

Adiponectin: Role in Physiology and Pathophysiology

Abstract

Adiponectin, an adipokine secreted by adipocytes, is a well-known homeostatic factor for regulating glucose levels, lipid metabolism, and insulin sensitivity through its anti-inflammatory, anti-fibrotic, and antioxidant effects. All these metabolic processes are mediated via two adiponectin receptors, AdipoR1 and AdipoR2. In addition, adiponectin is one of the hormones with the highest plasma concentrations. Weight loss or caloric restriction leads to increasing adiponectin levels, and this increase is associated with increased insulin sensitivity. Therefore, the adiponectin pathway can play a crucial role in the development of drugs to treat type 2 diabetes mellitus and other obesity-related diseases affected by insulin resistance like cancers or cardiovascular diseases. Adiponectin appears to increase insulin sensitivity by improving glucose and lipid metabolisms. The objective of this review is to analyze current knowledge concerning adiponectin and, in particular, its role in physiology and pathophysiology.

Keywords: *Adipokines, adiponectin, AdipoR, obesity, type 2 diabetes mellitus*

Introduction

Adiponectin was characterized, in 1995, as a protein abundantly secreted by 3T3-L1 adipocytes and present at high plasma concentrations in mice. Adiponectin is also referred to as ACRP30, AdipoQ, apM1, or GBP28. Four different teams working differently discovered that it is produced by the white adipose tissue almost at the same time.^[1-4] Of all this nomenclature, the name adiponectin (ApN) is the most widely accepted. Numerous studies have made it possible to establish the determining role of ApN in energy homeostasis, the metabolisms of lipids and carbohydrates, in particular in muscle and liver, as well as its anti-inflammatory and anti-atherogenic properties.^[5] ApN has also been detected in skeletal muscle,^[5] cardiomyocytes,^[6] osteoblasts,^[7] lymphocytes,^[8] adrenal gland,^[9] placenta,^[10] testis,^[11] ovary,^[12] pituitary gland,^[13] and liver tissue.^[14] The objective of this review is to analyze current knowledge concerning ApN and, in particular, its role in physiology and pathophysiology.

Adiponectin Structure and Biology

Structure of adiponectin

ApN is a specific protein in the adipose tissue of 247 amino acids with a molecular

weight of 30 kDa in mice and 244 amino acids with a molecular weight of 28 kDa in humans.^[1,4] The protein structure of ApN includes four parts: a signal region at the NH₂-terminus, a variable region that is species specific, a collagenous domain and a globular domain at the COOH-terminus.^[15]

Circulating ApN oligomers are present in plasma in three multimeric forms [Figure 1]. The assembly is carried out beforehand in the endoplasmic reticulum by post-translational modifications, such as hydroxylations and glycosylations of the ApN monomer. The globular domain allows the formation of low molecular weight trimers by hydrophobic bond, and the interactions at the level of the collagen domain by disulfide bonds allow the formation of medium molecular weight hexamers (association of two trimers), and high molecular weight multimers (4 to 6 trimers). ApN is also present in plasma in its globular form alone, resulting from proteolysis, but in very small quantities.^[16] The different forms of ApN have different biological properties and probably different tissue targets.

Synthesis of adiponectin

Unlike other adipokines, ApN has an inverse relationship with obesity.^[17] Several studies have shown that weight loss, including a reduction in body fat, is accompanied by an increase in circulating ApN levels.^[18]

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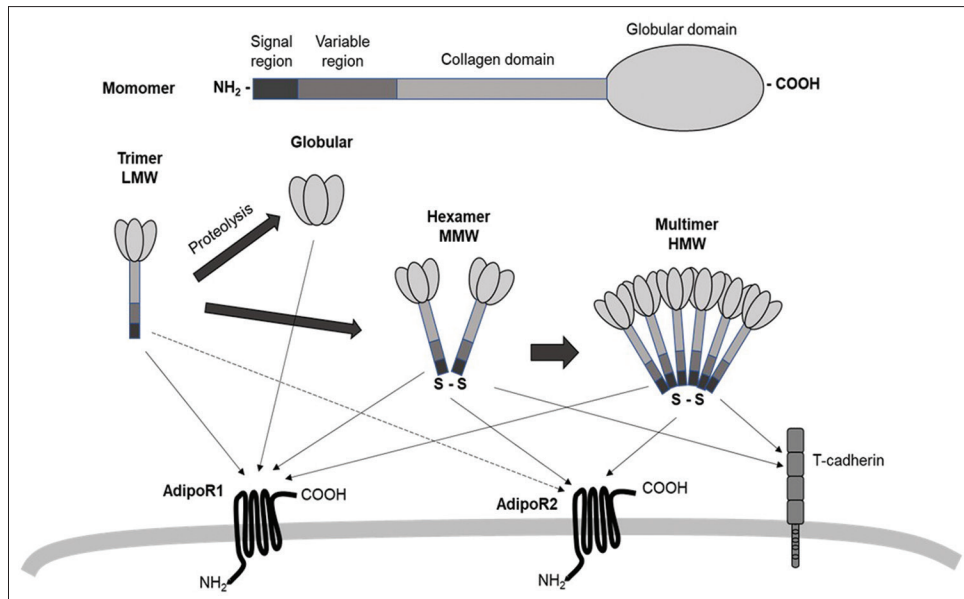


Figure 1: Adiponectin structure and receptors. Monomeric ApN consists of a globular domain, a collagenous domain, a species-specific domain, and a signal peptide. Oligomerization facilitates the formation of the trimers (LMW), hexamers (MMW), and multimer (HMW). S-S: disulfide bond. ApN interacts with ApN receptors: AdipoR1, AdipoR2, and T-Cadherin. The dotted line between AdipoR2 and globular ApN reflects that AdipoR2 is a relatively low-affinity receptor for globular ApN

The increase in circulating ApN induced by weight loss is not homogeneous but is in favor of the HMW form and to the detriment of the LMW and MMW forms.^[19] This is important, considering that the high molecular weight form is currently considered to be the active form of ApN, or at least more active than the LMW and MMW forms.^[20,21] During puberty, a notable decrease in the circulating ApN concentration is observed in males.^[22] In addition, circulating ApN levels also vary by ethnicity^[23] and are positively associated with age.^[24] Arai *et al.* (2006) showed that centenarians had higher circulating ApN levels than younger people with the same BMI.^[25] The body fat of the subjects was not measured in this study, however. The circadian variation profile of ApN shows that concentrations fluctuate by about 20% over 24 hours, with a slight decrease in rates overnight until a minimum in the early morning.^[26] This daily variation seems to be greater in women than in men and would not differ between thin and obese subjects.^[27]

Structure of adiponectin receptors

To exert its biological effects, ApN must bind to its specific receptors. The AdipoR1 and AdipoR2 receptors were first identified by Yamauchi *et al.* (2003),^[28] and T. Cadherin [Figure 1], a member of the cadherin family, has also been identified by Hugh *et al.* (2004) as a receptor of hexamers and HMW adiponectin oligomers.^[29]

The AdipoR1 and AdipoR2 receptor genes are located on chromosomes 1, locus 1p36.13-q41, and 12, locus 12p13.31, respectively. AdipoR1 and AdipoR2 are members of the progesterin and AdipoQ receptor superfamily, which possesses seven transmembrane domains. They are

topologically integral membrane proteins with intracellular N-terminus and extracellular C-terminus, which is the reverse topology of all other G-protein coupled receptors.^[28]

The AdipoR1 receptor has a higher affinity for the globular form, while the AdipoR2 receptor preferentially binds to the high molecular weight form [Figure 1]. It was initially shown that the AdipoR1 receptor was mainly expressed in skeletal muscles and AdipoR2 in the liver.^[28] Subsequently, the expression of these receptors has been identified in other tissues, such as the myocardium, macrophages, brain tissue, endothelial cells, lymphocytes, and adipose tissue,^[30] or in pancreatic β cells where the level of expression of AdipoR2 is even equivalent to that of its expression in the liver, and the level of expression of AdipoR1 higher than that of its muscle expression.^[31] Studies in mice have confirmed that these two receptors are the main ApN receptors *in vivo* and that they mediate the effects of ApN.^[32] Thus, KO mice for these two receptors develop glucose intolerance and hyperinsulinemia, showing their major involvement in carbohydrate homeostasis and insulin sensitivity. These effects appear to be receptor-specific, with in particular the involvement of AdipoR1 in the activation of AMPK while AdipoR2 is involved in the activation of PPAR α .^[30] More generally, a study to invalidate these receptors has shown that the involvements of the AdipoR1 and AdipoR2 receptors in metabolism are very different.^[33] In particular, they showed that AdipoR1 KO mice increase their adipose mass and insulin sensitivity, and decrease their glucose tolerance and energy expenditure. Conversely, AdipoR2 KO mice show better sensitivity to insulin and glucose, maintain normal body weight even under a fatty diet, spend more energy and improve their dyslipidemia.

T-cadherin is a glycoprotein involved in cell adhesion and a potential receptor for ApN. It is colocalized at the cellular level with ApN and is expressed in tissues like aorta, heart, or skeletal muscle, but almost none T-cadherin can be found in liver.^[34] Only the high molecular weight complexes of ApN are capable of binding T-cadherin, which implies that post-translational modifications of ApN are essential for its binding. It is therefore conceivable that T-cadherin, which is an extracellular protein without an intracellular domain, can act as an ApN binding protein rather than as a co-receptor.^[29] It has been shown by Fukuda *et al.* (2017) that T-cadherin has a role in adiponectin binding, especially the 130-kDa prodomain-bearing where T-cadherin is preferentially localized on the cell surface and bound more adiponectin than its 100-kDa form.^[35] Exosomes that contain adiponectin and T-cadherin are released in response to adiponectin in cells expressing T-cadherin.^[36]

Regulation of adiponectin receptor expression

Various factors regulate the expression of ApN receptors, which are thus expressed differently depending on the tissue. In the adipose tissue of transgenic mice for the ApN gene, with a targeted overexpression of ApN in adipose tissue, the level of expression of the AdipoR2 receptor is increased, but not that of AdipoR1.^[37] Furthermore, in adipose tissue, the expression levels of ApN receptors are associated with the level of tissue expression of ApN.^[38] The expression levels of AdipoR1 and AdipoR2 are inversely correlated with body fat and obesity.^[39,40] Unlike the expression of ApN itself, there is no sexual dimorphism in the expression of ApN receptors in adipose tissue.^[40] McAinch *et al.* (2006) showed that ApN up-regulates the AdipoR1 receptor in differentiated primary skeletal muscle cells from normal-weighted subjects, but not those from diabetic, obese, or having lost weight.^[41] The level of expression of the AdipoR2 receptor was not changed in this study. AdipoR1 and AdipoR2 receptors expression levels are also associated with age and aerobic capacity in skeletal muscle.^[42] Unlike adipose tissue, the expression of ApN receptors in muscle depends on gender, with men expressing more ApN receptors,^[42] this dimorphism thus appears to be tissue specific. Interestingly, circulating ApN levels are lower in men than women, which can be explained by the level of receptor expression in muscle. Finally, a study has shown that the expression of the three receptors is highly correlated, and positively associated with the expression of PPAR δ in human myocytes.^[43]

Adiponectin: Role in Physiology and Pathophysiology

Carbohydrate metabolism and insulin sensitization

Numerous studies have shown the existence of an inverse relationship between circulating ApN concentrations and insulin resistance in several pathologies with high cardiovascular risk such as obesity, metabolic syndrome,

and T2DM.^[44,45] The question is to know the meaning of this interaction. Mice disabled for the ApN gene develop hepatic, but not global resistance to insulin, with a 65% increase in hepatic glucose production. On a diet rich in saturated fatty acids, they also develop carbohydrate intolerance, which can be corrected by acute administration of recombinant ApN, without modification of muscle glucose uptake. Following this administration, the hepatic expression of the enzymes of gluconeogenesis, phosphoenol-carboxykinase and glucose-6-phosphatase is increased, with no change in insulinemia, which is a sign of insulin sensitization.^[46] In addition, the notion of an insulin-sensitizing activity of ApN is reinforced by the observation in individuals with extreme insulin resistance of a high ApN concentration.^[47]

In mice, injection of recombinant ApN induces an increase in circulating insulin levels.^[48] Indeed, it has been demonstrated that the treatment of pancreatic β cells with ApN induces an increase in insulin exocytosis, accompanied by an increase in expression of Pdx-1 and MafA genes, co-activators of transcription of the insulin gene.^[49] ApN promotes the consumption of glucose by stimulating the membrane translocation of GLUT4 in muscle cells and adipocytes following the phosphorylation of AMPK.^[50,51] This phenomenon is associated with the activation of the Rab5 protein by the APPL1 protein. Indeed, Rab5 is a GTPase involved in the biogenesis of endosomes, whose role seems crucial during the translocation of GLUT4 from endosomes to the plasma membrane.^[52] ApN also inhibits the formation of glucose and glycogen. In liver cells, glycogenolysis and gluconeogenesis are slowed down by ApN, following the decrease in the expression of two key enzymes in these pathways, glucose-6-phosphatase and PEPCK.^[53] In muscle cells, glycogen production is also reduced by ApN, following activation of AMPK.^[51] ApN induces a drop in blood sugar by its hypoglycemic action, it helps protect the body against the onset of T2DM.^[51]

Lipid metabolism

Mice homozygously disabled for the ApN gene exhibit hepatic steatosis in the long term, but not in the short term. Conversely, mice transfected with ApN gene have a reduced hepatic triglyceride content and, fed a diet rich in fat, limit the hepatic accumulation of triglycerides and lipid derivatives. Conversely, ApN promotes the differentiation of adipocytes, their sensitivity to insulin, and their accumulation of triglycerides.^[54] It therefore appears that ApN diverts fatty acids from ectopic (non-subcutaneous) lipid deposits towards deposits of young subcutaneous adipocytes, which generate less insulin resistance.^[55] Having found no mention in studies of the *in vitro* effects of ApN on lipoproteins, it is difficult for us to distinguish whether dyslipidemia linked to hypoadiponectinemia results from a direct hepatic effect of the hormone or from an indirect effect of insulin resistance.

ApN increases the transport of fatty acids into muscle cells, stimulating the expression of fatty acid translocase. It also promotes the catabolism of fatty acids by inducing the activity and expression of many enzymes involved in the β -oxidation process.^[50] In particular, via AMPK, ApN inactivates ACC by phosphorylation. This enzyme catalyzes the production of malonylcoA, an inhibitor of CPT-1. This protein transports fatty acids to the mitochondria.^[56] By lifting the inhibition of CPT-1, ApN promotes mitochondrial transport of fatty acids where they are degraded by the enzymes of β -oxidation. ApN also regulates the transcription of many genes involved in lipid catabolism, such as ACO, FABP3, and CPT-1 by inducing the expression of the transcription factor PPAR α .^[57]

ApN also promotes the accumulation of triglycerides in adipocytes.^[54] In the liver, on the other hand, it reduces the transport of fatty acids and the accumulation of triglycerides.^[58] ApN inhibits the expression of around thirty hepatic genes encoding proteins involved in the transport of fatty acids and lipogenesis.^[59] ApN therefore controls lipid metabolism by promoting the transport of fatty acids and β -oxidation in muscle cells, by inhibiting hepatic lipogenesis and by stimulating the storage function of adipose tissue. It therefore induces a decrease in circulating lipid levels, exerting a lipid-lowering role in the body.

Cardiovascular effects

In the cardiovascular system, the effects of ApN are not limited to carbohydrate metabolism alone. A role is indeed recognized for it in cardiovascular pathology in particular. Atherosclerosis is the result of a complex process in which the adhesion of circulating monocytes to endothelial cells, their differentiation into macrophagic cells, the accumulation of cholesterol within them, and their transformation into foam cells are key steps. Various receptors such as receptors of the R scavenger family and numerous adhesion molecules including VCAM-1 or ICAM-1 play important roles in it. ApN could suppress the expression of the scavenger type A receptor at the macrophagic level and, in this way, inhibit the lipid accumulation and the transformation into foamy cells of circulating monocytes.^[60] Likewise, it would antagonize the action of TNF α . The latter, via the NF- κ B pathway, stimulates the transcription of endothelial adhesion molecules and represents a factor in the pro-inflammatory reaction.^[61] We reported above that plasma ApN levels were significantly lowered in obese patients, who are also known to be at high cardiovascular risk. Measuring the plasma ApN level could therefore constitute an index to be taken into account in the assessment of coronary risk. In addition, there is a sexual dimorphism: the women have higher ApN levels than men and menopause does not affect their levels.^[62-64] Oophorectomy does not change plasma ApN levels and estrogen replacement has no effect

on them either. In contrast, castrated male mice expressed significantly decreased ApN levels, while, in cell cultures, adding testosterone reduced both circulating ApN and ApN secretion.^[63,65] This treatment also induces insulin resistance. In contrast, oophorectomy does not cause changes in ApN levels in female mice. Therefore, ApN may be involved in increasing the cardiovascular risk in men.

In addition, there is a close link between insulin resistance and atherosclerosis. ApN levels are further reduced in patients with T2DM complicated by atherosclerosis. Recently, a modulating effect on vascular remodeling has also been suggested by the suppressive activity of ApN on proliferation and migration of human aortic smooth muscle cells. A mouse model deficient in ApN showed a neointimal formation, in response to an external vascular lesion, twice as large than that observed in normal mice.^[66] This type of mouse exhibited moderate insulin resistance accompanied by glucose intolerance. Furthermore, the treatment of ApN-deficient mice with an ApN-producing adenovirus attenuated neointimal proliferation. ApN therefore seems to be a cytokine with an “anti-insulin resistance” and “anti-atherosclerosis” effect.

Therefore, manipulations of the ApN gene in mice have clarified its involvement in vascular and carbohydrate homeostasis. In the absence of ApN, the response to an external arterial injury is exacerbated, with thickening of the intima and excessive proliferation of smooth muscle cells.^[67] Conversely, administration of ApN reduces the extent of atherosclerotic lesions that appear spontaneously in apolipoprotein E-deficient mice.^[68] More recent studies suggest that ApN may also act as an antithrombotic factor and protect against ischemic damage to the myocardium.^[69,70] In humans, epidemiological studies clearly point to low circulating levels of ApN as a risk factor for cardiovascular disease, while high levels are associated with a reduced risk of myocardial infarction.^[67]

Adiponectin, obesity, insulin resistance, and T2DM

Conditions associating insulin resistance, T2DM and obesity, as in the case of lipodystrophy, present collapsed serum ApN levels.^[58] Studies carried out in knockout mice for the ApN gene (mice genetically deprived of the expression of this protein) provide different elements as to the role played by this adipocytokine. In KO mice, we can measure lower plasma acid clearance and levels of FATP-1, as well as increased TNF α levels in adipose tissue and in plasma. When these mice are put on a diet rich in glucose and lipids, they acquire insulin resistance, probably linked to a decrease in the substrate of the intracellular insulin type 1 receptor, thus causing reduction of intracellular uptake of glucose by insulin-sensitive tissues (mainly skeletal muscle).^[58] The restitution of ApN expression in this KO mouse corrects these various metabolic abnormalities. ApN therefore appears to be a hormone sensitizing the action of insulin and a decrease

in its production could be linked to the pathophysiology of insulin resistance. In human, many clinical studies indicate that increased ApN is a negative predictor of the development of insulin resistance and T2DM in BMI-adjusted subjects populations.^[71-73] A lowered plasma ApN level is a risk factor for progression of T2DM. The mechanisms by which ApN improves insulin sensitivity are unknown. Studies in lipotrophic mice and in animal obesity models suggest that ApN improves tissue sensitivity to insulin by lowering the plasma concentration of free fatty acids. The action of ApN could also involve stimulating the activity of AMPK.^[50] Insulin resistance causes stress in the endoplasmic reticulum, where the adiponectin multimer is formed, which in turn activates the unfolded protein response, and then suppresses adiponectin synthesis.^[74] In addition, obesity-induced inflammation and oxidative stress inhibit adiponectin maturation and secretion.^[75]

In addition, the insulin-sensitizing effects of new anti-diabetic molecules such as the PPAR γ nuclear receptor agonists (thiazolidinediones) are accompanied by an increase in adiponectinemia. Carriers of the Pro12Ala variant of the PPAR γ gene, which we know is protective against T2DM, have also high adiponectinemia. Conversely, diabetic, insulin-resistant, and hypertensive patients with mutants with a negative dominant effect of PPAR γ have collapsed adiponectinemia. Thus, in humans, hypoadiponectinemia is a risk factor for T2DM.^[76] These results are confirmed by studies in animal models showing unambiguously that insulin resistance and a high susceptibility to atherosclerosis accompany ApN deficiency. Conversely, the administration of ApN in lipodystrophic or obese mice corrects their insulin resistance.^[58] Recent genome studies have highlighted the ApN gene on the long arm of chromosome 3 (3q27). At this locus, a susceptibility to diabetes and dysmetabolic syndrome has been localized. Indeed, polymorphisms of this gene are associated with insulin resistance as well as a predisposition to T2DM, most certainly via an alteration in his expression which results in lowered ApN plasma levels.^[77] Therefore, the ApN gene has been proposed as a gene for susceptibility to T2DM. Studies in Pima Indians and in the general population also indicate that subjects with high concentrations of ApN are less at risk of developing T2DM than those with low concentrations.^[78] Genetic analyzes at the ApN locus on chromosome 3q27 also support the implication of low ApN levels in increasing the risk of T2DM.^[46] Thus, the decrease in adiponectinemia is now identified as a contributing factor in the pathogenesis of insulin resistance, T2DM, and cardiovascular pathologies.

ApN and its signal in cancer

Obesity, a disease characterized by significant excess of body fat, is a risk factor for many conditions like T2DM, cardiovascular diseases, as well as malignancies leading to cancers. Obesity decreases ApN while it is now

established that ApN helps against cancer by limiting tumor development and the metabolic dysfunctions that they can cause.^[79] ApN indeed reduces cancer cells migration and invasion abilities, stops their growth and proliferation, and helps in triggering apoptosis in them.^[80] ApN helps fighting endometrial cancer, and, as a corollary, a low ApN level is associated with a faster development of the illness.^[81] The analysis of serum of patients with ovarian cancer also show low levels of ApN.^[82] AdipoR1 and AdipoR2 are expressed in epithelial ovarian cancer cell, granulosa tumor cell, cancerous epithelial, and ovarian tissues.^[83-85] A positive AdipoR1 expression in patients with epithelial ovarian cancer is associated with a better life expectancy than a negative AdipoR1 expression.^[84] ApN decreased epithelial ovarian cancer cell proliferation independently from apoptosis.^[85] Thyroid cancer cells express both AdipoR1 and AdipoR2, while papillary thyroid carcinoma cell lines express a significantly lower number of receptors than normal thyrocytes.^[86] In prostate cancers, ApN and its receptors are known to be importantly involved but so far the results are partly contradictory.^[87] AdipoR1 and AdipoR2 receptor isoforms expression has thus been measured at a low level in prostate cancerous neoplastic tissue.^[88] ApN levels of patients with advanced prostate cancer were measured at a higher level than those at an earlier stage of the illness. Furthermore, AdipoR2 expression has also been reported to be directly associated with prostate cancer progression and metastatization.^[89] Recently, scientists have shown that treatment with adiponectin significantly inhibits the proliferation of human pancreatic cancer cells. Suppression of adiponectin receptors abolished the antiproliferative effect of adiponectin and clearly promoted the development of human pancreatic cancer xenografts in nude mice.^[90] ApN also inhibits the proliferation of cancer cells in the colon and changes the cell cycle in the G1/S transition phase.^[91]

Conclusions

Adiponectin is an adipokine produced and secreted by adipocytes. The biological actions of adiponectin are mediated through interactions with its receptor subtypes, AdipoR1, AdipoR2, and T-cadherin. ApN exerts multiple protective effects on various cell types, such as insulin-sensitizing, anti-inflammation, anti-proliferation, or anti-atherosclerotic actions and suppression of carcinogenesis. ApN is also a relatively abundant serum protein in human. Its levels are decreased in various pathological states including insulin resistance, T2DM, obesity, metabolic syndrome, or cardiovascular diseases. Many studies have shown the protective role of ApN in obesity-associated diseases and cancer. ApN modulates several signaling pathways to exert its physiological and protective functions. Figure 2 shows the involvement of APN in the signaling of its target cells. Focusing on ApN for new therapeutic strategies is full of promise regarding

ADIPONECTIN	
Liver	↓ Glycogenolysis; gluconeogenesis ↓ Lipogenesis; triglycerides
Pancrea	↑ Insulin exocytosis
Muscle	↓ Glycogen production ↑ Consumption of glucose ↑ Transport of fatty acid and fatty acid oxidation ↓ Triglycerides
Adipocytes	↑ Consumption of glucose ↑ Triglycerides ↑ Fat storage function of adipocytes

Figure 2: Summary of the involvement of Adiponectin in the signalling of its target cells

the aforementioned protective action against metabolic diseases.

Abbreviations

ApN	Adiponectin
ACRP30	Adipocyte complement-related protein of 30 kDa
ADIPOQ	Adiponectin, C1Q and Collagen Domain Containing
APM1	Adipose most abundant gene transcript 1
GBP28	Gelatin-binding protein 28
LMW	Low molecular weight
MMW	Medium molecular weight
HMW	High molecular weight
AdipoR1	Adiponectin receptor 1
AdipoR2	Adiponectin receptor 2
BMI	Body mass index)
KO	Knockout
AMPK	AMP-activated protein kinase
PPAR	Peroxisome proliferator-activated receptor
T2DM	Type 2 diabetes mellitus
GLUT4	Glucose transporter type 4
PEPCK	Phosphoenolpyruvate carboxy kinase
CPT-1	Carnitine palmitoyl transferase-1
ACO	Acetyl-CoA oxidase
ACC	Acetyl-CoA carboxylase
FABP3	Fatty-acid binding-protein 3
VCAM-1	Vascular cell adhesion molecule-1
ICAM-1	Intercellular adhesion molecule-1
TNF α	Tumor necrosis factor alpha
NF- κ B	Nuclear factor kappa B
FATP-1	Fatty acid transport proteins-1

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