Adiponectin in relation to malignancies: a review of existing basic research and clinical evidence\textsuperscript{1–4}

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ABSTRACT
Adiponectin, an adipocyte-secreted hormone that plays an important role in diabetes and cardiovascular disease, may also be of importance in the development and progression of several malignancies. Circulating adiponectin concentrations, which are determined mainly by genetic factors, nutrition, and adiposity, are lower in patients with breast, endometrial, prostate, and colon cancer. It has thus been proposed that adiponectin may be a biological link between obesity (especially central obesity) and increased cancer risk. Adiponectin may influence cancer risk through its well-recognized effects on insulin resistance, but it is also plausible that adiponectin acts on tumor cells directly. Several cancer cell types express adiponectin receptors that may mediate the effects of adiponectin on cellular proliferation. Therefore, we review recent evidence supporting a role of serum adiponectin concentrations as a novel risk factor and possible diagnostic marker for obesity-related malignancies, including cancers of the breast, endometrium, colon, and prostate. Further studies are needed to fully elucidate the potential role of adiponectin in cancer diagnostics and therapeutics.

KEY WORDS Adiponectin, ACRP30, AMPK, cancer, insulin resistance, obesity

INTRODUCTION
Adipose tissue, which is the largest endocrine organ in the body (1), plays an important role in regulating energy metabolism and inflammation and has also been associated with several cancers. Adiponectin, a 30-kDa complement C1q-related protein, is the most abundant gene product secreted by fat cells (2) and is a key regulator of insulin sensitivity (3, 4) and inflammation (5, 6). Adiponectin modulates several physiologic processes, such as metabolism of glucose and fatty acids (7), and decreases plasma adiponectin concentrations are associated with insulin resistance, type 2 diabetes (8), and atherosclerosis (9). In addition, it was recently shown that adiponectin may play a role in the development and progression of various types of malignancies, as reviewed herein.

ADIPONECTIN BIOLOGY
Adiponectin, which is also referred to as gelatin-binding protein-28 (GBP28) (10), AdipoQ (11), ACP30 (Acrp30) (12), or gene product of the adipose most abundant gene transcript-1 (apM1) (2), is secreted predominantly by white adipose tissue. The gene for adiponectin is located on human chromosome 3q27 (13), a region identified as a susceptibility locus for the metabolic syndrome and type 2 diabetes in whites (14).

Adiponectin is a 244–amino acid protein that circulates in human plasma as a homopolymer or as full-length adiponectin (fAd or Acrp30) that comprises up to 18 monomeric units. It has an N-terminal region with high structural homology to collagen VIII, X, and complement C1q and a C-terminal globular domain region that resembles the trimeric topology of tumor necrosis factor-α (15). Acrp30 is highly abundant in the circulation, with plasma concentrations in healthy humans of \(\approx10\ \mu\text{g/mL}\), and accounts for \(\approx0.01\%\) of total plasma protein.

At least 3 distinct and stable isoforms of Acrp30 have been isolated from \textit{Escherichia coli} or cultured mammalian cells in both mouse (16) and human (17) serum. Although most active adiponectin appears to exist in the form of full-length or high molecular weight (HMW) adiponectin in plasma (12, 18), low molecular weight (LMW) or trimeric complexes are also present in low abundance (17, 19). Proteolytic cleavage of the full-length molecule at amino acid 110 produces globular adiponectin (gAd or gAcrp30) (20), which is thought to have enhanced potency (21).

Oligomerization and posttranslational modifications (ie, glycosylation) of adiponectin are apparently critical for binding to its receptors (22) and determining biological activity (16, 23). Thus, different forms of adiponectin (ie, trimeric versus hexamic and HMW, or globular versus full-length) show distinct biological effects through differential activation of downstream signaling pathways (16, 23, 24). Recent evidence suggests that the HMW adiponectin complex may be the active form of the hormone (25, 26), but this remains to be confirmed. HMW adiponectin correlates more strongly with postload glucose concentrations than does total adiponectin (26), and changes in the ratio of HMW to total adiponectin are closely associated with improvements in insulin sensitivity during thiazolidinedione

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treatment in humans, whereas changes in total adiponectin concentrations are not (25).

Full-length adiponectin, but not gAd, down-regulates genes involved in gluconeogenesis through 5’-AMP-activated protein kinase (AMPK) in the liver (27). In one study, trimeric Acrp30 was the most potent isoform in terms of suppression of hepatocyte glucose production and reduction of serum glucose concentrations as compared with the higher order oligomeric forms (28). Other studies have suggested that both fAd and gAd stimulate fatty acid oxidation, glucose uptake, and lactate production through AMP activation in C2C12 myocytes (29). However, further evidence suggests that trimeric Acrp30 and gAcrp30, but not hexamer and HMW Acrp30, increase phosphorylation and activation of AMPK in skeletal muscle (23). Thus, this remains an active area of research.

Two adiponectin receptor isoforms (AdipoR1 and AdipoR2) have been cloned (30). Structurally, these 7-transmembrane-region proteins have an internal N terminus region and an external C terminus, as opposed to the usual topology of G protein-coupled receptors (30). Both have unique distributions and affinities for the different forms of circulating adiponectin. AdipoR1 is a high-affinity receptor for gAd with a low affinity for fAd. AdipoR1 is expressed ubiquitously; it is most abundant in skeletal muscle but is also expressed in endothelial cells and other tissues. AdipoR2 is predominantly expressed in the liver and has intermediate affinity for both forms of adiponectin (18, 21). Both adiponectin receptors are markedly expressed in pancreatic β-cells, at levels similar to liver for AdipoR2 and even greater than in muscle for AdipoR1 (31).

Of note, several tumor cell lines express AdipoR1 and AdipoR2, which suggests that adiponectin could exert direct effects on these cells via signaling through its receptors. Adiponectin receptors are expressed not only by prostate (32–34) and hepatocellular (32) carcinoma cell lines, but also by breast cancer cells (35–38), normal (39) and cancerous endometrial cells, and colon and neuroblastoma cancer cell lines (C Mantzoros, unpublished data, 2007). Although it has not yet been clarified whether the presence of adiponectin receptors in tumor cells has any functional relevance, initial studies indicate that activation of adiponectin receptors by adiponectin limits the proliferation of breast cancer cells in vitro (37). Finally, T-cadherin, a cell-surface receptor involved in calcium mediated cell–cell interactions and signaling located in endothelial and smooth muscle cells, was also found to bind strongly to HMW adiponectin. Because T-cadherin does not have an intracellular domain, however, it is believed that it does not signal internally but may act as a co-receptor (22).

The expression of adiponectin receptors is negatively regulated by insulin through activation of phosphoinositide 3 kinase and inactivation of Foxo1 (40). Thus, the expression of AdipoR1/R2 is inversely correlated with plasma insulin concentrations in vivo under physiologic (ie, increase with fasting and decrease with feeding) and pathologic conditions (40). Reduced expression or down-regulation of adiponectin receptors has been reported in skeletal muscle and adipose tissue in leptin-deficient ob/ob (40) and db/db (41) mice, as well as in fa/fa Zucker rats (42), which suggests that leptin may also play a role in adiponectin receptor regulation. We recently reported that aging and prolonged exposure to high-fat feeding down-regulate adiponectin concentrations and up-regulate the expression of adiponectin receptors (43). In addition, adiponectin receptor expression is also regulated by peroxisome proliferator-activated receptor-α and peroxisome proliferator-activated receptor-γ, with increased expression in adipose tissue and cultured adipocytes but not in cultured myocytes (40, 44, 45).

ADIPONECTIN PHYSIOLOGY AND PATHOPHYSIOLOGY

Certain polymorphisms of the adiponectin gene promoter have been associated with lower serum adiponectin concentrations in persons with diabetes (46), but whether these polymorphisms are also associated with risk of malignancies remains to be studied. Dietary factors may also modulate plasma adiponectin concentrations (47). Adiponectin concentrations have been inversely associated with glycemic load in a dose-dependent manner (48). Higher intakes of fiber and magnesium have been associated with increased plasma adiponectin concentrations in diabetic men (48). Also, above and beyond any effect of specific food items, we recently showed that closer adherence to a Mediterranean-style dietary pattern is significantly associated with circulating adiponectin concentrations (49).

Women have higher adiponectin concentrations than do men independently of fat mass or distribution, most likely as the result of differences in circulating estrogens or androgens (3, 50). Testosterone administration suppresses serum total adiponectin concentrations in mice and in men (51, 52) and also limits adipocyte production of HMW adiponectin in vivo and in cultured adipocytes (52). These sex-specific differences in circulated adiponectin concentrations may reflect differences in end organ adiponectin sensitivity or adiponectin production rates, and their pathophysiologic significance remains to be determined.

Circulating concentrations of adiponectin are reduced in obesity and type 2 diabetes (53, 54) and in congenital lipodystrophic syndromes (55) and have a strong inverse association with parameters of central and overall obesity, independently of age, menopausal status, and estradiol concentrations (56, 57). Chronic caloric restriction leading to weight loss increases adiponectin concentrations (48, 58, 59); however, plasma adiponectin concentrations are more closely related to insulin sensitivity and fasting insulinemia than to adiposity (60), and low adiponectin concentrations at baseline (before and after adjustment for body fat) precede a decrease in insulin sensitivity (61). Cross-sectionally, adiponectin concentrations are associated with hormonal markers of insulin sensitivity (62).

In addition to the strong and consistent inverse association between adiponectin and insulin resistance (63, 64), adiponectin has also been linked to several inflammatory markers, such as C-reactive protein and fibrinogen (1, 65). Plasma adiponectin concentrations in humans have also been found to be positively correlated with HDL cholesterol and negatively correlated with triacylglycerols and apolipoprotein B-100 (65). Higher adiponectin concentrations are associated with a moderate decrease in risk of coronary artery disease in diabetic men (66) and with improved glycemic control and lipid concentrations and reduced inflammation in diabetic women (67).

ADIPONECTIN AND CANCER EPIDEMIOLOGY

Studies conducted by our research group found lower circulating adiponectin concentrations to be associated with an increased risk of breast cancer in postmenopausal women, independent of body mass index (BMI), leptin, and insulin-like
growth factor-I (IGF-I) concentrations (37, 68). Others have confirmed this association regardless of menopausal status (69, 70). We also conducted a large, prospective case-control study nested within the Nurses’ Health Study and Nurses’ Health Study II cohorts to examine the association between plasma adiponectin concentrations and breast cancer risk (62). Similar to our previous results in a retrospective study (68), the inverse association between adiponectin concentrations and breast cancer was statistically significant in postmenopausal women only. The lower estrogen concentrations in postmenopausal women may partially explain the lower adiponectin concentrations in these women. This finding suggests that adiponectin may play a role in breast cancer etiology, particularly in a low-estrogen environment. It remains unclear whether stage or grade of disease is associated with adiponectin concentrations; one study reported an inverse correlation (69), but another 2 studies did not confirm these results (62, 70).

Our research group has also shown that adiponectin is inversely associated with risk of endometrial cancer; in addition, women with high BMI and low plasma adiponectin have a risk of endometrial cancer that is 6.5-fold that in women with normal BMI and higher adiponectin concentrations (71). This relation is independent of variation in IGF-1, IGF-2, IGF binding protein-3, leptin, BMI, and other known risk factors of the disease in women under 65 y of age (72). Recent studies have confirmed these findings (73, 74). More recently, a large, case-control, prospective study nested within the European Prospective Investigation into Cancer and Nutrition (EPIC) Study confirmed the relation between lower pre-diagnostic plasma adiponectin concentrations and a higher risk of endometrial cancer in both pre- and postmenopausal women regardless of BMI status (obese versus nonobese) or other obesity-related risk factors, such as endogenous insulin concentrations, IGF binding proteins, or hormonal status (74).

Another large, prospective, nested case-control study conducted by our group found that plasma adiponectin concentrations were inversely associated with risk of colorectal cancer in men (75). Men with the highest concentrations had an ≈60% reduced risk for colorectal cancer compared with those with the lowest concentrations, even after adjustment for body size, waist circumference, and physical activity (75). This prospective study design provides the time sequence criterion for causality, although observational studies cannot prove causation beyond any doubt. In addition, we have found that colorectal tumors express adiponectin receptors, and that this expression is significantly higher in notinmorous colorectal tissue from colorectal cancer patients (C Mantzoros, unpublished data, 2007). The elevated expression of AdipoR1 and AdipoR2 further indicate a potential role of adiponectin in the pathogenesis of colorectal cancer.

A small case-control study (76) also reported that plasma adiponectin concentrations are significantly lower in subjects with prostate cancer than in patients with benign prostatic hyperplasia or in healthy control subjects. We replicated these results in a larger study (77), in which we found an ≈70% reduced risk for men with the highest relative to men with the lowest adiponectin concentrations. This association was independent of age, BMI, and other classic risk factors. In addition, our group (77) and others (76) have shown that plasma adiponectin concentrations are negatively correlated with histologic grade and disease stage. Although one prospective study in prostate cancer (78) did not find any association between adipokines (and adiponectin in particular) and prostate cancer, it is of note that the technology used to measure adiponectin concentrations was not standard; in addition, the small sample size could have prevented the results from reaching statistical significance.

Adiponectin may also play a role in gastric (79) and renal (80) cancer and in leukemia (73, 81). Plasma adiponectin concentrations have been found to be lower in patients with gastric cancer than in healthy control subjects and to be inversely correlated with tumor size, depth of invasion, and tumor stage (79). In a small, case-control, retrospective study of patients with histologically confirmed renal cell carcinoma and healthy control subjects matched by sex and age, we found that serum adiponectin concentrations were significantly and inversely associated with renal cell carcinoma after control for BMI; however, after adjustment for central obesity (waist-to-hip ratio), the association between adiponectin and renal cell carcinoma became not significant. This finding indicates that altered concentrations of adiponectin may mediate the effect of intraabdominal obesity (80). Finally, in a case-control study, we found that adiponectin concentrations were lower in patients with acute myeloblastic leukemia than in healthy control subjects (81), which agrees with the observation that adiponectin treatment suppresses the growth of myelomonocytic cell lines (82).

In summary, evidence from case-control studies indicates that circulating adiponectin concentrations in vivo are inversely associated with the risk of obesity-related malignancies, including breast (71, 72, 83), endometrial (71, 72, 83), and prostate (76, 78, 84) cancer, and may also play a role in gastric cancer (79) and leukemia (73, 81). In addition, prospective studies have detected an increased risk of postmenopausal breast (62), endometrial (74), and colorectal (75) cancer with low adiponectin concentrations (Table 1). Thus, both prospective observational and interventional studies are warranted to fully elucidate the mechanisms underlying the effects of adiponectin.

**POTENTIAL MECHANISMS UNDERLYING THE PROTECTIVE ROLE OF ADIPOnectin IN CARCINOGENESIS**

Accumulating evidence suggests that adiponectin is an important regulator of cell proliferation. Adiponectin may act either directly on cancer cells or indirectly by regulating whole-body insulin sensitivity.

**Antiproliferative effects**

Adiponectin has been shown to drastically suppress the growth of myelomonocytic leukemia cells in vitro (82). Moreover, adiponectin induces apoptosis in myelomonocytic progenitor cells (M1 leukemia lines) in a dose-dependent manner, likely by down-regulating antiapoptotic genes (82). Other recent studies report that adiponectin can suppress cell growth in the MDA-MB-231 (38, 85), MCF-7 (35, 86), and T47D (37, 38) breast cancer cell lines. Interestingly, only the HMW form of fAd (not LMW fAd or gAd) inhibited the proliferation of androgen-dependent (LNCaP-FGC) and androgen-independent (DU145 and PC-3) prostate cancer cell lines as well as hepatocellular carcinoma cells (HepG2) (34) at subphysiologic concentrations (1 μg/mL). In the same study, HMW adiponectin was also found to inhibit dihydrotestosterone- or IGF-1–stimulated cell growth and to enhance doxorubicin inhibition of prostate cancer cell
TABLE 1
Epidemiologic studies that show an inverse, independent association between adiponectin concentrations and risk of different types of cancers shown as odds ratios (ORs)

<table>
<thead>
<tr>
<th>Cancer and study</th>
<th>Type of study</th>
<th>No. of cases/controls and population</th>
<th>OR (95% CI) or significance</th>
<th>Additional results, analysis, and comments</th>
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<tbody>
<tr>
<td>Breast cancer</td>
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<tr>
<td>Mantzoros et al, 2004 (68)</td>
<td>Retrospective case-control</td>
<td>174/167 Greek</td>
<td>0.84 (0.71, 0.99) for 1-SD increase in adiponectin</td>
<td>Association found only in postmenopausal women.</td>
</tr>
<tr>
<td>Miyoshi et al, 2003 (69)</td>
<td>Retrospective case-control</td>
<td>102/100 Japanese</td>
<td>3.63 (1.61–8.19) for highest tertile vs lowest tertile of adiponectin</td>
<td>Association present in pre- and postmenopausal women. Lower adiponectin concentrations with more advanced stage disease.</td>
</tr>
<tr>
<td>Chen et al, 2005 (70)</td>
<td>Retrospective case-control</td>
<td>100/100 Taiwanese</td>
<td>P &lt; 0.009</td>
<td>Lower adiponectin concentrations in cases (pre- and postmenopausal women)</td>
</tr>
<tr>
<td>Korner et al, 2006 (37)</td>
<td>Retrospective case-control</td>
<td>74/76 Greek</td>
<td>0.35 (0.14–0.87) for highest vs lowest tertile of adiponectin</td>
<td>Lower adiponectin concentrations in cases; HMW adiponectin measurements produced similar results.</td>
</tr>
<tr>
<td>Tworoger et al, 2007 (62)</td>
<td>Prospective case-control</td>
<td>NHS and NHSII 1477/2196</td>
<td>0.89 (0.71–1.11) for all</td>
<td>The first prospective study of adiponectin in breast cancer; adiponectin was found to be inversely associated with postmenopausal breast cancer risk only.</td>
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<tr>
<td>Endometrial cancer</td>
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<tr>
<td>Dal Maso et al, 2004 (71)</td>
<td>Retrospective case-control</td>
<td>87/132 Italian</td>
<td>0.42 (0.19–0.94) for 1-SD increase in adiponectin</td>
<td>BMI and adiponectin showed multiplicative effects on endometrial carcinogenesis (OR = 6.45 for highest level of BMI and lowest of adiponectin).</td>
</tr>
<tr>
<td>Petridou et al, 2003 (72)</td>
<td>Retrospective case-control</td>
<td>84/84 Greek</td>
<td>0.44 (0.24–0.81) for 1-SD increase in adiponectin</td>
<td>Adjusted OR per quintile increase in adiponectin was 0.74 (0.56–0.97) for all.</td>
</tr>
<tr>
<td>Soliman et al, 2006 (83)</td>
<td>Retrospective case-control</td>
<td>117/238 American</td>
<td>10.5 (4.49–24.57) for lowest tertile of adiponectin vs controls</td>
<td>Confirms the previously published case-control studies from Europe. The association was also strong in nonobese women.</td>
</tr>
<tr>
<td>Cust et al, 2007 (74)</td>
<td>Prospective case-control</td>
<td>284/548 European</td>
<td>0.56 (0.36–0.86) for highest vs lowest quartile of adiponectin</td>
<td>First prospective study of adiponectin in endometrial cancer. The inverse association was independent of other obesity-related risk factors.</td>
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<tr>
<td>Prostate cancer</td>
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<tr>
<td>Freedland et al, 2005 (84)</td>
<td>Retrospective case-control</td>
<td>236 cases American</td>
<td>0.94 (0.87–1.01) for high-grade disease vs controls</td>
<td>Shows association between adiponectin and high-grade disease only in overweight and obese (80 advanced stage/160 organ-confined cases).</td>
</tr>
<tr>
<td>Goktas et al, 2005 (76)</td>
<td>Retrospective case-control</td>
<td>30/36 Turkish</td>
<td>P &lt; 0.001</td>
<td>Lower adiponectin concentrations in cases and negative association with histologic grade and disease stage.</td>
</tr>
<tr>
<td>Baillargeon et al, 2006 (78)</td>
<td>Prospective case-control</td>
<td>125/125 San Antonio Center for Biomarkers of Risk of Prostate Cancer</td>
<td>0.87 (0.46–1.65) for highest vs lowest tertile of adiponectin</td>
<td>Nonstatistically significant results observed; the method used is not the standard one because questions about sensitivity of the assay used remain.</td>
</tr>
<tr>
<td>Michalakis et al, 2007 (77)</td>
<td>Retrospective case-control</td>
<td>75/150 Greek</td>
<td>0.29 (0.10–0.89) for highest vs lowest quartile of adiponectin</td>
<td>Association was independent of age, BMI, smoking, alcohol, insulin, and testosterone.</td>
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<tr>
<td>Colon cancer</td>
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<tr>
<td>Wei et al, 2005 (75)</td>
<td>Prospective case-control</td>
<td>179/556 American Health Professionals Follow-up Study</td>
<td>0.48 (0.25–0.90) for highest vs lowest quintile of adiponectin</td>
<td>The first prospective study, on adiponectin in relation to colorectal malignancy in men.</td>
</tr>
<tr>
<td>Gastric cancer</td>
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<tr>
<td>Ishikawa et al, 2005 (79)</td>
<td>Retrospective case-control</td>
<td>75/52 Japanese</td>
<td>0.89 (0.84–0.95) for highest vs lowest tertile of adiponectin</td>
<td>The stage was inversely related to adiponectin concentrations in undifferentiated gastric cancer (n = 32).</td>
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(Continued)
growth (34), but the mechanisms underlying these effects remain unknown.

In contrast with findings in breast and prostate cancer cell lines, both full-length and globular adiponectin stimulated colonic (HT-29) epithelial cell proliferation (87). Also, study of the effects of adiponectin on the apoptosis of cancer cells in vitro, which may well differ from the in vivo condition, remains inconclusive. In some studies (35, 38, 85), apoptosis was increased by adiponectin treatment, but this was not observed in other studies (34, 86). Although experimental conditions can vary, it is of note that all these in vitro proliferation studies have limitations; one is the fact that these studies were performed in a serum-free environment, which may be sufficient to decrease cell proliferation or inhibit cell growth.

Only 2 studies to date have explored the physiologic relevance of the above data by examining the effects of in vivo adiponectin administration on tumor growth (38, 88). In vivo intratumoral administration of murine adiponectin to mice resulted in significant suppression of T241 fibrosarcoma tumor growth (60% reduction of tumor volumes and weights after 6 weeks of treatment (88). More recently, mammary tumorigenesis of MDA-MB-231 cells in female nude mice was substantially reduced by either supplementation with recombinant adiponectin or adenovirus-mediated overexpression of adiponectin at 7 or 14 d after initial tumor implantation (38). A reduction in lung metastasis was also observed in the adiponectin-treated group, but it was not possible to discriminate whether this decrease was caused by the direct suppressive effects of adiponectin on cell migration and invasion or was secondary to the reduced size of primary tumors in the adiponectin-treated group (38). These data clearly support a role of adiponectin in breast carcinogenesis.

Despite the mounting experimental data, the mechanisms underlying the antiproliferative effects of adiponectin are not fully understood. It has been hypothesized that the beneficial actions could be explained in part through activation of the AMPK pathway. AMPK activation suppresses cell proliferation through multiple mechanisms, including inhibition of enzymes implicated in the regulation of protein (mammalian target of rapamycin) and fatty acids and triacylglycerol synthesis (acyetyl-CoA carboxylase and fatty acid synthase). It also decreases the expression of the transcriptional regulator sterol-regulatory-element-binding-protein 1c (SREBP-1c), which inhibits de novo fatty acid synthesis. In addition, activated AMPK positively regulates 2 proteins that are important for the control of growth arrest and apoptosis: p21 and p53 (89).

Most of the available data support the observation that AMPK may constitute a general intracellular response to adiponectin, because it is activated in response to adiponectin treatment in myocytes and hepatocytes (29), adipocytes (90), pancreatic β-cells (91), cardiomyocytes (92, 93), and endothelial cells (94, 95). This has also been confirmed in MCF-7 breast cancer cells (35), and we found that adiponectin activates AMPK and one of its major downstream targets acetyl-CoA carboxylase in LNCaP and CWR22Rv1 prostate cell lines (C Mantzoros, unpublished data, 2007). Similarly to previous studies, the activation of the AMPK pathway was rapid and transient (the effect is maximum in the first 10 min and gone within 30–60 min).

In addition to AMPK activation in MCF-7 cells, longer treatment with adiponectin (over a period of 2 to 6 h) was also shown to decrease the mRNA expression of the growth regulatory gene c-myc and one of the important G1 regulatory cyclins, cyclin D1 (35). Adiponectin-mediated suppression of cyclin D1 expression and inhibition of cell-cycle progression was observed in MDA-MB-231 cells with prolonged treatment (24 h), possibly through modulation of the β-catenin–Wnt pathway.

The stabilization and nuclear translocation of β-catenin and overexpression of cyclin D1 have been observed in many types of human cancer (96). Glycogen synthase kinase-3β (GSK-3β) is one of the enzymes of the β-catenin degradation complex, which facilitates ubiquitination and proteolysis of β-catenin by phosphorylation at N-terminal sites (97). Akt can phosphorylate
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FIGURE 1. A summary of the factors that contribute to increased risk of obesity-associated malignancies, including decreased concentrations of adiponectin. Reduced release or impaired secretion of adiponectin can directly or indirectly through development of insulin resistance or by promoting inflammation (as well decreased sequestration of growth factors not depicted here) contribute toward a higher risk of tumor development. Insulin resistance is the product of decreased adiponectin as well as increased concentrations of other adipokines (eg, tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6)) in obesity. Compensatory hyperinsulinemia can in turn reduce liver synthesis and serum concentrations of insulin-like growth factor binding proteins (IGFBPs) and thus increase concentrations of bioavailable IGF-1 (free IGF-1). Chronic hyperinsulinemia also causes a decrease in the hepatic synthesis of sex hormone–binding globulin (SHBG), thus contributing to increased free sex steroid concentrations. In addition, in obese individuals there is an increase in the activity of enzymes aromatase and 17β-hydroxysteroid dehydrogenase (17βHSD) in adipose tissue, both of which lead to increased conversion of androgens to estrogens (aromatase activity) and increased conversion of “weak” or less biologically active sex hormones to more active hormones, ie, estradiol (E2) and testosterone (T). Altered concentrations of adiponectin, insulin, IGF-1 and sex hormones alter cellular proliferation and inhibit apoptosis. FFA, free fatty acid.

and inactivate GSK-3β, leading to stabilization and increased concentrations of β-catenin (96).

Although there was no direct evidence in this study of direct alteration of Akt phosphorylation status by adiponectin, chronic recombinant adiponectin treatment suppressed serum-induced phosphorylation of Akt and GSK-3β in MDA-MB-231 cells; subsequently, the intracellular accumulation and nuclear translocation of β-catenin and the expression of one of its transcriptional targets, cyclin D1, was decreased (38). However, these effects do not seem to be mediated through adiponectin receptors, because simultaneous down-regulation of both AdipoR1 and AdipoR2 had no effects on adiponectin-mediated inhibition of cell proliferation or β-catenin accumulation in MDA-MB-231 cells (38); action at the prereceptor level, ie, by sequestration of growth factors (see paragraph below) may be one possibility. In addition, this suppressive effect of adiponectin on β-catenin in MDA-MB-231 breast cells may be cell type specific, ie, adiponectin treatment did not alter β-catenin concentrations in T47D cells (38). These findings, however, support the hypothesis that adiponectin modulation of the GSK-3β/β-catenin signaling pathway might play a critical role in mediating the inhibitory effects of adiponectin on breast cancer (38). Nevertheless, the fact that adiponectin may modulate the GSK-3β/β-catenin pathway could be especially important in cancers that are PTEN deficient and subsequently have constitutive activation of the phosphoinositide 3 kinase–Akt pathway, which may contribute to Wnt-1–induced β-catenin stabilization (ie, advanced prostate cancer).

Finally, another potential mechanism by which adiponectin may exert antiproliferative, and thus anticarcinogenic, effects in vitro and in vivo could be by regulating the bioavailability of certain growth factors, as was recently and thoroughly reviewed elsewhere (98). In cultured smooth muscle cells, adiponectin in physiologic concentrations significantly reduces DNA synthesis, cell proliferation, and migration induced by several growth factors (99, 100). Another study also showed that adiponectin selectively binds not only platelet-derived growth factor-BB (PDGF-BB), but also heparin-binding epidermal growth factor–like growth factor (HB-EGF) and basic fibroblast growth factor. It also inhibits the interaction of these factors with their membrane receptors (100), which suggests that the antiproliferative effect of adiponectin is at least partly due to its selective sequestration of growth factors at a prereceptor level (100). The binding of these growth factors by adiponectin is specific and involves different oligomeric forms and binding sites of adiponectin for each growth factor; ie, HB-EGF binds all 3 oligomeric complexes of adiponectin (HMW, MMW, and LMW), PDGF-BB binds to the HMW and MMW forms but not the LMW form of adiponectin, and fibroblast growth factor binds preferably HMW. This affirms that oligomerization may play an essential role in determining the biological activities of adiponectin (100). Clearly, there is more to be studied to better understand the mechanisms underlying the antiproliferative effects of adiponectin. A summary of the possible mechanisms reviewed herein is presented in Figure 1.

Insulin-sensitizing and antiinflammatory effects

Adiponectin’s anticancer properties are also likely explained, at least in part, by its antiinflammatory and insulin-sensitizing effects (8). Intraperitoneal injection of ACRP30 lowers glucose concentrations in mice (101) and eliminates hyperglycemia in ob/ob, nonobese diabetic and streptozotocin-treated mice (27) by inhibiting both the expression of hepatic gluconeogenic enzymes and the rate of endogenous glucose production (27, 101). Although the mechanisms underlying the insulin-sensitizing effects of adiponectin are not completely understood, adiponectin-induced phosphorylation and activation of AMPK (27, 29), p38 mitogen-activated protein kinase (MAPK), and peroxisome proliferator-activated receptor-α effects (29, 30, 102) have been proposed to account for increased insulin sensitivity and fatty acid oxidation in response to adiponectin treatment. Moreover,
Adiponectin administration has been shown to increase whole-body insulin sensitivity through increased insulin-induced tyrosine phosphorylation of the insulin receptor in rodents (61). Thus, the insulin-sensitizing properties of adiponectin may modulate obesity-associated malignancies that have also been closely correlated with an insulin-resistant state (103).

Adiponectin also plays a role in inflammatory processes. It has been shown to inhibit the growth of macrophage precursors and also to suppress in vitro mature macrophage phagocytic activities and tumor necrosis factor-α production (82, 104). In addition, adiponectin reduces the induction of adhesion molecules, such as intercellular adhesion molecule-1 and circulating vascular cell adhesion molecule-1 (105, 106), inhibits interleukin (IL)-6 and IL-8 (6) production, and induces the antiinflammatory cytokines IL-10 and IL-1 receptor antagonist (5, 107). Inhibition of nuclear factor κB by adiponectin might explain some of these effects (6, 108). Whether these antiinflammatory effects of adiponectin play a role in carcinogenesis remains to be elucidated.

Regulation of angiogenesis

Tumor growth is angiogenesis-dependent (109), and suppression of angiogenesis has been shown to inhibit tumor growth (88, 110). Contradictory results have been reported (21) on the effect of adiponectin to alter neovascularization, possibly because of differences in the cell types used as well as differences in the microenvironments between in vivo versus in vitro studies, as recently reviewed elsewhere (98).

CONCLUDING REMARKS AND FUTURE DIRECTIONS

In summary, accumulating clinical and experimental evidence supports a role of low adiponectin concentrations in obesity-associated malignancies. Adiponectin’s ability to increase insulin sensitivity in conjunction with its antiproliferative properties associated malignancies. Adiponectin’s ability to increase insulin sensitivity through increased insulin-induced tyrosine phosphorylation of the insulin receptor in rodents (61). Thus, the insulin-sensitizing properties of adiponectin may modulate obesity-associated malignancies that have also been closely correlated with an insulin-resistant state (103).

Further investigations to address a potential role of adiponectin in cancer pathogenesis, as well as additional studies designed to fully elucidate the mechanisms underlying the effects of adiponectin, are warranted. These may include 1) studies of the expression and activation of adiponectin receptors and studies that fully describe adiponectin signaling in vitro; 2) in vivo animal studies that directly assess adiponectin’s anticarcinogenic action, ie, adiponectin-deficient mice (8) could be used to test the anti-tumor effects of adiponectin in addition to high-fat diet-induced obese mice, a model that most closely resembles human obesity; and 3) observational studies in humans designed to quantify the different forms of circulating adiponectin, including the development of reliable laboratory techniques (eg, enzyme-linked immunosorbent assays) for measuring total, HMW, and LMW adiponectin. Large prospective studies assessing the various forms of adiponectin as diagnostic and prognostic markers in several malignancies are clearly needed.

Therapeutic strategies to increase adiponectin concentrations, such as up-regulation of plasma concentrations, up-regulation of adiponectin receptor, or development of adiponectin receptors agonists, as well as administration of human recombinant adiponectin should be considered in the context of potentially enhancing our pharmacologic armamentarium for treating malignancies in the not so distant future.

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REFERENCES


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