Cell Metabolism
Review

Adiponectin Receptor as a Key Player in Healthy Longevity and Obesity-Related Diseases

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Adiponectin is a fat-derived hormone whose reduction plays central roles in obesity-linked diseases including insulin resistance/type 2 diabetes and atherosclerosis. The cloning of Adiponectin receptors AdipoR1 and AdipoR2 has stimulated adiponectin research, revealing pivotal roles for AdipoRs in pleiotropic adiponectin actions, as well as some postreceptor signaling mechanisms. Adiponectin signaling has thus become one of the major research fields in metabolism and clinical medicine. Studies on AdipoRs will further our understanding of the role of adiponectin in obesity-linked diseases and shortened life span and may guide the design of antidiabetic and antiaging drugs with AdipoR as a target.

Background

Roles of Adipokines in Obesity-Related Diseases

The prevalence of obesity has increased dramatically in recent years (Friedman, 2000). It is commonly associated with type 2 diabetes, dyslipidemia, and hypertension, and the coexistence of these diseases has been termed metabolic syndrome, which is related to atherosclerosis (Reaven, 1997; Matsuzawa, 1997). In addition to metabolic syndrome and atherosclerosis, obesity has been reported to be associated with a wide spectrum of health problems such as cancer, fatty liver, and Alzheimer's disease.

Insulin resistance is a key feature of these diseases and is defined as a state in which greater than normal insulin levels are required to maintain glucose homeostasis. To compensate for this insulin resistance, insulin secretion is increased, leading to hyperinsulinemia. Thus, insulin resistance and hyperinsulinemia are seen to coexist in obesity. The reduced cellular insulin response due to insulin resistance results in insufficient inhibition of gluconeogenesis in the liver and decreased glucose uptake in skeletal muscle, leading to type 2 diabetes, thereby forming "the vicious circle." In contrast, the excessive insulin levels result in cell proliferation and increased cellular stress such as oxidative stress and ectopic fat accumulation in vascular smooth muscle cells, cancer cells, hepatocytes, and neuronal cells, leading to atherosclerosis, cancer, dyslipidemia, fatty liver, and Alzheimer's disease.

Before "the vicious circle" is formed, what is the mechanism by which obesity first results in insulin resistance (and then induces hyperinsulinemia)? White adipose tissue (WAT) is a major site of energy storage and is important for energy homeostasis: it stores energy in the form of triglycerides during nutritional abundance and releases it as free fatty acids (FFAs) during nutritional deprivation (Kahn, 2000; Spiegelman and Flier, 2001). While WAT provides a survival advantage in times of starvation, excess WAT is now linked to obesity-related health problems in the current nutritionally rich environment. Regulated by multiple hormonal signals, nuclear hormone receptors, and the central nervous system, WAT has been increasingly recognized as an important endocrine organ that secretes a number of biologically active "adipokines" (Hotamisligil et al., 1993; Zhang et al., 1994; Lazar, 2006). Some of these adipokines have been shown to directly or indirectly affect insulin sensitivity through modulation of insulin signaling and the molecules involved in glucose and lipid metabolism. Of these adipokines, adiponectin has recently attracted much attention because of its antidiabetic and antiatherogenic effects as well as its antiproliferative effects in cancer cells and is expected to be a therapeutic tool for diabetes, metabolic syndrome, cardiovascular diseases, and cancers (Kadowaki and Yamauchi, 2005; Kadowaki et al., 2006).

Biology, Physiology, and Pathophysiology of Adiponectin

Identification of Adiponectin

Adiponectin, also termed Acrp30 (Scherer et al., 1995), AdipoQ (Hu et al., 1996), apM1 (Maeda et al., 1996), or GBP28 (Nakano et al., 1996), was originally identified independently by four groups using different approaches. The *Adiponectin* gene encodes a secreted protein expressed exclusively in both WAT and brown adipose tissue. Adiponectin has a carboxyl-terminal globular domain and an amino-terminal collagen domain and is structurally similar to complement 1q (Shapiro and Scherer, 1998), which belongs to a family of proteins that form characteristic multimers (McCormack et al., 1997). In contrast to the expression of adipokines such as tumor necrosis factor-α (TNF-α) and MCP-1, which cause insulin resistance, adiponectin expression is reduced in obese, insulin-resistant rodent models (Hu et al., 1996). Plasma adiponectin levels have also been reported to be reduced in obese humans (Arita et al., 1999). Importantly, decrease in plasma adiponectin levels preceded the onset of diabetes in obese rhesus monkey model, in parallel with the observation of decreased insulin sensitivity (Hotta et al., 2001).

Discovery of the Insulin-Sensitizing Action of Adiponectin

Using DNA chips, we screened for secreted molecules in WAT, the expressions of which were increased in small adipocytes from insulin sensitive mice such as heterozygous peroxisome proliferator-activated receptor γ (PPARγ)-deficient mice, and we found that increased expression of adiponectin correlates with increased insulin sensitivity in mouse models of altered

insulin sensitivity. We next assessed whether adiponectin was able to improve insulin resistance in KKAy mice (KK mice overexpressing the agouti protein), as a model of the metabolic syndrome and type 2 diabetes linked to obesity. Plasma adiponectin levels were decreased in KKAy mice fed a high-fat diet (HFD). Replenishment of adiponectin significantly ameliorated HFD-induced insulin resistance and hypertriglyceridemia, which led us to propose that adiponectin is an insulin-sensitizing adipokine (Yamauchi et al., 2001). These data also strongly suggested that the HFD-induced, obesity-linked decrease in adiponectin level is causally involved in obesity-linked insulin resistance and the metabolic syndrome. Scherer and colleagues reported that an acute increase in the level of circulating adiponectin triggers a transient decrease in basal glucose level by inhibiting both the expression of hepatic gluconeogenic enzymes and the rate of endogenous glucose production in both wild-type and type 2 diabetic mice, and they proposed that adiponectin sensitizes the body to insulin, which is associated with inhibition of endogenous glucose production (Berg et al., 2001; Combs et al., 2001). Lodish and colleagues reported that a proteolytic cleavage product of adiponectin, which structurally resembles globular adiponectin, increases fatty acid oxidation in muscle, decreases plasma glucose, and causes weight loss in mice (Fruebis et al., 2001).

Subsequently, the long-term effects of adiponectin on insulin resistance in vivo were investigated through the use of adiponectin transgenic mice (Yamauchi et al., 2003a; Combs et al., 2004) or adiponectin-deficient mice (Kubota et al., 2002; Maeda et al., 2002; Ma et al., 2002; Nawrocki et al., 2006). Adiponectin transgenic mice showed amelioration of insulin resistance and diabetes. Adiponectin-deficient mice showed mild insulin resistance with glucose intolerance. Adiponectin-deficient mice also exhibited other features of metabolic syndrome, such as dyslipidemia and hypertension (Kubota et al., 2002).

Scherer and his colleagues reported that adiponectin transgenic mice displayed increased expression of PPARγ target genes and became morbidly obese with improvement in insulin sensitivity (Kim et al., 2007).

Proposal of the Adiponectin Hypothesis in Obesity-Related Diseases

Plasma adiponectin levels have also been reported to be reduced in obese humans, particularly those with visceral obesity, and to correlate inversely with insulin resistance (Arita et al., 1999; Matsuzawa, 2010). Prospective and longitudinal studies (Lindsay et al., 2002; Spranger et al., 2003) have shown that lower adiponectin levels are associated with a higher incidence of diabetes. Adiponectin has been shown to be significantly related to the development of type 2 diabetes in Pima Indians (Lindsay et al., 2002). Hypoadiponectinemia has also been demonstrated to be independently associated with metabolic syndrome—indeed, more strongly than are any other inflammatory markers (Matsushita et al., 2006). Reduced plasma adiponectin levels are also commonly observed in a variety of states frequently associated with insulin resistance, such as dyslipidemia (Matsushita et al., 2006), cardiovascular disease (Matsuzawa, 2010; Pischon et al., 2004), and hypertension (Adamczak et al., 2003).

The reduction of plasma concentrations of adiponectin is not only closely related to disease states such as type 2 diabetes and cardiovascular diseases, but is also implicated in cancer development in human obesity. Recent clinical studies involving several independent cohorts have demonstrated that plasma concentrations of adiponectin are inversely correlated with the risk of several types of cancer (Paz-Filho et al., 2011).

Plasma adiponectin levels are reduced in obesity and are even lower in patients with hepatic steatosis or nonalcoholic steatohepatitis (NASH) (Belfort et al., 2006). Interestingly, there was an inverse relationship between the reduction in hepatic fat content and the increase in the plasma adiponectin level when patients were treated with thiazolidinedione (TZD) (Belfort et al., 2006).

From these data, we proposed adiponectin hypothesis (Kadowaki et al., 2006). According to this hypothesis, reduced plasma adiponectin levels in obesity play causal roles in obesity-linked diseases such as type 2 diabetes, cardiovascular diseases, and NASH.

Regulation of Biosynthesis and Secretion of Adiponectin

Biosynthesis and Secretion Pathways of Adiponectin Multimers

Adiponectin exists in a wide range of multimer complexes in plasma and combines via its collagen domain to create 3 major oligomeric forms: a low-molecular-weight (LMW) trimer, a middle-molecular-weight (MMW) hexamer, and a high-molecular-weight (HMW) 12- to 18-mer (Pajvani et al., 2003; Waki et al., 2003). Importantly, HMW adiponectin has been shown to be able to activate AMP kinase most potently (Kobayashi et al., 2004; Hada et al., 2007).

A truncated form of adiponectin that includes the globular domain cleaved proteolytically from full-length adiponectin has been reported to exist in plasma, although in very small amounts (Fruebis et al., 2001). The *Adiponectin* gene expressed exclusively in adipocytes has been reported to be regulated by transcriptional factors including C/EBPs (Saito et al., 1999), sterol regulatory element binding protein 1c (SREBP1c) (Seo et al., 2004), and PPARγ (Maeda et al., 2001) (Figure 1). Farmer and his colleagues reported that during adipocyte differentiation, SirT1 levels are decreased and PPARγ levels are increased, both of which increase endoplasmic reticulum (ER) oxidoreductase Ero1-L, thereby stimulating secretion of HMW adiponectin (Qiang et al., 2007). Scherer and his colleagues showed that there is an abundant pool of properly folded adiponectin in the secretory pathway through thiol-mediated retention and that adiponectin is covalently bound to the ER chaperone ERp44. They also showed that another ER chaperone, Ero1-Lα, plays a critical role in the release of adiponectin from ERp44 and that these chaperones play a major role in the assembly of HMW adiponectin. They also reported that one mechanism for increasing circulating levels of specific adiponectin complexes by PPARγ agonists may be selective upregulation of rate-limiting chaperones such as ERp44 and Ero1-Lα (Wang et al., 2007) (Figure 1).

Several observations support the hypothesis that HMW adiponectin is the more active form of the protein and has a more relevant role in insulin sensitivity and in protecting against diabetes. First, rare mutations—G84R and G90S—in the collagen domain are closely associated with type 2 diabetes (Waki et al., 2003). Subjects with either of these two mutations have extremely low levels of HMW adiponectin, although total plasma adiponectin

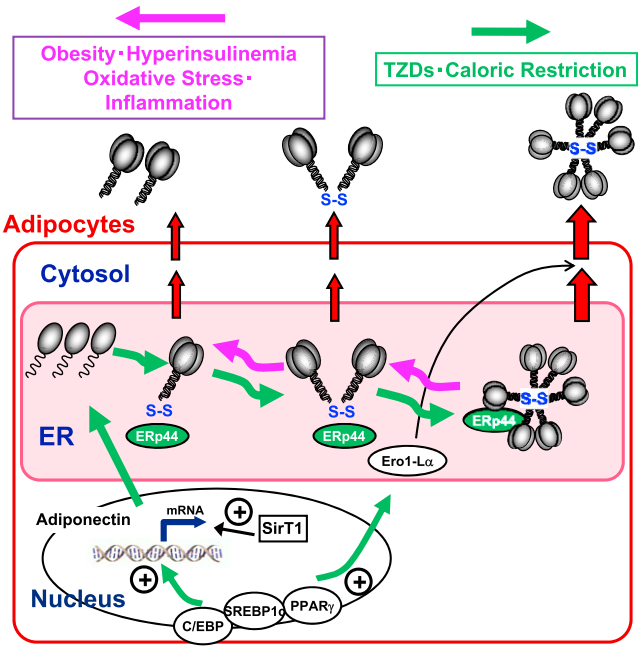

Figure 1. Regulatory Mechanisms of Adiponectin Multimer Formation

The *Adiponectin* gene expressed exclusively in adipocytes has been reported to be regulated by transcriptional factors, including C/EBPs, sterol regulatory element binding protein 1c (SREBP1c), and peroxisome proliferator-activated receptor γ (PPARγ). SirT1 has recently been reported to deacetylate Lys268 and Lys293 of PPARγ and to cause selective PPARγ modulation, leading to upregulation of adiponectin. There is an abundant pool of properly folded adiponectin in the secretory pathway through thiol-mediated retention, and that adiponectin is covalently bound to the ER chaperone ERp44. Another ER chaperone, Ero1-Lα, plays a critical role in the release of adiponectin from ERp44, and that these chaperones play a major role in the assembly of HMW adiponectin. Hyperinsulinemia, oxidative stress and inflammation observed in obesity have been reported to reduce HMW adiponectin, whereas TZDs and caloric restriction have been reported to increase HMW adiponectin.

levels were not significantly changed. Moreover, the two mutant adiponectins recombinantly expressed in NIH 3T3 fibroblasts were not able to form the HMW form of adiponectin (Waki et al., 2003). Second, increases in the ratio of plasma HMW adiponectin levels to total adiponectin levels correlate with improvement in insulin sensitivity during treatment with an insulin-sensitizing drug, TZD, in both mice and human diabetes, whereas increases in total serum adiponectin levels do not show good correlations with improvement in insulin sensitivity during treatment with TZD (Pajvani et al., 2004). Third, the level of plasma HMW adiponectin was reported to be associated with parameters related to glucose homeostasis in a cohort study (Lara-Castro et al., 2006). It is noteworthy that the ratio of plasma HMW adiponectin to total adiponectin correlated more significantly with glucose and insulin levels than did the total adiponectin level (Lara-Castro et al., 2006), suggesting that alterations in plasma HMW adiponectin level may be more relevant to the prediction of insulin resistance than are total plasma adiponectin alterations. Consistent with this, levels of total adiponectin, HMW adiponectin, and the HMW-to-total adiponectin ratio all inversely correlated with key features of central obesity and positively correlated with the insulin-stimulated glucose disposal rate. However, HMW adiponectin levels, not total adiponectin levels, are primarily responsible for these relationships, suggesting that measurement of the HMW adiponectin level may be superior to measurement of total adiponectin (Fisher et al., 2005). Using an ELISA system for selective measurement of HMW adiponectin, we also found HMW adiponectin and the HMW-to-total adiponectin ratio to have significantly better power for the prediction of insulin resistance and the metabolic syndrome in humans (Hara et al., 2006). Thus, HMW adiponectin level may be the superior biomarker for insulin resistance, metabolic syndrome, and type 2 diabetes. However, Blüher et al. failed to observe the superiority of HMW over total adiponectin in assessing metabolic variables at baseline or in response to physical training (Blüher et al., 2007), suggesting that further studies are required for clinical effectiveness and usefulness of measuring HMW adiponectin.

Physiological and Pathophysiological Regulation of Plasma Adiponectin

Caloric restriction/starvation/fasting have been reported to result in upregulation of plasma adiponectin levels (Figure 1). Accili and his colleagues indeed showed that SirT1 gain of function increases adiponectin messenger RNA (mRNA) levels, protein levels, and both HMW and MMW adiponectin in mice fed either a standard diet or HFD, which resulted in increased insulin sensitivity in the liver (Banks et al., 2008). SirT1 has recently been reported to deacetylate Lys268 and Lys293 of PPARγ and to cause selective PPARγ modulation, leading to upregulation of adiponectin and repression of proinflammatory cytokines (Qiang et al., 2012). As for insulin in the regulation of adiponectin levels, it is reported that adipocyte-specific insulin receptor knockout mice exhibited increased adiponectin expression levels in adipose tissue (Blüher et al., 2002). In this context, it is noteworthy that subjects with mutations in the insulin receptor, despite having the most severe degree of insulin resistance, had elevated plasma adiponectin (Semple et al., 2006). Moreover, Scherer and his colleagues proposed that an increase in serum insulin levels may trigger the induction or activation of a serum reductase that triggers the dissociation of the HMW adiponectin, leading to the transient appearance of the lower-molecular-weight adiponectin (Pajvani et al., 2003).

In contrast to caloric restriction/starvation/fasting, obesity results in decreased adiponectin levels via multiple mechanisms, including decreased levels of SirT1, hyperinsulinemia, oxidative stress, and inflammation (Furukawa et al., 2004). Conversely, TZDs reverse hyperinsulinemia, oxidative stress, and inflammation, thereby increasing adiponectin levels especially those of HMW adiponectin. Moreover, TZDs directly increase the expression of adiponectin gene itself via peroxisome proliferator response element (PPRE) (Maeda et al., 2001). Scherer et al. reported that one mechanism for increasing circulating levels of HMW adiponectin by TZDs may be selective upregulation of rate-limiting chaperones such as ERp44 and Ero1-Lα (Wang et al., 2007) (Figure 2).

There is a sexual dimorphism in the circulating levels of adiponectin. Indeed, females have higher plasma adiponectin levels than males in humans and rodents, suggesting that sexual hormones regulate the production of adiponectin, although it is controversial how these hormones, such as estrogen and testosterone, are involved in the regulation of plasma adiponectin level

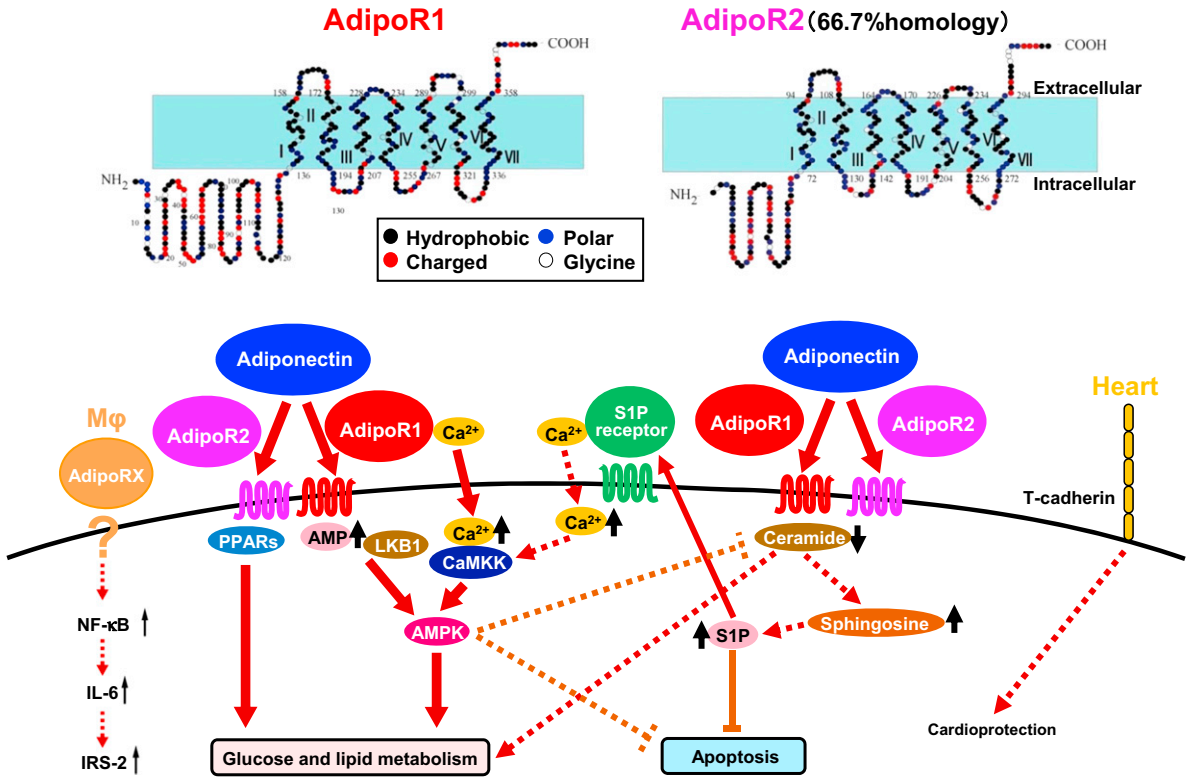

Figure 2. Cloning and Functional Analysis of Adiponectin Receptors

Adiponectin receptors AdipoR1 and AdipoR2 were identified by expression cloning in 2003. AdipoR1 and AdipoR2 are significantly homologous (67% amino acid identity). AdipoR1 and AdipoR2 appear to be integral membrane proteins; the N terminus is internal and the C terminus is external—opposite to the topology of all reported GPCRs. AdipoR1 and AdipoR2 serve as receptors for adiponectin and mediate increased AMP-activated kinase (AMPK) and PPARs activities, thereby regulating glucose and lipid metabolism. Both Ca^{2+}/CaMKKβ and AMP/LKB1 are necessary for adiponectin-induced full AMPK activation. Adiponectin via AdipoR1 and AdipoR2 decreased ceramide, increased sphingosine-1-phosphate (S1P), and protected from apoptosis. T-cadherin is critical for adiponectin-mediated cardioprotection in mice. Adiponectin increases IL-6 in macrophages via activation of NF-κB through a still unidentified adiponectin receptor AdipoRX but not AdipoR1 or AdipoR2, leading to increased IRS-2 in hepatocytes under a fasted state.

(Combs et al., 2003; Nishizawa et al., 2002; Xu et al., 2005). Nevertheless, this may partly account for the fact that females are more sensitive to insulin than are males.

Concentrations of serum adiponectin were higher in a hyperthyroid state than in a hypothyroid state. A strong positive correlation of adiponectin with thyroid hormones has been noted. Thus, the plasma adiponectin level is affected by multiple factors, such as insulin (insulin signaling in adipocytes and insulin-dependent reductase), intracellular stress in adipocytes (inflammation and oxidative stress), other hormones (estrogen, testosterone and thyroid hormone), sex, aging, and lifestyle.

Adiponectin Receptors AdipoR1/AdipoR2: Molecular Structure and Their Functions

Identification and Molecular Cloning of Adiponectin Receptors AdipoR1 and AdipoR2

Identification and molecular cloning of adiponectin receptors AdipoR1 and AdipoR2 have opened up an avenue of fundamental understanding of adiponectin actions and their physiological and pathophysiological significance. AdipoR1 and AdipoR2 are significantly homologous (67% amino acid identity), and they are structurally conserved from yeast to humans (especially in the seven transmembrane domains) (Yamauchi et al., 2003b). Interestingly, the yeast homolog (YOL002c) plays a key role in metabolic pathways that regulate lipid metabolism, such as fatty acid oxidation (Karpichev et al., 2002). AdipoR1 is ubiquitously expressed, including abundant expression in skeletal muscle, whereas AdipoR2 is most abundantly expressed in the mouse liver. AdipoR1 and AdipoR2 appear to be integral membrane proteins; the N terminus is internal and the C terminus is external—opposite to the topology of all reported G protein-coupled receptors (GPCRs) (Yamauchi et al., 2003b) (Figure 2).

Demonstration of Pivotal Roles of AdipoR1 and AdipoR2 in Adiponectin Actions

AdipoR1and AdipoR2 have been shown to serve as the major adiponectin receptors in vivo, since AdipoR1•AdipoR2 double-knockout mice showed abrogation of adiponectin binding (Yamauchi et al., 2007). AdipoR1 and AdipoR2 mediate metabolic actions of adiponectin, since AdipoR1•AdipoR2 double-knockout mice showed abrogation of glucose-lowering effects of adiponectin. Moreover, since AdipoR1•AdipoR2 double-knockout mice showed glucose intolerance and hyperinsulinemia, AdipoR1 and AdipoR2 play physiological roles in regulation of normal glucose metabolism and insulin sensitivity. For example, in the liver, AdipoR1 is involved in activation of AMP-activated kinase (AMPK), and AdipoR2 is involved in activation

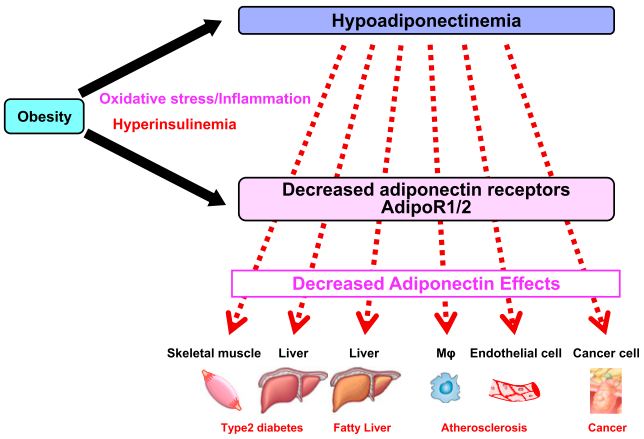

Figure 3. Impaired Adiponectin Action Is a Hallmark of Obesity-Related Diseases

Decreased adiponectin effects in obesity play causal roles in the development of obesity-related diseases such as type 2 diabetes, fatty liver, atherosclerosis, cancers, and so on, in which there are two mechanisms about disturbed adiponectin effects; one is the absolute decrease of adiponectin, and the other is decreased adiponectin receptors AdipoR1/R2, both of which appear to be caused, at least in part, by increased oxidative stress, inflammation, and hyperinsulinemia in obesity.

of PPARα, leading to increased insulin sensitivity. Expression of AdipoR1 and AdipoR2 or suppression of AdipoR1 and AdipoR2 expression supports our conclusion that AdipoR1 and AdipoR2 serve as receptors for globular and full-length adiponectin and mediate increased AMP-activated kinase (AMPK), PPARα ligand activities, fatty acid oxidation, and glucose uptake by adiponectin (Yamauchi et al., 2007; unpublished data) (Figure 2).

Signal Transduction Mechanisms

AMPK Activation via AdipoR1. With respect to the molecular mechanisms underlying the insulin-sensitizing action of adiponectin, we found that full-length adiponectin stimulated AMPK phosphorylation and activation in both skeletal muscle and the liver, while globular adiponectin did so in skeletal muscle (Yamauchi et al., 2002) (Figure 2). Blocking AMPK activation by use of a dominant-negative mutant inhibited these effects of full-length or globular adiponectin, indicating that stimulation of glucose utilization and fatty acid combustion by adiponectin occurs through activation of AMPK (Yamauchi et al., 2002). Lodish, Ruderman, and colleagues also showed that the adiponectin globular domain could enhance muscle fat oxidation and glucose transport via AMPK activation and acetyl-CoA carboxylase inhibition (Tomas et al., 2002). Consistent with the proposed roles of AMPK activation by adiponectin in the liver (Yamauchi et al., 2002), Scherer et al. reported that in adiponectin transgenic mice (Combs et al., 2004), reduced expression of gluconeogenic enzymes such as phosphoenolpyruvate carboxylase and glucose-6-phosphatase is associated with elevated phosphorylation of hepatic AMPK. We showed by using LKB1 deletion that adiponectin suppresses hepatic SREBP1c expression in an AdipoR1/LKB1/AMPK-dependent pathway. However, by using inducible hepatic deletion of LKB1, Birnbaum et al. reported that LKB1- and AMPK-dependent and independent signaling pathways may exist in vivo (Miller et al., 2011).

PPAR Activation via AdipoR2. Adiponectin activated the PPAR pathway via AdipoR2 (Figure 2) and also increased fatty acid combustion and energy consumption, in part via increased molecules involved in these functions such as ACO and UCP, respectively (Yamauchi et al., 2003b, 2007). To clarify the mechanisms by which adiponectin increased the expressed levels of ACO and UCP, we measured endogenous PPARα ligands activities, because the ACO and UCP genes possess PPRE in its promoter regions. Interestingly, adiponectin increased PPARα ligands activities and also expression of PPARα itself (Yamauchi et al., 2003a).

AMPK, Ca^{2+}, Fatty Acid Combustion, Mitochondrial Biogenesis, Mitochondrial OXPHOS, and ROS via AdipoR1. Adiponectin induces extracellular Ca^{2+} influx by AdipoR1, which is necessary for the subsequent activation of Ca^{2+}/calmodulin-dependent protein kinase kinase β (CaMKKβ), AMPK (Figure 3). This pathway then activated SirT1, increased expression and decreased acetylation of PPARγ coactivator1α (PGC-1α), and increased mitochondria in myocytes. In fact, muscle-specific disruption of AdipoR1 suppressed the adiponectin-mediated increase in intracellular Ca^{2+} concentration and decreased the activation of CaMKK, AMPK, and SirT1 by adiponectin. Suppression of AdipoR1 also resulted in decreased PGC-1α expression and deacetylation, decreased mitochondrial content and enzymes, decreased oxidative type I myofibers, and decreased oxidative stress-detoxifying enzymes in skeletal muscle that were associated with insulin resistance and decreased exercise endurance. Decreased levels of adiponectin and AdipoR1 in obesity may have causal roles in the mitochondrial dysfunction and insulin resistance seen in diabetes (Iwabu et al., 2010).

APPL. A two-hybrid study revealed that the C-terminal extracellular domain of AdipoR1 interacted with adiponectin, whereas the N-terminal cytoplasmic domain of AdipoR1 interacted with APPL (adaptor protein containing pleckstrin homology domain, phosphotyrosine-binding domain, and leucine zipper motif) (Mao et al., 2006). Moreover, it has been reported that interaction of APPL with AdipoR1 in mammalian cells was stimulated by adiponectin binding and this interaction played important roles in adiponectin signaling and adiponectin-mediated downstream events such as AMPK activation, lipid oxidation, and glucose uptake. Furthermore, these data are consistent with that the N terminus of adiponectin receptors is internal and the C terminus is external (Mao et al., 2006).

Ceramide Pathway. Although it was shown that AdipoR1and AdipoR2 regulate glucose and fatty acid metabolism partly via activation of AMPK, Ca^{2+}, and PPARα signaling pathways, it seems likely that additional signaling pathways also participate at the pleiotropic actions of adiponectin (Figure 2). In fact, Scherer and his colleagues added ceramide signaling as a pathway involved in mediating such pleiotropic effects (Holland et al., 2011). Interestingly, they demonstrated that adiponectin lowers cellular ceramide levels via activation of ceramidase, which converts ceramide to sphingosine, leading to reduced hepatic ceramide levels and improved insulin sensitivity (Figure 2). Conversely, deficiency of adiponectin increases hepatic ceramide levels, which may be implicated insulin resistance.

Adiponectin increased sphingosine 1-phosphate (S1P) and protects from apoptotic cell death induced by either palmitate

or C2-ceramide in cardiac myocytes and pancreatic β cells (Holland et al., 2011) (Figure 2). Because this protection is reversed by either an inhibitor of ceramide biosynthesis or S1P itself, it seems likely that adiponectin-induced S1P generation protects cardiac myocytes and β cells from cell death. Most importantly, this ceramide pathway, which appears to be activated adiponectin is totally dependent on AdipoR1/AdipoR2, which was shown by the observations that overexpression of adiponectin, AdipoR1, and AdipoR2, reduced hepatic ceramide levels and improved insulin sensitivity.

AdipoR1 and AdipoR2 belong to the progesterone and adipoQ receptor (PAQR) family. Some PAQR family members have been reported to contain sequence homology with alkaline ceramidase (Holland et al., 2011). An important issue to be solved by analyses of 3D structure of AdipoR1/AdipoR2 is whether the ceramidase activity is intrinsic to the receptor or whether ceramidase is indirectly activated upon adiponectin stimulation via an unknown mechanism.

Based upon the work of our laboratory, as well as other laboratories such as Scherer's laboratory, we would like to propose the potential signal mechanisms downstream of AdipoR1 and AdipoR2, which collectively lead to pleiotropic biological actions; adiponectin appears to regulate more diverse and complex pathways, such as ceramide and S1P downstream of AdipoR1 and AdipoR2, in addition to those originally identified, such as AMPK, Ca^{2+}, and PPARα (Holland et al., 2011; Iwabu et al., 2010; Kadowaki et al., 2006; Kadowaki and Yamauchi, 2011; Yamauchi et al., 2003b, 2007)(Figure 2).

Potential Existence of Other Receptors and Action Mechanisms Such as T-Cadherin and Nonreceptor Pathways

Lodish's group reported that T-cadherin was capable of binding adiponectin in C2C12 myoblasts and muscle; however, T-cadherin was not expressed in hepatocytes or the liver (Hug et al., 2004), another important target organ (Combs et al., 2001; Kubota et al., 2006; Nawrocki et al., 2006). Moreover, T-cadherin by itself was thought to have no effect on adiponectin cellular signaling or function, because T-cadherin is without an intracellular domain. These data raised the possibility that T-cadherin may be one of the adiponectin-binding proteins. Consistence with this, in T-cadherin-deficient mice, adiponectin failed to associate with cardiac tissue, and its levels dramatically increased in the circulation. Interestingly, T-cadherin is critical for adiponectin-mediated cardioprotection in mice (Denzel et al., 2010) (Figure 2).

As for adiponectin-binding proteins, adiponectin was reported to modulate inflammatory reactions via calreticulin (Takemura et al., 2007). Walsh et al. showed that both calreticulin and CD91 are involved in the adiponectin-mediated uptake of apoptotic cells (Takemura et al., 2007). Moreover, Ouchi and his colleagues reported that pretreatment with anti-calreticulin antibodies reduced the binding of adiponectin to cardiac myocytes and blocked the adiponectin-stimulated increase in Akt activation and survival in cardiomyocytes.

The different properties of adiponectin from those of other bioactive substances such as hormones and cytokines are very important issues. Adiponectin is a unique bioactive substance in sense of very high concentrations in plasma. There are several possibilities that could explain the high concentrations of adiponectin in plasma. One possibility is the unique molecular structure of HMW adiponectin, which displays more-potent bioactivities than trimer or hexamer adiponectin. Because HMW adiponectin is thought to be composed of 18-mer or 36-mer, it is possible that effective molar concentrations of adiponectin in plasma may be substantially low as compared with those calculated from mass concentrations.

Another possibility could be the unique action mode of adiponectin, which may be different from that of other bioactive substances. Adiponectin has been reported to bind to non-signaling molecules such as extracellular collagens and some adhesion molecules in injured tissues presumably via low-affinity high-capacity binding. It is important to clarify the potentially cytoprotective role of adiponectin that accumulates in injured tissue.

Transcriptional Control of AdipoR in Physiology and Obesity

The expression of AdipoR1/R2 in insulin target organs, such as skeletal muscle and liver, significantly increases in fasted mice and decreases in refed mice. Consistent with this, in vitro studies revealed that insulin reduced the expression of AdipoR1/R2 via the phosphoinositide 3 kinase/FoxO1-dependent pathway. The expression levels of both AdipoR1 and AdipoR2 were significantly decreased in the muscle and adipose tissue of insulin-resistant *ob*/*ob* mice, probably in part because of obesity-linked hyperinsulinemia via FoxO (Tsuchida et al., 2004) (Figure 3). Moreover, adiponectin-induced activation of AMPK was impaired in the skeletal muscle of *ob*/*ob* mice. These data suggest that adiponectin resistance is present in *ob*/*ob* mice, presumably due to the decreased expression of AdipoR1 and AdipoR2 (Tsuchida et al., 2004). Thus, obesity decreases not only plasma adiponectin levels but also AdipoR1/R2 expression, thereby reducing adiponectin sensitivity and leading to insulin resistance, which in turn leads to hyperinsulinemia, creating a "vicious cycle" (Tsuchida et al., 2004). Adiponectin receptor expression in the skeletal muscle of type 2 diabetic patients has been reported to be decreased (Civitarese et al., 2004). In addition, a correlation has been reported between adiponectin receptor gene expression and insulin sensitivity in nondiabetic Mexican Americans with or without a family history of type 2 diabetes (Debard et al., 2004).

Biological Functions of AdipoR in Various Tissues

Suppression of NASH. Nonalcoholic steatohepatitis (NASH) is one of the most frequent causes of liver dysfunction associated with the dysregulation of synthesis and oxidation of fatty acids. Plasma adiponectin levels have been reported to be reduced in obesity and even more reduced in patients with NASH (Belfort et al., 2006). Interestingly, there seemed to be an inverse relationship between the reduction in hepatic fat content and the increase in the plasma adiponectin level when patients were treated with TZD (Belfort et al., 2006). These data suggested that low adiponectin levels may relate to the development of NASH. Adiponectin receptors (AdipoR1/R2) are known as modulators of fatty acid metabolism in the liver. Yukawa and his colleagues reported that after feeding a high-fat and high-cholesterol diet to obese *fa*/*fa* Zucker rats for 8 weeks, they develped fatty liver spontaneously with inflammation and fibrosis that are characteristic of NASH. The expression levels of AdipoR1/R2 are significantly decreased in NASH (Matsunami

et al., 2011), which was associated with decreased AMPKα1/α2 and PPARα. Taken together, increased synthesis and decreased oxidation of fatty acids by downregulation of AdipoR may contribute to the progression of NASH (Matsunami et al., 2011) (Figure 3).

Regulation of Inflammation: M1/M2 Macrophage Polarization. Walsh and his colleagues reported that adiponectin promotes macrophage polarization toward an anti-inflammatory phenotype (Ohashi et al., 2010). Nagy and his colleagues showed that adiponectin potently shifted the polarization of Kupffer cells and RAW264.7 macrophages to an M2/anti-inflammatory phenotype in an IL-4/STAT6-dependent mechanism. M2 polarization was also partially dependent on AMP-activated kinase (Mandal et al., 2011).

Recently, it has been reported that saturated fatty acid-induced AMPK inactivation results in decreased activation of unc-51-like kinase-1 (ULK1), the mammalian homolog of autophagy-related-1 (Atg1), leading to decreased autophagy, thereby inducing mitochondrial ROS generation that activates the NLRP3-ASC inflammasome, causing caspase-1, IL-1β, and IL-18 production, which finally leads to insulin resistance (Wen et al., 2011). It is interesting to clarify whether AMP kinase activation in macrophages by adiponectin/AdipoR1 could regulate these pathways (Figure 3).

NF-κB Signaling Pathways: Yin and Yang Regulation. It is well known that adiponectin suppresses inflammatory stimuli-induced nuclear factor κB (NF-κB) activation (Ouchi et al., 2000), which is thought to contribute considerably to the antidiabetic and antiatherogenic effects of adiponectin. Importantly, PPAR and AMPK, downstream mediators of AdipoR1 and AdipoR2, have been reported to antagonize inflammatory responses by transrepression of NF-κB target genes, including COX2 (Chandrasekar et al., 2008), which could account for the anti-inflammatory effects of adiponectin, at least in part.

However, unexpectedly, adiponectin has also been reported to activate NF-κB transcription factor under basal conditions in a variety of cell types including C2C12 myocytes and myotubes (Tsao et al., 2002). Adiponectin has been reported to cause elevated expression of COX-2 by stromal cells and induce release of prostaglandin E(2), and at the same time block fat cell formation in long-term bone marrow cultures and inhibit the differentiation of cloned stromal preadipocytes. As one clue of the significance of NF-κB pathway activation by adiponectin, we have shown that adiponectin increases IL-6 in macrophages via activation of NF-κB through a still-unidentified adiponectin receptor AdipoRX but not AdipoR1 nor AdipoR2, which results in activation of STAT3 in hepatocytes, leading to increased IRS-2 under a fasted state, thereby increasing insulin sensitivity (Awazawa et al., 2011) (Figure 2).

Researchers in this field might wish to clarify how adiponectin-induced suppression of NF-κB activated by inflammatory stimuli as well as adiponectin-induced mild activation of NF-κB under a basal state coordinately maintain in vivo homeostasis (Yin and Yang regulation).

Cardiovascular Function. Walsh et al. examined the role of adiponectin in myocardial remodeling in response to acute injury. Ischemia-reperfusion in adiponectin-deficient (APN-KO) mice resulted in increased myocardial infarct size, myocardial apoptosis, and TNF-α expression compared with wild-type mice. Administration of adiponectin diminished infarct size, apoptosis, and TNF-α production in both APN-KO and wild-type mice. They suggest that adiponectin protects the heart from ischemia-reperfusion injury through both AMPK- and COX-2-dependent mechanisms (Shibata et al., 2005).

Because COX-2 is also an important modulator of endothelial function, Walsh and his colleagues investigated the possible contribution of COX-2 to adiponectin-mediated vascular responses in a mouse hind limb model of vascular insufficiency. Disruption of the adiponectin-COX-2 regulatory axis in endothelial cells could participate in the pathogenesis of obesity-related vascular diseases (Ohashi et al., 2009).

Adiponectin receptors are expressed by cardiac myocytes and heart tissue. Hyperinsulinemia related to obesity has been reported to decrease myocardial AdipoR1 expression via PI3K/Akt and FoxO1 pathway (Cui et al., 2012). Moreover, through the use of RNA interference, decreased AdipoR1 has been reported to result in decreased AMPK-dependent angiogenic response (Shimano et al., 2010). These data suggested that downregulation of adiponectin receptor pathway could be causally implicated in decreased cardiovascular function (Figure 3).

Suppression of Carcinogenesis. It has been shown that adiponectin may exert antineoplastic activity in gastric, breast, esophageal, and prostate cancer cells, through suppression of tumor proliferation and neoangiogenesis and through induction of apoptosis. Recent clinical studies involving several independent cohorts have demonstrated that plasma concentrations of adiponectin are inversely correlated with the risk of several types of cancer, including gastric, colorectal, breast, endometrial, and prostate cancers (Paz-Filho et al., 2011).

In addition, the expression of adiponectin receptors has been documented in several human cancer cell lines, such as gastric, breast, prostate, and endometrial cancer cells (Barb et al., 2007). An in vitro experiment using two gastric cancer cell lines, MKN-74 and NUGC-3, showed that the expression levels of AdipoR1 and AdipoR2 were significantly decreased by transforming growth factor-β in a dose-dependent manner (Otani et al., 2010). In gastric cancer tissue, as compared to findings in the normal counterparts, AdipoR1 mRNA expression tended to be decreased and AdipoR2 expression was significantly decreased (Ishikawa et al., 2007). In endometrial adenocarcinoma tissues, decreased expression of adiponectin receptors is implicated in the development, invasion, and metastasis (Yamauchi et al., 2012). Adiponectin/AdipoRs is thought to reduce cancer risk at least in part through amelioration of hyperinsulinemia as well as through direct effects on tumor cells such as via inhibition of the mammalian target of the rapamycin (mTOR) pathway by activating AMP kinase (Fujisawa et al., 2008) (Figure 3).

Taken together, as shown in Figure 3, we would like to propose a hypothesis that impaired adiponectin action is hallmark of obesity-related diseases. According to this hypothesis, obesity is not only accompanied by hypoadiponectinemia, but also decreased adiponectin receptors AdipoR1 and AdipoR2. Impaired adiponectin actions via AdipoR1 in muscle, liver, and macrophages may cause type 2 diabetes and atherosclerosis. Impaired adiponectin actions via AdipoR1 and AdipoR2 in liver and cancer cell may cause fatty liver and cancer. Impaired adiponectin actions via AdipoR2 in endothelial cell may cause atherosclerosis.

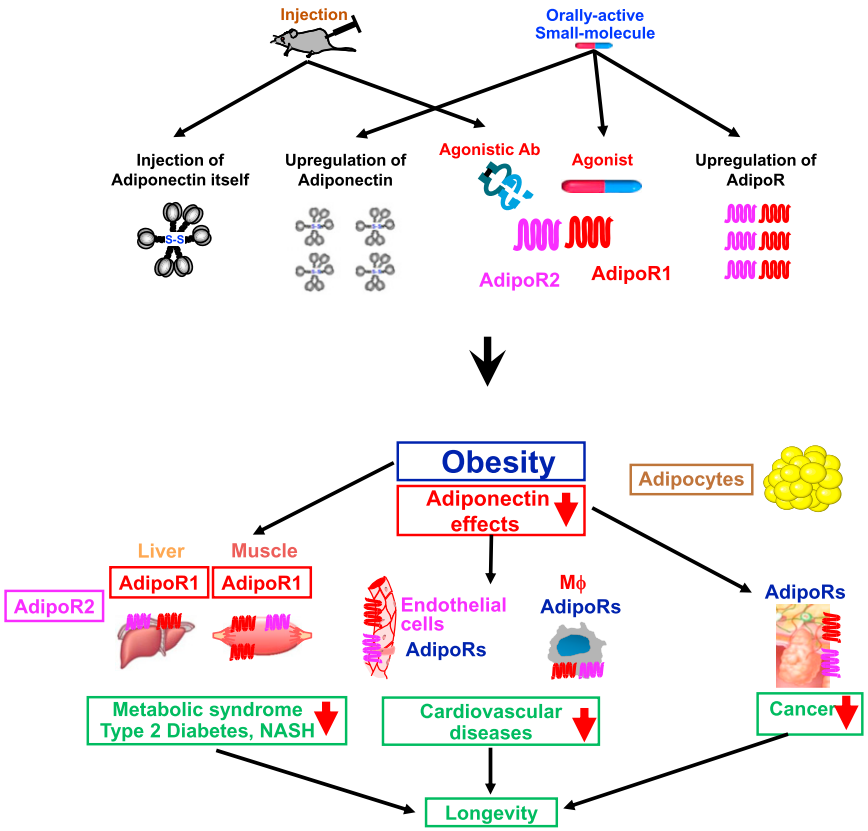

Figure 4. Strategies to Increase Adiponectin Effects and Pathophysiological Roles of Adiponectin/AdipoR in Obesity

There are several strategies to increase adiponectin effects. One is to increase levels of adiponectin itself, such as through the injection of adiponectin. The second is use of compounds to increase adiponectin expression. The third is to activate AdipoRs, such as small-molecule compounds and activating antibodies against AdipoRs. The fourth is to increase levels of AdipoRs. Increased activation of adiponectin and AdipoRs pathways like exercise may have beneficial effects on healthy longevity and lifestyle-related diseases, such as type 2 diabetes, metabolic syndrome, cardiovascular diseases, cancers, NASH, and so on.

Thus impaired adiponectin actions due to reduced adiponectin and downregulation of adiponectin receptors can cause a variety of obesity-related diseases.

Regulation of Life Span. Exercise has been reported to have beneficial effects on obesity-related disorders such as type 2 diabetes and to contribute to healthy longevity. Activation of AMPK occurs with exercise and has been proposed as a longevity strategy for mammals. We previously demonstrated that adiponectin also activates AMPK via AdipoR1 in skeletal muscle, which in turn activates SirT1, implicated in longevity. Therefore, AdipoR1 agonists and strategies to increase AdipoR1 in muscle tissues could be used as exercise mimetics and hopefully to extend life span.

Overexpression of human adiponectin (4- to 6-fold) in transgenic mice indeed results in the prevention of premature death by a high-calorie diet (Otabe et al., 2007). It is interesting to determine whether APN-KO or AdipoR1•AdipoR2 double-knockout mice show shortened life span. Results on whether the replenishment of adiponectin or adiponectin actions could indeed prolong the shortened life span under the HFD are awaited.

Therapeutic Strategy Targeted to the Adiponectin Pathway

Decreased adiponectin effects in obesity have been reported to play causal roles in the development of obesity-related diseases such as diabetes and cardiovascular diseases.

There are several strategies to reverse reduced adiponectin effects (Figure 4). One is to increase levels of adiponectin itself, such as through the injection of adiponectin. As for injection of adiponectin, there are many difficulties, such as very high plasma concentrations of adiponectin and HMW adiponectin multimers as the highest activity form.

The second is use of compounds to increase adiponectin expression. The TZDs, which also have pleiotropic effects on cardiovascular diseases and lipid metabolism, are known to exert its effects partly through increasing the levels of HMW adiponectin (Kubota et al., 2006; Yamauchi et al., 2001). TZDs could increase adiponectin expression very potently; however, TZDs also have other effects besides increasing adiponectin levels, such as increasing body weight, retention of water, and bone resorption. In this context, non-TZD selective PPARγ agonists such as INT 131 that increase adiponectin levels seem to be superior to TZD, because INT131 has been reported to normalize insulin signaling defects and increase bone mass in diet-induced obese mice (Lee et al., 2012).

Some dietary factors, such as soy protein, fish oils, and linoleic acid, are also suggested to increase plasma adiponectin levels, which is consistent with the fact that intake of these factors is thought to have a protective effect on the development of diabetes. In contrast, a carbohydrate-rich diet appears to decrease plasma adiponectin levels (Pischon et al., 2005).

The third is to activate AdipoRs, such as small-molecule compounds and activating antibodies against AdipoRs.

The fourth is to increase levels of AdipoRs. In pathophysiology, the expression levels of adiponectin receptors are relatively low, compounds that can increase the numbers of adiponectin receptors are required for the full activation of AdipoRs. In this context, PPARα activation by its agonist, Wy-14,643, upregulated expression of AdipoR1 and AdipoR2 in WAT (Tsuchida et al., 2005).

We have recently shown that chromatin immunoprecipitation sequencing analysis together with other analyses, including the gel-shift assay and luciferase assay, revealed a cluster of multiple functional PPAR/RXR binding sites PPRE in the intron 1, downstream of the transcription start site of AdipoR2 (Waki et al., 2011).

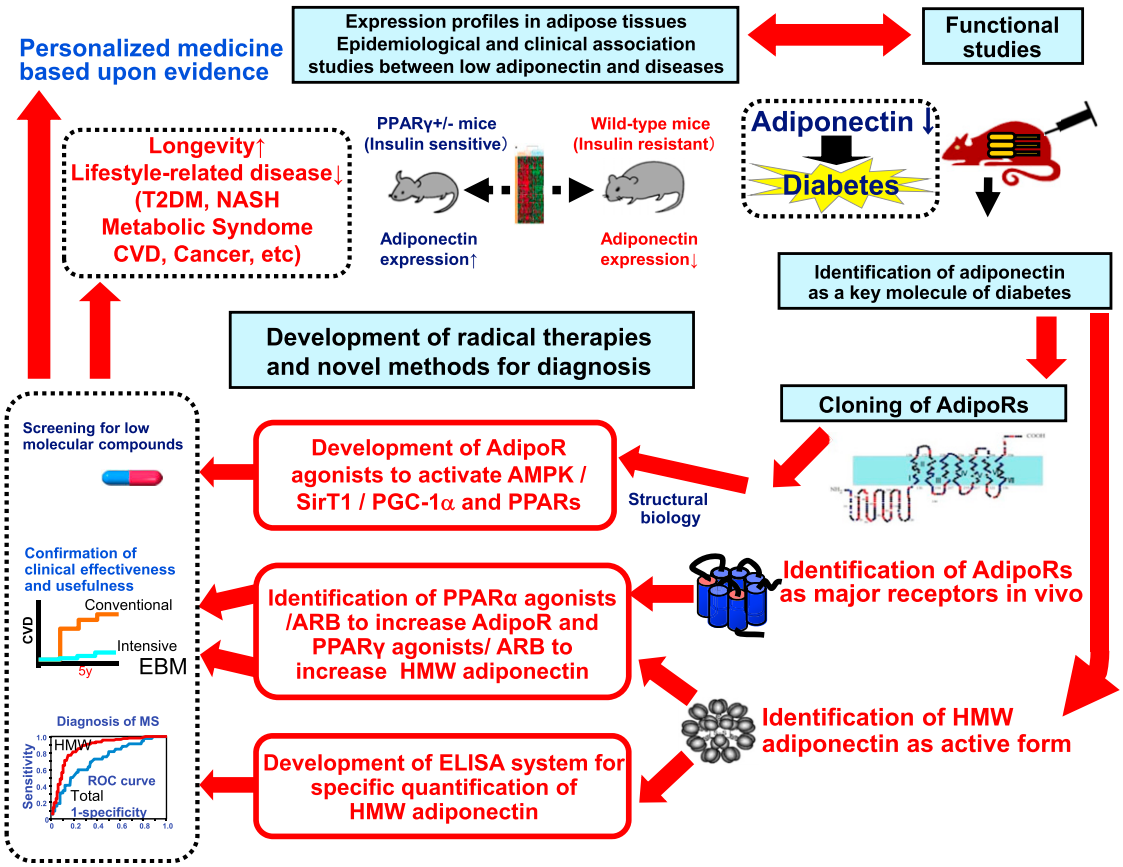

Figure 5. Translational Research Targeted to Adiponectin and AdipoRs
Combination of expression profiles in adipose tissues and epidemiological and clinical association studies between low adiponectin and diseases and functional studies led to identification of adiponectin as a key molecule of lifestyle-related disease such as diabetes. Then, AdipoR1 and AdipoR2 were identified by expression cloning. Disruption of AdipoR1 and AdipoR2 revealed that AdipoR1 and AdipoR2 are required for specific binding of adiponectin and glucose-lowering effects of adiponectin, indicating that AdipoR1 and AdipoR2 are major adiponectin receptors in vivo. PPARα agonists and ARB increase AdipoR expression. Human mutation analyses revealed that HMW adiponectin is the more active form of the protein and has a more relevant role in insulin sensitivity. PPARγ agonists and ARB increase total and HMW adiponectin. For development of methods for diagnosis, methods for specific quantification of HMW adiponectin were developed and clinical effectiveness and usefulness are now under investigation. For development of radical therapies, low-molecular-weight compounds are screened for AdipoR agonists.

Summary and Perspectives

Adiponectin is a fat-derived hormone that appears to play a crucial role in protecting against insulin resistance/diabetes and atherosclerosis (Yamauchi et al., 2001, 2002; Fruebis et al., 2001; Berg et al., 2001; Kubota et al., 2002; Maeda et al., 2002). Decreased adiponectin levels are thought to play a central role in type 2 diabetes and have been reported to be the most powerful predictor of diabetes, as well as cardiovascular disease, linked to obesity in humans (Kadowaki et al., 2006; Shetty et al., 2009; Matsuzawa, 2010). In the past 10 years, the receptors AdipoR1 and AdipoR2 were discovered and cloned, which was the starting point of fundamental understanding of adiponectin actions. In fact, pivotal roles of AdipoR1 and AdipoR2 in pleiotropic adiponectin actions have been demonstrated. Postreceptor signaling mechanisms downstream of AdipoR1 and AdipoR2 have also been progressively elucidated, albeit not completely.

As depicted in Figure 5, using DNA chips, we screened for secreted molecules in WAT, the expressions of which were increased in small adipocytes from insulin sensitive mice such as heterozygous PPARγ-deficient mice, and we found that increased expression of adiponectin correlates with increased insulin sensitivity in mouse models of altered insulin sensitivity. Combination of these expression profiles and epidemiological association studies between low adiponectin and clinical parameters, as well as functional analyses using transgenic or knockout mice led to identification of adiponectin as a key molecule of lifestyle-related disease such as diabetes. Then, AdipoR1 and AdipoR2 were identified by expression cloning. Disruption of AdipoR1 and AdipoR2 revealed that AdipoR1 and AdipoR2 are required for specific binding of adiponectin and glucose-lowering effects of adiponectin, indicating that AdipoR1 and AdipoR2 are major adiponectin receptors in vivo. Moreover, disruption of AdipoR revealed that adiponectin could activate AMPK/SirT1/PGC-1 and PPARs via AdipoR. Interestingly, PPARα agonists and angiotensin II receptor blocker (ARB) increase AdipoR expression. Human mutation analyses revealed that HMW adiponectin is the more active form of the protein and has a more relevant role in insulin sensitivity. Importantly, PPARγ agonists (TZDs and non-TZDs) and ARB increase total

and HMW adiponectin. For development of methods for diagnosis, methods for specific quantification of HMW adiponectin were developed and clinical effectiveness and usefulness are now under investigation. For development of radical therapies, low-molecular-weight compounds are screened for AdipoR agonists. Parallel to first-in-class drug development of low-molecular-weight compounds targeted to AdipoR, the analysis of 3D conformation of AdipoR is also under investigation. Toward development of best-in-class drugs for lifestyle-related diseases, AdipoR agonists are optimized based on three-dimensional conformation of AdipoR agonists-AdipoR complex.

We believe that further work on AdipoRs should facilitate both the understanding of the molecular mechanisms of adiponectin actions and obesity-related diseases such as diabetes and shortened life span, and also focus on the designing of antidiabetic and antiaging drugs with AdipoR agonist as a target.

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