Published in final edited form as:
Placenta. 2013 March ; 34 Suppl: S40–S45. doi:10.1016/j.placenta.2012.11.024.

Review: Adiponectin – The Missing Link between Maternal Adiposity, Placental Transport and Fetal Growth?

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Abstract

Adiponectin has well-established insulin-sensitizing effects in non-pregnant individuals. Pregnant women who are obese or have gestational diabetes typically have low circulating levels of adiponectin, which is associated with increased fetal growth. Lean women, on the other hand, have high circulating levels of adiponectin. As a result, maternal serum adiponectin is inversely correlated to fetal growth across the full range of birth weights, suggesting that maternal adiponectin may limit fetal growth. In the mother, adiponectin is predicted to promote insulin sensitivity and stimulate glucose uptake in maternal skeletal muscle thereby reducing nutrient availability for placental transfer. Adiponectin prevents insulin-stimulated amino acid uptake in cultured primary human trophoblast cells by modulating insulin receptor substrate phosphorylation. Furthermore, chronic administration of adiponectin to pregnant mice inhibits placental insulin and mammalian target of rapamycin complex 1 (mTORC1) signaling, down-regulates the activity and expression of key placental nutrient transporters and decreases fetal growth. Preliminary findings indicate that adiponectin binds to the adiponectin receptor-2 on the trophoblast cell and activates p38 MAPK and PPAR-α, which inhibits the insulin/IGF-1 signaling pathway. In contrast to maternal adiponectin, recent reports suggest that fetal adiponectin may promote expansion of adipose tissue and stimulate fetal growth. Regulation of placental function by adiponectin constitutes a novel physiological mechanism by which the endocrine functions of maternal adipose tissue influence fetal growth. These findings may help us better understand the factors determining birth weight in normal pregnancies and in pregnancy complications associated with altered maternal adiponectin levels such as obesity and gestational diabetes.

1. Introduction

It is well established that birth weight is positively correlated with maternal pre-pregnancy body mass index (BMI) [1]. Moreover, both small and large size at birth is associated with obesity later in life, indicating a generational transmission of risk for metabolic diseases [2]. Fetal growth is largely dependent on the delivery of oxygen and nutrients across the placenta. The ability of the placenta to supply nutrients to the fetus is determined by a multitude of factors, including the nutritional state of the mother, utero-placental blood flow,

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Conflict of Interest Statement
The authors declare no conflict of interest.

and the expression and function of trophoblast nutrient transporters [3]. However, the placenta is not merely a passive conduit for nutrients; growing evidence indicates that the placenta acts as a nutrient sensor, integrating signals from mother and fetus to balance fetal demand with maternal substrate supply by modulating placental growth and function [4–6]. To better understand the mechanisms governing maternal-fetal resource allocation it is important to identify the maternal and fetal factors that regulate placental function.

In recent years, adipocyte-derived signaling molecules referred to as ‘adipokines’, including leptin, resistin, adiponectin and pro-inflammatory cytokines, have been implicated in various pregnancy disorders [7]. Of these, only adiponectin is produced exclusively in adipose tissue in non-pregnant subjects and may therefore be considered a ‘true’ adipokine [8, 9]. In pregnancy, the placenta secretes an array of adipokines. Although some investigators have reported that adiponectin is produced by the placenta [10, 11], other studies have not confirmed these findings [12–14]. It is therefore likely that the adiponectin influencing placental function predominantly originates from maternal adipose tissue.

Several studies, including data from our laboratory (Figure 1), have demonstrated that serum levels of maternal adiponectin are negatively correlated with birth weight in healthy pregnant women with varying early pregnancy BMI [15, 16], as well as in women with gestational diabetes mellitus (GDM) [17]. Based on these clinical observations, we hypothesized that maternal adiponectin plays a causative role in regulating fetal growth by modulating placental nutrient transport. Here, we review the latest information on adiponectin receptors and signaling, summarize what is known with respect to maternal adiponectin in pregnancy, discuss recent findings demonstrating that adiponectin regulates placental function and briefly review emerging data implicating a role of fetal adiponectin in fetal adiposity and growth.

2. Adiponectin and adiponectin signaling

Adiponectin was discovered by four independent groups using different approaches [8, 9, 18, 19]. Three of these labs identified the gene encoding adiponectin (known as AdipoQ) exclusively in adipose tissue [8, 9, 18], while another group reported circulating adiponectin [19]. Adiponectin was also reported to be the most abundantly expressed transcript in adipose tissue [18]. The AdipoQ gene encodes a protein (full-length adiponectin, fADN) with 248 amino acids and four domains based on the primary amino acid sequence [20]: an N-terminal signal peptide, a variable region, a collagenous domain and a globular domain at the C-terminal end [18]. The shorter globular adiponectin (gADN) possesses potent biological activities, which in many tissues display similar properties to fADN [21, 22]. In contrast, gADN and fADN have distinct, and sometimes opposing, biological effects in other tissues including the placenta [23, 24]. The physiological significance of gADN is currently unclear given that almost all circulating adiponectin exists as fADN [25], whereas gADN is only present in very low concentrations in human plasma [25, 26]. However, it has been proposed that gADN may be released by locally active proteinases and exert local paracrine effects [27].

Adiponectin exerts a multitude of tissue-specific effects, in part depending on its unique, tightly regulated multimerization behavior. fADN assembles into three oligomeric isoforms: low molecular weight (LMW) trimers, medium molecular weight (MMW) hexamers and high molecular weight (HMW) oligomers [28]. Low serum levels of HMW adiponectin, rather than the total or other oligomeric forms, are associated with several metabolic disorders including type 2 diabetes mellitus [29], childhood obesity [30] and the metabolic syndrome across different populations [31].

The biological properties of adiponectin are mediated via two receptors: AdipoR1 and AdipoR2. While adiponectin is secreted exclusively by the adipose tissue, adiponectin receptors display widespread tissue expression. Both AdipoRs are predicted to contain 7 helices, resembling an inverse transmembrane architecture of G-protein coupled receptors [32]. Although the amino acid sequence of AdipoR1 and AdipoR2 show extensive homology, the two receptors exhibit diverse tissue expression patterns and activity. AdipoR1 is ubiquitously expressed with high levels in the skeletal muscle, whereas AdipoR2 expression is more restricted, with high expression in the liver [33]. AdipoR1 binds gADN with high affinity and fADN with low affinity, whereas AdipoR2 binds both gADN and fADN with intermediate affinity (Figure 2).

AdipoR signaling can be further modulated by the interaction with two adaptor proteins: Adaptor Protein Containing Pleckstrin Homology Domain, Phosphotyrosine Binding Domain and Leucine Zipper Motif 1 (APPL1) and APPL2 (Figure 2). Following adiponectin–AdipoR1 binding, APPL1 mediates a number of downstream signaling events associated with adiponectin function [34]. When the receptor is inactive APPL2 binds and inhibits APPL1 function, but APPL2 binding is displaced upon activation of AdipoR1 [35].

Adiponectin was also shown to bind to T-cadherin in myoblasts [36], implicating this protein as a novel adiponectin receptor. However, T-cadherin is absent in liver (a major site of adiponectin action) and because it lacks an intracellular domain it is not believed to mediate signal transduction. Hence T-cadherin may act as an adiponectin antagonist by competing for adiponectin binding.

Adiponectin activates three key signaling pathways in muscle and liver: AMP-activated protein kinase (AMPK), p38 mitogen-activated protein kinase (p38 MAPK) and peroxisome proliferator-activated receptor α (PPARα). Activation of these pathways results in fatty acid oxidation and glucose uptake in skeletal muscle, and inhibition of gluconeogenesis in liver [37]. These effects are believed to mediate the insulin-sensitizing actions of adiponectin. In skeletal muscle both gADN and fADN can induce the cellular energy sensor AMPK resulting in increased glucose utilization [37] and import of free fatty acids into mitochondria for β-oxidation [38]. The promoter activity of key genes regulating fatty acid transport and oxidation is controlled by the transcription factor PPARα [33]. p38 MAPK, which responds to cytokines and metabolic stress, is also activated by adiponectin. Recently, Yoon and coworkers demonstrated that adiponectin sequentially activates AMPK/p38 MAPK and PPARα in skeletal muscle [39]. In myotubes, inhibition of AMPK or p38 MAPK prevented PPARα activation by adiponectin [39].

In the liver fADN, but not gADN, increased AMPK phosphorylation [37]. Furthermore, disruption of adiponectin signaling using selective AdipoR knockout mice has implicated AdipoR2 in modulating PPARα activity in the liver, while AMPK was without effect [40]. Hence PPARα activity in the liver is likely to be dependent on adiponectin-mediated p38 MAPK signaling whereas in the muscle AMPK plays a dominant role.

3. Adiponectin in the pregnant mother

Accumulating evidence suggests that adiponectin plays disparate roles in maternal, placental and fetal physiology. This may be due to differential expression of AdipoRs and APPLs in the three compartments. Although mechanistic studies are largely lacking, clinical observations suggest that adiponectin plays a physiological role in the pregnant mother. In humans, early pregnancy is associated with metabolic changes resulting in the accumulation of fat. This is followed by the development of an insulin-resistant state to support increased hepatic gluconeogenesis and reduced glucose uptake in maternal skeletal muscle and adipose tissue, and increased lipolysis in adipose tissue, thereby making glucose and lipids

available to the fetus. Interestingly, changes in serum adiponectin track changes in maternal insulin sensitivity. Compared to the pre-gravid state, serum adiponectin is increased in early gestation [41]. Subsequently, adiponectin levels in serum and adipose tissue decline over the second half of gestation [42]. These observations are consistent with the possibility that high levels of adiponectin in early pregnancy enhance maternal accretion of nutrients, whereas declining adiponectin levels later in gestation promotes allocation of nutrients to the fetus.

In line with a role in regulating insulin sensitivity in the mother, lower adiponectin levels were reported in mothers with gestational diabetes mellitus (GDM) [17], a condition characterized by insulin-resistance and glucose intolerance. Furthermore low adiponectin levels in these women are typically associated with increased risk of delivering large for gestational age or macrosomic infants [17]. In otherwise healthy pregnant women, maternal serum adiponectin was also inversely correlated with birth weight [16].

4. Adiponectin signaling in the placenta: effects on placental function and fetal growth

Unlike skeletal muscle and liver, adiponectin signaling in the placenta is relatively unknown. Although adiponectin has been reported to be expressed in the placenta [10, 11] a number of studies have not been able to confirm these findings [12–14]. The human placenta was also proposed to secrete adiponectin in abundance [10, 11]. However, recent reports using more sensitive techniques suggest that it is unlikely that adiponectin is expressed and produced in the placenta, and indicate that contamination by adiponectin from the maternal circulation or fetal bovine serum used in cell cultures may explain previous positive findings [14, 43].

AdipoR1 and AdipoR2 are expressed in placental trophoblasts at the mRNA level [10], but only AdipoR2 protein is reported in human [44] and mouse trophoblast plasma membranes [45]. In agreement with the differential expression of AdipoRs in human placenta, gADN and fADN often display distinct biological effects in primary human trophoblasts (PHTs) (Table 1 and [24]). However, almost all studies to date addressing the role of adiponectin in placental function have utilized gADN. McDonald and Wolfe demonstrated that gADN attenuates mRNA expression and/or production of placental lactogen, chorion gonadotropin and progesterone in trophoblast cells [14]. Adiponectin has been reported to promote syncytialization in BeWo cells and in PHTs isolated from early first trimester placentas [46], but inhibit syncytialization in PHT isolated later in gestation [14, 46]. Furthermore, fADN was shown to inhibit cell proliferation in placental cell lines [47]. These observations may provide an additional mechanism by which adiponectin limits fetal growth. Our laboratory recently explored the distinct effects of gADN and fADN in cultured PHTs from term placentas [24]. Treatment with gADN increased secretion of IL-6 and TNF-α from PHTs, while fADN increased TNF-α but decreased IL-6 production. The effects of gADN on cytokine secretion were corroborated by findings of others demonstrating a pro-inflammatory action of gADN in PHTs [48].

Whereas the role of adiponectin in modulating insulin responsiveness in skeletal muscle and liver is well established, the factors regulating insulin sensitivity in the placenta are largely unknown. Recent findings indicate unique interactions between adiponectin and placental insulin signaling. In the absence of physiological concentrations of insulin, gADN stimulated trophoblast System A mediated amino acid transport, whereas fADN was without effect [24].

However, fADN prevented insulin stimulated System A activity, indicating a role for fADN in placental insulin-resistance. Moreover, fADN attenuated insulin-dependent activation of

insulin receptor substrate-1 (IRS-1), as well as preventing the downstream activation of protein kinase B/Akt. In contrast, gADN did not modulate insulin signaling in PHTs. Full length adiponectin did not affect AMPK phosphorylation but increased phosphorylation of PPARα in PHTs. Collectively, these data suggest that the effects of fADN in trophoblasts are mediated by AdipoR2 signaling [33]. This conclusion is also supported by preliminary findings demonstrating that incubation of PHTs in fADN leads to p38 MAPK phosphorylation (unpublished observations).

In agreement with the findings in cultured PHTs, chronic infusion of fADN in pregnant mice decreased placental amino acid transport resulting in a 19% reduction in fetal weight [45]. Insulin signaling, as evidenced by IRS-1 and Akt phosphorylation, was also attenuated in the placentas of dams chronically infused with fADN. The mechanisms underlying the effect of fADN on insulin-mediated amino acid transport may involve mTORC1 signaling. Functional readouts of mTORC1 activity, including phosphorylation of ribosomal protein S6K1, ribosomal protein S6 and eukaryotic translation initiating factor 4E-binding protein 1, were attenuated in the placentas of fADN-infused dams. Because mTORC1 is a downstream target of insulin signaling and constitutes a positive regulator of System A transporter activity in the placenta [49] mTORC1 signaling may provide a link between fADN signaling and nutrient transport. Similar to the findings in PHTs, maternal infusion of fADN in mice led to increased PPARα phosphorylation but not to activation of AMPK. Collectively, the data obtained in mice *in vivo* support the findings in cultured PHTs.

PPARα regulates the transcription of genes involved in fatty acid oxidation and thus adiponectin provides beneficial effects in the liver and skeletal muscle partly through reduction in triglyceride levels [33]. However, several lines of evidence indicate that PPARα also influences sphingolipid metabolism. For example, rats treated with PPARα agonists show increased expression of enzymes associated with ceramide biosynthesis including sphingosine palmitoyl transferase in the liver [50] and sphingomyelinase in the heart [51], concomitant with elevated ceramide concentrations in these tissues. Therefore, we hypothesize that fADN-mediated activation of PPARα in the placenta leads to elevation in ceramide levels, which impairs insulin-signaling and down-regulates amino acid transport. In support of this hypothesis, PHTs treated with ceramide display decreased Akt phosphorylation, which is downstream of IRS-1 [52]. Moreover, ceramide exposure decreased System A activity and protein synthesis in L6 myotubes [53]. Recently, Holland et al. demonstrated a role for sphingolipids in mediating the beneficial effects of adiponectin in mice liver and heart [54], implicating sphingolipids as critical intermediaries in adiponectin and insulin-signaling in a variety of tissues.

Based on the evidence presented above we propose a working model of fADN-mediated attenuation of insulin-stimulated amino acid transport in placental trophoblasts (Figure 3). Insulin signals via its receptor and activates IRS-1 and Akt, which results in increased System A activity mediated by mTORC1 signaling and other mechanisms. fADN signals via AdipoR2 and APPL1/2 to activate p38 MAPK and PPARα. We postulate that the activation of PPARα leads to transcription of genes favoring ceramide biosynthesis. Changes in sphingolipid metabolism may then promote ceramide-dependent inhibition of IRS-1 signaling and its downstream effects on amino acid transporter activity (Figure 3).

5. Emerging role of fetal adiponectin in fetal adiposity and growth

In contrast to the adult, neonatal concentrations of adiponectin positively correlate with several anthropometric indices of adiposity [12, 55]. Higher levels of cord blood adiponectin are associated with increased birth weight [55]. These findings suggest that maternal and fetal adiponectin have opposite roles in regulating fetal growth. At birth, cord blood

concentrations of adiponectin are approximately 4–7 fold higher than maternal serum [56]. However, this is followed by a progressive decline in adiponectin levels in the first year of life [57]. Since maternal adiponectin does not cross the placenta [41], the associations between cord blood adiponectin and measures of fetal adiposity reflect an independent role of fetal adiponectin.

While the above studies were based on clinical associations, Qiao et al. recently used genetic approaches to manipulate fetal adiponectin gene expression in mice and reported data supporting a direct link between elevated adiponectin and increased size of fat depots in early life [58]. Similar to the findings in humans, neonatal adiposity in mice was positively correlated with circulating neonatal adiponectin concentrations, whereas adiponectin knockout fetuses displayed lower body weight and fat content. However, the effect of adiponectin gene-knockout on body weight and body fat was no longer observable after the 15^{th} postnatal day. While the mechanisms underlying the delayed expansion of adipose tissue in adiponectin knockout fetuses remain unclear, it may be related to decreased transcription of lipogenic genes in the fetal liver.

6. Summary and future perspectives

Despite numerous clinical studies in the last decade reporting an inverse association between maternal adiponectin and birth weight, the underlying mechanisms remain largely unknown. Based on studies in cell-lines and non-pregnant animals, adiponectin signaling in skeletal muscle and liver of pregnant women would be expected to enhance insulin sensitivity (Figure 4). However, recent findings suggest that adiponectin has the opposite function in the placenta, i.e. promotes insulin resistance. Treatment of trophoblast cells *in vitro* as well as chronic adiponectin-infusion in pregnant mice impairs insulin signaling and attenuates insulin-stimulated amino acid transport, resulting in fetal growth inhibition *in vivo*. Regulation of placental function by adiponectin constitutes a novel physiological mechanism by which the endocrine functions of maternal adipose tissue influence fetal growth. The functional significance of fetal adiponectin is largely unknown; however, recent data suggest that fetal and neonatal adiponectin may promote expansion of adipose tissue and stimulate growth in early life. Mechanistic studies in both animal models and *in vitro* models such as PHTs will be instrumental in elucidating the precise role of adiponectin on maternal, placental and fetal physiology.

Acknowledgments

This work was supported by NIH grant HD065007.

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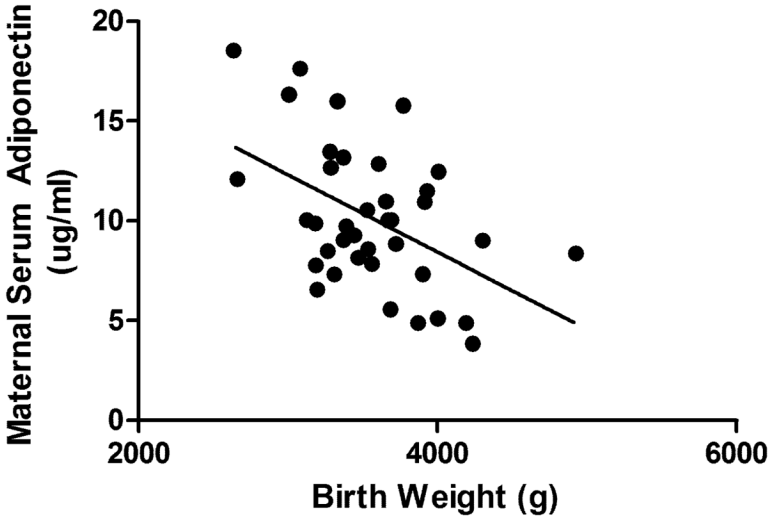

Figure 1. Relationship between maternal serum adiponectin and birth weight

Maternal serum adiponectin was determined at 36 weeks of gestation in women with normal term pregnancies and varying early pregnancy BMI (16.9 – 44.44; Mean = 25.42). r = −0.4879, p = 0.0019, n = 39. Data from Jansson et al. 2008 [23].

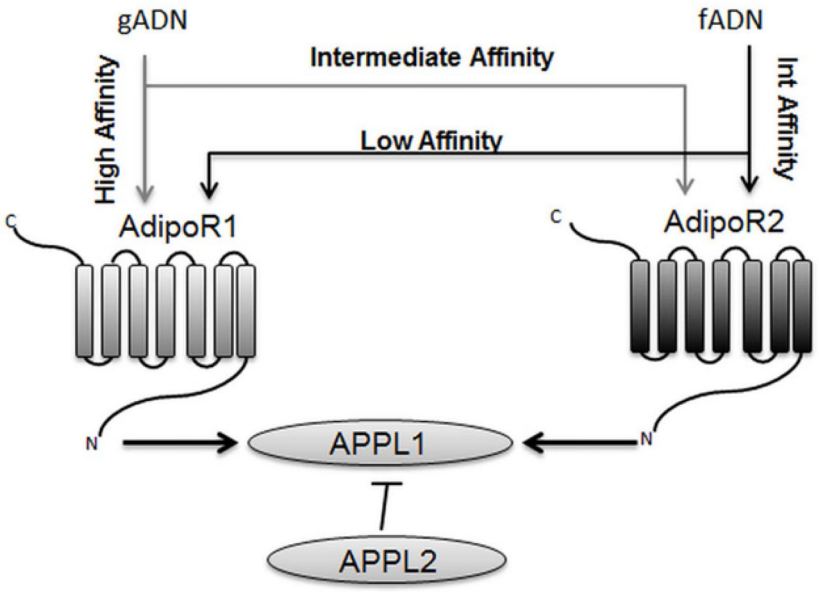

Figure 2. Adiponectin receptors and adaptor proteins

Adiponectin-signaling is mediated via AdipoR1 and AdipoR2. AdipoR1 binds gADN with high affinity and fADN with low affinity, whereas AdipoR2 binds both gADN and fADN with intermediate affinity. Adaptor protein APPL1 interacts with adiponectin receptors and mediates the activation of downstream targets, while APPL2 is bound to APPL1 in the receptor inactive state and inhibits signaling activity. AdipoR1/2, adiponectin receptor 1/2; APPL1/2, adaptor protein containing pleckstrin homology domain, phosphotyrosine binding domain and leucine zipper motif 1/2; fADN, full-length adiponectin; gADN, globular adiponectin; Int, intermediate.

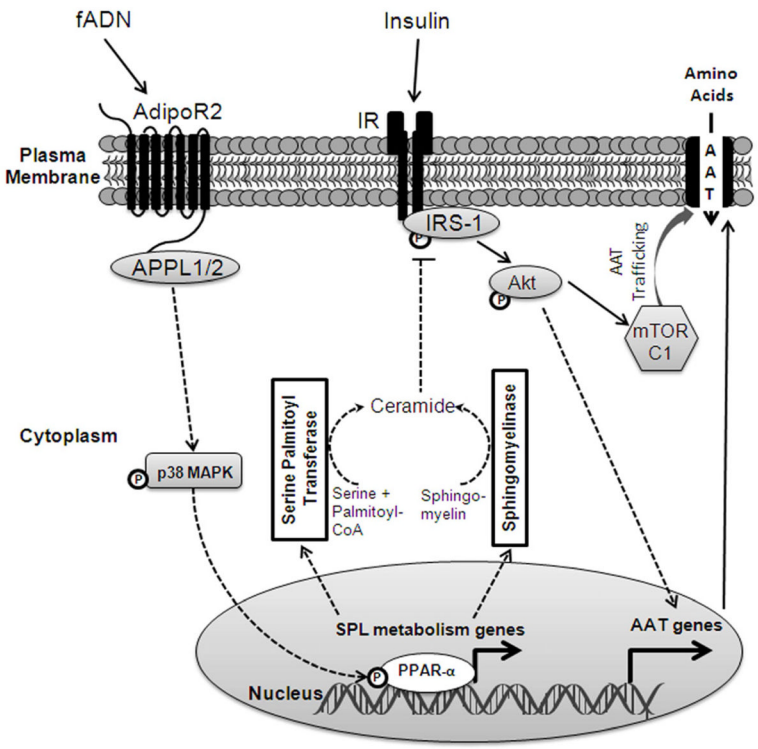

Figure 3. Proposed model of adiponectin signaling in syncytiotrophoblast cells

fADN interacts with AdipoR2 on the syncytial plasma membrane. Mediated by interaction with APPLs, this results in the activation of p38 MAPK and PPARα. Activation of PPARα dependent gene transcription leads to changes in sphingolipid metabolizing enzymes promoting ceramide biosynthesis. Consequently, elevated intracellular ceramide impairs IRS-1 activity and its downstream signaling of Akt and mTORC1, thereby inhibiting amino acid transport. Solid lines represent previously established processes, dashed lines indicate hypothetical mechanisms. AAT, amino acid transporters; AdipoR1/2, adiponectin receptor 1/2; APPL1/2, adaptor protein containing pleckstrin homology domain, phosphotyrosine binding domain and leucine zipper motif 1/2; fADN, full-length adiponectin; IR, insulin receptor; IRS-1, insulin receptor substrate-1; mTORC1, mammalian target of rapamycin complex 1; p38 MAPK, p38 mitogen-activated protein kinase; PPARα, peroxisome proliferator-activated receptor alpha; SPL, sphingolipid.

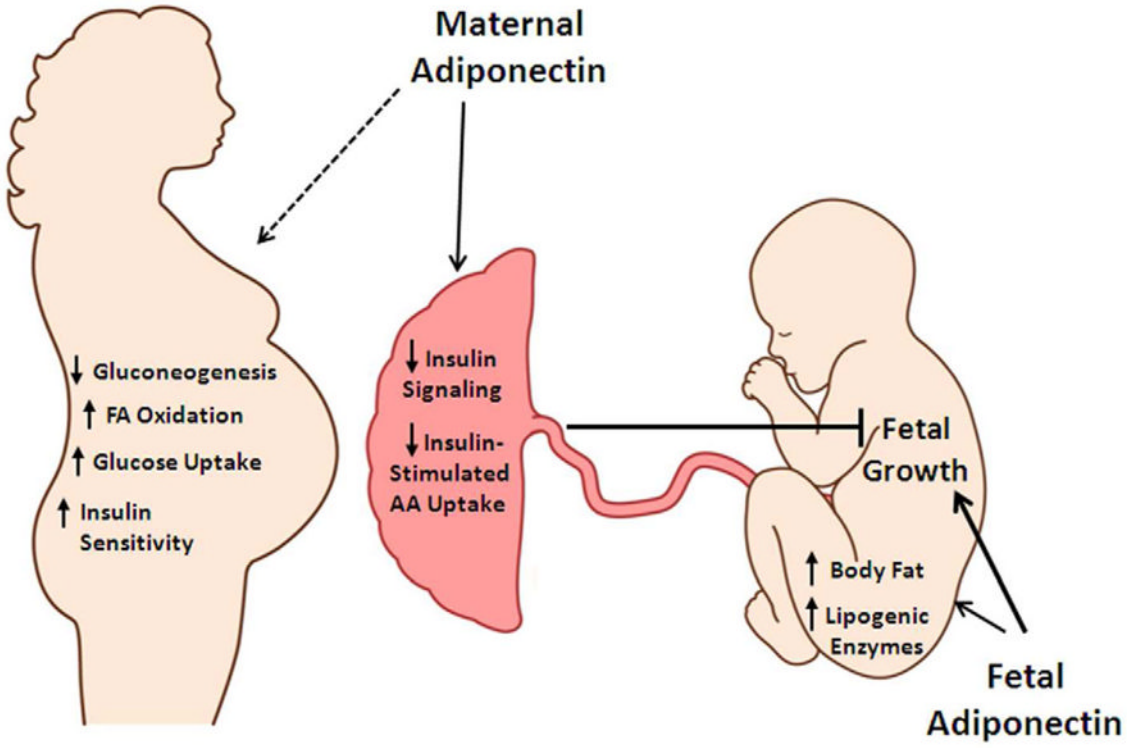

Figure 4. Specific roles of adiponectin in maternal, placental and fetal physiology

Maternal adiponectin is predicted to decrease gluconeogenesis in maternal liver, increase fatty acid oxidation and glucose utilization, and improve insulin sensitivity in liver and skeletal muscle. In the placenta, maternal adiponectin decreases placental insulin-signaling and reduces insulin-stimulated amino acid transport and subsequently decreases fetal growth. Fetal adiponectin is proposed to increase fetal adiposity and growth, possibly via increased lipogenic enzyme expression in the fetal liver. AA, amino acid; FA, fatty acid.

Table 1
Effects of globular and full-length adiponectin in primary human trophoblasts

The table summarizes findings in Jones et al. [33].

Biological Effect	Globular Adiponectin	Full-Length Adiponectin
Cell Signaling		
Insulin-stimulated IRS-1 phosphorylation (Tyr612)	**?**	↓
Insulin-stimulated Akt phosphorylation (Thr308 and Ser473)	↔	↓
AMPKα phosphorylation (Thr172)	↑	↔
PPARα phosphorylation (Ser21)	**?**	↑
p38 MAPK phosphorylation (Thr180/Tyr182)	**?**	↑*
Inflammation		
IL-6 secretion	↑	↓
TNF-α secretion	↑	↑
Nutrient Transport		
Basal System A activity	↑	↔
Insulin-stimulated System A activity	↔	↓
Basal System L activity	↔	↔
Basal SNAT2 protein expression	↑	↔
Insulin stimulated SNAT2 protein expression	↔	↓

AMPK, AMP-activated protein kinase; fADN, full-length adiponectin; gADN, globular adiponectin; IL-6, interleukin-6; IRS-1, insulin-receptor substrate-1; p38 MAPK, p38 mitogen-activated protein kinase; PPARα, peroxisome proliferator-activated receptor alpha; Thr, Threonine; TNF-α, tumor necrosis factor alpha; Tyr, tyrosine; Ser, serine; **?** unknown; * unpublished observation; ↔ no change; ↑ increases; ↓ decreases.