The effect of Adiponectin Receptors AdipoR1/AdipoR2 in Obesity and type II Diabetes, Cancer, and Cardiovascular and as potential therapeutics (Part two)

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Abstract

Adiponectin (Acrp30) is a novel polypeptide classified among adipokines that are chiefly secreted by adipocytes within adipose tissue. Besides the adipose tissue, levels of the adipocytokine also circulate in human plasma.

Recent studies strongly indicate that adipose tissue is an active endocrine organ that secretes bioactive factors such as adipokines. Adiponectin appears to have a regulatory role in the mechanism of insulin resistance and in the development of atherosclerosis.

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.

Adiponectin, the most abundant protein secreted by adipose tissue, exhibits insulin-sensitizing, antiinflammatory, antiatherogenic, proapoptotic, and antiproliferative properties.

Recent in vitro studies demonstrate the antiangiogenic and tumor growth-limiting properties of adiponectin. Studies in both animals and humans have investigated adiponectin and adiponectin receptor regulation and expression in several cancers.

Current evidence supports a role of adiponectin as a novel risk factor and potential diagnostic and prognostic biomarker in cancer. In addition, either adiponectin per se or medications that increase adiponectin levels or up-regulate signaling pathways downstream of adiponectin may prove to be useful anticancer agents.

In this article, I discuss Adiponectin Receptors AdipoR1/AdipoR2, Signal Transduction Mechanisms, Molecular Characteristic of Adipocytes, Cell Biological Functions of Adiponectin,

Adiponectin and endothelial function, Regulation of adiponectin expression, Adiponectin in obesity and type II diabetes, Adiponectin in cancer and Therapeutic role of adiponectin

Key Word: Adiponectin Receptors AdipoR1/AdipoR2, Signal Transduction Mechanisms, Molecular Characteristic of Adipocytes, Cell Biological Functions of Adiponectin, obesity, type II diabetes and cancer

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1. Introduction

Adiponectin, also known as Acrp30 (1), AdipoQ (2), GBP-28 (3), and apM1(4), and independently identified by four groups using different approaches (1),(2),(4),(3), was originally cloned as an adipocyte-enriched protein highly induced upon 3T3-L1 adipocyte differentiation (1). The human adiponectin gene encodes a 244-amino acid protein of 30 kDa (247 amino acids for the mouse ortholog), whose primary structure includes a signal peptide, a variable region, a collagen-like domain, and a globular domain (5). The full-length adiponectin protein shares structural similarity with complement factor C1q, tumor necrosis factor-a, and collagens VIII and X. Adipocytes synthesize and secrete multiple forms of adiponectin: low-molecular weight (LMW) trimers (the most basic form), medium-molecular weight (MMW) hexamers, and high-molecular weight (HMW) oligomers of 4–6 trimers (6),(7),(8),(9). A proteolytic adiponectin fragment, known as globular adiponectin (gAd), also occurs in human plasma (10),(8). During the past 20 years, a large body of work established important roles of adiponectin in metabolic regulation and inflammatory/antiinflammatory processes. Notably, each adiponectin formappears to have distinct target tissue specificity andmodulates unique biological processes (11),(12). Adiponectin is an insulin sensitizer (13),(14),(15),(16), and reduced adiponectin levels (17),(18),(19),(20),(21), and /or ratios of HMW/LMW (7),(22),(23), are linked to insulin resistance and metabolic syndrome. When supplied exogenously

(13),(14),(15),(24), or overexpressed as a transgene (25),(26),(27),(28), adiponectin suffices topromote insulin action andameliorates insulinresistance.While adiponectin exerts pro-inflammatory activities in some contexts (29),(30),(31),), it can suppress inflammatory Responses (32),(33),(34),(35),(36). Adiponectin enhances the secretion of the anti-inflammatory cytokine IL-10 by cultured human monocyte-derived macrophages and stromal vascular fraction cells prepared from human adipose tissue (37). Intriguingly, adiponectin promotes macrophage polarization toward the anti-inflammatory M2 phenotype (33). On the other hand,macrophage polarization phenotype regulates the expression of adiponectin receptors (AdipoRs) in ways that classical activation(M1) ofmacrophages suppresses the expression of AdipoRs, and alternative activation (M2) preserves it (38). Remarkably, adiponectin elicits antagonistic responses in the two macrophage polarization phenotypes. In M1 macrophages, adiponectin induced the expression of pro-inflammatory cytokines including TNF-a, IL-6, and IL-12, as well as AdipoRs. In M2 macrophages, adiponectin triggered the expression of the anti-inflammatory cytokine IL-10 without affecting AdipoR levels (38). Recent studies have also begun to reveal mechanisms of adiponectin actions and the cellular circuitry downstream of the adiponectin receptors. While these advances offer novel opportunities for diabetes treatment, multiple considerations limit the development of adiponectin as a pharmacological agent in a clinical setting. First, under physiological conditions, the circulating plasma concentrations of adiponectin in humans range from 2 to 20 mg/ml (39), more than 1000-fold higher than other hormonal regulators suchas insulin. This abundance would make its development for clinical use unlikely. Second, adiponectin circulates in multiple forms of oligomers, each with its unique cellular target(s) and signaling pathways (12). Currently, selective enrichment of a particular multimeric form of adiponectin in vivo remains a challenge. Lastly, various forms of adiponectin have relatively short half-life: 32 min for trimers and 83 min for HMW and MMW proteins (40). Conceptually, these characteristics necessitate multiple high doses of adiponectin if used as a therapeutic agent, a measure with potentially high clinical risks. Thus, understanding the mechanistic details of adiponectin signal transduction could reveal new opportunities for clinical treatment, tailored to its underlying biology and pathophysiology. Here, we consider five aspects of adiponectin action and signal transduction with the potential for drug development: (i) tissue-specific functions of adiponectin; (ii) adiponectin receptors AdipoR1, AdipoR2, and T-cadherin; (iii) adiponectin receptor signaling; (iv) adiponectin signaling pathway cross talks with other pathways involved in metabolic regulation; and (v) adipo R independent pathways. Our goal is not to comprehensively review these areas, but rather, to identify recent advancements and updates in adiponectin biology and explore the therapeutic potential of targeting adiponectin signal transduction.

2. Adiponectin 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) (41). Interestingly, the yeast homolog (YOL002c) plays a key role in metabolic pathways that regulate lipid metabolism, such as fatty acid oxidation (42). 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 proteincoupled receptors (GPCRs) (41).

3. 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 (43), 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 (43). 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 (44). Consistent with the proposed roles of AMPK activation by adiponectin in the liver (43), Scherer et al. reported that in adiponectin transgenic mice (25), reduced expression of gluconeogenic enzymes such as phosphoenol pyruvate 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 (45). PPAR Activation via AdipoR2. Adiponectin activated the PPAR pathway via AdipoR2 and also increased fatty acid combustion and energy consumption, in part via increased molecules involved in these functions such as ACO and UCP, respectively (41),(46). To clarify the mechanisms by which adiponectin increased the expressed levels of ACO and UCP, we measured endogenous PPARa ligands activities, because the ACO and UCP genes possess PPRE in its promoter regions. Interestingly, adiponectin increased PPARa ligands activities and also expression of PPARa itself (47). AMPK, Ca2+, Fatty Acid Combustion, Mitochondrial Biogenesis, Mitochondrial OXPHOS, and ROS via AdipoR1. Adiponectin induces extracellular Ca2+ influx by AdipoR1, which is necessary for the subsequent activation of Ca2+/calmodulin dependent protein kinase kinase b (CaMKKb), AMPK. This pathway then activated SirT1, increased expression and decreased acetylation of PPARg coactivator1a (PGC-1a), and increased mitochondria in myocytes. In fact, muscle-specific disruption of AdipoR1 suppressed the adiponectin-mediated increase in intracellular Ca2+ concentration and decreased the activation of CaMKK, AMPK, and SirT1 by adiponectin. Suppression of AdipoR1 also resulted in decreased PGC-1a 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 (48). 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) (49). 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 (49). Ceramide Pathway. Although it was shown that AdipoR1and AdipoR2 regulate glucose and fatty acid metabolism partly via activation of AMPK, Ca2+, and PPARa signaling pathways, it seems likely that additional signaling pathways also participate at the pleiotropic actions of adiponectin. In fact, Scherer and his colleagues added ceramide signaling as a pathway involved in mediating such pleiotropic effects(50). 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. 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 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. or C2-ceramide in cardiac myocytes and pancreatic b cells (50). 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 b 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 (50). 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 mAdipoR2, 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, Ca2+, and PPARa (50),(48),(51),(52),(41),(46).

4. Molecular Characteristic of Adipocytes

To elucidate the molecular mechanism of visceral obesityrelated diseases, we have investigated the biological characteristics of adipose tissue by analyzing the gene expression profile in visceral and subcutaneous fat. We initiated a systemic analysis of active genes by constructing a 3_- directed cDNA library, in which the mRNA population is faithfully reflected. Of approximately 1000 independent clones, 60% of the whole genes were already identified as known human genes by searching in the non-expressed sequence tags (EST) division of the Gen Bank (53). The remaining 40% of genes were novel and unidentified genes. We found unexpectedly high frequency of the genes encoding secretory proteins in adipose tissue, most of which are important bioactive substances (54). In subcutaneous adipose tissue, approximately

20% of all known genes were the genes encoding secretory protein (Figure 1). Furthermore, its frequency came up to approximately 30% in visceral adipose tissue. Leptin and tumor necrosis factor (TNF)-_ have been well recognized as bioactive substances from adipose tissues, which control the functions of other organs. We classified these adipose tissue– derived bioactive substances as adipo-cytokines, although some of them are not cytokines according to the classical category. The genes for plasminogen activator inhibitor type 1(PAI-1) and heparin binding endothelial growth factor–like growth factor are found to be highly expressed in adipose tissue (55),(56). PAI-1 mRNA levels increased up to 10 times in visceral adipose tissue during development of fat accumulation in ventromedial hypothalamic lesioned rats, which is an experimental animal model of obesity, whereas it remained unchanged in the subcutaneous adipose tissue. We also demonstrated that plasma levels of PAI-1 were significantly correlated with visceral adiposity determined by CT scan in human subjects. Circulating PAI-1 has been considered to be a strong risk factor of coronary artery disease (57). These data suggest that the secreted PAI-1 from accumulated visceral fat may contribute to the determination of plasma PAI-1 levels, and increased secretion of PAI-1 from accumulated visceral adipose tissue may have an important role in the development of thrombotic disorders and atherosclerosis frequently found in obesity, especially visceral obesity.

5. Cell Biological Functions of Adiponectin

A large amount of adiponectin flows with the blood stream inside of vascular walls. It would be interesting to know whether adiponectin can enter into vascular walls. Immunohistochemical examination using anti-adiponectin antibody demonstrated that there is no existence of adiponectin in the untreated normal vascular walls in rabbit. However, markedly positive immunohistochemical stain was detected in the balloon-injured vascular walls (58). Because adiponectin has been shown to have an ability to bind subendothelial collagen, such as collagen V, VIII, and X, endothelial injury may induce the entering of adiponectin into subendothelial space by binding to these collagens. Atherosclerotic cellular changes consist of basically the following 3 cellular phenomena: monocyte adhesion to endothelial cells by the expression of adhesion molecules, oxidized LDL uptake of macrophages through scavenger receptors, and proliferation of migrated smooth muscle cells by the action of platelet-derived growth factors or heparinbinding endothelial growth factor–like growth factor. Adiponectin has potential inhibitory activities of these atherogenic cellular phenomena. Physiological concentration of adiponectin was demonstrated to strongly inhibit the expression of adhesion molecules, including intracellular adhesion molecule-1, vascular cellular adhesion molecule-1, and E-selectin (59). Adiponectin was shown to inhibit the TNF-_– induced nuclear factor-_B activation through the inhibition of I_B phosphorylation, which might be a major molecular mechanism for the inhibition of monocyte adhesion to endothelial cells (58). Adiponectin also inhibits the expression of the scavenger receptor class A-1 (SR-A) of macrophages, resulting in markedly decreased uptake of oxidized LDL and inhibition of foam cell formation (60). In addition, adiponectin inhibits the proliferation and migration of smooth muscle cells. This inhibition was shown to be attributable to the binding competition to platelet-derived growth factor-BB receptor of adiponectin and the inhibition of signal transduction through extracellular signal-related kinase (ERK) (61). From these vascular cellular functions, adiponectin may have a potential antiatherogenicity. In humans, many offensive factors are present, including oxidized LDL, inflammatory stimuli, and chemical substances that may induce vascular injuries. At that time, adiponectin secreted from adipose tissues may go into the injured arteries

and protect against the development of atherogenic vascular changes. Therefore, adiponectin might be likened firefighters who put out the fire of the vascular walls while it is still small. When the plasma levels of adiponectin are decreased in the subjects with visceral fat accumulation, the small fire may become bigger and bigger because of the shortage of firefighters.

6. Adiponectin and endothelial function

It has been shown that adiponectin exerts direct effects on vascular endothelium, diminishing the inflammatory response to mechanical injury and enhancing endothelium protection in cases of apolipoprotein E deficiency (62),(63),(64). Regarding other lipids, cross-sectional studies showed, after adjusting for gender and adiposity, that adiponectin levels present a inverse correlation with triglycerides (65), while they are directly correlated with HDL-cholesterol (66). It has been found that adiponectin plasma concentrations are lower in individuals with CAD compared to age- and obesity-matched controls (59), and that individuals with adiponectin levels under 4 μg/ml were at increased risk of CAD and presented more factors for MS (67). Conversely, while prospectively evaluating men without CAD, it was found after a 6 year-follow up that individuals in the highest percentile of plasma adiponectin were at a lower risk of MI, compared with those in the lowest percentile (68). Adiponectin levels are also decreased in people with hypertension, regardless the presence of insulin resistance (69). These subjects are characterized by a decreased endothelium-dependent vasodilation, which could be one of the mechanisms involved in central obesity-associated hypertension (70). It is well established that adiponectin has an anti -atherosclerotic effect via inhibition of adhesion molecules production, such as vascular cell adhesion protein 1 (VCAM-1) and selectin E (71),(72). The adiponectin mediated suppression of nuclear factor kB, could be an important molecular mechanism for inhibiting monocytes adhesion to endothelial cells (72). Immunohistochemistry studies show that adiponectin is not incorporated into the normal and intact vessel wall, while it presents a marked adherence to previously damaged vessel walls, like those mechanically injured by balloon catheters (58), and adiponectin may also act as a modulator for macrophage-tofoam cell transformation, slowing or inhibiting the process (60). Moreover, experimental and clinical investigations indicate that adiponectin promotes endothelial repair and angiogenesis by increasing the number and function of endothelial progenitor cells (EPCs) (73),(74),(75). This EPCsmediated endothelial repair involves several stages, beginning with mobilization of EPCs from bone marrow or spleen into the bloodstream, followed by recruitment and adhesion of EPCs to the injured blood vessel wall, and finally, differentiation and tubule formation. Thus, adiponectin modulates almost every step of endothelial repair via EPCs (76),(77).

7. Regulation of adiponectin expression

Adiponectin an adipose tissue-specific protein is normally under transcriptional control of adipogenesis regulators comprising; PPAR-γ (peroxisome-proliferator activated receptor gamma), SREBP-1c (sterol regulatory element binding protein-1c), C/EBP-α, (CCAAT enhancer binding protein alpha) and ID-3 protein (78),(79),(80),(81). Receptors that serve to mediate effects of Acrp30 comprise AdipoR1 and R2 (82),(41). It is noteworthy that various anti-diabetes drugs more specifically thiazolidinedione (TZD) class to which pioglitazone and rosiglitazone (PPAR-γ agonists) belong, are characterized with Acrp30 high inducing capacity (83),(84, 85). Therefore, increased Acrp30 expression modulates beneficial effects of this class of therapeutic

agents. More importantly, wide ranging post-translational modification which entails hydroxylation and glycolysation is critical for Acrp30 assembly and subsequent formation of functional oligomeric complexes (86),(87), (88),(89). Hence, following Acrp30 secretion that is regulated particularly by endoplasmic reticulum (ER) proteins ERp44 and oxidoreductase Ero1-Lα (90),(91), the adipocytokine is found circulating freely within plasma in three oligomeric forms namely, high molecular weight (HMW; oligomer), medium molecular weight (MMW; hexamer) and low molecular weight (LMW; trimer) (92). However, host circulating levels of this adipocytokine are dependent on various factors including sex, metabolic status and body fat distribution (93),(51),(94). Additionally, the state of oligomerisation is vital as it regulates both signal transduction pathway and overall biological functioning of Acrp30 (86),(88),(12),(95). The three oligomeric complexes together are collectively termed as full-length adiponectin (fAd) (82). Schematic representation of the steps involved in transcription, translation, post-translation modification, oligomerization and secretion of Acrp30. Several transcription factors (top left) which mediate adiponectin gene transcription are regulated to increase (thiazolidinedione, TZD) or decrease (tumor necrosis factor-alpha, TNF-α) adiponectin expression. Monomeric adiponectin (mAd) is post-translationally modified and further oligomerized to form trimers (low molecular weight, LMW), hexamers (medium, MMW) and oligomeric (high, HMW) forms. Various mechanisms (bottom right) mediate this oligomerization and secretion resulting in secretion of HMW, MMW, and LMW forms (96).

8. Adiponectin in obesity and type II diabetes

A steep rise in the prevalence of obesity has occurred over the past few decades. Obesity is inversely related to adiponectin, making adiponectin a negative marker of metabolic syndrome. Furthermore, the expression of the receptors AdipoR1 and AdipoR2 decline by 30% in the subcutaneous fat of obese individuals, while they normalize following weight loss (97). It is by now well established that adiponectin plays an important role in type II diabetes, hypertension, multiple sclerosis (MS), and the dyslipidaemias. The most significant role played by adiponectin is that of Adiponectin: Regulation of its production and its role in human diseases 17 its insulin-sensitizing effect. Adiponectin levels in the diabetic's blood are lower than normal, whereas higher levels of adiponectin in plasma minimize the risk of developing type II diabetes.(98). Additionally, adiponetin relates negatively to blood glucose and insulin levels. Total adiponectin, HMW adiponectin, and the HMW ratio all are inversely related to homeostasis model assessment (HOMA) insulin resistance index. The HMW ratio is considered to be a better indicator of insulin resistance than total plasma adiponectin levels, this being supported by the fact that mutations, which affect the multimerization of adiponectin, render a person more susceptible to diabetes (99). The role of adiponectin in insulin resistance was determined by using knockout mice. These mice had normal plasma insulin levels but its role in lowering the blood glucose level was severely impaired, this clearly pointing to the role of adiponectin in glucose tolerance (100). Likewise, the absence of serum adiponectin in lipoatrophic mice causes hyperglycaemia and hyperinsulinaemia, which can be normalized by adiponectin injections. The ability of adiponectin to ameliorate insulin resistance has been documented in db/db mice (101). All studies on the putative role of adiponectin in insulin resistance and type II diabetes suggest that decreased levels of adiponectin cause susceptibility to these disorders.

9. Adiponectin in cancer

A good deal of compelling evidence has shown that circulating adiponectin levels are inversely associated with the risk of malignancies linked to obesity and insulin resistance, including endometrial cancer, postmenopausal breast cancer, leukaemia, and colon, gastric, and prostate cancer. Adiponectin modulates several intracellular signaling pathways and stimulates AMPK, PPARγ, and MAPK in classical insulin target organs such as the liver and skeletal muscles (102) Adiponectin is a well-known insulin sensitizing hormone that inhibits cancer progression and invasion through its receptors (AdipoR1, AdipoR2). The expression of adiponectin receptors in lung tissues was apparent only in the areas of cancerous lesions (64.2% AdipoR1 and 61.9% AdipoR2) (103). Studies have shown that individuals with low levels of adiponectin (hypoadiponectinaemia) could be at a higher risk of developing tumors, including those suffering from polycystic ovary syndrome (PCOS). It should be noted here that PCOS is characterized by hyperandrogenism, most probably because the circulating high levels of insulin stimulate the ovary to produce more androgens.(104), Hyperinsulinaemia stimulates androgen production, while at the same time it decreases the production of sex hormone binding globulin (SHBG), leading to an even higher hyperandrogenic environment (104). The aforementioned description supports the finding that adiponectin is negatively correlated with insulin sensitivity in women with PCOS.

10. Therapeutic role of adiponectin

A range of studies have demonstrated reduced Acrp30 expression to be linked to diabetes mellitus (105),(17), while recovery of this adipocytokine controls insulin resistance by enhancing free fatty acid oxidation, glucose uptake and subsequent utilization (43). Hence, diabetes medicaments including pioglitazone and rosiglitazone belonging to the TZD class of PPAR-γ agonists are observed to be potent inducers of Acrp30 expression (106),(107),(108). This induction of Acrp30 has both metabolic and cardio-protective effects against diabetes mellitus and cardiovascular disease respectively. The proposed mechanisms that regulate Acrp30 expression by PPAR-γ agonists involves a reduction in triglyceride amounts within the muscle and liver cells as well as preventing adipocyte hypertrophy (109). Additionally, it's also possible that TZD's heighten Acrp30 mRNA expression through the CCAAT/enhancer-binding protein sites (110). Essentially, the high expression of Acrp30 is a fundamental mechanism of action that mediates beneficial effects of this diabetes controlling drug class. Clinical trials involving administration of Acrp30 therapy on animal models controlled for obesity reveals hyper-glycaemia and hyperinsulinaemia regulation without even inducing weight loss or gain in a number of this studies (111). To add further, Acrp30 therapy has been demonstrated to reverse insulin resistance in mice manifesting obesity and lipoatrophy (109), which further potentiates the adipocytokine adoption among therapeutic interventions (Acrp30 replacement therapy) to

be considered in HIV-infected lypodystrophic patients as well as obesity subjects during instances of metabolic abnormalities.

11. Conclusion

Adiponectin carries out its roles for preventing development of vascular changes and the impairment of glucose and lipid Molecular mechanism of anti-atherogenic functions of adiponectin. Metabolism, which may be induced by a variety of attacking factors, such as chemical subjects, mechanical stress, or nutritional loading, like a firefighter who is putting out small fires to keep them from becoming big. 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, PPARa 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.The main metabolic effects of adiponectin are suppression of hepatic glucose production and modulation of suppressing inflammatory responses in other cell types, including macrophages. Despite the beneficial role of adiponectin on vascular homeostasis, studies suggest that increased levels of circulating adiponectin are associated with increased cardiovascular mortality in patients with coronary artery disease.

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