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Adiponectin receptors: A review of their structure, function and how they work

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The discovery of adiponectin and subsequently the receptors it acts upon have lead to a great surge forward in the understanding of the development of insulin resistance and obesity-linked diseases. Adiponectin is a hormone that is derived from adipose tissue and is reduced in obesity-linked diseases including insulin resistance/type 2 diabetes and atherosclerosis. Adiponectin exerts its effects by binding to adiponectin receptors, two of which, AdipoR1 and AdipoR2, have been cloned. This has enabled researchers to carry out detailed studies elucidating the role played by these receptors and the metabolic pathways that are involved following their activation. Such studies have clearly shown that the stimulation of these receptors is associated with glucose homeostasis and ongoing research into their role will clarify the underlying molecular mechanisms of adiponectin. Such knowledge can then be used to provide therapeutic targets aimed at managing obesity-linked diseases including type 2 diabetes and metabolic syndrome.

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The anti-diabetic actions of adiponectin

Animal studies have been pivotal in providing evidence clarifying the role and mechanism of action of adiponectin and its receptors. Mouse models of increased insulin sensitivity such as the heterozygous peroxisome proliferator-activated receptor (PPAR)γ deficient mice have been used to screen for

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molecules secreted by white adipose tissue (WAT). Results demonstrate that the increased expression of adiponectin seen in these mice is associated with increased insulin sensitivity. Additional knowledge regarding the role adiponectin plays in glucose homeostasis was gained following an investigation into the effect of increasing the expression of adiponectin in insulin resistant mice (KKAy mice: KK mice overexpressing the agouti protein). A high-fat diet (HFD) was fed to KKAy mice, which resulted in decreased plasma adiponectin levels. The addition of adiponectin to these adiponectin-low mice resulted in significant improvement in the insulin resistance and hypertriglyceridemia, which they had developed in response to the HFD. Therefore adiponectin was recognized as an insulin-sensitizing adipokine [1]. An acute increase in the level of circulating adiponectin was also shown to trigger a transient decrease in basal glucose. This decrease in glucose levels, seen in both wild-type and type-2 diabetic mice, was associated with a reduction in hepatic gluconeogenic enzymes. Researchers proposed that adiponectin inhibits endogenous glucose production by sensitizing the body to insulin [2,3]. These findings were supported by evidence showing that a product of adiponectin increases fatty-acid oxidation in muscle, decreases plasma glucose, and causes weight loss in mice [4].

The direction of research then turned to investigating the long-term effects of adiponectin on insulin resistance. Adiponectin transgenic mice showed a reduction in insulin resistance and diabetes [5,6], while adiponectin-deficient mice showed mild insulin resistance with glucose intolerance, as well as dyslipidemia and hypertension [7–10].

Adiponectin receptors; structure and functions

Full length adiponectin undergoes proteolytic cleavage to form globular adiponectin, which has increased binding in myocytes and skeletal muscle membranes, but reduced binding in hepatocytes and liver membranes. The cDNA for adiponectin receptors was isolated from retrovirally infected Ba/F3 cells and was shown to encode a protein called AdipoR1 (Fig. 1). Two types of adiponectin receptor were identified with different binding affinities for globular or full-length adiponectin (AdipoR1 and AdipoR2) with human and mice sharing 96.8% and 95.25 of AdipoR1 and AdipoR2 identity, respectively. Human and mouse AdipoR1 is located at chromosome 1p36.13-q41 and 1 E4, whereas AdipoR2 is located at chromosome 12p13.31 and 6 F1, respectively. The molecular structure of both receptor forms are significantly homologous, with an internal N-terminus and external C-terminus [11]. AdipoR1 and AdipoR2 are part of the progesterone and adiponectin Q receptor (PAQR) family, some members of which contain sequence homology with alkaline ceramidase [12].

Mice studies have confirmed that AdipoR1 and AdipoR2 are major adiponectin receptors in vivo [13] and mediate metabolic actions of adiponectin. These effects have been confirmed, with AdipoR1·AdipoR2 double knockout mice shown to be glucose intolerant and hyperinsulinemic, indicating that AdipoR1 and AdipoR2 help to regulate normal glucose metabolism and insulin sensitivity. These effects are also dependent on specific tissues with liver AdipoR1 involved in activating AMP-activated kinase (AMPK), while AdipoR2 is involved in activation of PPARα, leading to increased insulin sensitivity. Therefore AdipoR1 and AdipoR2 serve as receptors for globular and full-length adiponectin and mediate increased AMPK, PPARα ligand activities, fatty-acid oxidation, and glucose uptake by adiponectin ([13]; unpublished observations). At present it is not clear whether the ceramidase activity exhibited by these receptors is integral to their structure or occurs via activation of another pathway. It has been proposed that the potential signal mechanisms are 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 [11–16] (Fig. 1).

Signaling mechanisms outlined

Full-length adiponectin stimulates the phosphorylation and subsequent activation of AMPK in both skeletal muscle and the liver, compared to globular adiponectin which only exerts its effect in skeletal muscle [17] (Fig. 1). When AMPK activation is blocked, glucose utilization and fatty-acid combustion is also inhibited, indicating that the action of adiponectin occurs through activation of AMPK [17]. In addition, muscle fat oxidation and glucose transport are enhanced by globular adiponection causing
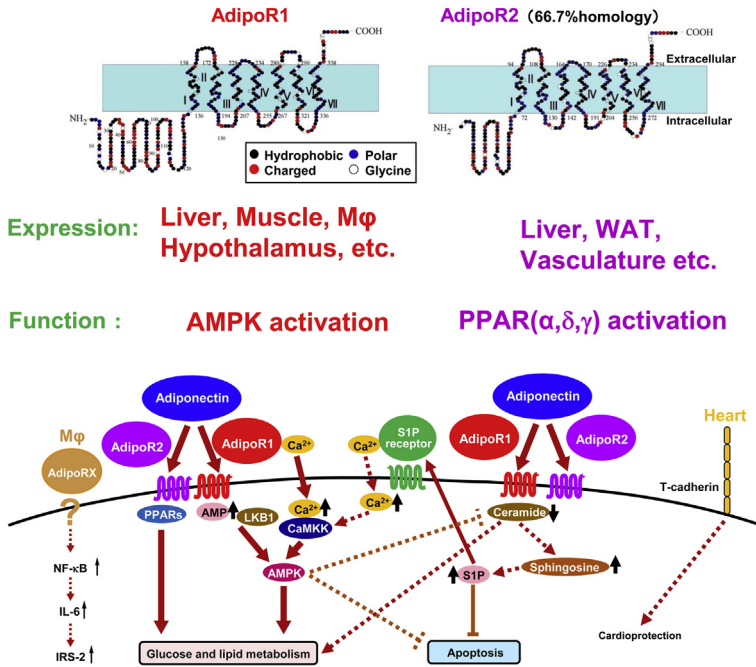
Fig. 1. Cloning and functional analysis of adiponectin receptors. Adiponectin receptors, AdipoR1 and AdipoR2 were identified by expression cloning in 2003. AdipoR1 and AdipoR2 are significantly homologous (67% amino acid identity). AdipoR1 and AdipoR2 appear to be integral membrane proteins; the N-terminus is internal and the C-terminus is external — opposite to the topology of all reported G protein–coupled receptors (GPCRs). AdipoR1 is abundantly expressed in liver, skeletal muscle, macrophages, hypothalamus and so on, while AdipoR2 is expressed in liver, white adipose tissue (WAT), vasculature and so on. 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-kappaB through a still unidentified adiponectin receptor AdipoRX but not AdipoR1 nor AdipoR2, leading to increased IRS-2 in hepatocytes under a fasted state.

AMPK activation and acetyl-CoA carboxylase inhibition [18]. Studies have also shown that the reduced expression of gluconeogenic enzymes such as phosphoenolpyruvate carboxylase and glucose-6-phosphatase that are found in adiponectin transgenic mice are associated with elevated phosphorylation of hepatic AMPK [6]. Results following deletion of LKB1 indicate that adiponectin suppresses hepatic SREBP1c expression in an AdipoR1/LKB1/AMPK dependent pathway. Investigating this pathway in more detail hasdemonstrated that LKB1- and AMPK-dependent and independent signaling pathways may exist *in vivo* [19].

Adiponectin, via AdipoR2, activates and increases the expression of PPARα ligands [5] (Fig. 1) and increases fatty-acid combustion and energy consumption [11,13]. This is partly done via increased expression of ACO and UCP, because the ACO and UCP genes possess peroxisome proliferator response element (PPRE) in their promoter regions.

Adiponectin also works on AdipoR1, inducing extracellular Ca^{2+} influx necessary for activation of Ca^{2+}/calmodulin-dependent protein kinase kinase (CaMKK)β, AMPK (Fig. 1). This step is then followed by activation of SirT1 and increased expression and decreased acetylation of PPARγ coactivator (PGC)-1α, and increased mitochondria in myocytes. Specifically disrupting the AdipoR1 in muscle results in suppression of the adiponectin-mediated increase in intracellular Ca^{2+} concentration, and decreases

the adiponectin-activation of CaMKK, AMPK and SirT1. Suppression of AdipoR1 also decreases the expression and deacetylation of PGC-1α, decreases mitochondrial content and enzymes, decreases oxidative type I myofibers, and decreases oxidative stress-detoxifying enzymes in skeletal muscle, which are associated with insulin resistance and decreased exercise endurance. These results support the proposal that decreased adiponectin and AdipoR1 levels in obesity may be causally associated with the mitochondrial dysfunction and insulin resistance seen in diabetes [14].

In addition to adiponectin activating AMPK, Ca^{2+}, and PPARα signaling pathways, it is also likely to be involved in other signaling pathways, possibly including ceramide signaling [12]. Adiponectin lowers cellular ceramide levels via activation of ceramidase, which is associated with an increase in sphingosine, leading to reduced hepatic ceramide levels and improved insulin sensitivity. Conversely a reduction in adiponectin levels increases hepatic ceramide, which may be implicated in insulin resistance (Fig. 1). The increased levels of sphingosine 1-phosphate (S1P) seen with increased levels of adiponectin, protect cells from apoptosis induced by either palmitate or C2-ceramide in cardiac myocytes and pancreatic beta cells [12] (Fig. 1). Either an inhibitor of ceramide biosynthesis or S1P itself reverses this effect. Therefore, adiponectin-induced S1P is likely to protects cardiac myocytes and beta cells from cell death. The importance of this ceramide pathway is supported by evidence the fact that it showing it to be totally dependent on adiponectin activating AdipoR1/AdipoR2, with an over-expression in adiponectin, AdipoR1 and AdipoR2 reducing hepatic ceramide levels, with improved insulin sensitivity.

Pathway regulation

AdipoR1 is found in many tissues, being particularly abundant in skeletal muscle, whereas AdipoR2 is most commonly found in the liver. The expression of these receptors in insulin target organs, such as skeletal muscle and liver, significantly increases in fasted mice and decreases in refed mice and *in vitro* studies have shown the expression of AdipoR1/R2 is reduced by insulin via the phosphoinositide 3-kinase/FoxO1-dependent pathway. AdipoR1 and AdipoR2 levels are significantly decreased in the muscle and adipose tissue of insulin-resistant *ob/ob* mice, probably partly due to obesity-linked hyperinsulinemia via FoxO [20] (Fig. 2). Additionally, adiponectin-induced activation of AMPK is reduced in the skeletal muscle of *ob/ob* mice, suggesting that the reduced expression of AdipoR1 and AdipoR2 seen in *ob/ob* mice is associated with insulin resistance [20]. This indicates that obesity not only decreases plasma adiponectin levels but also AdipoR1/R2 expression, thereby reducing adiponectin sensitivity and leading to insulin resistance, creating a "vicious cycle" [20].
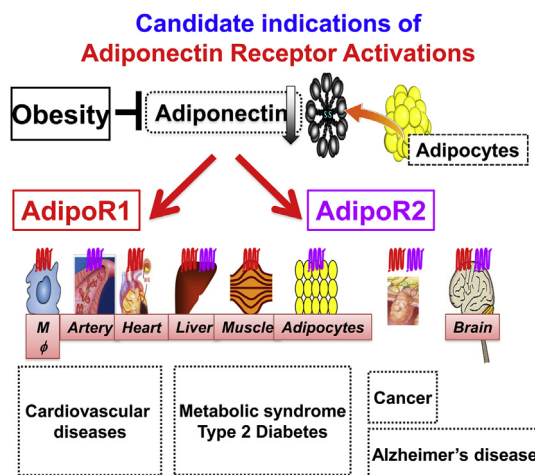

Fig. 2. Impaired adiponectin action is hallmark of obesity-linked diseases. Increased activation of adiponectin and AdipoRs pathways like exercise may have beneficial effects on healthy longevity and life-style related diseases, such as type 2 diabetes, metabolic syndrome, cardiovascular diseases, cancers, NASH, and so on.

Genetic factors

Data from the Québec Family Study has been used to investigate the association between ADIPOR1 and ADIPOR2 polymorphisms with energy metabolism and adiposity. One single-nucleotide polymorphism (SNP) each in the putative promoter of ADIPOR1 (i.e., −3882T→C) and ADIPOR2 (i.e., IVS1 −1352G→A) was associated with RQ (P = 0.03 and 0.04, respectively), and the association was even stronger in nonobese persons (P = 0.02 and 0.003). Carriers of the common alleles (ADIPOR1 T and ADIPOR2 G alleles) had a lower RQ than did the rare homozygotes. A significant genotype-by-genotype interaction (P = 0.0002–0.02) was found between SNPs in the promoters of ADIPOQ (−3971A→G) and ADIPOR1 (−3882T→C). Subjects carrying the minor ADIPOQ allele (G allele) who were rare homozygotes (C/C) for the ADIPOR1 SNP had a higher RQ (P = 0.003) and greater overall (P < 0.03) and abdominal (P < 0.05) adiposity than did persons with other genotype combinations. Thus variants in the promoter region of both ADIPOR genes contribute to substrate oxidation.

The Cebu Longitudinal Health and Nutrition Survey (CLHNS) genome-wide association study investigated the genetic loci associated with plasma adiponectin in 1776 unrelated Filipino women. Adiponectin was strongly associated with three genetic positions: the gene CDH13 (rs3865188, $P \leq 7.2 \times 10^{-16}$), near the ADIPOQ gene (rs864265, $P = 3.8 \times 10^{-9}$) and 100 kb upstream near KNG1 (rs11924390, $P = 7.6 \times 10^{-7}$). All three signals were also observed in 1774 young adult CLHNS offspring and in combined analysis including all 3550 mothers and offspring samples (all $P \leq 1.6 \times 10^{-9}$). An uncommon haplotype of rs11924390 and rs864265 (haplotype frequency = 0.050) was strongly associated with lower adiponectin compared with the most common C-G haplotype in both CLHNS mothers ($P = 1.8 \times 10^{-25}$) and offspring ($P = 8.7 \times 10^{-32}$). This is the first genome-wide study to provide evidence associating plasma adiponectin at the CDH13 locus, and with the KNG1-ADIPOQ haplotype with adiponectin levels in Filipinos [21].

Further genetic investigations were performed, looking at Mexican-American families with type 2 diabetes from the Veterans Administration Genetic Epidemiology Study (VAGES). Results revealed that heritability for plasma triglycerides was $46 \pm 7\%$ ($P < 0.0001$) with the strongest evidence for linkage of plasma triglycerides near marker D12S391 on chromosome 12p (logarithm of odds [LOD] = 2.4). Results from San Antonio Family Diabetes Study (SAFDS) also demonstrated a linkage signal on chromosome 12p. Combining results from the VAGES and SAFDS studies demonstrated significant evidence for linkage of plasma triglycerides to a genetic location between markers GATA49D12 and D12S391 on 12p (LOD = 3.8, empirical P value = 2.0×10^{-5}). The gene-encoding AdipoR2 has also been confirmed on 12p [22].

Possible other receptors and pathways

T-cadherin has been reported to bind adiponectin in C2C12 myoblasts and muscle although it is not expressed in the liver [3,10,23,24]. Since T-cadherin does not have an intracellular domain it is not thought to exert a direct effect on adiponectin cellular signaling or function, but rather may be an adiponectin-binding protein. This is supported by studies showing that adiponectin failed to associate with cardiac tissue in T-cadherin–deficient mice. Interestingly, T-cadherin is critical for adiponectin-mediated cardioprotection in mice [25] (Fig. 1). Adiponectin has been reported to modulate inflammatory reactions via calreticulin, which along with CD91 are involved in the adiponectin-mediated uptake of apoptotic cells [26]. Pretreatment with anti-calreticulin antibodies has also been demonstrated to reduce the adiponectin binding to cardiac myocytes and inhibited adiponectin-stimulated increase in Akt activation and survival in cardiomyocytes.

Adiponectin and receptors in disease

AdipoR1 and AdipoR2 modulate fatty acid metabolisms in the liver. This is demonstrated by the development of nonalcoholic steatohepatitis (NASH, fatty liver with inflammation and fibrosis) in obese *fa/fa* Zucker rats fed a high-fat/high-cholesterol diet. Expression of AdipoR1/R2 is significantly decreased in NASH, which was associated with decreased AMPKα1/α2 and PPARα. Increased synthesis

and decreased oxidation of fatty acids by down-regulation of AdipoR may contribute to the progression of NASH [27] (Fig. 2).

Adiponectin has also been reported to promote the development of an anti-inflammatory phenotype of macrophages, Kupffer cells and RAW264.7 macrophages, in a mechanism that is partially dependent on AMP-activated kinase [28,29]. The AMPK inactivation induced by saturated fatty acids decreased activation of unc-51–like kinase-1 (ULK1) resulting in decreased autophagy, and the generation of mitochondrial ROS. This then activates the NLRP3-ASC inflammasome, causing caspase-1, IL-1β, and IL-18 production, which finally leads to insulin resistance [30].

Adiponectin also suppresses inflammatory stimuli-induced NF-kappaB activation, which may significantly contribute to the anti-diabetic and anti-atherogenic effects of adiponectin (Ouchi et al., 2000). The downstream mediators of AdipoR1 and AdipoR2, RPPAR and AMPK increase inflammatory responses by transrepression of nuclear factor kappa B (NF-kappaB) target genes including COX2, which may partly account for the anti-inflammatory effects of adiponectin [31]. However, countering this is evidence showing that adiponectin activates NF-kappa B transcription factor in a variety of cell types including C2C12 myocytes and myotubes [32]. Adiponectin also elevates expression of COX-2 by stromal cells and release of prostaglandin E(2), while also blocking the formation of fat cells in bone marrow and inhibits the differentiation of cloned stromal preadipocytes. Adiponectin increases IL-6 in macrophages via activation of NF-kappaB through an adiponectin receptor (not AdipoR1/R2). This activates STAT3 in hepatocytes, ultimately increasing IRS-2 and insulin sensitivity [33] (Fig. 1).

Cardiac myocytes and heart tissue express adiponectin receptors which are decreased in hyperinsulinemia related to obesity, via the PI3K/Akt and FoxO1 pathway [34]. A decrease in AdipoR1 also decreases AMPK-dependent angiogenic response, and the down regulation of the adiponectin receptor pathway may be causally related to decreased cardiovascular function [35] (Fig. 2).

Adiponectin receptors are expressed in gastric, breast, prostate, and endometrial cancer cells [36]. The expression of AdipoR1 and R2 are decreased in a dose-dependent manner in gastric cancer cell lines, MKN-74 and NUGC-3, via transforming growth factor (TGF)-β [37]. AdipoR1 mRNA expression is also decreased in gastric cancer cells and AdipoR2 expression significantly decreased [38]. The decrease in adiponectin receptor expression in endometrial adenocarcinoma tissues is implicated in the development, invasion, and metastasis of the carcinoma [39]. The mechanism by which adiponectin and its receptors reduces cancer risk is probably indirectly through reduction in hyperinsulinemia as well as directly on tumor cells [40] (Fig. 2).

These results have led to the hypothesis that impaired adiponectin action is a hallmark of obesity-linked diseases, with hypoadiponectinemia and downregulation of adiponectin receptors. 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.

Exercise is associated with activation of AMPK and subsequent increased longevity. Adiponectin also activates AMPK via AdipoR1 in skeletal muscle, which in turn activates SirT1, implicated in longevity. Therefore, increasing activation of AdipoR1 provides a potential strategy to mimic the beneficial effect of exercise with increased life span.

Adiponectin also has a central action in regulating energy homeostasis by enhancing AMP-activated protein kinase activity in the arcuate hypothalamus (ARH) via its receptor AdipoR1 by stimulating food intake. Adiponectin also decreases energy expenditure. Fasting results in an increase in serum and cerebrospinal fluid levels of adiponectin and expression of AdipoR1 in the ARH, with this countered by refeeding. Therefore adiponectin stimulates food intake and decreases energy expenditure during fasting through its effects in the central nervous system [41].

Therapeutic strategies using adiponectin and its receptors

A reduction in the effect of adiponectin appears to have a causal role in the development of obesity-related diseases such as diabetes and cardiovascular diseases. To counteract this it has been proposed that strategies aimed at increasing adiponectin receptors would be useful. Therefore PPARα activation by its agonist, Wy-14,643 would be a potential strategy as it results in increased expression of AdipoR1

and AdipoR2 in WAT [42]. A cluster of multiple functional PPAR/RXR binding sites PPRE in the intron 1, downstream of the TSS of AdipoR2 have also been identified [43]. Another mechanism would be to activate AdipoRs, using small-molecule compounds and activating antibodies against AdipoRs.

Practice points

- A correlation has been reported between adiponectin receptor gene expression and insulin sensitivity.
- Down regulation of adiponectin receptor pathway could be causally implicated in decreased cardiovascular function.
- Increased synthesis and decreased oxidation of fatty acids by down-regulation of AdipoR may contribute to the progression of NASH.
- 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 mTOR pathway by activating AMP kinase.

Research agenda

- Drug development of small-molecule compounds targeted to AdipoR.
- Analysis of 3D structure of AdipoR.
- Optimization of ARA(Adiponectin receptor agonist)s based on 3D structure of ARA-AdipoR complex.
- Development of best in class drugs for type 2 diabetes and obesity-linked diseases with AdipoR as a target.

Summary

Adiponectin plays an important role in protecting against insulin resistance/diabetes and atherosclerosis [1,2,4,7,8,17]. Therefore a decrease in adiponectin is thought to play a central role in type 2 diabetes and is strongly associated with the likelihood of developing obesity-induced diabetes and cardiovascular disease [15,44,45]. The cloning of adiponectin receptors AdipoR1 and AdipoR2 has allowed research to be performed which have proven the pivotal actions AdipoR1 and AdipoR2, confirming they are necessary for binding of adiponectin and subsequent glucose-lowering effects of adiponectin. Moreover, disruption of AdipoR has shown that adiponectin could activate AMPK/SIRT1/PGC-1 and PPARs via AdipoR. Therapeutic strategies could screen low molecular compounds for AdipoR agonists and along with this, the 3D conformational analysis of AdipoR could provide potential treatment approaches. In order to develop best in class drugs for lifestyle-related diseases, AdipoR agonists are optimized based on 3D analysis of AdipoR agonist-AdipoR conformation. Further research clarifying AdipoRs should facilitate both the understanding of the molecular mechanisms of adiponectin actions and obesity-linked diseases such as diabetes and reduced longevity, and focus on the designing of novel antidiabetic and anti-aging drugs with AdipoR agonist as a target.

Acknowledgments

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