Adiponectin: ceramidase activity and stress control of the endoplasmic reticle in obesity

Adiponectina: actividad ceramidasa y control del estrés del retículo endoplásmico en la obesidad

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Abstract

Adiponectin is a cytokine synthesized by adipocytes, which acts through receptors (AdipoR1, AdipoR2) and T-cadherin. Recently, it has been identified an endosomal protein, APPL1, that binds to AdipoRs to mediate signaling and nuclear factors of adiponectin. The expression of these receptors depends on the activation phenotype of the macrophages: classical activation (M1) suppresses the expression, and alternative activation (M2) maintains the expression of AdipoRs. Adiponectin regulates the metabolism of carbohydrates and lipids and reducing the production of hepatic glucose and the oxidation of fatty acids; it is also considered a biomarker of endothelial function due to its correlation with endothelial alterations, dyslipidemia, and atherosclerosis. There is a new protective function of Adiponectin against metabolic disorders and organic damage through T- cadherin that facilitates the exosomic release of inadequately folded proteins, controls cellular stress, decreases ceramide levels, and maintains cellular homeostasis. Another essential function of adiponectin is to protect cells from apoptosis induced by endoplasmic reticulum stress and the reduction of the inflammation in adipocytes, hepatocytes, endothelial cells, and pancreatic beta cells as it blocks mitochondrial apoptosis through the activation of the pathway of the protein kinase signal. Adiponectin is a potential biochemical biomarker and an anti-inflammatory in metabolic disorders since it modulates the pathogenesis of overweight and diabetes mellitus type 2, thus considered key to the prognosis and therapeutic intervention of these pathologies.

Keywords: obesity, adiponectin, adiponectin receptors, ceramidas, endoplasmic reticulum stress

Resumen

La adiponectina es una citocina sintetizada por los adipocitos, que actúa a través de los receptores AdipoRs (AdipoR1, AdipoR2) y T-cadherina, recientemente se ha identificado APPL1, una proteína endosomal que se une a los receptores AdipoRs, para mediar la señalización y los factores nucleares de la adiponectina. La expresión de estos receptores depende del fenotipo de activación de los macrófagos, activación clásica (M1) suprime la expresión y la activación alternativa (M2) mantiene la expresión de AdipoRs. La adiponectina regula el metabolismo de carbohidratos y lípidos, reduce la producción de glucosa hepática y la oxidación de ácidos grasos, además se considera un biomarcador de la función endotelial por su correlación con alteraciones endoteliales, dislipidemia y aterosclerosis. Existe una nueva función protectora de la adiponectina contra los trastornos metabólicos y el daño orgánico, a través de T-cadherina facilitando la liberación exosómica de proteínas plegadas inadecuadamente, controlando el estrés celular, disminuyendo los niveles de ceramida y manteniendo la homeostasis celular. Otra función importante de la adiponectina es la protección de las células de la apoptosis inducida por el estrés del retículo endoplásmico y la reducción de la inflamación en adipocitos, hepatocitos, células endoteliales y células beta pancreáticas bloqueando la apoptosis mitocondrial a través de la activación de la vía de la señal de la proteína quinasa. La adiponectina es un potencial biomarcador bioquímico y antiinflamatorio en los trastornos metabólicos, ya que modula la patogénesis del sobrepeso y la diabetes mellitus tipo 2, considerándose clave para el pronóstico e intervención terapéutica de estas patologías.

Palabras clave: obesidad, adiponectina, receptores de adiponectina, ceramidas estrés del retículo endoplásmico.

Introduction

Adiponectin is a protein hormone synthesized by mature adipocytes. It is also known as adipocyte complement-related protein of 30-kDa (Acrp30), because its homology with the C1q complement system factor (a subcomponent of the complement 1)[1-3]. Adiponectin is an hormone adipokine with the highest expression in adipose tissue. Its synthesis redominates in subcutaneous white adipose tissue, and it is a potential biochemical and anti-inflammatory biomarker in metabolic disorders. Adiponectin levels are negatively correlated with fat accumulation[4-7].

Adiponectin is a protein of 244 amino acids (247 amino acids in the mouse), whose primary structure includes four distinct regions: a signal peptide, a variable region, a collagen-like domain and a globular domain. The primary structure is similar to C1q since, the basic structural unit of adiponectin is a strongly associated trimer, formed by the conjunction of three units into the globular domain. In turn, these trimers can be associated in groups of 4 to 6 through the collagen domain, forming highly ordered structures or oligomers[8-10]. Recently, adiponectin production has been demonstrated in cells other than adipocytes such as osteoblasts, hepatocytes, myocytes, epithelial cells, and placental tissue[11-14].

Adiponectin is synthesized as a 28-30 kDa monomer. After post-translational modifications, the adiponectin is assembled in oligomers that control its biological activity. These oligomers are found in three different molecular weights forms: low molecular weight trimer, medium molecular weight hexamer, and high molecular weight multimer[15,16].

Adiponectin represents 0.01% of the total serum proteins. Its concentration in plasma (5-30 µg/ml), which depends on gender, as males show lower levels compared to women[17]. Regarding to differences in androgen concentrations, men with hypogonadism present higher levels of adiponectin compared to men with eugonadal status[18,19].

Genetic factors determine around 39-70% of the variability in adiponectin levels. The primary genetic determinant of adiponectin is the ADIPOQ (Adiponectin, C1Q And Collagen Domain Containing), which is located in chromosome 3q27; it contains three exons with the start codon in exon 2 and the stop codon in exon 3 and is related to susceptibility to type 2 diabetes and metabolic syndrome[20-22]. Approximately 15.8 kb and three exons form adipose most abundant transcript 1 gene (APM1), several polymorphisms of this gene have been associated with adiponectin levels and have been linked to susceptibility to metabolic syndrome, type 2 diabetes,

and cardiovascular disease[20-23].

The ADIPOQ gene negatively correlates with fasting glucose results and insulin sensitivity. Epigenetic modifications such as methylation in the promoter region of the DNA adiponectin gene may result in repressed transcriptional activity with low levels of adiponectin in plasma and a significant association with lower levels of adiponectin in patients with type 2 diabetes[24,25].

Adiponectin receptors

Adiponectin acts through two receptors: AdipoR1 and AdipoR2 in the regulation of energy homeostasis and anti-inflammatory responses. AdipoR1 is the most abundant form in skeletal muscle, whereas AdipoR2 is the most abundant form in the liver[26]. AdipoR1 and AdipoR2 have seven transmembrane domains, which are homologous with the G protein-coupled receptors. The N-terminal is located in the cytoplasmic region of the cell while the C-terminal end is external. Besides, a zinc ion is found in the transmembrane domains, which plays a vital role in the stimulation of adenosine monophosphate-activated kinase (AMP-K) that allows the action of adiponectin. These characteristics of adiponectin receptors are being used for the development of AdipoR agonists, which may be included in the future treatment of obesity and type 2 diabetes[27], since adiponectin modulates the pathogenesis of overweight and diabetes mellitus type 2[28,29].

Adiponectin acts through AMP-K, a critical regulatory kinase of glucose and lipid metabolism, and by the activation of the peroxisome proliferator-activated gamma receptor (PPAR-γ), which inhibits gluconeogenesis and stimulates glucose uptake[30,31]. Recent research has identified an adiponectin receptor adapter protein named Adaptor Protein, Phosphotyrosine Interacting With PH Domain And Leucine Zipper 1 (APPL1), that is an adapter protein with a Pleckstrin homology domain and a phosphotyrosine binding domain. This is an endosomal protein that binds to the AdipoR1 and AdipoR2 to positively mediate the signaling and nuclear transcription factors of adiponectin[31].

APPL1 has three functional domains, which play essential role in the intracellular signal transduction of receptors, and it is expressed in insulin target tissues: skeletal muscles, liver, and adipose tissue. APPL1 interacts directly with adiponectin receptors mediating the actions of adiponectin in the regulation of metabolic energy and insulin sensitivity; adiponectin signaling through APPL1 is necessary to exert its anti-inflammatory as well as cytoprotective effects on endothelial cells, reducing the formation of neointima through the inhibition of smooth muscle proliferation[32]. The suppression of APPL1 expression in skeletal myoblast culture cells decreases adiponectin- induced glucose uptake and translocation of GLUT4 (glucose transporters 4), while its over-expression enhances the stimulatory actions of adiponectin in the glucose metabolism[33].

In addition to the effects on glucose metabolism, adiponectin acts as a cardioprotective molecule, by suppressing the expression of interleukin-8 (IL-8) in human aortic endothelium cells stimulated by tumor necrosis factor Alfa (TNFα)[34]. Also, adiponectin reduces the expression of adhesion molecules in endothelial cells, prevents the binding of monocytes, stimulates the production of interleukin-10 (IL-10), and suppresses the expression of proinflammatory mediators in monocytes and macrophages, such as TNFα and the chemo-attractant protein of monocytes 1 (MCP-1) in various cell types (macrophages derived from human monocytes -cells of the stromal vascular fraction of human subcutaneous fat pads). Furthermore, Adiponectin controls the expression of the vascular adhesion molecule-1 (VCAM-1) and TNFα in atherosclerotic lesions[35,36]. It also prevents the transformation of the macrophage into foam cells by inhibiting the expression of the scavenger receptor and coenzyme-A: cholesterol acyltransferase, responsible for the storage of lipids and the development of atherosclerotic plaques. Adiponectin performs an anti-apoptosis activity in cardiac ventricular myocytes and a protective effect on glomerular podocytes[37,38]. Low serum content of adiponectin is considered a biomarker of endothelial function due to its correlation with endothelial alterations, dyslipidemia, and atherosclerosis[39]. Adiponectin suppresses the activation of M1 macrophages (classically activated macrophages) that produce proinflammatory cytokines such as TNFα, the macrophage migration inhibiting factor (MIF), interleukin 6 (IL-6), the monocyte chemotactic protein-1 (MCP-1) and promotes the proliferation of M2 macrophages (alternatively activated macrophages) that secrete anti-inflammatory cytokines such as IL-10 and transforming growth factor β (TGF-β). Adiponectin deficiency leads to a classical activated M1 macrophage phenotype, while recombinant adiponectin acts promoting an anti-inflammatory phenotype in macrophages[40,41]. The macrophage polarization phenotype regulates the expression of adiponectin receptors (AdipoR), suppressing the expression of AdipoRs, and in M2 macrophages maintains the expression of those receptors[42,43].

Since the circulating levels of adiponectin, particularly the high-weight form, are elevated in mice with T-cadherin deficiency, T-cadherin has been postulated as a binding protein for adiponectin, which plays a crucial role in its signaling[44,45]. T-cadherin has also been identified as a potent receptor for hexamers and high molecular weight oligomers of adiponectin[46]; this protein is highly expressed in the vasculature and to a lesser extent, in the muscle. However, the liver, a significant target for adiponectin, does not show high expression of that protein of T-cadherin expression[47].

The active forms of multimeric and hexameric adiponectin, accumulate in tissues such as heart, vascular endothelium and skeletal muscles through

the interaction with T-cadherin. Studies in mice with T cadherin deficiency have shown that the association of adiponectin and T-cadherin plays a protective vascular role suppressing atherosclerotic plaque formation and neointimal proliferation[48]; therefore, demonstrating that T-cadherin is essential for cardiovascular protection mediated by adiponectin[49].

Recent research in mice vascular tissue helped to establish a new function for adiponectin meditate by T-cadherin in the regulation of exosomal release. The importance of this function is based on the fact that exosomes are vesicles that intervene in cell-to-cell communication under normal and pathological conditions by transferring active proteins, mRNA and small non-coding RNAs. They also serve as an alternative way for the elimination of lysosomes of inadequately folded proteins; this exosomal release controls cell stress and maintains homeostasis by exporting various unnecessary or harmful materials. In this regard, adiponectin decreases ceramide levels establishing a protective function, since the intracellular accumulation of ceramides is implicated in the pathogenesis of insulin resistance and endothelial dysfunction and leading the creation of new therapeutic strategies[50].

Ceramidase activity of adiponectin

Adiponectin induces ceramidase activity through its receptors resulting in the hydrolysis of ceramide to form sphingosine and free fatty acid. Sphingosin produced in this reaction is further phosphorylated by sphingosine kinase to produce sphingosine 1-phosphate (S1P). This molecule functions as an essential signaling molecule in several different cellular processes. The ceramidase activity induced by activation of AdipoR1 and AdipoR2 determines the adiponectin activity in the metabolism of sphingolipids[51].

In transgenic mice with overexpression of adiponectin receptor isoform (AdipoR1, AdipoR2) was demonstrated that adiponectin could induce ceramidase activity, which produced increment in hepatic sphingosine-1-phosphate levels and improves hepatic steatosis in adult mice with diet-induced obesity[52].

The degradation of ceramide in the liver by adiponectin is a local phenomenon leading to decreased hepatic lipid absorption and expression of lipogenic. In addition, the effects of adiponectin mediated through AdipoR1 and AdipoR2 within adipocytes, contribute to greater local lipid purification to protect adipocytes from excess exposure to lipids[52-53].

The receptors of adiponectin decrease the length of the chain of ceramides in obesity, suggesting a possible novel therapeutic objective, since ceramide metabolism influences predominantly in the sensitizing effects to insulin by adiponectin in the liver and adipose tissue. In other words, overexpression of AdipoR1 and AdiopoR2 increases the activity of ceramidase in visceral adipose tissue. When sphingosine kinase phosphorylates Sphingosine, it produces sphingosine 1-phosphate (S1P), which it acts as a signaling molecule[54]. Other groups have shown that overexpression of S1P avoids the accumulation of ceramide and improves muscle insulin resistance in mice fed with a high-fat diet[55] Overexpression of S1P acid ceramides seems to have the same effect on adipose tissue preventing hepatic steatosis and systemic insulin resistance[56].

Ceramides are a critical factor in understanding the regulation of weight gain and intolerance to glucose, as they increase during obesity and promote insulin resistance. Ceramides are synthesized by the enzyme ceramide synthetase (CerS)[56,57]. Overexpression of CerS correlates with insulin resistance and CerS deficient mice are protected from high-fat diet induced obesity and glucose intolerance[58].

The accumulation of ceramide in skeletal muscles is associated with altered insulin sensitivity, so the concentration of ceramide decreased by adiponectin may be a mechanism to increase insulin sensitivity in skeletal muscle[59].

Adiponectin through the activity of ceramidase can avoid apoptosis. It has been considered that the reducing activity of ceramide is an important mechanism of adiponectin to fight metabolic diseases and protect against organic damage[60]. This finding was supported by the induction of AdipoRs overexpression in the liver, which was accompanied by better glucose metabolism. The crystalline structures of AdipoR2 sphingosine have provided additional support for the concept of ceramides in the action of adiponectin[61].

T-cadherin can regulate the cellular content of ceramide in response to the multimeric adiponectin of high molecular weight, as an additional mechanism for the adiponectin/AdipoR axis that improves the biogenesis and secretion of exosome leading to decrease of cellular ceramides[62]. Adiponectin actions in the metabolism of carbohydrates and lipids in adipose tissue, adiponectin increases basal glucose uptake and glucose uptake through AMP-activated protein kinase (AMPK) activation, which plays a vital role in the regulation of cellular lipid metabolism and systemic adipose deposits regulating lipolysis, fatty acid transport and β-oxidation[63].

Adiponectin not only inhibits lipolysis, but also preferentially promotes fat storage in adipocytes of subcutaneous adipose tissue, instead of visceral or ectopic adipose tissue in the liver and avoids subcutaneous morphological alterations of fat (adipocytes hypertrophy, degenerative changes, infiltration of macrophages, and necrosis of adipocytes). Consequently, circulating levels of adiponectin and infiltration of macrophages in adipose tissue are among the most potent clinical predictors of insulin sensitivity in obese individuals[64,65].

Rabbit blastocysts cultured in vitro with adiponectin, showed that the insulin-like growth factor-I receptor (IGF1R) and insulin receptor were up-regulated after incubation with adiponectin. These results imply an increase in the availability and sensitivity of insulin, due to a more significant expression of the receptor as a response to adiponectin[66].

Anti-inflammatory actions of adiponectin could contribute to the "metabolically healthy obese," a subpopulation of obese individuals with normal insulin sensitivity since there is information regarding to high level of adiponectin in obese women with a profile standard metabolic[67].

Adiponectin regulates the metabolism of carbohydrates and lipids, reduces the production of hepatic glucose and improves the oxidation of fatty acids in skeletal muscle. Unlike most other adipokines, circulating adiponectin levels are typically reduced in obesity, type 2 diabetes, and associated conditions. Besides, mice lacking adiponectin or humans with polymorphisms that compromise adiponectin production a metabolic dysfunction and type 2 diabetes. Therefore, therapeutic strategies to reverse hypoadiponectinemia are attractive[68]. The growing evidence indicates that resistance to adiponectin also contributes to the development of metabolic and cardiovascular diseases[69].

Adiponectin is a well-described anti-inflammatory adipokine very abundant in serum. Previous reports have found that adiponectin deficiency promotes cardiovascular and metabolic dysfunction in murine models while its overexpression is protective[70]. In addition to the circulatory system, skeletal muscle is a peripheral target for adiponectin to exert its anti-inflammatory metabolic effects by improving the utilization of glucose and the oxidation of fatty acids in myocytes and by increasing the uptake of glucose in skeletal muscle through the translocation of glucose transporter 4 (GLUT-4). AdipoR1 is the most abundant adiponectin receptor in skeletal muscle, and globular adiponectin has a high affinity to AdipoR1; for this reason, most of the effects of adiponectin in skeletal muscle are carried out by the globular form[71].

Recent research in obese mice demonstrated that adiponectin improves the oxidation of fatty acids in muscle cells by stimulating the transcriptional activity of PPARγ (peroxisome proliferator-activated gamma receptor), a nuclear receptor that modulates the transcription of multiple genes. This receptor intervenes in the effect of adiponectin on glucose and the metabolism of fatty acids in skeletal muscle to decrease the content of muscular lipids as a controlling mechanism of insulin resistance[72].

Adiponectin reduces endoplasmic reticulum stress

The endoplasmic reticulum is an organelle that participates in the storage of intracellular calcium, in assembly, folding and post-translational modifications of proteins that must then be adequately folded through special proteins called chaperones[73].

When endoplasmic reticulum homeostasis is altered, three events known as the stress of the reticulum occur: accumulation of misfolded proteins in the lumen, decrease of protein transport towards the Golgi apparatus and depletion of calcium. This stress triggers a repair process called "unfolded protein responses (UPR)"[74].

In order to protect the cell and restore cellular homeostasis. The signals capable of activating reticule stress include calcium availability, presence of pathogens or alterations in nutrients. In addition, the endoplasmic reticulum is a sensor in the detection of cellular and metabolic alterations[75].

The reticulum stress produces an inflammatory response through the activation of NF-κB (nuclear factor enhancer of the light chains kappa of activated B cells) and translocation to the nucleus, promoting the expression of a variety of genes involved in the expression of inflammatory cytokines such as TNF-α, IL-1β and IL6, which induce lipogenesis, low-grade inflammatory status in obesity, insulin resistance and hepatic steatosis[76]. In addition to the inflammatory process, the interaction between the endoplasmic reticulum and the mitochondria, plays a vital role in metabolic homeostasis and oxidative stress, in the case that those adaptation mechanisms were insufficient to restore the activity of the endoplasmic reticulum, and the cell suffers apoptosis[77].

Adiponectin protects cells from endoplasmic reticulum stress-induced apoptosis and reduces inflammation in adipocytes, hepatocytes, endothelial cells, and pancreatic beta cells. These actions block mitochondrial apoptosis through the activation of protein kinases pathway signal and the suppression of transcription activating transcription factor-2 (ATF2), which plays a crucial role in the regulation of apoptosis and lipogenesis[76,77]. Adiponectin improves the cellular availability of Ca^{2+} and eliminates the deposit of free fatty acids induced by endoplasmic reticulum stress in adipocytes, decreases mitochondrial apoptosis and improves the cellular activity of the reticulum[78-80].

Conclusions

AdipoR1 and AdipoR2 receptors have seven transmembrane domains, which are homologous with the G protein-coupled receptors, a zinc ion that plays a fundamental role in the stimulation of the adenosine monophosphate- activated kinase, which allows the action of adiponectin. These characteristics of adiponectin receptors are being used for the development of AdipoR agonists, which may be included for the treatment of obesity and type 2 diabetes in the future since adiponectin modulates the pathogenesis of overweight and diabetes mellitus type 2, and it is considered a prognostic marker and a therapeutic intervention.

Recent research has helped to identify an adaptor protein of adiponectin receptors called APPL1, which binds to AdipoR1 and AdipoR2, to positively mediate the signaling and nuclear factors of adiponectin and the actions of adiponectin in the regulation of energy metabolism and insulin sensitivity. Adiponectin signaling through APPL1 is necessary to exert its anti- inflammatory and cytoprotective effects on endothelial cells so reducing the formation of arterial neointima via a dependent inhibition of the oligomerization of smooth muscle proliferation.

The ceramidase activity of AdipoR1 and AdipoR2 determines the hydrolysis of ceramide to form sphingosine 1-phosphate, which acts as an adiponectin signaling molecule. The latter allows lipid clearance by protecting adipocytes from their excess in visceral adipose tissue and decreases the absorption of hepatic lipids and the expression of lipogenic genes. This suggests that it is a possible novel therapeutic objective as the metabolism of ceramide predominantly influences the insulin-sensitizing effects of adiponectin in the liver and adipose tissue.

Recent research using vascular tissue of mice established a new function for adiponectin through T-cadherin in the exosomal release to control cell stress and maintain homeostasis by exporting several unnecessary or harmful materials. This adiponectin protective function against metabolic disorders and organ damage can lead to the creation of new therapeutic strategies.

Adiponectin protects cells from endoplasmic reticulum stress-induced apoptosis and reduces inflammation in adipocytes, hepatocytes, endothelial cells, and pancreatic beta cells by blocking mitochondrial apoptosis through the activation of the signal pathway of the protein kinases and suppression of activating transcription factor ATF2, which has a vital role in the regulation of apoptosis and lipogenesis.

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