 but did not affect necrosis or apoptosis. Lin *et al.* (2003) evaluated the effect of leptin on MKN 28 gastric cancer cells and found both increased cell proliferation and ERK2 and STAT3 phosphorylation. Hardwick *et al.* (2001) detected leptin receptor expression in both tumor tissue and colon cancer cell line HT29 and showed that leptin induced cell proliferation and p42/44 MAPK phosphorylation. These results were confirmed by Rouet-Benzineb *et al.* (2004). Additionally, leptin treatment induced downstream NFκB signaling pathway, increased the number of HT29 cells in S and G_2/M phase, increased cyclin D1 expression in G_0/G_1 and prevented HT29 cells from sodium butyrate-induced apoptosis. Altogether, leptin acted as a potent mitogen and anti-apoptotic cytokine in colon cancer cell line HT29 through NFκB and ERK1/2 signaling pathways.

Attoub *et al.* (2000) showed that leptin promoted the invasiveness of familial adenomatous colonic cells PC/AA/C1 and the human adenocarcinoma colonic cells LoVo and HCT-8/S11 cells *in vitro*.

Despite such a significant amount of *in vitro* data, direct and convincing evidence about the role of circulating leptin in the development of gastrointestinal tract cancer is not available. Numerous studies demonstrated that diets rich in fat that increase circulating leptin promote carcinogenesis by stimulating colon cell proliferation (Lin *et al.* 1998, Bahceci *et al.* 1999, Baile *et al.* 2000) while diets rich in dietary fibers that reduce leptin levels have an opposite effect (Agus *et al.* 2000). Whether leptin is directly involved in the process of

gastrointestinal carcinogenesis needs to be proven.

Adiponectin and gastric cancer

Ishikawa *et al.* (2005) found lower serum adiponectin levels in patients with gastric cancer especially an upper gastric cancer when compared to healthy controls and showed an inverse relation to gastric cancer risk.

Adipocytokines and hematological malignancies

Leptin receptor mRNA was detected in acute myeloid leukemia (AML), acute lymphocytic leukemia (ALL) and chronic myeloid leukemia (CML) but were not detected in chronic lymphocytic leukemia (CLL) cells (Cioffi *et al.* 1996, Nakao *et al.* 1998, Lindsay *et al.* 2003). Both short and long isoforms were expressed in acute myeloid leukemia. The incidence of leptin receptor expression was higher in recurrent cases of AML and myelodysplastic syndrome than in newly diagnosed cases (Konopleva *et al.* 1999). Expression of the long but not short isoform occurred more frequently in the primary AML than in secondary AML or the myelodysplastic syndrome. Higher leptin receptor expression was observed in blast crisis patients than in the chronic phase of CML. Overexpression of the leptin receptor was observed in K562, HEL, and MO7E cell lines (Nakao *et al.* 1998). Leptin stimulated proliferation of human myeloid leukemia cell lines OCI/AML2 and MO7E in a dose-dependent manner. The proliferative response did not correlate with leptin receptor expression (Konopleva *et al.* 1999). Leptin also induced growth of primary leukemic cells from some AML patients. Combination of leptin with other hematopoetic factors such as granulocyte-macrophage colony-stimulating factor (GM-CSF) and G-CSF (granulocyte colony-stimulating factor), induced a synergistic response in blast crisis CML patients and additive and synergistic response in some AML patients, respectively (Konopleva *et al.* 1999). In contrast, adiponectin administration inhibited proliferation of myelomonocytic lineage cells by induction of apoptosis (Yokota *et al.* 2000). We have measured circulating leptin levels in patients undergoing mobilization of peripheral blood stem cells before autologous stem cell transplantation. Serum leptin levels decreased significantly at the leucopenia phase and remained suppressed in the stem cell harvest phase, which could possibly be explained either by direct effect of G-CSF administration or by increased leptin consumption by activated stem cells (Haluzík *et al.* 2002).

Conclusions

Adipocytokines were shown to participate to some extent in the process of carcinogenesis, however most if not all of these positive data come from *in vitro* studies on cancer cell lines. It is well documented that obesity increases the risk of some types of cancer such as that of the colon, breast and prostate. Leptin, the most widely studied member of a family, stimulates growth, migration and invasion of cancer cells *in vitro* and also potentiates angiogenesis, thus displaying a capacity for promoting malignant biological behavior of cancer *in vitro*. The influence of other members of adipocytokine family on cancer is less clear. Further studies using more specific animal models lacking respective adipocytokines such as leptin-deficient *ob/ob* mice or adiponectin-knockout mice are clearly needed to dissect the importance of adipocytokines in the cancer development. It still has to be elucidated whether disturbances of adipocytokines are directly linked to the cancer development or whether they are just a correlate of adipose tissue endocrine dysfunction seen in obesity.

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