The roles of Adiponectin in Insulin sensitivity, Modulates inflammatory responses, Regulation of energy metabolism and Several key signaling pathways as potential therapeutics on Cancer, and Metabolic Disorders (Part three)

By Dr. Zelalem Kiros Bitsue MD, PhD, Immunologist
United States of African Health Organization "US-AHO", International

Abstract

Adiponectin, the most abundant adipokine produced by the human adipose tissue, is linked to obesity, metabolic syndrome, insulin resistance, type 2 diabetes, coronary heart disease, inflammation, and several types of cancer.

Recent study demonistrated that adiponectin-based short peptide, ADP 355, mimicking adiponectin action, restricted proliferation in a dose-dependent manner in several adiponectin receptor-positive cancer cell lines, modulated several key adiponectin signaling pathways (AMPK, Akt, STAT3, ERK1/2), and suppressed the growth of orthotopic human breast cancer xenografts

Adiponectin, an abundant adipocyte-secreted factor with a wide-range of biological activities, improves insulin sensitivity in major insulin target tissues, modulates inflammatory responses, and plays a crucial role in the regulation of energy metabolism.

However, adiponectin as a promising therapeutic approach has not been thoroughly explored in the context of pharmacological intervention, and extensive efforts are being devoted to gain mechanistic understanding of adiponectin signaling and its regulation, and reveal therapeutic targets.

In this article, I discuss Adiponectin Pathophysiology, breast cancer, endometrial cancer, pancreatic cancer, liver cancer, renal cancer, and lung cancer

Key Word: Adiponectin, breast cancer, endometrial cancer, pancreatic cancer, liver cancer, renal cancer, and lung cancer

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1. Introduction

Adiponectin, alsoknownas Acrp30 (1) AdipoQ (2), GBP-28 (3), and apM1 (4), and independently identified by four groups using different approaches (1),(2),(4),(3), was originally cloned as an adipocyte-enriched protein highly induced upon 3T3-L1 adipocyte Differentiation (1). The human adiponectin gene encodes a 244-amino acid protein of 30 kDa (247 amino acids for the mouse ortholog), whose primary structure includes a signal peptide, a variable region, a collagen-like domain, and a globular domain (5). The full-length adiponectin protein shares structural similarity with complement factor C1q, tumor necrosis factor-a, and collagens VIII and X. Adipocytes synthesize and secrete multiple forms of adiponectin: low-molecular weight (LMW) trimers (the most basic form), medium-molecular weight (MMW) hexamers, and high-molecular weight (HMW) oligomers of 4–6 trimers (6),(7),(8),(9). A proteolytic adiponectin fragment, known as globular adiponectin (gAd), also occurs in human plasma (10),(8). During the past 20 years, a large body of work established important roles of adiponectin in metabolic regulation and inflammatory/ anti-inflammatory processes. Notably, each adiponectin formappears to have distinct target tissue specificity andmodulates unique biological processes (11),(12). Adiponectin is an insulin sensitizer (13),(14), (15),(16), and reduced adiponectin levels (17),(18),(19), (20),(21), and/or ratios of HMW/LMW (7),(22),(23), are linked to insulin resistance and metabolic syndrome. When supplied exogenously (13),(14),(15),(24), or overexpressed as a transgene (25),(26), (27),(28), adiponectin suffices topromote insulin action andameliorates insulinresistance. While adiponectin exerts pro-inflammatory activities in some contexts (29),(30),(31), it can suppress inflammatory responses (32),(33),(34),(35),(36). Adiponectin enhances the secretion of the anti-inflammatory cytokine IL-10 by cultured human monocyte-derived macrophages and stromal vascular fraction cells prepared from human adipose tissue (37). Intriguingly, adiponectin promotes macrophage polarization toward the anti-inflammatory M2 phenotype (33). On the other hand,macrophage polarization phenotype regulates the expression of adiponectin receptors (AdipoRs) inways that classical activation(M1) ofmacrophages suppresses the expression of AdipoRs, and alternative activation (M2) preserves it (38). Remarkably, adiponectin elicits antagonistic responses in the two macrophage-polarization phenotypes. In M1 macrophages, adiponectin induced the expression of pro-inflammatory cytokines including TNF-a, IL-6, and IL-12, as well as AdipoRs. In M2 macrophages, adiponectin triggered the expression of the anti-inflammatory cytokine IL-10 without affecting AdipoR levels (38). Recent studies have also begun to reveal mechanisms of adiponectin action(31)s and the cellular circuitry downstream of the adiponectin receptors. While these advances offer novel opportunities for diabetes treatment, multiple considerations limit the development of adiponectin as a pharmacological agent in a clinical setting. First, under physiological conditions, the circulating plasma concentrations of adiponectin in humans range from 2 to 20 mg/ml (39), more than 1000-fold higher than other hormonal regulators such as insulin. This abundance would make its development for clinical use unlikely. Second,

adiponectin circulates in multiple forms of oligomers, each with its unique cellular target(s) and signaling pathways (12). Currently, selective enrichment of a particular multimeric form of adiponectin in vivo remains a challenge. Lastly, various forms of adiponectin have relatively short half-life: 32 min for trimers and 83 min for HMW and MMW proteins (40). Conceptually, these characteristics necessitate multiple high doses of adiponectin if used as a therapeutic agent, a measure with potentially high clinical risks. Thus, understanding the mechanistic details of adiponectin signal transduction could reveal new opportunities for clinical treatment, tailored to its underlying biology and pathophysiology. Here, we consider five aspects of adiponectin action and signal transduction with the potential for drug development: (i) tissue-specific functions of adiponectin; (ii) adiponectin receptors AdipoR1, AdipoR2, and T-cadherin; (iii) adiponectin receptor signaling; (iv) adiponectin signaling pathway cross talks with other pathways involved in metabolic regulation; and (v) adipo Rindependent pathways. Our goal is not to comprehensively review these areas, but rather, to identify recent advancements and updates in adiponectin biology and explore the therapeutic potential of targeting adiponectin signal transduction.

2. Adiponectin Pathophysiology

A. Adiponectin to Cancer

Our group and others have recently shown that hypoadiponectinemia *in vivo* is inversely linked to the risk of obesity- associated malignancies and insulin resistance (41),(42), that is, endometrial cancer (43),(44), postmenopausal breast cancer (41),(45),(46). colon cancer (47), renal cancer (48), leukemia (49), and other hematological malignancies (50),(51),(52),(53),(54). Furthermore, low adiponectin concentrations have been reported in gastric (55), and prostate cancer (56). Table 1 portrays recent comparative epidemiological studies that depict associations between serum adiponectin levels and risk of different types of cancer. Table 2 depicts epidemiological studies showing association between genetic variation (SNPs) in adiponectin (*ADIPOQ*) and adiponectin receptors (*ADIPOR1/R2*) and risk of different types of cancer.

B. Adiponectin and breast cancer

Adult weight gain and excess adiposity are positively associated with breast cancer in postmenopausal women and inversely associated in premenopausal women (57),(58). Case-control studies conducted by our group linked lower total or HMW adiponectin levels to an increased risk for postmenopausal breast cancer independently of classical risk factors including leptin and the IGF-I system (41),(45),(46). A larger, prospective study in the context of the Nurses' Health Study (NHS) later confirmed these observations (59), which were independently confirmed by Miyoshi *et al.(60),* (232) in both premenopausal and postmenopausal women. Other studies conducted in Chinese, Taiwanese, and Malaysian women found significantly low serum adiponectin levels in breast cancer patients compared with their matched controls (61),(62),(63), especially in postmenopausal women (46),(61). Moreover, a very recent study by Macis *et al. (64),* in premenopausal women identified lower plasma circulating adiponectin levels as a risk biomarker for progression from intraepithelial neoplasia to invasive cancer independently of age, BMI, and treatment group (64),(65). Because adipose tissue cells represent the predominant breast stromal element, adiponectin exerts a major paracrine influence in mammary epithelium. Adiponectin may play a role in breast

cancer etiopathogenesis, particularly in the lowestrogen environment observed in postmenopausal women. In a study by our group, we have also shown that AdipoR1/R2 were expressed in breast cancer cell lines and tissue samples and that adiponectin may act not only via altering the hormonal milieu but directly through inhibition of breast cancer cell proliferation *in vitro* (41). Jeong *et al.* *(66),* found also that high adiponectin and AdipoR expression may be associated with breast cancer invasiveness. Nevertheless, one retrospective and one very recent prospective study failed to detect lower circulating adiponectin levels in breast cancer patients compared with their controls (67),(68). Specifically, a case-control study by Kang *et al.* (67), evaluated 41 newly diagnosed breast cancer female patients compared with 43 age- and BMImatched controls and found no significant difference in adiponectin in either the pre- or postmenopausal group. The limitations of this study included its small sample size and the fact that risk factors for breast cancer were not controlled for. In a nested case-control study of 234 postmenopausal women and 234 controls within a cohort of U.S. women with prospectively collected serum samples, breast cancer risk was not associated with circulating adiponectin levels independently from other known risk factors (68). According to this study, the lack of association may be attributed to measurement errors of the laboratory assays. Karaduman *et al.*(69), measured adiponectin lev-els specifically in breast tissue samples of 27 breast cancer patients, which presented significantly increased adiponectin levels, compared with tissues of 33 controls with fibroadenoma. However, this group's findings of high adiponectin levels as a risk factor for breast cancer are in contrast with most other studies reported to date and could be due to measuring adiponectin levels in a very small group of tissue samples instead of serum and to not controlling for known confounding factors. Interestingly, a very recent study by the same group reported that serum adiponectin levels in 53 patients with breast cancer were significantly inversely correlated with tumor tissue adiponectin (70), pointing out that when tumor tissue adiponectin was increased, serum adiponectin levels were decreased. These data need to be replicated, and their implications remain to be elucidated. Additionally, some but not all studies have suggested that breast tumors arising in women with hypoadiponectinemia may present a more aggressive phenotype [large size of tumor, higher histological grade, and estrogen receptor (ER) negativity] (60),(60),(62). It is unclear why hypoadiponectinemia is observed predominantly in ER /progesterone receptor (PR)-negative cancer. Probably, the effects of hypoadiponectinemia could be the deregulation of circulating sex steroids. Only five studies to date have addressed this issue. Two investigations found a significant association with receptor-negative breast cancer (60),(71), another with receptor-positive breast cancer (72), whereas two studies found no significant associations in regard to hormonal receptor status (59),(73). The interrelationship of estrogen and progesterone signaling pathway with insulin and adipose tissue hormones could be responsible for adiponectin secretion and action that in turn affects sex steroid levels and action in a true endocrine loop manner (74),(75). Low adiponectin concentrations are associated with lymph node metastases (61),(67), and increased breast cancer mortality in breast cancer survivors after adjustment for covariates (73). In a very recent study by Oh *et al.* (71), serum adiponectin levels in ER/PR-negative breast cancer presented an inverse association with the risk of recurrence regardless of other factors, including obesity and insulin resistance. Finally, in a large retrospective case-control study focusing on adiponectin genetic variants (*ADIPOQ*) and adiponectin receptor genes (*ADIPOR1*) and breast cancer risk, our group found that two *ADIPOQ*SNP, rs2241766 and rs1501299, related with circulating levels of adiponectin, and one *ADIPOR1* SNP (rs7539542) was also associated with breast cancer risk (76). Based on the known function of rs2241766 and rs1501299, individuals with intermediate and low adiponectin

signaling presented a greater breast cancer risk than high adiponectin signalers (76). However, two other American studies (one prospective study in postmenopausal women and one population-based case-control study among Whites and African-American women) showed no association between polymorphisms in *ADIPOQ*, *ADIPOR1* (including rs7539542), and *ADIPOR2* SNP and breast cancer risk (77),(78). The discrepancy of results may be attributed to the different panels of SNP, the different menopausal status and race of women, and the different pathological subtypes of breast cancer examined in these studies.

C. Adiponectin and endometrial cancer

Excess BMI and adiposity are associated with an increased risk of developing endometrial cancer (57), especially in premenopausal women (79), contrary to that of breast cancer risk. Our group has shown that lower adiponectin levels were associated with a higher risk of endometrial cancer, particularly in women younger than 65 yr, independently from BMI, leptin, the IGF system, and other known risk factors (43). This is in accordance with an *in vitro* study by our group reporting that adiponectin suppressed endometrial cancer cell proliferation acting through AdipoR increasing the adaptor molecule LKB1, responsible for the adiponectin-mediated activation of AMPK/S6 axis (80). It is worth noting that adiponectin receptors R1 and R2 are highly expressed in the endometrium during the midluteal period of the menstrual cycle (81). We have also found that AdipoR1 is higher than AdipoR2 in human endometrial cancer tissue, but the expression of AdipoR is similar to that from nonneoplastic tissues (80). Additionally, a combination of obesity and lower adiponectin constitutes a greater risk for endometrial cancer occurrence (43),(44),(60). Very recent retrospective case-control studies have confirmed the above findings (82),(83),(84), in both pre- and postmenopausal women. These findings were later confirmed by a larger, prospective, nested case-control study within the European Prospective Investigation into Cancer and Nutrition (EPIC) study showing that lower prediagnostic plasma adiponectin levels predispose to an elevated risk of endometrial cancer regardless of BMI status, measures of central obesity, and other obesity-related biological risk factors such as circulating levels of C-peptide (a marker of pancreatic insulin production), endogenous sex steroid hormones, and IGF binding protein 1 (IGFBP-1) and IGFBP-2, particularly among obese and peri-/postmenopausal Women (85). However, a second prospective study from the NHS showed that prediagnostic adiponectin was not predictive of endometrial cancer risk, controlling for endometrial cancer risk factors such as BMI, par-ity, age at last birth, and diabetes (86). This discrepancy of results, especially between the two large prospective studies, might be attributed to the different interval of time from blood draw to endometrial cancer diagnosis [shorter in the study by Cust *et al.*(85), to a higher proportion of premenopausal women in the study by Soliman *et al.* (86), and to the smaller sample size of cases in the NHS (146 cases and 377 controls) compared with the EPIC study (284 cases and 548 controls). Further studies are needed to define the association between adiponectin and endometrial cancer and to determine the duration of insulin resistance that must be present to increase the risk of endometrial cancer among women. Finally, in a large Chinese retrospective case-control study focusing on adiponectin genetic variants (*ADIPOQ*) and adiponectin receptor genes and endometrial cancer risk, Chen *et al.*(87), found that three *ADIPOQ* SNP were associated with reduced endometrial cancer risk.

D. Adiponectin and pancreatic cancer

Obesity, diabetes mellitus type 2, and insulin resistance, particularly in men, are associated with an increased risk for PaC (88). Evidence for the association between PaC and adiponectin levels is conflicting and depends mainly on the study design (*i.e.*, prospective *vs.* retrospective). Serum adiponectin in PaC patients has been reported to be elevated in retrospective studies (89),(90), (91), decreased in a prospective study on male Finnish smokers (92), and in the EPIC prospective study among never smokers (93), and unchanged in the EPIC prospective study among current smokers (93), and in a study examining adiponectin amid patients suffering from different pancreatic pathologies (94). Specifically, our group investigated Greek subjects with PaC and hospital controls and found that hyperadiponectinemia was associated with PaC risk adjusting for age, gender, BMI, smoking status, alcohol consumption, history of diabetes, family history of gastroin-testinal cancer or PaC, and leptin concentrations. In our data, further stratification by smoking status revealed that among never-smokers, the strength of the association between hyperadiponectinemia and PaC was more pronounced than among smokers [for never-smokers, odds ratio (OR), 1.154; 95% confidence interval (CI), 1.016– 1.31; P = 0.027; and for current smokers, OR, 1.077; 95% CI, 1.002–1.158; P _ 0.045). Hyperadiponectinemia observed in case-control studies could be compensating for insulin resistance and/or inflammation and weight loss due to cancer-associated cachexia, a complex metabolic state characterized by loss of adipose and muscle tissue (89), that develops after cancer develops. Indeed, higher levels of adiponectin are seen in cases of anorexia nervosa and prolonged voluntary weight loss (57). An alternative, probably less likely explanation for the association between elevated adiponectin levels and PaC could be adiponectin resistance produced by a down-regulation of adiponectin receptors or signaling pathways downstream of the receptors leading to subsequent counter-regulatory increased adiponectin secretion. However, we have reported that adiponectin receptors were present in PaC and that both adiponectin receptors were strongly expressed in the vast majority of studied subjects (89). In disagreement with the previous study, a Finnish prospective nested case-control study by Stolzenberg-Solomon *et al.* (92), examining the association of prediagnostic adiponectin concentration and risk for PaC found that higher adiponectin levels were inversely related to PaC risk specifically in male smokers. Despite the prospective design and the large number of incident PaC cases, this study population represents a homogenous group of male smokers and cannot be generalized to nonsmokers and females. Finally, in a study byChang*et al.* (90), serum adiponectin was able to differentiate between states of chronic pancreatitis and PaC, suggesting that this hormone may be used as a more specific tumor marker for PaC compared with the usual serum tumor markerCA19-9. Further prospective studies are needed to clarify the role of adiponectin in PaC development, specifically taking into account the smoking status, insulin resistance, and the time of adiponectin measurement in relation to diagnosis. It is possible that lower adiponectin levels predispose to PaC, but it is also possible that adiponectin levels increase when the disease becomes overt in a compensatory manner.

E. Adiponectin and liver cancer

Evidence suggests an association between adiponectin and liver tumorigenesis (95). To date, very few studies have explored the link between serum adiponectin and hepatocellular carcinoma (HCC) risk. In a Japanese prospective nested case-control study, individuals with a higher percentage of circulating LMW adiponectin multimers tended to have a reduced liver cancer risk after controlling for age, gender, area, BMI, smoking, alcohol, coffee consumption, diabetes history, and hepatitis C virus-antibody positivity (95). This is in line with the finding that

adiponectin has an antioncogenic potential in HCC cell lines HepG2 and Huh7, especially by inhibiting the oncogenic actions of leptin (96). Obesity and metabolic syndrome are recognized risk factors for hepatic steatosis (97), severe fibrosis (98), andHCCin patients with chronic hepatitisC(CHC) (99),(100). In a large-scale retrospective cohort study, Arano *et Al (101).* investigated the association of serum adiponectin levels and the risk ofHCCin patients withCHCand found that higher adiponectin levels were an independent risk factor for HCC, particularly in female subjects, suggesting that adiponectin may possess oncogenic functions after accumulation in the fibrotic liver. Another possible explanation is the adiponectin resistance phenomenon caused by down-regulation of adiponectin receptors; however, further studies are needed to elucidate this mechanism. Moreover, in the aforementioned study, the middle and low molecular weight (MLMW) adiponectin isoform was an independent risk factor for HCC. In contrast to these results, Nkontchou *et al. (102),* reported that serum adiponectin was not associated with HCC occurrence in a cohort study of 248 Japanese patients with compensated hepatitis C cirrhosis. Sumie *et al. (103),* reported similar serum total and HMW adiponectin between 97 Japanese patients with CHC who developed HCC and 97 controls with only CHC. These discrepancies may be attributed to the different liver pathologies (liver cirrhosis *vs.* CHC) examined in relation to HCC occurrence in the previous studies. In the study by Sumie *et al. (103),* serum total and HMW adiponectin were predictors of liver fibrosis, and low total andHMWadiponectin levels were independent risk factors for worse HCC histological grades (103). Moreover, microarray analysis of tissue adiponectin expression levels in HCC patients revealed that adiponectin expression was inversely correlated with tumor size, supporting the hypothesis that adiponectin may inhibit proliferation and dedifferentiation (104). Finally, fasting hyperinsulinemia but not serum adiponectin was associated with a poorer prognosis of early stage HCC in a cohort of 140 Japanese patients with incident HCC (105).

F. Adiponectin and renal cancer

Our group showed that lower levels of adiponectin were positively associated with renal cell carcinoma risk controlling for BMI; however, after adjustment for central obesity [waist-to-hip ratio (WHR)], the association be-came not statistically significant. This finding suggests that altered concentrations of adiponectin may mediate the effect of visceral obesity (48),(106). Furthermore, lower plasma adiponectin levels were associated with larger tumor size and metastasis in clear-cell renal carcinoma (107). Both total and HMW adiponectin were decreased in patients with metastatic renal cancer compared with those with localized disease (108), suggesting that adiponectin may be a possible biomarker of renal cancer progression. Nonetheless, the authors speculated that antihypertensive and/or antilipidemic medications taken by the study group may be a confounding factor for these results. Both adiponectin receptors, particularly AdipoR1, are expressed in normal renal tissue as well as in renal cancer cells, whereas adiponectin receptors (especially AdipoR2 in metastatic tumors) may be down-regulated, reducing the potential protective effect of adiponectin on tumor cells (107).

G. Adiponectin and lung cancer

Previous studies have evaluated the association between adiponectin and obesity-associated cancers, and little or no focus has been given to non-obesity-associated cancers, such as lung cancer. A case-control study by our group (109), found that serum adiponectin was not significantly different in patients with lung cancer compared with controls, but it was

significantly lower in patients with advanced disease stage, suggesting that adiponectin could be a potential marker for lung cancer progression. When examining archival lung specimens, we found that both adiponectin receptors were expressed only in cancerous lung tissue, whereas AdipoR2 was mainly expressed in the non-small-cell lung carcinoma (NSCLC) tissues and in the advanced disease stage tissues (109). In a subsequent study, Petridou *et al. (110),* found that serum adiponectin was not a major predictor of lung cancer risk, with insulin resistance representing a meaningful risk factor for lung cancer taking into account anthropometric and lifestyle variables as well as metabolic parameters. Another study has reported that serum adiponectin presented no significant differences in 101 advanced NSCLC patients compared with 51 healthy controls and could not be used as a predictive parameter for overall survival (111). Finally, in a Chinese retrospective case-control study focusing on adiponectin genetic variants (*ADIPOQ*) and NSCLC risk, Cui *et al. (112),* found that an *ADIPOQ* SNP (rs2241766) was associated with susceptibility to NSCLC, adjusting for age, gender, BMI, and smoking status.

3. Conclusion

Adiponectin, the most abundant adipokine produced by the human adipose tissue, is linked to obesity, metabolic syndrome, insulin resistance, type 2 diabetes, coronary heart disease, inflammation, and several types of cancer. Furthermore, similar to many new assays, international standardization of levels and assay procedures is also needed in the future before full commercialization of adiponectin as a potential diagnostic for obesity-related malignancies. Because it is extremely difficult to synthesize adiponectin and to convert its full-size protein into a viable drug to be used in humans, research efforts should be directed toward identifying ways to increase endogenous circulating adiponectin levels, to possibly moderate the obesitycancer link. Interestingly, a new adiponectin-based short peptide, ADP 355, mimicking adiponectin action, restricted proliferation in a dose-dependent manner in several adiponectin receptor-positive cancer cell lines, modulated several key adiponectin signaling pathways (AMPK, Akt, STAT3, ERK1/2), and suppressed the growth of orthotopic human breast cancer xenografts AdipoRon improves metabolic parameters and prolongs life span in db/db mice, a genetic mouse model for diabetes. Thus, small molecules that enhance adiponectin signaling may be viable options for the treatment of obesity-linked metabolic diseases including type 2 diabetes. Certain metabolic diseases, such as type 1 diabetes and IR antibody-induced type B insulin resistance, exhibit high plasma concentrations of adiponectin.

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