Adiponectin in insulin resistance: lessons from translational research

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ABSTRACT
Adiponectin is an adipose tissue–secreted endogenous insulin sensitizer, which plays a key role as a mediator of peroxisome proliferator-activated receptor γ action. Adiponectin alters glucose metabolism and insulin sensitivity, exhibits antiinflammatory and antiatherogenic properties, and has been linked to several malignancies. Circulating concentrations of adiponectin are determined primarily by genetic factors, nutrition, exercise, and abdominal adiposity. Adiponectin concentrations are lower in subjects with obesity, metabolic syndrome, and cardiovascular disease. Adiponectin knockout mice manifest glucose intolerance, insulin resistance, and hyperlipidemia and tend to develop malignancies especially when on high-fat diets. Animal studies have also shown beneficial effects of adiponectin in rodents in vivo. Circulating concentrations of adiponectin are lower in patients with diabetes, cardiovascular disease, and several malignancies. Studies to date provide promising results for the diagnostic and therapeutic role of adiponectin in obesity, insulin resistance, diabetes, cardiovascular disease, and obesity-associated malignancies.

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IDENTIFICATION AND MOLECULAR STRUCTURE
Adiponectin [also known as Acrp30 (adipocyte complement-related protein of 30 kDa) or AdipoQ] is a 244–amino acid protein secreted mainly by the adipose tissue. It was identified almost simultaneously by 4 different groups in the mid-1990s as an adipocyte-secreted hormone but remained in obscurity until the early 2000s. Scherer et al (1) were the first to report isolating adiponectin cDNA in mice by a differential display method in adipocytes, and their data were soon thereafter confirmed by Hu et al (2). Human adiponectin cDNA was also independently identified from adipose tissue by Maeda et al (3), and human adiponectin was finally purified from plasma by Nakano et al (4) as a gelatin-binding protein. The adiponectin gene is located on chromosome 3q26, a region associated with susceptibility to developing metabolic syndrome and type 2 diabetes mellitus (5).

Adiponectin circulates in multimers, ie, as full-length or high-molecular-weight (HMW), medium-molecular-weight (or hexamer), and low-molecular-weight (or trimer) adiponectin complexes. Additionally, full-length adiponectin may be cleaved to form a smaller, globular fragment, which has been proposed to have greater potency than full-length adiponectin (1). Adiponectin contains an N-terminal collagen-like hypervariable region at the NH₂ terminal and a C-terminal globular domain, which is similar in structure to tumor necrosis factor-α, another adipose tissue–secreted adipokine with an action opposite that of adiponectin (5). Adiponectin primarily circulates in human plasma as a homomultimer or full-length structure (fAd or Acrp30). Posttranslational modifications are critical determinants of activity, although consensus on the biological activity of the specific circulating forms of adiponectin is lacking. The HMW isoform was proposed to have a stronger association with insulin resistance, metabolic syndrome, and cardiovascular disease as the biologically more active form of the hormone (7). We have shown, however, that the additional predictive value provided by HMW adiponectin in humans is minimal (6, 7).

REGULATION OF ADIPONECTIN EXPRESSION
Adiponectin is synthesized primarily in white adipose tissue and, at lower concentrations, in brown adipose tissue (8). Much lower concentrations of expression have been reported in skeletal muscle, liver, colon, cardiac tissue, salivary glands, and placenta. Adiponectin is even detected in cerebrospinal fluid and breast milk at much lower concentrations (9). Normal plasma adiponectin concentrations range between 5 and 30 μg/mL (depending on the assay used), are 1000 time higher than leptin concentrations, and are inversely proportional to those of abdominal adiposity (9), insulin resistance, and type 2 diabetes. Adiponectin has also been shown to have distinct effects on lipid metabolism as well as antiinflammatory and antiatherogenic effects (10). In addition to its peripheral actions, adiponectin may act centrally to modulate food intake and energy expenditure (11). Women have higher adiponectin concentrations than do men (a measure that is independent of fat mass or distribution), which is possibly linked to differences in estrogen or androgen concentrations (12). We have reported that in growing mice adiponectin initially increases in proportion to accumulating adipose tissue until the age of ~8–10 wk and then starts decreasing. Environmental factors act as modulators of adiponectin (13), as shown by a cross-sectional evaluation of diabetic women from the Nurses’ Health Study...
Health Study that has linked a Mediterranean-type diet and its components, primarily whole grains, moderate alcohol consumption, and nuts, to higher adiponectin concentrations (14). A recent prospective cohort study reports that coffee consumption is associated with higher plasma adiponectin concentrations (15). In vitro and in vivo studies in mice and humans have shown that adiponectin expression and secretion is up-regulated by thiazolidinediones (16–18) and/or selective peroxisome proliferator-activated receptor γ (PPARγ) modulators, predominantly the HMW form. Although head-to-head comparisons have not been performed, it appears that the selective PPARγ modulator INT131 is a relatively more potent enhancer of adiponectin secretion (19).

**ADIPONECTIN RECEPTORS**

Two different receptor isoforms, AdipoR1 and AdipoR2, have been described to date (20). Both are 7-transmembrane proteins, and in contrast to the G protein–coupled receptor family, these receptors have internal N-terminal and external C-terminal regions (20). AdipoR1 has a high affinity for globular adiponectin and a low affinity for full-length adiponectin and is abundantly expressed in skeletal muscle and endothelial cells among other tissues. AdipoR2 has intermediate affinity for both forms of adiponectin and is predominantly expressed in the liver (21, 22). Although both receptors are present in almost every tissue, including pancreatic β cells and malignant cells, one or the other receptor usually predominates. Interestingly, HMW adiponectin has also been proposed to be a ligand for T-cadherin, but this remains to be fully elucidated.

Studies in mice link aging and high-fat feeding to increased receptor expression in muscle and liver (P < 0.001) (23). We have shown that both leptin and melanocortin agonists alter AdipoR1/R2 expression in mice (24). Low adiponectin concentrations increase the risk of developing insulin resistance and possibly diabetes (25). Yamauchi et al (26) observed in a lipoatrophy mouse model that replenishing physiologic doses of adiponectin reverses insulin resistance. Adiponectin knockout mice show increased platelet aggregation and thrombus formation, apoptosis, and tumor necrosis factor-α concentrations (27, 28). Adiponectin receptors are expressed in both fat and muscle tissues in humans (27). We have also shown that both receptors are expressed in subcutaneous and visceral adipose tissues and at significantly lower concentrations (P < 0.001) than in skeletal muscle. AdipoR1/R2 in muscle is inversely associated with circulating adiponectin concentrations whereas AdipoR2 in subcutaneous fat is positively associated with circulating adiponectin concentrations (29, 30). Receptor expression in both fat and muscle is further increased in insulin-resistant states accompanied by hypoadiponectinemia. Physical activity up-regulates adiponectin receptors (29), which suggests that the adiponectin hormone system may mediate exercise-associated improvements in insulin resistance (29, 30). Interestingly, PPARγ agonists, used as insulin sensitizers in the treatment of type 2 diabetes, stimulate adiponectin production and secretion. More specifically, these drugs (rosiglitazone, pioglitazone, and ciglitazone as well as the selective PPARγ model INT131) increase the HMW/total adiponectin concentrations (19), but further clinical studies are needed to investigate hypoadiponectinemia in hyperinsulinemic states to determine the potential therapeutic effects of this hormone.

**SIGNALING**

Adiponectin binding to its receptors activates several intracellular signaling pathways, mainly AMP-activated protein kinase (AMPK) but also mTOR, nuclear transcription factor-κB (NF-κB), STAT3, and JNK. AMPK phosphorylation promotes glucose utilization that results in increased fatty acid oxidation, increased glucose uptake in the muscle, and reduced glucoseogenesis in the liver. AMPK activation also regulates several downstream targets, which include enzymes (involved in regulating the synthesis of protein, fatty acids, and triglycerides such as acetyl-CoA carboxylase and fatty acid synthase) as well as transcription factors and other regulatory proteins. AMPK is an upstream regulator of mTOR and is linked with several cancers (31) by directly inhibiting this pathway that results in suppression of cell proliferation (32). The JNK- and STAT3-signaling pathways are also proposed as mediators of adiponectin’s effects on the metabolic syndrome and cancer (33).

**OBESITY, METABOLIC SYNDROME, DIABETES, AND CARDIOVASCULAR DISEASE**

Adiponectin concentrations are low in obese patients and markedly increase after prolonged caloric restriction, such as in dieting and anorexia nervosa (34), and are significantly lower (P < 0.001) in obese subjects when compared with nonobese males and females (35). Adiponectin is more closely associated with visceral fat than with subcutaneous fat (12) and is lower in type 2 diabetes, cardiovascular disease, hypertension, and metabolic syndrome (24, 35, 36), conditions that are often associated with insulin resistance. A recent meta-analysis of prospective studies with a total of 14,598 subjects and 2623 cases of type 2 diabetes indicated that higher adiponectin concentrations were associated with a lower risk of type 2 diabetes. The estimated absolute risk difference (cases/1000 person-years)/1-log μg/mL increment in adiponectin concentrations was 3.9 for elderly Americans and 30.8 for Americans with impaired glucose tolerance (36). Furthermore, adiponectin is positively correlated with HDL cholesterol and negatively associated with serum triglycerides and apolipoprotein B-100 (37). Adiponectin shows antiinflammatory effects by enhancing nitric oxide production and activating endothelial nitric oxide synthase (38) and may act as a modulator of vascular remodeling by suppressing smooth muscle cell migration (39), which possibly plays a role in the regulation of atherosclerosis.

**ADIPONECTIN AND CANCERS**

We have proposed that adiponectin is a link between obesity and obesity-related malignancies mainly on the basis of our original observations that adiponectin concentrations are lower in patients with these types of cancers. Case-control studies conducted by our group linked lower adiponectin concentrations to an increased risk of breast cancer (40) and these observations were later independently confirmed (42, 43). Similarly, the risk of colorectal cancer has been inversely associated with lower adiponectin in a prospective study in the context of the Health Professionals Follow-Up Study (41). Case-control studies showed that lower adiponectin concentrations are associated with a higher risk of endometrial cancer in both pre- and postmenopausal women (42, 43), and these findings were later confirmed by a larger case-
control study nested within the European Prospective Investigation into Cancer and Nutrition Study (44). In addition, several groups have reported similar inverse associations with prostate cancer (45), myelodysplastic syndromes, a preleukemic condition linked with obesity (46), as well as gastric (47) and renal cancers. Lower concentrations of adiponectin were positively associated with renal cell carcinoma and tumor aggression (48) and were shown to be even lower in patients with metastasis when compared with those with localized disease (49). In contrast, a hospital-based case-control study showed that adiponectin concentrations are positively associated with pancreatic cancer, and a substudy of tissue samples showed increased expression of adiponectin receptors (50); however, further studies are needed to determine whether this is a compensatory mechanism for high adiponectin concentrations observed during cancer progression. Several single-nucleotide polymorphisms within the 5′ flanking region of the ADIPOQ gene are associated with the risk of breast and colorectal cancer (51). Adiponectin’s direct effects are exerted by receptor-mediated stimulation of signaling pathways and indirectly by moderating insulin sensitivity at the level of target tissue. Adiponectin acts through receptors R1/R2 to stimulate signaling pathways, mainly AMPK, but also PPARα, MAPK, and NF-κB (52). AMPK activation regulates cell proliferation, decreases expression of transcriptional regulators, and positively regulates important proteins associated with controlling growth arrest and apoptosis (p21, p53). It is suggested that adiponectin may regulate tumor cells by directly inhibiting proangiogenic factors such as basic fibroblast growth factor and interleukin-8 produced by tumors or platelet-derived growth factor BB produced by endothelial cells (39). Several case-control studies showed that adiponectin receptors, especially AdipoR1, are up-regulated in malignancies that include prostate (48), breast (51), pancreatic (50), colorectal (53), and endometrial cancers (CS Mantzoros, unpublished data, 2009).

Adiponectin also exerts an indirect action through an insulin-sensitizing, antiinflammatory, and antiangiogenic effect. Hyperinsulinemia results in high concentrations of circulating insulin-like growth factor I, which leads to increased cell proliferation, decreased apoptosis, and increased inflammation (54). In vitro studies to date show that adiponectin decreases cell viability and proliferation in breast, colorectal, prostate, and endometrial cancers. Recently, in vivo studies in mice evaluated adiponectin’s role in suppression of colon cancer cell proliferation and its possible therapeutic use for colon cancer (55). Although promising, further studies are needed in animals and humans to better delineate the effects of adiponectin and cell proliferation, apoptosis, inflammation, and insulin sensitization in relation to obesity-associated cancers.

CONCLUDING REMARKS AND FUTURE DIRECTION

Adiponectin, an endogenous insulin-sensitizing hormone and the most abundant adipokine produced by the human adipose tissue, is linked to obesity, metabolic syndrome, insulin resistance, type 2 diabetes, and inflammation as well as several types of cancers. Genetic factors such as single nucleotide polymorphism 276 in the adiponectin gene and environmental factors such as a high-fat diet and inactivity are associated with low adiponectin concentrations and may contribute to the development of insulin resistance, type 2 diabetes, and athero-sclerosis. A Mediterranean-type diet, reduction of body weight, and consumption of nuts, coffee, and/or moderate amounts of alcohol have a well-established association with increased plasma adiponectin concentrations and a decreased risk of developing insulin resistance, metabolic syndrome, diabetes, and cardiovascular disease. More specifically, adiponectin could play a potential role in the treatment of insulin-resistant states, which include type 2 diabetes. Accumulating evidence from research studies conducted in both animals and humans links adiponectin and its receptors to several malignancies, which suggests a potential role in regulating cell proliferation and a possible key role in cancer prevention and/or therapy. Thus, adiponectin could prove to be an effective therapeutic agent. Alternatively, pharmacologic agents that could directly increase adiponectin’s circulating concentrations (including novel or existing medications such as PPARα agonists) and/or compounds that could directly act on specific tissue targets, such as adiponectin receptor agonists that induce signaling pathways downstream of adiponectin receptors, would be an important addition to our therapeutic armamentarium. (Other articles in this supplement to the Journal include references 56–59.)

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REFERENCES