# Adiponectin: Obesity and Development of Different Diseases

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## ABSTRACT

Adiponectin is an adipokine abundantly expressed in adipose tissue, which has been well characterized, demonstrating its beneficial effect on human health, circulates in the bloodstream in various isoforms, playing different roles in the balance of energy homeostasis. Adiponectin is an insulin sensitizing hormone that exerts its action through AdipoR1, AdipoR2 and T-cadherin receptors. AdipoR1 is abundantly expressed in muscle, whereas AdipoR2 is expressed predominantly in the liver. Adiponectin is inversely proportional to obesity, diabetes and other states of insulin resistance; this review presents current findings regarding regulation, production and biological effects. Adiponectin acts by activating AMPk (AMP-activated protein kinase) and thus the enzymatic modulation so that the signaling pathways play an important role in the regulation, in addition to the above it has been demonstrated that the deregulation in the biogenesis and function of the miRNAs contributes to the appearance and development of diverse diseases.

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## ABBREVIATIONS

HER2 : Human epidermal growth factor receptor 2.
HER3 :  Human epidermal growth factor receptor 3.
RTKN : Rhotekin coding gene.
ESR1 : Estrogen receptor coding gene 1.
ER : Estrogen receptor.
H-RAS : Gene encoding HRAS proteins.
HMGA2 : High-mobility group AT-hook 2.
LIN28 : Encodes a LIN-28 family RNA-binding protein.
PEBP1 : Encodes a member of the phosphatidylethanolamine-binding family of proteins and has been shown to modulate multiple signaling pathways.
ERBB3 : Receptor tyrosine-protein kinase, also known as HER3.
CDC25C :  encodes a conserved protein that plays a key role in the regulation of cell division.
EVI-1 :  Ecotopic viral integration site 1 (EVI1) regulates multiple cellular processes.
BCL-2 : Protein family that regulates apoptosis.
TIPM1 : Metallopeptidase inhibitor 1.
PDCD4 : Programmed cell death 4.
PTEN : phosphatase and tensin homolog.
MASPIN : mammary serine protease inhibitor.
RHOA : Family of genes homologous to Ras, member A.
FOXO2 : Forkhead Box Protein O2.
E-CADHERIN : Calcium-dependent cell adhesion proteins.
FOXO3a : Forkhead Box Protein 3A.
ERα : Estrogen receptor alpha.
HOXD10 : homeobox D10.
NF-Kappa B : Nuclear factor kappa-light-chain-enhancer of activated B cells.

## 1. INTRODUCTION

Obesity is a multifactorial disease produced by the interaction of genetic and environmental factors, caused by lifestyle, characterized by an excessive increase of body fat, produced by an imbalance between ingestion and energy expenditure [1,2]. Obesity has become a public health problem worldwide and its prevalence has increased dramatically in developed and developing countries [2,3]. In this sense, Mexico ranks second in the world prevalence of obesity, where over 70% of the adult population is overweight and obese, and resulting in economic and public health repercussions [4].

Epidemiological studies have shown that due to the physiological condition that occurs in obesity, it is a risk factor for the development of different diseases, such as cardiovascular, diabetes mellitus, hypertension and different types of cancer, including breast cancer [1,5]. In this sense, accumulation of fat causes a deregulation in the production of adipokines which contributes strongly to the onset of obesity related to the development of various diseases, the indisputable protagonist in the pathophysiological process of these diseases is adipose tissue, which is an endocrine organ that produces biologically active molecules defined as "adipokines", involved in the homeostasis of various physiological processes [6,7]. Therefore, alterations in adipose tissue, causes changes in the serum concentrations of adipokines, [6] and against this background, much of the scientific research is directed towards the understanding of the pathological mechanisms of obesity, allowing to establish clear associations between biochemical and anthropometric indicators with the risk of complications derived from obesity. However, an emerging field is the strong relationship between adipokine serum concentrations, particularly adiponectin, with obesity and its involvement in pathophysiological processes [8].

## 2. OVERVIEW OF ADIPONECTIN

Adiponectin, one of many hormones secreted by adipose tissue, was characterized in the 1990s and has received various names according to the description of various research groups [9]. Plasma concentrations of adiponectin in the human are ~ 5-30 μg / ml, this is one of the most

abundant proteins in circulation (0.01% of total proteins) [10]. The biological effects of adiponectin not only depend on blood concentrations, but also important the expression of different isoforms of receptors in different tissues [11].

Adiponectin plays critical roles in metabolism, regulation and maintenance for energy throughout the body, the main target organs are liver and skeletal muscle, however, during the last few decades numerous studies have shown that adiponectin exerts several effects on other organs in different contexts [12] (Fig. 1).

Adiponectin is a 30 kDa protein, composed of 244 amino acids and encodes the long arm of chromosome 3 (locus 3q27). The adiponectin gene consists of 3 exons and 2 introns, structurally containing 4 domains [15,16], it is synthesized as a single subunit and by processes of hydroxylation and glycosylation, various isoforms circulating in the plasma as trimer (low molecular weight LMW), hexamers (MMW average molecular weight) or multimers (high molecular weight HMW) are originated. The monomer form lacks biological activity, whereas HMW is the main active form, and is strongly associated with insulin resistance, metabolic syndrome and cardiovascular disease [15,16,17,19].

The action of adiponectin is mediated by 3 types of receptors: AdipoR1, AdipoR2 and T- Cadherin. The first two consist of 7 transmembrane domains, with the internal N-terminal region and the outer C-terminal region, structurally and functionally different from the G- protein coupled receptor family [15,20]. AdipoR1 is abundantly expressed in skeletal muscle and endothelial cells, AdipoR2 is expressed predominantly in the liver. The third is T-cadherin, lacking a transmembrane domain and exhibiting affinity for MMW and HMW isoforms, furthermore involved in cell adhesion and calcium-mediated cellular interactions [14,16,20,21].

## 2.1 Signaling Routes

AdipoR1 and ADipoR2 receptors are able to bind to adiponectin, their subsequent signaling is mediated primarily by AMPK phosphorylation and subsequent activation of mTOR (mammalian Target of Rapamycin), PI3k (phosphoinositide-3-kinases) / AKT (protein kinase B), MAPK, PPAR-α (peroxisome proliferator-activated receptor alpha), STAT3 (Signal transducer and activator of transcription 3) and NK-kβ (nuclear factor kappa-

light-chain-enhancer of activated B cells). AMPK is activated by the adapter protein APPL-1 (adaptor protein, phosphotyrosine interaction, PH domain and leucine zipper containing 1) and kinase β1 (LKB1), the activity of LKB1 (liver kinase B1) depends on the interaction with two proteins STE 20 (STRAD) and MO25, this complex phosphorylates AMPK and regulates several pathways, such as apoptosis, proliferation, angiogenesis and energy metabolism. AMPK phosphorylates the TSC2 (Tuberous Sclerosis Complex 2) protein, which negatively regulates protein synthesis and cell proliferation. Adiponectin also affects PI3K / AKT signaling, which is involved in cell growth and proliferation, AKT phosphorylates TSC2 which in turn stimulates mTOR signaling by neutralizing the effects of activated AMPK. In treatment with adiponectin in breast cancer cells the phosphorylation of PI3k and AKT induces the activation of AMPK and suppresses the mTOR pathway thereby inhibiting cell growth. Low doses of adiponectin inhibit ERK1 (extracellular signal–regulated kinases) / 2 signaling and reduce viability in breast cancer cells, and adiponectin induces cell cycle arrest through down-regulation of C-myc, cyclin D, and Bcl levels. Increases the expression of P53 (cellular tumor antigen), P21 (cyclin-dependent kinase inhibitor 1) and Bax [22,23,24,25,26].

## 2.2 Adiponectin Regulation

White adipose tissue, under normal physiological conditions, controls the use of substrates in other tissues by releasing hormones such as adiponectin that is transported through the bloodstream to other organs, where through signaling pathways mediated by their receptors, they activate key enzymes of lipid and glucose metabolism [27]. Both adiponectin receptors (Adipor1 and Adipor2), are capable of binding to adiponectin; Its subsequent signaling is mediated, mainly by the phosphorylation of AMPK and the activation of the activated receptor of peroxisome alpha proliferator (PPAR), in order to exert modifications in the metabolism of glucose and lipids of liver and muscle cells, as well as in inflammatory processes, vascular endothelial injury, and some are associated with intracellular signaling such as APPL1. In this context, signaling networks play an important role in regulation, activating AMPK and thereby modulating enzymatic activity at the post-transcriptional level; and acting on gene expression through the PPARS nuclear receptors. Similarly, the release of this adipokine

has a paracrine effect on the adipocytes themselves, in which activation of AMPK also occurs, thus establishing a self-regulation of this organ [27,28].

As mentioned above, the control of energy metabolism falls to several molecular and cellular systems, which interact in a coordinated way establishing a network of communication between different organs. This explains the impact of a disturbance in one of them on the whole organism, endocrine-metabolic disorders such as obesity, type II diabetes, heart failure, characterized by important alterations in energy metabolism, are necessarily related to alterations in this energy signaling pathway (Table 1).
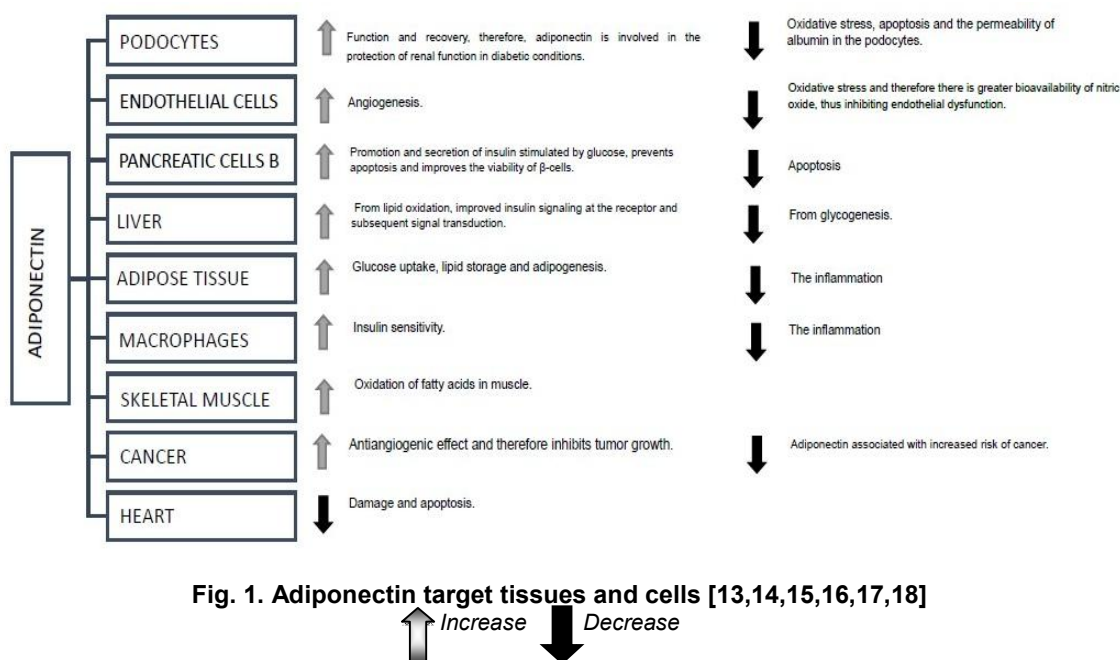


**Fig. 1. Adiponectin target tissues and cells [13,14,15,16,17,18]**
⬆ *Increase* ⬇ *Decrease*

**Table 1. Expression inhibitors and main adiponectin signaling ways**

| Inhibitors of Adiponectin Expression [29, 30, 31, 32, 33] | |
|---|---|
| **TNF-α (Tumor Necrosis Factor alpha)** | Inhibits the production of adiponectin in adipose tissue. |
| **IL-6 (Interleukin 6)** | Inhibits the expression and secretion of adiponectin genes in 3T3-L1 adipocytes |
| **CRP (C- reactive protein)** | Inhibits adiponectin mRNA levels in adipose tissue. |
| **Insulin** | Suppresses adiponectin gene expression in adipocytes. |
| **Glucocorticoids** | Suppress adiponectin gene expression in adipocytes. |
| **B-adrenergic agonists** | Inhibit adiponectin gene expression. |
| | **Inhibitors of the Adiponectin Signaling Ways** |
| **AMPK (activaded protein kinase p38)** | DORSOMORPHIN [34] SB203580 [35] LY2228820 [36] |
| **P38 MAPK (mitogen-activated protein kinases)** | VX-702 [37] LOSMAPIMOD [38] BIRB796 (P38α) [39] Skepinone-L(p38 α) [40] HS-173 (P110 α) [41] |

| | |
|---|---|
| **PI3K (PI3K: phosphatidylinositol 3-kinase)** | TGX-221 (P110β) [42] |
| | CZC244832 (P110Y) [43] |
| | CAL-110 (P110δ) [43] |
| **AKT ( protein Kinase B)** | A-674563 (AKT 1) [44] |
| | CCT128930 (AKT 2) [44] |
| | Pifithrin- α (PFT α) [45] |
| **P53 (Cellular Tumor Antigen)** | ReACp53 [46] |
| | Pifithrin-μ [47] |

## 3. ADIPONECTIN ASSOCIATED WITH PHYSIOPATHOLOGICAL PROCESSES

Adiponectin plays an important role against the development of various pathophysiological disorders, including metabolic and vascular diseases, several endocrine pathologies that share some common parameters such as increased insulin resistance, obesity and high blood glucose levels are closely related to low levels of adiponectin. Plasma adiponectin has shown a beneficial effect on human health. However, low levels of adiponectin in pathological conditions such as hypoadiponectinemia, is an important risk factor for the development of various diseases [48] (Table 2).

In contrast to hypoadiponectinemia, hyperadiponectinemia is caused by high concentrations of plasma asiponectin and leads to pulmonary, renal and cardiac diseases (Table 3), however, factors contributing to the development of hyperadiponectinemia remain unknown [62].

**Table 2. Diseases associated with hypoadiponectinemia**

| | |
|---|---|
| **Obesity** | The expression of adiponectin in adipose tissue and its plasma concentration is reduced in overweight and obese individuals, the plasma adiponectin concentration in addition to being negatively correlated with body mass index, also with the concentration of triglycerides [49,50]. |
| **Diabetes Mellitus Type 2 and Resistance to Insulin** | Studies conducted in various populations revealed that low adiponectin concentrations are related to the development of insulin resistance and Type 2 diabetes mellitus [51,52]. |
| **Hypertension** | There is a positive correlation between hypoadiponectinemia and hypertension, obese individuals with low plasma adiponectin levels are prone to hypertension [53]. |
| **Dyslipidemia** | Dyslipidemia is a disorder of lipid metabolism characterized by elevated levels of serum triglycerides, low density lipoprotein (LDL cholesterol) and low levels of high density lipoprotein (HDL) cholesterol. Several studies have shown that the level of adiponectin indicates an inverse relationship with the level of low-density lipoprotein, triglycerides and a positive correlation with high-density lipoprotein levels [54]. |
| **Metabolic Syndrome** | It is a group of conditions, such as abdominal obesity, insulin resistance, dyslipidemia, hyperglycemia and hypertension, which increase the risk of developing diabetes, stroke and heart disease. Decreased plasma adiponectin levels are associated with an increase in the number of metabolic syndrome components [55]. |

| Cardiovascular Disease and Aterosclerosis | Low levels of adiponectin play an important role in the development of atherosclerosis and cardiovascular disease, due to the fact that adiponectin plays a protective role in the pathogenesis of vascular diseases by promoting the production of nitric oxide, as well as the inhibition of inflammation and oxidative stress. So adiponectin deficiency shows deterioration of endothelium-dependent vasodilation [56, 57]. |
|---|---|
| Cancer | Hypoadiponectinenia plays a key role in the development and progression of obesity-related cancer, low plasma levels of adiponectin are directly associated with the risk of developing various types of cancer [58, 59, 60]. |
| Hepatic Disease Non Alcoholic Fat | Disease caused by the deposition of extra fat in liver cells regardless of alcohol consumption and can lead to fibrosis and cirrhosis, adiponectin limits excess lipid deposition in the liver and protects it from inflammation and fibrosis, so Hypoadiponectinemia may play a crucial role in the progression of non-alcoholic fatty liver disease and nonalcoholic steatohepatitis [61]. |

**Table 3. Diseases related to hyperadiponectinemia**

| Chronic Renal Disease | Chronic kidney disease consists of progressive loss of renal function over time and is an independent risk factor for the development of cardiovascular disease. High plasma adiponectin levels were found in patients with chronic kidney disease compared to healthy subjects due to low rate of clearance of adiponectin by the kidney [63]. |
|---|---|
| Lung Disease | Hyperadiponectinemia is associated with loss of body weight, systemic inflammation and hyperinflation in patients with COPD [64]. |
| Chronic Heart Failure | Adiponectin exerts protective effects on CHF (chronic heart failure) and patients with cardiovascular disease. However, controversy exists over the role of adiponectin and CHF, in some studies, high levels of plasma adiponectin were found in patients with CHF and increased plasma adiponectin levels correlated directly with the severity or mortality in CHF despite the protective effect of high plasma adiponectin on CHF in mice [65]. |

## 3.1 Strategies for Maintaining Healthy Plasma Adiponectin Levels

There are several strategies to increase the levels of adiponectin although the difficulty of converting adiponectin into a viable drug has been demonstrated [3]. e.g: PPAR agonists: thiazolidinediones (TZD) but TZD: INT131, induce the expression of adiponectin [7], in this sense a healthy dietary pattern like the mediterranean diet increases the adiponectin plasma levels, in the same context, the activation of AdipoRs is shown one of the most promising therapeutic approaches for treating disorders related to obesity. Nine agonists have recently been demostrated., four of them, mataresinol, arctiin, (-) - arctigenin and gramine, show a high affinity for AdipoR1. Four of these

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compounds, parthenolide, taxifolol, deoxyschizandrin, syringing, show high affinity for AdipoR2 and recently, Okada-Iwabu et al. identified a small agonist AdipoRs, AdipoRon which, in vitro, binds to AdipoR1 and AdipoR2 with high affinity [7,66].

## 4. REGULATION OF ADIPONECTIN BY MICRORNAs

MicroRNAs (miRNAs) are small non-coding RNAs that regulate the expression profiles of different genes. Consequently miRNAs are key molecules in the regulation of various processes within which it is possible to cite; proliferation, differentiation, mobility, invasion, cell death, among others. The miRNAs are sequences of a length of 19-25 nucleotides, which regulate the transcription of a white RNA, inhibiting its translation, stabilizing it or leading to its degradation. They are expressed in serum, plasma and other body fluids in a stable form, which makes them attractive for use as biomarkers. Coupled with the above, it is demonstrated that deregulation in the biogenesis and function of miRNAs contributes to the emergence and development of important diseases such as diabetes, cardiovascular diseases and cancer [67].

However, there is currently little data available on the regulation of adiponectin by miRNAs. Adiponectin is a marker protein for the expression and secretion of adipose tissue in adipocyte differentiation. Studies report that miRNAs play an important role in the differentiation of adipocytes and in their function. For example, in adipocyte differentiation, miR-27 expression is down-regulated, and its overexpression may specifically inhibit adipocyte differentiation, miR-143 expression is upregulated, and the inhibition of its expression may reduce differentiation of the adipocyte. These data suggest that the expression profiles of the miRNAs may change the adipocyte differentiation. This has been tested by Kang M et al. where they report that overexpression of some miRNAs such as miR-2 can significantly promote adipocyte differentiation, and increase the expression of marker genes such as adiponectin. Similarly, in an investigation conducted by Belarbi et al. observed that overexpression of miR-193b, miR-126 and miR-26a increased secretion of adiponectin in human adipocytes [68,69,70].

## 5. ROLE OF microRNAs IN BREAST CANCER

Among the different types of neoplasias, breast cancer is currently the cancer with the highest incidence and mortality in the female population both in Mexico and worldwide. The development of breast cancer is divided into initiation, formation, promotion, progression, metastasis, therapeutic resistance and recurrence of malignant tumors. The miRNAs are part of each of these processes and can act as oncogenes, tumor suppressors or metastatic regulators [71,72,73] (Table 4).

**Table 4. Principal miRNAS modulated in breast cancer, white gene and functionality**

| Tumor suppressor miRNA | | |
|---|---|---|
| miRNA | Target gen | Associated function in breast cancer |
| miR-125a/b | HER2, HER3 | Growth dependent anchorage |
| miR-145 | RTKN, Mucin | Its overexpression inhibits the cell growth of MCF-7 and induces apoptosis. |
| miR-206 | ESR1, ER (Decreased in ER-positive breast cancer tissues) | ER signaling |
| miR let-7 | H-RAS, HMGA2, LIN28, PEBP1 | Proliferation, differentiation. |
| miR-22 | ERBB3, CDC25C, EVI-1 | Tumor suppressor and metastasis inhibitor. |
| *miRNA oncogenes* | | |
| miRNA | Target gen | Associated function in breast cancer |
| miR-21 | BCL-2, TIMP1, TIMP3, PDCD4, PTEN, MASPIN | Adiponectin inhibitor |
| miR-155 | RHOA, FOXO2, E-CADHERIN, FOXO3a | Signaling of TGF-β, inhibitor of apoptosis |
| miR-125b | PROAPOPTOTIC Bcl-2 | MiR125b confers resistance to cancer cells in the breast cancer to paclitaxel. |

| miR-22 | ERα | It represses the expression of estrogen receptor α |
|---|---|---|
| miR-206 | ERα | Induces proliferation |
| miR-10b | HOXD10 | Metastasis |
| miR-146a/b | NF-Kappa B | Its deregulation is involved in breast cancer; Its increase forms part of the altered expression of BRCA1. |

To date, several studies have been reported to identify differentially regulated miRNAs between the tumor and normal mammary tissue, suggesting its potential use as disease classifiers and prognostic tools in this field. In an analysis of 76 breast tumors and 34 normal specimens, Lorio et al. identified 29 miRNAs that were differentially expressed in breast cancer tissue compared to normal [72,73,74].

## 6. CONCLUSION

Clinical and experimental studies indicate that a normal level of adiponectin helps the body counteract various pathologies related to obesity, which in turn, triggers the onset of metabolic and cardiovascular diseases. Alterations in the plasma adiponectin concentration are a biomarker useful in obesity, diabetes mellitus, dyslipidemia and hypertension, so that several studies suggest that adiponectin supplementation could be used as a potential therapeutic tool, improving the expression and function of receptors when they are present in pathophysiological conditions related to adiponectinemia. Therefore, it is necessary to continue studying the effects and precise mechanisms of action of adiponectin to give way to the development of effective drugs aimed at improving the complications associated with imbalance of this hormone.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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