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Deep Insight Section

Adiponectin and cancer

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Abstract

Deep insight on adiponectin and cancer.

Obesity and cancer

Obesity has increased worldwide, becoming a major global health issue with epidemic proportions. Obesity is implicated in many diseases such as cardiovascular disease, type 2 diabetes mellitus and various cancers (Hubert et al., 1983; Mokdad et al., 2003; Ogden et al., 2007; Renehan et al., 2008; Dalamaga et al., 2012; Dalamaga et al., 2013b) such as colon cancer, postmenopausal breast cancer, endometrial cancer, renal cell cancer, esophageal adenocarcinoma, non-Hodgkin's lymphoma, leukemia, multiple myeloma (Pischon et al., 2008; Lichtman, 2010; Dalamaga et al., 2009a; Dalamaga et al., 2010), thyroid cancer, pancreatic cancer (Dalamaga et al., 2009b), gallbladder cancer, high-grade prostate cancer and ovarian cancer (Renehan et al., 2008; Larsson et al., 2007; Wiseman, 2008; Hsing et al., 2007; Dalamaga et al., 2012).

The main mechanisms associating obesity to cancers are: i) abnormalities of the insulin-like growth factor-I (IGF-I) system; ii) hyperinsulinemia and insulin resistance; iii) obesity-driven chronic low-grade systemic inflammation; iv) the influence of obesity in sex hormones biosynthesis; and v) variations in the levels of adipokines (Park et al., 2011; van Kruijsdijk et al., 2009).

Adiponectin biology, physiology and pathophysiology

Adiponectin is mainly produced by white adipose tissue (Ziemke and Mantzoros, 2010; Maeda et al., 2012), although other tissues express lower quantities of adiponectin. Adiponectin is alternatively called AdipoQ (Hu et al., 1996), Acrp30 (adipocyte complement-related protein of 30 kDa) (Scherer et al., 1995), apM1 (gene product of the adipose most abundant gene transcript-1) (Maeda et al., 2012), and GBP28 (gelatin-binding protein-28) (Nakano et al., 1996), and was first described in the mid-1990s.

The adiponectin gene is located on chromosome 3q27 and consists of three exons and two introns (Takahashi et al., 2000). Some polymorphisms of the adiponectin gene have been shown to present functional consequences of the adiponectin protein and have been associated with clinical manifestations (Dalamaga et al., 2012).

Adiponectin is a 244-amino acid protein encompassing four structural domains: an amino-terminal signal peptide followed by a variable domain, a collagen-like region of 22 Gly-X-Y repeats, and a carboxyl-terminal globular domain that binds to the adiponectin receptors and resembles tumor necrosis factor-α (TNF-α) (Dalamaga et al., 2012).

Adiponectin is firstly synthesized as a single subunit that forms trimers, hexamers, and multimers before secretion. The monomeric form of adiponectin is thought to be present only in the adipocyte (Chandran et al., 2003), whereas adiponectin is mainly circulating as a trimer. Adiponectin can be found into five different configurations with different biological effects: the globular adiponectin (gAPN), full-length adiponectin (fAPN), low-molecular-weight adiponectin, medium molecular-weight adiponectin, and high-molecular-weight adiponectin (HMW) (Dalamaga et al., 2012).

Adiponectin binds to two main receptors, adiponectin receptor 1 and 2 (AdipoR1 and AdipoR2) encoded by genes located on chromosomes 1p36.13-q41 and 12p13.31, respectively (Yamauchi et al., 2003). AdipoR1 is expressed ubiquitously but most abundantly in skeletal muscle, whereas AdipoR2 is predominantly expressed in the liver. Although both receptors are expressed in almost every tissue, including pancreatic β-cells, one or the other receptor usually prevails (Dalamaga et al., 2012). A plethora of cancer cell lines express adiponectin receptors, suggesting that adiponectin may exhibit direct effects on these cells and limit their proliferation at least in vitro (Kim et al., 2010). The two main receptors are integral membrane proteins with seven transmembrane domains with an internal N-terminal collagenous domain and an external C-terminal globular structure. AdipoR1 has high affinity for gAPN whereas AdipoR2 mainly recognizes fAPN (Kadowaki and Yamauchi, 2005). T-cadherin has also been proposed as an adiponectin receptor, acting as a co-receptor by competing with AdipoR1/R2 and binding to the hexameric and HMW forms of adiponectin; though its pathophysiological importance is not yet elucidated in humans (Hug et al., 2004). The two classical adiponectin receptors, AdipoR1 and AdipoR2, are structurally very related and share 67% identity in their protein sequence. They are also highly conserved sharing 95% homology between humans and mice (Dalamaga et al., 2012). Adiposity is considered to downregulate the expression of AdipoR1/R2, which results to a decrease in adiponectin sensitivity, leading to insulin resistance (Ouchi et al., 2000). On the other hand, physical exercise upregulates adiponectin receptors in muscles and adipose tissue, and increases the levels of circulating adiponectin (Blüher et al., 2006).

Adiponectin exerts diverse effects on different tissues and organs, and the various isoforms present various biological effects on different target tissues (Ziemke and Mantzoros, 2010). Adiponectin is considered to be a protective hormone, exhibiting insulin-sensitizing, anti-inflammatory, anti-atherogenic and cardioprotective properties. Adiponectin plays also an important role in lipid metabolism (Barb et al., 2007; Ziemke and Mantzoros, 2010) by redirecting fatty acids to the muscles to undergo oxidation, decreasing the liver uptake of fatty acids and the total triglyceride content resulting in increased insulin sensitivity in liver and skeletal muscle. Particularly in the liver, these actions are considered to be achieved by HMW adiponectin (Hada et al., 2007). Adiponectin presents anti-atherogenic actions by direct inhibition of atherosclerosis and plaque formation. Adiponectin presents also central actions by modulating food intake and energy expenditure (Dalamaga et al., 2012).

Circulating adiponectin levels are generally measured in the range of 2 to 20 μg/mL. Depending on the assay methodology, race and gender, median adiponectin levels in healthy individuals with a body mass index (BMI) between 20 and 25 kg/m^2 are approximately 8 μg/mL for men and 12.5 μg/mL for women (Dalamaga et al., 2012; Fabian, 2012). Circulating adiponectin levels are regulated by factors like genetic background, anthropometric characteristics, hormonal profile, inflammation, nutritional habits, and pharmacologic parameters. In obesity, serum adiponectin is decreased, in contrast to other hormones secreted by the adipose tissue, and presents, generally, a negative correlation with BMI, waist and hip circumference, waist-to-hip ratio, and visceral fat (Barb et al., 2007; Ziemke and Mantzoros, 2010).

Hypoadiponectinemia related to genetic and environmental factors, such as diet and obesity, may be implicated in the pathogenesis of insulin resistance (Weyer et al., 2001), metabolic syndrome, type 2 diabetes (Weyer et al., 2001), gestational diabetes (Mazaki-Tovi et al., 2009), hypertension and cardiovascular disease (Trujillo and Scherer, 2005). Low adiponectin levels are the common pathodenominator of the constellation of risk factors that synthesize the metabolic syndrome such as hypertension, dyslipidemia, obesity, hyperglycemia, hyperinsulinemia and insulin resistance (Dalamaga et al., 2012).

Adiponectin and carcinogenesis mechanisms

A growing body of evidence suggests that adiponectin presents anti-neoplastic effects via two mechanisms. First, adiponectin can act directly on tumor cells by enhancing receptor-mediated signaling pathways. Secondly, adiponectin may act indirectly by regulating inflammatory responses, influencing cancer angiogenesis and regulating insulin sensitivity at the target tissue site (Dalamaga et al., 2012).

In vitro and *in vivo* studies have shown the expression of AdipoR1 and AdipoR2 in various

cancer cell types, suggesting that adiponectin can exhibit direct receptor-mediated effect. Adiponectin has shown to restrain proliferation of most obesity-related cancer types with some conflicting published data. For example, in the case of liver carcinoma, esophageal adenocarcinoma, gastric, endometrial and prostate carcinoma, adiponectin presented clear anti-carcinogenic effects, whereas it had no effect on melanoma cell proliferation (Dalamaga et al., 2012). However, inhibition of proliferation or no effect on proliferation of colorectal cancer cell lines was noted after treatment with adiponectin (Williams et al., 2008). Also, in vitro studies on breast cancer cell lines have been conflicting pointing towards cell line dependent effects (Dalamaga et al., 2012). Potential reasons for these discrepancies may be biological variations between the several lines of the respective cells used in various laboratories, differences in culture conditions, glucose availability medium, incubation time or adiponectin dosage, the specific isoform of adiponectin used, etc.

The signaling pathways linking adiponectin to inhibition of tumorigenesis involve several intracellular signaling pathways, including 5' AMP-activated protein kinase (AMPK), mammalian target of rapamycin (mTOR), phosphatidylinositol 3-kinase (PI3K)/v-Akt murine thymoma viral oncogene homolog (Akt), mitogen-activated protein kinase (MAPK), signal transducer and activator of transcription 3 (STAT 3), nuclear factor-κB (NFκB) and the sphingolipid metabolic pathway. Furthermore, inhibition of β-catenin, activation of c-AMP/protein kinase A and reduction of reactive oxygen species (ROS) may also contribute to the response of tumor cells to adiponectin (Dalamaga et al., 2012). Nevertheless, most of the effects of adiponectin on cancer cells are mediated through AMPK. Collectively, the adiponectin anti-neoplastic effects result in decreased protein and fatty acid synthesis, reduced cellular growth, proliferation and DNA-mutagenesis as well as enhanced cell cycle arrest and apoptosis (Dalamaga et al., 2012). The interplay between the mentioned pathways adds further complexity to the adiponectin signaling network. Interestingly, recent evidence has indicated that adiponectin can stimulate ceramidase activity independently of AMPK via the classical adiponectin receptors (Holland et al., 2011), contributing to increased amounts of prosurvival sphingosine 1 phosphate (S1P). Elevated S1P is associated with enhanced cell survival and higher local pro-angiogenic activity as observed in mammary tumor mouse models (Landskroner-Eiger et al., 2009).

Adiponectin can also present receptor-independent, anti-proliferative actions through controlling the bioavailability of certain growth and inflammatory factors related to carcinogenesis. Finally, *in vitro* studies have shown interactions between adiponectin and other hormonal signaling pathways such as sex steroids and leptin, underscoring the complex mechanisms that regulate carcinogenesis *in vivo* (Dalamaga et al., 2012).

Animal experiments have been conducted in order to further evaluate the *in vitro* adiponectin findings. Animal models testing the role of adiponectin in carcinogenesis have elucidated the anti-tumorigenic action of adiponectin, particularly in obesity-associated cancer types. The diet-mediated influences have also been tested in animal models and have contributed to the knowledge of the role of adiponectin *in vivo*. Importantly, adiponectin presents the strongest effect under the high-fat diet condition, which is characterized by insulin resistance and a pro-inflammatory state. Generally, inhibition of tumor growth has been shown for colon, gastric, liver, breast and lung cancer as well as melanoma (Dalamaga et al., 2012). Finally, the role of adiponectin in tumor angiogenesis remains to be defined as both pro-angiogenic (Ouchi et al., 2004) and anti-angiogenic activities (Bråkenhielm et al., 2004) have been described with a prevailing pro-angiogenic function (Dalamaga et al., 2012).

Adiponectin and cancer: epidemiologic evidence

Epidemiological evidence has linked adiponectin to the risk of obesity-associated cancers, including but not limited to breast, endometrial, prostate, gastric, colon, pancreatic, and hematologic malignancies. Moreover, many studies have reported adiponectin receptors and their expression in specific cancer tissues. Few epidemiologic studies have related specific gene polymorphisms of adiponectin and adiponectin receptors with cancer risk presenting variable associations (Dalamaga et al., 2012).

Hypoadiponectinemia has been proposed as a biological link between obesity, insulin resistance and colorectal cancer as well as colorectal adenoma. Two meta-analyses and a large, prospective study in the context of the Health Professionals Study examining the association between circulating adiponectin and the risk of CC and adenoma have found significantly lower adiponectin levels than healthy controls and an elevated risk for colorectal cancer associated with hypoadiponectinemia (Wei et al., 2005; Xu et al., 2011; An et al., 2012). Determining serum adiponectin levels and assessing the expression of adiponectin receptors in colorectal cancer tissue could be useful in predicting the risk of colorectal cancer, establishing the prognosis and recurrence of colorectal cancer.

Hypoadiponectinemia has also been found in patients with gastric cancer, especially upper gastric cancer, esophageal adenocarcinoma and esophageal

squamous cell carcinoma in comparison to healthy controls (Ishikawa et al., 2005; Yildirim et al., 2009). In particular, lower plasma adiponectin levels were inversely correlated with tumor size, depth of invasion and tumor TNM stage, underscoring a potential role for adiponectin in gastric cancer progression (Ishikawa et al., 2005).

Evidence for the relationship between pancreatic adenocarcinoma and adiponectin levels is conflicting and depends mainly on the study design (retrospective versus prospective). In general, circulating adiponectin levels have been reported decreased in prospective studies (Bao et al., 2013) and increased in retrospective case-control studies (Dalamaga et al., 2009a; Dalamaga et al., 2009b). Elevated adiponectin levels seen in retrospective studies for pancreatic cancer may be a compensatory response to inflammation, insulin resistance and the disease-induced weight loss due to cancer cachexia, a metabolic state characterized by adipose and muscle tissue loss (Dalamaga et al., 2009b). Moreover, cachectic patients may exhibit glucose intolerance and insulin resistance due to alterations in fat metabolism, hypoleptinemia, a pro-inflammatory state and an increased activity of the Cori cycle (Dalamaga, 2013).

The majority of epidemiologic evidence has linked lower total or HMW adiponectin levels to an increased risk for breast cancer independently of classical risk factors, including leptin and the IGF-I system in both premenopausal and postmenopausal women (Mantzoros et al., 2004; Dalamaga et al., 2011; Dalamaga et al., 2012). Macis et al. identified hypoadiponectinemia in premenopausal women as a risk biomarker for progression from intraepithelial neoplasia to invasive breast cancer independently of age, BMI, and treatment group (Macis et al., 2012). Because adipocytes constitute the predominant breast stromal element, adiponectin may exert a major paracrine and autocrine influence in mammary epithelium. Since AdipoR1/R2 are expressed in breast cancer tissue samples and cell lines, adiponectin could act not only through altering the hormonal milieu but directly through suppression of breast cancer cell proliferation. In addition, some studies have pointed out that breast tumors arising in women with low adiponectin levels may present a more aggressive phenotype characterized by a higher histologic grade, a large size of tumor and estrogen-receptor negativity (Dalamaga et al., 2012). Hypoadiponectinemia was also associated with lymph node metastases and increased mortality in breast cancer survivors after adjustment for parameters, including obesity and insulin resistance (Duggan et al., 2011). Finally, some studies focusing on adiponectin genetic variants (ADIPOQ) and adiponectin receptor genes (ADIPOR1) and breast cancer risk have reported associations of ADIPOQ single nucleotide polymorphisms (SNPs) and ADIPOR1 SNP with breast cancer risk. However, other studies did not find such associations (Dalamaga et al., 2012).

Hypoadiponectinemia was associated with an elevated risk of endometrial cancer, particularly in women younger than 65 years, independently from BMI, leptin, the IGF system and other known risk factors (Petridou et al., 2003). Interestingly, a combination of obesity and hypoadiponectinemia constitutes a greater risk for endometrial cancer occurrence. In particular, among obese and peri-/postmenopausal women, lower pre-diagnostic circulating adiponectin levels may predispose to a higher risk of endometrial cancer independently from BMI, measures of central obesity and other obesity-related biological risk factors such as circulating levels of C-peptide, a biomarker reflecting pancreatic insulin production, endogenous sex steroid hormones, and IGF binding proteins (Cust et al., 2007).

Although the relationship between adiponectin concentrations and prostate cancer has not been consistently shown, there is growing evidence that hypoadiponectinemia is not only associated with prostate cancer risk (Dalamaga et al., 2012) but also with the histologic grade and disease stage (Michalakis et al., 2007). Indeed, in a 25-year prospective study, men with elevated pre-diagnostic adiponectin levels presented lower risk for developing high-grade or metastatic prostate cancer (Li et al., 2010).

Finally, circulating adiponectin levels have been related mainly to the risk of hematologic malignancies of the "myeloid" cell line (Dalamaga et al., 2012) such as childhood acute myeloblastic leukemia, myelodysplastic syndromes (Dalamaga et al., 2007; Dalamaga et al., 2008; Dalamaga et al., 2013a), and myeloproliferative disorders including chronic myelogenous leukemia (Avcu et al., 2006). Interestingly, lower serum adiponectin and free leptin, and elevated fetuin-A levels, may mediate effects of excess body weight on insulin resistance and risk for myelodysplastic syndromes (Dalamaga et al., 2013a). These findings are in accordance with a previous hypothesis showing that adiponectin induces apoptosis and inhibits the proliferation of myeloid cell lineage predominanltly (Yokota et al., 2000). Controversial data exist in the literature in relation to circulating adiponectin levels as a biomarker of hematologic malignancies from "lymphoid" origin. A decrease, no change and even an elevation in adiponectinemia have been reported (Dalamaga et al., 2012). In addition, no prospective epidemiologic studies have been performed examining the association of pre-diagnostic adiponectin levels and non-Hodgkin lymphomas due to the rarity of these malignancies in the general population. Lower levels of adiponectin were associated with a greater risk for multiple

myeloma adjusting for age, gender, BMI, serum leptin and resistin (Dalamaga et al., 2009a) in accordance with a recent research by Fowler et al., which reported a significant percent decrease in circulating HMW adiponectin concentrations in patients with monoclonal gammopathy of undetermined significance that either progress or do not progress to multiple myeloma from age-, gender-, and BMI-matched controls (Fowler et al., 2011). This is in accordance with the finding that adiponectin can induce apoptosis of myeloma cells through an activation of AMPK, and that myeloma cell apoptosis is reduced in myeloma-bearing adiponectin-deficient mice (Fowler et al., 2011). Augmenting adiponectin via an apolipoprotein peptide mimetic, L-4F, increased apoptosis of myeloma cells in vivo and prevented myeloma bone disease (Fowler et al., 2011).

Therefore, adiponectin could not only represent a biomarker for cancer development in obesity, but could also act as a molecular mediator relating adipose tissue with carcinogenesis. The mechanisms underlying the actions of adiponectin and its potential diagnostic, prognostic and/or therapeutic utility need further investigation (Dalamaga et al., 2012).

Future perspectives

The action of adiponectin in ameliorating insulin sensitivity synergistically with its anti-proliferative and pro-apoptotic properties has rendered this adipokine a promising potential diagnostic and prognostic biomarker, and a novel therapeutic tool in the pharmacologic armamentarium for cancer treatment. In the future, based on circulating adiponectin determinations and specific combinations of adiponectin pathway SNPs, a high-risk population for developing cancer could be identified and benefit from adiponectin replacement therapy.

Research efforts could be directed towards identifying ways to augment endogenous adiponectin levels in order to moderate the obesity-cancer relationship. Adiponectin-mimetics, agonists of AdipoR1/R2 and strategies to increase adiponectin receptors and to modulate their sensitivity to adiponectin could provide novel therapeutic approaches for insulin resistance, diabetes type 2 and obesity-associated cancers. Pharmacologic agents such as full and selective PPAR-γ agonists increasing circulating adiponectin levels or stimulating adiponectin signaling are at the forefront of future therapeutic modalities for obesity-linked cancers. Nonetheless, further basic research, in vivo animal studies, observational human studies, and prospective and longitudinal studies are required in order to clearly determine the mechanisms underlying the actions of adiponectin in cancer.

At present, lifestyle amelioration remains the most important component in preventing obesity-related cancer.

Physical exercise, reduction of body-weight, a Mediterranean-based diet with consumption of fruits, nuts, coffee and/or moderate amounts of alcohol present a well-established association with increased adiponectin levels, and a lower risk of developing insulin resistance, diabetes type 2, cardiovascular disease and malignancies.

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