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Review

Adiponectin: Regulation of its production and its role in human diseases

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ABSTRACT

Adiponectin is a white and brown adipose tissue hormone, also known as gelatin-binding protein-28 (GBP28), AdipoQ, adipocyte complement-related protein (ACRP30), or apM1. Adiponectin circulates in the bloodstream in trimeric, hexameric, and high-molecular-mass species, while different forms of adiponectin have been found to play distinct roles in the balance of energy homoeostasis. Adiponectin is an insulin sensitizing hormone that exerts its action through its receptors AdipoR1, AdipoR2, and T-cadherin. AdipoR1 is expressed abundantly in muscle, whereas AdipoR2 is predominantly expressed in the liver. Adiponectin is inversely proportional to obesity, diabetes, and other insulin-resistant states. In this review we present the current findings regarding the regulation of its production and several new findings pertaining to its biological effects. Adiponectin enhances AMPK and the PPARα pathway in the liver and skeletal muscle. Adiponectin increases fatty acids oxidation, which lowers circulating free fatty acids and prevents insulin resistance. Adiponectin has been reported to exert an antiatherosclerotic effect. It inhibits macrophage activation and foam cell accumulation, while it also augments endothelial nitrous oxide production and protects the vasculature by reducing platelet aggregation and vasodilation. Apart from causing metabolic dysfunction, adiponectin deficiency may also contribute to coronary heart disease, steatohepatitis, insulin resistance, nonalcoholic fatty liver disease, and a wide array of cancers. In this study, we present ample evidence that adiponectin mediates multiple molecular pathways. We therefore support the concept that it shows distinct potential for being of therapeutic value in the treatment of obesity related diseases, ranging from metabolic syndrome to malignancies.

Key words: Adiponectin, Regulation, Insulin, Inflammation, Atherosclerosis, Fatty acid, Obesity, Liver disease

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INTRODUCTION

Adiponectin, which is mainly produced in white adipose tissue (WAT), characteristically differs from most adipokines as it is negatively correlated with obesity. Adiponectin, a hormone, exerts multiple

biological effects throughout the body mediated by the specific receptors AdipoR1, AdipoR2, and T-cadherin.[1]

In 1995, Lodish et al. identified a secretory protein from murine 3T3-L1 adipocytes and named it adipocyte complement-related protein of 30 kDa (Acrp30). It is a structural homolog to complement factor C1q and to a hibernation-specific protein isolated from the plasma of Siberian chipmunks.[2] It forms large homo-oligomers that undergo a series of posttranslational modifications. Using the mRNA differential display technique, it was cloned and called adipoQ. The adipoQ cDNA encodes a polypeptide of 247 amino acids, with a secretory signal sequence at the amino terminus, a collagenous region (Gly-X-Y repeats), and a globular domain.[3]

The human adiponectin gene was cloned through systematic sequencing of an adipose-tissue library. The apM1 gene encodes a 244 amino acid open reading frame containing a putative signal sequence repeat (66 amino acids) followed by a cluster of aromatic residues near the C terminus having high local resemblance to collagens X and VIII and complement factor C1q.[4] In 1999, a group at Osaka University isolated the human adipose-specific transcript, the apM1 gene product, which was found to be a soluble matrix protein, and named it adiponectin. It was identified as a distinct protein among the adipokines because the plasma concentration of adiponectin decreases upon accumulation of visceral fat. Adiponectin was observed to be abundant in the plasma of healthy volunteers at a range of 1.9 to 17.0 mg/mL.[5]

In 2003, a group from Japan isolated complementary DNAs encoding the adiponectin receptors 1 and 2 (AdipoR1 and AdipoR2) by expression cloning. These two adiponectin receptors have seven-transmembrane domains, but they are distinct from the topology of G-protein-coupled receptors. The AdipoR1 gene encodes for a 375-amino-acid protein with an estimated molecular mass of 42.4 kDa, whereas AdipoR2 encodes for a 311-amino-acid protein of 35.4 kDa. Suppression or expression of AdipoR1 and AdipoR2 revealed that AdipoR1 is a high-affinity receptor for globular adiponectin and a low-affinity receptor for full-length adiponectin, whereas AdipoR2 has an intermediate affinity for both.[6]

In 2004, Lodish and colleagues identified adiponectin-binding proteins through retroviral expression of a C2C12 myoblast cDNA library in Ba/F3 cells. Subsequent DNA analysis revealed T-cadherin as an adiponectin-binding protein. T-cadherin is a unique cadherin molecule that lacks the transmembrane and cytoplasmic domains and is bound to the surface membrane through a glycosylphosphatidylinositol (GPI) anchor. The expression of T-cadherin was observed to confer binding of hexameric and HMW multimers but not trimeric adiponectin.[1]

The physiological role of adiponectin has not yet been fully elucidated, but it is believed that it has the ability to reduce glucose, triglycerides, and free fatty acids and that it plays a major role in the pathogenesis of metabolic syndrome. Metabolic syndrome comprises a cluster of metabolic disorders that give rise to such metabolic risk factors as visceral obesity, insulin resistance, hyperglycaemia, dyslipidaemia, and hypertension. In addition, numerous experimental and clinical observations have shown decreased adiponectin bioactivity in obesity and obesity-related complications, including insulin resistance, diabetes, cardiovascular diseases, and non-alcoholic fatty liver disease (NAFLD). The current review summarizes the recent progress made in our understanding of adiponectin production and biological effects. We also describe the latest experimental and clinical studies regarding this fascinating molecule.

Adiponectin receptors

The regulation of AdipoR1 and AdipoR2 is important for facilitating essential physiological functions. AdipoR1 is ubiquitously expressed and exhibits high affinity to the ligand, whereas AdipoR2 exhibits intermediate affinity. The expression of adiponectin and its receptors has been investigated in streptozotocin (STZ)-induced diabetic rat heart and in mouse skeletal muscle. STZ-induced diabetes up-regulates adiponectin receptors in the heart.[7] Despite an increase in cardiac adiponectin receptor 1 expression, there is an elevated cardiac inflammatory response and a decreased GLUT4 protein expression associated with a reduction in circulating adiponectin. In addition, AdipoR1 mRNA was increased in the skeletal muscle of streptozotocin (STZ)-induced diabetic mice and normal AdipoR1 levels were restored by insulin

administration, while hepatic AdipoR2 gene expression was unaltered in STZ-induced diabetic mice.[7,8]

Some evidence suggests that T-cadherin can bind to the hexameric and HMW forms of adiponectin but not to monomer globular and trimeric forms. T-cadherin is ubiquitously expressed, with the highest expression found in the heart and the aortic, carotid, iliac, and kidney arteries.[1] T-cadherin is bound to adiponectin and is critical for the association of adiponectin protection against cardiac stress in mice. Denzel et al. concluded that deletion of T-cadherin abolished adiponectin cardioprotective effects in cardiac hypertrophy as well as in myocardial ischaemia-reperfusion injury. Recently, clinical and laboratory studies confirmed that myocyte expression of PPARδ and the adiponectin receptors is highly coordinated.[9] The mRNA levels of the three adiponectin receptors, AdipoR1, AdipoR2, and T-cadherin, were strongly interrelated ($r \geq 0.91$) and these receptors were positively associated with PPARδ expression ($r \geq 0.75$). The myocyte expression levels of AdipoR1 and T-cadherin were inversely associated with the donors' fasting plasma triglycerides ($P < .03$).[10] A relation between adiponectin receptors was also confirmed in the muscle tissue of 24 h fasted pigs in which the expression of T-cadherin was decreased, suggesting that the expression of T-cadherin can be regulated by metabolic status. Additionally, T-cadherin was expressed in smooth muscle cells and visceral adipose tissue, but only muscle mRNA expression was decreased by fasting.[11] These data suggest that T-cadherin can also participate in AdipoR1 and AdipoR2 adiponectin binding as well as initiate adiponectin signal transduction.

PART ONE: REGULATION OF ADIPONECTIN PRODUCTION

Effect of insulin

Though the relationship between plasma insulin and adiponectin levels has been studied extensively, the exact role of insulin in adiponectin biosynthesis and secretion remains contentious. In 3T3-L1 adipocytes, insulin has a direct stimulatory effect on adiponectin gene expression.[12] Studies have also demonstrated the selectivity of insulin in adiponectin regulation and secretion. Furthermore, exposing cultured 3T3-L1 adipocytes to insulin leads to an increased adiponectin secretion into the culture media.[13] The precise mechanism by which insulin stimulates adiponectin biosynthesis remains obscure.

It has been suggested that insulin suppresses the activity of FoxO1, a transrepressor (suppressor) of PPARγ, which is an inducer of adiponectin biosynthesis. However, still to be explained is the well-documented negative correlation between insulin and adiponectin levels in-vivo. Indeed, serum adiponectin levels are elevated in type I diabetic patients (i.e. patients with reduced levels of circulating insulin) as well as in patients with genetically defective insulin receptors when compared with healthy controls.[14] In contrast to several other adipokines, which cause insulin resistance, adiponectin expression is reduced in obese and insulin-resistant models. Increase in insulin resistance depresses the levels of circulating adiponectin.

Oxidative stress has been found to augment insulin resistance, at the same time inhibiting the expression of adiponectin. Although the mechanism underlying this regulation is unclear, it may contribute to the decrease in plasma adiponectin in obesity, which is associated with increased oxidative stress in adipose tissue.[15] Furthermore, hyperinsulinaemia significantly lowers plasma adiponectin levels under euglycaemic conditions.[16] In addition, the HMW form of adiponectin is selectively down-regulated in hyperinsulinaemia and type II diabetes. The reason that insulin has a different in-vitro and in-vivo effect on adiponectin levels remains unknown, but it is possible that insulin may activate some signaling pathways that indirectly suppress adiponectin biosynthesis and secretion. Further investigations should yield insights into this possibility.

REGULATION OF ADIPONECTIN AT THE TRANSCRIPTIONAL AND POST-TRANSLATIONAL LEVEL (Figure 1)

PPARγ

PPARγ is a member of the PPAR subfamilies of transcription factors, which is expressed mainly in adipose tissue and which is considered to be a positive regulator of adiponectin gene expression. Targeted deletion of PPARγ in adipose tissue of mice results in marked adipocyte hypocellularity and

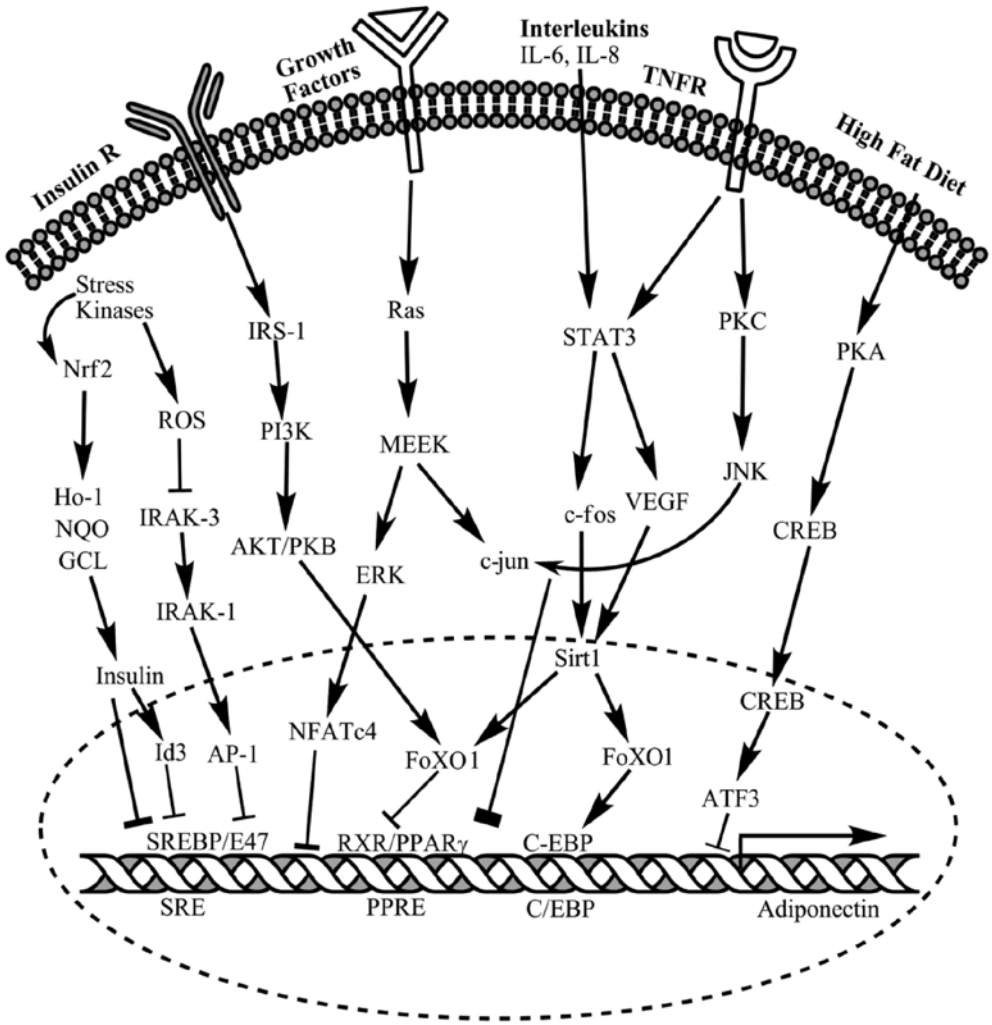

Figure 1. Regulation of adiponectin transcription by inflammatory mediators such as TNFα, IL-6, and IL-18 negatively regulates adiponectin gene expression. These inflammatory cytokines activate several pathways, including the JNK and ERK1/2 pathways, which have a major role in adiponectin regulation. Oxidative stress inhibits the expression of IRAK-3 and activates IRAK-1, which in turn activates activator protein 1 (AP-1) and decreases adiponectin activity. High fat diet induced obesity also suppresses adiponectin expression by increasing intracellular levels of PKA-mediated activation of CREB. Evidence suggests that insulin positively regulates adiponectin gene expression by activating PPARγ via suppressing FoxO1 activity, while a negatively correlated relationship has also been documented between insulin and adiponectin levels. FoxO1 increases adiponectin transcription via interaction with C/EBP. Regulation of FoxO1 by insulin and Sirt1 may provide a mechanism to dynamically regulate adiponectin gene expression.

hypertrophy, elevated levels of plasma free fatty acids and triglyceride, and decreased levels of adiponectin.[17] Furthermore, a putative PPARγ obligatory binding (PPAR-responsive element) site is present in human and mouse adiponectin promoters, and point mutations at this site lead to reduced basal and TZD-induced adiponectin promoter transactivation.[18] PPARγ increases adiponectin levels and secretion by stimulating the expression of proteins involved in adiponectin assembly and secretion such as Erol-Lα and DsbA-L. Activation of PPARγ enhances the expression levels of Ero1-Lα in mature adipocytes. PPARγ also elevates cellular levels of DsbA-L, a multifunctional factor in adiponectin multimerization and secretion.[19,20]

C/EBPα

The C/EBPs belong to the basic leucine zipper family and are comprised of six members, of which three (C/EBPα, -β, and -δ) have a role in adipogenesis.

An early study demonstrated that phosphorylation of C/EBPα at a consensus ERK/glycogen synthase kinase 3 (GSK3) site regulates adiponectin gene expression during the C/EBPα-facilitated differentiation of mouse fibroblasts into adipocytes. It should be noted that the NIH 3T3 cells produce a modest amount of adiponectin. Induction of the expression of both PPARγ and C/EBPα in these cells stimulates the production of adiponectin.[21] In addition, overexpression of endogenous C/EBPα increases and siRNA-mediated knockdown of C/EBPα decreases adiponectin mRNA levels in differentiated human Chub-S7 adipocytes, while neither C/EBP -β nor -δ significantly affect adiponectin expression in mature adipocytes. Thus, C/EBPα appears to be a key transcription factor for full activation of human adiponectin gene transcription in mature adipocytes through interaction with response elements in the intronic enhancer.[22] However, C/EBPα does not appear to be the major player in the regulation of adiponectin gene expression and no difference is observed in C/EBPα expression in the adipose tissues of subjects with insulin resistance compared to normal control subjects.[18,23] This study corroborates the finding that the expression of C/EBPα is reduced by caloric restriction in subjects with metabolic syndrome, which has been shown to increase cellular levels of adiponectin in rats.[24] Additionally, C/EBPα negatively correlates with BMI, waist-hip ratio, and plasma glucose levels.[25] However, the exact physiological role of C/EBPα in regulating adiponectin expression in-vivo remains an open question.

SREBPSs

Sterol-regulatory-element-binding proteins (SREBPs) are unique members of the basic helix-loop-helix leucine-zipper family of transcription factors. The binding of SREBPs to sterol response elements (SREs) promotes transcription and up-regulation of enzymes involved in lipid metabolism.[26] Out of three subunits, SREBP1c is hypothesized to control adiponectin gene expression in differentiated adipocytes. The levels of adiponectin mRNA and protein are reduced in the white adipose tissue of ob/ob and db/db mice and there is a concomitant reduction of adipocyte determination and differentiation-dependent factor 1 ADD1/SREBP1c transcription factor.[18] In a study of 3T3-L1 adipocytes, adenoviral overexpression of SREBP-1c increased adiponectin mRNA and protein levels. SREBP-1c also promotes adiponectin transcription by association with another bHLH factor E47 and subsequent binding to E-boxes within the adiponectin promoter.[27] However, a differential role of SREBP-1c has been observed in hepatocytes and adipocytes. Activation of this transcription factor in the liver leads to insulin resistance and steatosis, whereas activation of this gene in adipocytes may improve insulin sensitivity by activating the adiponectin gene.

FoxO1

FoxO1 is a member of the forkhead box O transcription factor family. FoxO1 is involved in the regulation of adipocyte differentiation and positively regulates adiponectin transcription. The protein levels of FoxO1 and Sirt1 (sirtuin, silent mating type information regulation 2 homolog)1 are greatly reduced in fat tissues from high fat diet-induced obese and type II diabetic mouse models. It should be mentioned that the formation of a FoxO1-C/EBPα complex is stimulated by overexpression of Sirt1 resulting in adiponectin promoter activation.[28] Two FoxO1-responsive elements have been identified in the mouse adiponectin promoter. In addition, PPARγ positively regulates adiponectin gene expression and secretion and FoxO1 has been found to suppress PPARγ gene expression.[29]

CREB

cAMP response element binding protein (CREB) regulates glucose homoeostasis and contributes to hyperglycaemia and insulin resistance in diabetes and obesity. Adipose-tissue specific expression of a dominant-negative CREB transgene increased the levels of adiponectin mRNA and circulating HMW adiponectin protein compared with wild-type controls, but had no effect on plasma concentrations of resistin, retinol binding protein 4 (RBP4), TNFα, and IL-1. The constitutively active form of CREB increases the promoter activity of the mouse adiponectin gene.[30] Transfection studies using 5' serial deleted promoters revealed the presence of a putative CRE location between the -1,250 and -1,000bp region. In addition, IGF-1 stimulates adiponectin expression through CREB phosphorylation via the ERK pathway and CREB is a positive regulator of mouse adiponectin gene expression in adipocytes.[31]

CREB plays an important role in the regulation of adiponectin expression in response to growth factors.

NFAT

NFAT comprises a family of transcription factors that have a definite role in 3T3-L1 adipocytes. NFATc4 and ATF3 negatively regulate adiponectin gene expression. The binding activities of these transcriptional factors are significantly increased in WATs of the ob/ob and db/db mice compared to controls, which is consistent with a negative role of these transcriptional factors in adiponectin expression in obesity and type II diabetes.[32]

TNFα and Interleukins

It is now well established that TNF-α and IL-6 expression and secretion increases in the adipose tissue of obese subjects and are negatively associated with adiponectin. In 3T3-L1 and human adipocyte cultures, insulin strongly enhances adiponectin expression (by approximately twofold) and secretion (threefold). It is believed that insulin up-regulates adiponectin expression and that TNFα suppresses the expression levels of activators involved in promoting adiponectin gene expression, such as PPARγ and Super Conserved Receptors Expressed mainly in Brain SREBs).[33] The suppressive effect of TNFα on adiponectin transcription may be mediated by c-Jun N-terminal kinase (JNK), which phosphorylates PPARγ and decreases its DNA-binding activity. TNFα also suppresses the transcription of the adiponectin gene by inhibiting transcriptional Sp1-binding activity. In addition, TNFα activates the expression of IGFBP-3, which suppresses adiponectin transcription and induces insulin resistance.[34,35]

Several inflammatory cytokines such as IL-6, in concentrations similar to that circulating during metabolic syndrome, suppress in-vitro the levels of adiponectin transcript as well as its secretion by 3T3-L1 adipocytes. This inhibition is partially reversed by pre-treatment of cells with the inhibitors of mitogen-activated protein kinase (MAPK).[36] Adiponectin expression is up-regulated via a mechanism that implicates PPARγ concomitantly with the decrease in TNF-α and IL-6 mRNA expression, suggesting that drugs as potential antagonists of TNF-α and IL-6 should be considered prospective candidates for the treatment of metabolic diseases.[37] Unlike IL-6, IL-18 levels also increase with obesity and metabolic diseases and are inversely correlated with the plasma levels of adiponectin. IL-18 suppresses adiponectin expression in 3T3-L1 adipocytes via a signal transduction pathway involving extracellular-signal-regulated kinase 1/2 (ERK1/2)-dependent NFATc4 phosphorylation.[38] IL-18 induces ERK 1/2-dependent phosphorylation and activation of NFATc4, which has a major role as a repressor of adiponectin transcription. The inhibitory effect of IL-18 on adiponectin promoter activity was diminished by inactivation of ERK1/2 or RNA interference-mediated suppression of NFATc4.[39] Furthermore, a population-based sample of 1,059 Chinese men and women aged 35-54 years was performed to measure plasma IL-18, glucose, insulin, lipid profile, inflammatory markers, and adiponectin. Elevated plasma IL-18 was associated with higher metabolic syndrome prevalence in apparently healthy Chinese independent of traditional risk factors, fat mass index, inflammatory markers, and HMW-adiponectin.[40] It was thus hypothesized that IL-18 may have a mild effect on obesity-induced suppression of adiponectin gene expression.

DsbA-L

Disulfide-bond A oxidoreductase-like protein (DsbA-L), also known as glutathione transferase (GST) Kappa, is a 25-kDa adiponectin-interactive protein. DsbA-L is expressed in various mouse tissues such as liver, kidney, pancreas, and heart, but the highest expression of this protein is detected in adipose tissue, where adiponectin is synthesized and secreted.[41] DsbA-L facilitates adiponectin folding and assembly and provides a protective effect against ER stress-mediated adiponectin down-regulation in obesity. Additionally, DsbA-L plays a critical role in the promoting effect of natural polyphenolic drugs on adiponectin multimerization and cellular levels.[20,41] The cellular levels of DsbA-L are significantly reduced in adipose tissues of obese mice and human subjects. Like adiponectin, DsbA-L expression in 3T3- L1 adipocytes is stimulated by the insulin sensitizer and inhibited by the inflammatory cytokine. Overexpression of DsbA-L promotes adiponectin multimerization, while suppressing DsbA-L expression selectively reduces adiponectin expression levels in 3T3-L1 adipocytes.[42]

ER and Oxidative Stress

Obesity leads to ER stress, which has been linked to the inhibition of adiponectin production in adipose tissue. Adiponectin mRNA expression in adipose tissue of obese mice was negatively correlated with the expression levels of an ER stress marker, such as C/EBP homologous protein (CHOP).[43] In cultured adipocytes, induction of increased mitochondrial biogenesis (via adenoviral overexpression of nuclear respiratory factor-1) augmented adiponectin synthesis, whereas impairment of mitochondrial function decreased it. Impaired mitochondrial function increased ER stress, and pharmacological agents causing mitochondrial or ER stress reduced adiponectin transcription via activation of JNK and following induction of ATF3.[44] Furthermore, reducing ER stress and inactivation of JNK by PPARα/γ and macelignan treatment elevated adiponectin expression in adipose tissue of obese diabetic db/db mice.[45] The expression levels of adiponectin also decrease during oxidative stress and are negatively correlated with the production of ROS. Increased ROS generation augmented expression of NADPH oxidase and decreased expression of antioxidative enzymes. During oxidative stress, the expression of adiponectin mRNA is inhibited by glucose oxidase and a significant inverse correlation has been observed between 4-HNE formation and adiponectin secretion.[46] The mechanism involved in obesity-mediated suppressed expression of adiponectin has been studied in 3T3L1-cells. It appears that H_2O_2 markedly suppresses adiponectin mRNA expression and protein secretion, while it enhances plasminogen activator inhibitor (PAI-1) and IL-6 production in mature adipocytes. Adiponectin expression was reduced by H_2O_2 via the Akt and JAK/STAT pathway. Increased fat mass results in a hypoxic microenvironment, which has been associated with the decreased levels of adiponectin.[47] During obesity, insulin-like growth factor binding protein-3 (IGFBP-3) mediated the inhibition of adiponectin transcription by the hypoxia inducible factor-1 (HIF-1α) dependent pathway.

PART TWO: THE PLEIOTROPIC EFFECTS OF ADIPONECTIN

The pleiotropic roles of adiponectin have been studied in multiple in-vitro and in-vivo models. In short, the multiple molecular targets of adiponectin mediate multiple pharmacological actions (Figure 2). There follows a discussion of the different therapeutic roles of adiponectin under relevant headings

Adiponectin in non-alcoholic fatty liver disease (NAFLD)

NAFLD is characterized by insulin resistance and is commonly associated with obesity and type II diabetes. The histology of NAFLD comprises a broad range of liver injuries ranging from simple nonalcoholic fatty liver to nonalcoholic steatohepatitis (NASH) and NASH-related cirrhosis complications. Hypoadiponectinaemia might be a risk factor for nonalcoholic fatty liver disease. Serum adiponectin level has been found to be significantly lower in the early-stage NASH group compared to the simple steatosis group ($P < 0.001$).[48,49] It is believed that adiponectin attenuates liver inflammation and fibrosis, possibly through the decrement in the hepatic and insulin resistance. Adiponectin is considered to have insulin sensitizing, antifibrogenic, and anti-inflammatory properties by acting on hepatocytes, hepatic stellate cells, and hepatic macrophages (Kupffer cells), respectively. In the liver, adiponectin acts through the activation of the AMPK and PPAR-α pathways and inhibition of toll-like receptor-4 mediated signaling.[50] Adiponectin decreased gluconeogenesis, decreased free FFA influx into the liver, and increased FFA oxidation. In addition, adiponectin has antifibrotic action in the liver, mainly through down-regulating the expression of aldehyde oxidase, TGF and CTGF, and anti-inflammatory action by suppressing TNF-α and other proinflammatory cytokines and by inducing anti-inflammatory cytokines, such as IL-10.[51]

In clinical studies, expression of adiponectin is suppressed in the liver of obese patients and in NASH patients when compared with fatty liver, which has been observed with a higher grade of hepatic inflammation and liver fibrosis.[52] Furthermore, increased serum level of adiponectin has been observed in liver cirrhosis. Adiponectin in cirrhosis correlates to the clinical stage of the disease. Furthermore, plasma levels of adiponectin are markedly reduced in visceral obesity and states of insulin resistance such as NASH and type II diabetes. A negative association between serum levels of adiponectin and liver enzymes has been demonstrated in 'healthy' subjects. Patients

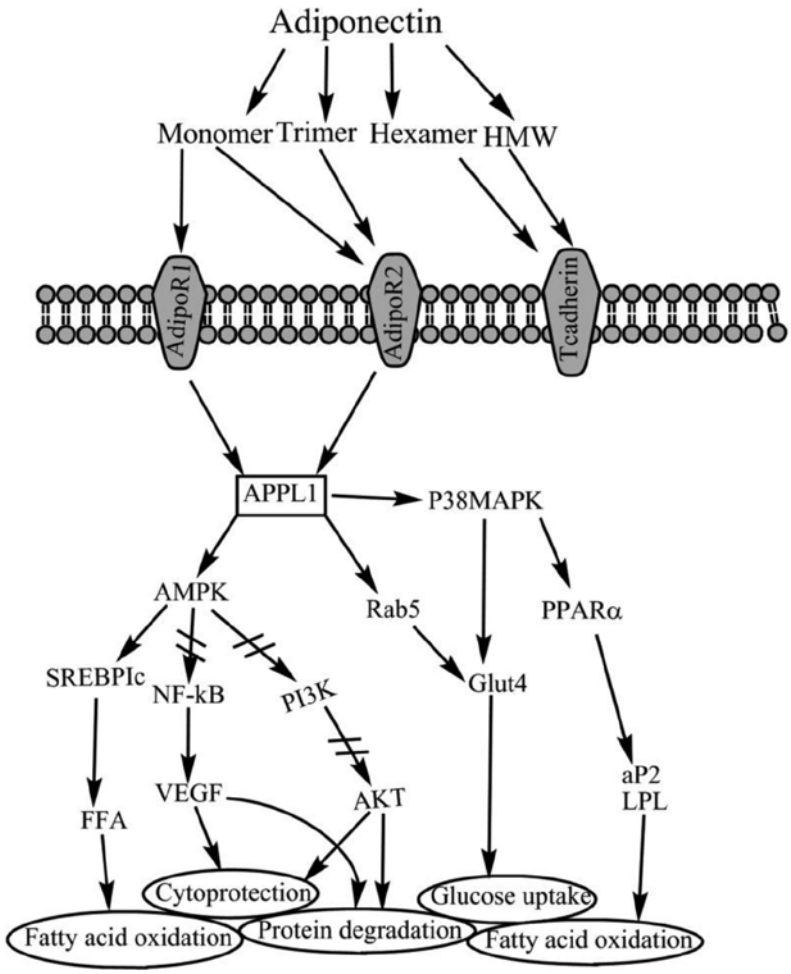

Figure 2. Adiponectin exerts its action through its receptors AdipoR1, AdipoR2, and T-cadherin. T-cadherin is a truncated receptor that can bind the hexameric and HMW oligomeric forms of adiponectin. AdipoR1 and AdipoR2 interact with the adaptor protein containing a pleckstrin homology domain, a phosphotyrosine domain, and a leucine zipper motif (APPL1), which binds the N-terminal intracellular domains of the receptors. The binding of adiponectin to its receptors provokes the activation of adenosine monophosphate AMPK and the activation of various signaling molecules, such as p38 mitogen-activated protein kinase p38 MAPK, PPAR, the RAS-associated protein Rab5, phosphatidylinositol 3-kinase (PI3K), and Akt. Activation of AMPK mediates pharmacological actions of adiponectin, including fatty acid oxidation, protein degradation, cytoprotection, and glucose uptake.

with both steatosis and NASH have decreased serum levels of adiponectin.[53] Rosiglitazone therapy raises plasma adiponectin levels in type II diabetes with proteinuria. A negative correlation has been observed between plasma adiponectin concentrations and the degree of proteinuria after a four-week treatment. Moreover, a three-week treatment of non-diabetic, insulin-resistant subjects with pioglitazone improves insulin sensitivity in parallel to an elevation of the levels of circulating total and HMW adiponectin, whereas circulating lipids are not affected.[54] In adipocytes, both adiponectin and adipoR2 expression increased. Serum adiponectin does not appear to increase following metformin therapy compared to a 16-week treatment with rosiglitazone. Several studies from different centers have shown that two adiponectin gene single nucleotide polymorphisms (SNPs) (45GT and 276GT) were associated with NASH and predicted the severity of liver disease. In addition, SNP in the PPAR-γ gene was associated with NAFLD, possibly through the adiponectin pathway.[55,56] In animal models of NASH, the absence of adiponectin was found to initiate the progression of hepatic tumor formation, but in humans the role of

adiponectin in the progression from NASH to HCC is still unresolved.

Adiponectin in cardiovascular diseases

Cardiovascular diseases are associated with obesity and other metabolic disorders. Obesity is characterized by low serum adiponectin levels. The potential role of adiponectin in cardiovascular diseases has been observed in patients with coronary artery diseases (CAD), as they have lower levels of adiponectin irrespective of ethnic group.[57] Intriguingly, HWM adiponectin has been linked to CAD. However, the hexamers are not affected and trimers increase, underlining the importance of HMW adiponectin in CAD in addition to the other obesity-related disorders/diseases, perhaps due to the functional priorities and tissue specificity shown by the adiponectin isoforms.[58,59] The severity of hypoadiponectinaemia correlates to coronary lesions. Indeed, adiponectin levels are lower in patients suffering from CAD.[60] Furthermore, plasma adiponectin levels can be helpful in identifying patients susceptible to CAD.[61] It is of interest that adiponectin reshapes myocardial infarction during acute injury.[62] Adiponectin deficiency in ischaemia-reperfusion mice caused myocardial infarct and aggravation was up to 78%, with a surge in TNFα levels and a decrease in activation of AMPK activity. This resulted in increased apoptosis of myocytes and stromal cells. Treatment of mice with adiponectin abrogates the extent of infarction, while the levels of TNFα are suppressed. These effects involve COX-2, prostaglandin E synthase (PGES), through the PGE receptor 4 dependent pathway. It should be noted here that mice deficient in adiponectin suffer from myocardial ischaemia and injury due to reduced levels of cyclooxygenase-2 (COX-2), suggesting that adiponectin regulates COX-2 production. It is also of interest that Shingosine kinase (SphK) affects COX-2 production via adiponectin in neonatal rat cardiomyocytes.[62,63] A possible role of adiponectin in atherosclerosis has been observed, in which activated macrophages attach to the vascular walls and convert into foam cells. These cells mass lipid droplets and recruit other macrophages to the site, ultimately leading to localized inflammation. Adhesion of monocytes to human aortic endothelial cells (HAECs), facilitated by TNFα, is inhibited by adiponectin by reducing the expression of vascular cell adhesion molecule-1 (VCAM-1), E-selectin, and intercellular adhesion molecule-1 (ICAM-1) on the surface of HAECs.[64] Adiponectin also binds to collagen (I, III and V) present in vascular walls but only in injured vessels.[65] Adiponectin inhibits the transformation of human monocyte-derived macrophages into foam cells by inhibiting the class A macrophage scavenger receptor. Some findings suggest a role of adiponectin in atherosclerosis by inhibiting binding of LDL to biglycan, which is a vascular proteoglycan. This ultimately decreases lipid accumulation in the subendothelial space, the cause of atherosclerotic plaque formation.[66] In addition, single nucleotide polymorphisms (SNPs) at position +276 in the adiponectin gene have been associated with CAD. T/T homozygous is at a lower risk of developing CAD than G/G or G/T variants of the genes. A "C" to "G" variant at position 11,377 in the promoter region of adiponectin has been linked to coronary atherosclerosis and other related diseases. T-cadherin expression is higher in athero-resistant than atherosclerosis susceptible coronary arteries, which indicates that its expression is involved in the progression of atherosclerosis.[67,68] Both T-cadherin and adiponectin have been found in the vicinity of injured vessels, which suggests that they have a role in atherosclerosis.

Adiponectin has been shown to activate both the AMPK and PPAR-α pathways and to increase the expression of AdipoR1 in CAD. In patients with coronary heart failure, however, despite increased muscle and circulating adiponectin levels, the PPAR-α/AMPK pathway is deactivated, resulting in decreased AdipoR1 and fatty acid and glucose metabolism enzymes. All these observations argue in favor of a state of adiponectin resistance in this disease.[69]

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.[70] 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

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.[71] 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.[72] 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.[73] 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.[74] 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.

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.[75] 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).[76] 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.[77] 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.[77] The aforementioned description supports the finding that adiponectin is negatively correlated with insulin sensitivity in women with PCOS.

Future prospects

In conclusion, adiponectin exerts an insulin-sensitizing action via an enhancement of AMPK and PPARα, this having profound effects on fatty acid oxidation and inflammation. Drugs affecting the levels of adiponectin may have a role in the treatment of NAFLD, cardiovascular disease, type II diabetes, and possibly in preventing metabolic syndrome-related cancers. Significantly, modulation of adiponectin actions through expression of adiponectin receptors may be a novel and promising therapeutic strategy.

Several in-vitro and in-vivo studies have marked progress in exploring the physiological mechanism via which adiponectin exerts its action. In particular, knowledge concerning the pleiotropic roles of adiponcetin has been accumulating at a rapid pace. Clinical studies aimed at reducing the deleterious effects of a number of ailments have been undertaken and this, in conjunction with a better understanding of the adiponectin genetic bases for these processes and the cellular events that underlie them should enhance our ability to devise new and better approaches aimed at minimizing the adverse effects of these diseases. However, many questions need to be addressed before adiponectin can be used as a potent therapeutic target. For example, the presence of different adiponectin oligomeric isoforms and production sites, the sexual dimorphism in adiponectin concentration and oligomeric isoform distribution, and the identification of multiple receptors with differing affinity for adiponectin oligomers all add to the complexity of adiponectin actions across an array of physiological processes and diseases. Nevertheless, studies in animal models of diabetes, obesity, and atherosclerosis clearly demonstrated that adiponectin can indeed have beneficial effects on those disease states. These findings therefore

suggest that adiponectin is a promising therapeutic option in obesity-related diseases.

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