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Up- and down-regulation of adiponectin expression and multimerization: Mechanisms and therapeutic implication

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Abstract

Adiponectin has been receiving a great deal of attention due to its potential therapeutic use for metabolic and cardiovascular disorders. Adiponectin expression levels and multimerization are down-regulated in obesity and up-regulated by insulin sensitizers such as thiazolidinediones (TZDs), metformin, sulfonylurea and resveratrol (RSV). The precise mechanisms underlying adiponectin up- and down-regulation remain largely unknown, but recent studies indicate that the cellular and plasma levels of adiponectin could be regulated at both transcriptional and post-transcriptional levels. At the post-translational level, TZDs and resveratrol promote adiponectin levels and multimerization via up-regulation of disulfidebond-A oxidoreductase-like protein (DsbA-L). Adiponectin levels are also stimulated by FOXO1 and AMP-activated protein kinase (AMPK), and are suppressed by PKA or silencing mediator of retinoid andthyroid hormone receptors (SMRT). Since multimerization is important not only for adiponectin function but also for stability, increasing adiponectin multimerization has become a promising drug target for the treatment of metabolic diseases and other related disorders.

Keywords

Adiponectin; TZDs; Resveratrol; Metformin; DsbA-L

1. Introduction

Adiponectin, a 30 KD adipokine predominantly secreted from adipose tissue, exerts multiple protective properties against obesity[1–4], insulin resistance [5,6], inflammation [7–9], and cardiovascular diseases [10–12]. Adiponectin exists in cells and in the plasma in three major forms: trimers, hexamers, and the high-molecular-weight (HMW) *forms*, and the HMW form of adiponectin has been shown to be the most bioactive with respect to insulin action[4,13]. Reduction of the HMW form, rather than the total levels of adiponectin, has been shown to be associated with various metabolic disease states [14,15], suggesting that enhancing adiponectin multimerization could be an effective approach for the treatment of insulin resistance and related metabolic diseases.

Adiponectin expression, multimerization and secretion are increased by agonists of the nuclear receptor peroxisome proliferator-activated receptors γ (PPARγ) such as

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thiazolidinediones (TZDs) [15–18] and TZD structurally related compounds such as vitamin E vitamers α- and γ-tocopherol [19]. Adiponectin multimerization and cellular levels are also induced by MRL24, a PPARγ ligand that has been shown to protect adiponectin from obesity-induced down-regulation [20]. In addition to these PPARγ activators, several other small molecules such as resveratrol (RSV), a stilbenoid natural compound with an anti-diabetic property[21–23], and metformin [24] are also reported to stimulate adiponectin expression and secretion.

In this review, we have summarized our current understanding on the mechanisms by which the above-mentioned PPARγ activators and small molecules that promote adiponectin expression levels and multimerization. We will also discuss how phosphorylation and interaction with other nuclear receptors (NRs) positively or negatively regulate PPARγ activity and subsequent adiponectin expression.

2. Transcriptional and post-transcriptional regulation of adiponectin by PPARγ

The stimulatory effect of TZDs on adiponectin cellular levels[15–17] and multimerization [25,26] are well established. One possible mechanism underlying the promoting effect of TZDs is to promote PPARγ binding to a putative PPARγ-responsive element (PPRE) on the adiponectin gene promoter, thus leading to increased adiponectin gene transcription [15]. Adiponectin transcription is also stimulated by TZD structurally relevant compounds such as vitamin E vitamers, α- and γ-tocopherol [27], as well as PPARγ ligand anandamide [28]. However, the underlying mechanisms by which adiponectin gene is stimulated by these molecules remain to be further determined.

In addition to promoting adiponectin gene transcription, some recent studies suggest that activation of PPARγ can up-regulate adiponectin levels and secretion via a post-translational mechanism. Several recent studies indicate that activation of PPARγ induces the transcription of genes coding for proteins in the endoplasmic reticulum (ER) involved in the post-translational process such as adiponectin multimerization (Fig. 1) [18,29,30]. It has been shown that treating 3T3-L1 adipocytes with troglitazone had little effect on the mRNA levels of adiponectin [29]. On the other hand, this PPARγ agonist significantly enhanced the cellular levels of ER oxidoreductase Ero1-Lα, leading to increased secretion of the HMW complex of adiponectin [29]. Adiponectin levels and multimerization are also stimulated by a different TZD compound, rosiglitazone [18]. Interestingly, the promoting effects of rosiglitazone on adiponectin multimerization and cellular levels are greatly reduced in 3T3-L1 adipocytes in which the expression levels of disulfide-bond A oxidoreductase-like protein (DsbA-L) are suppressed by siRNA. In addition, overexpression of DsbA-L enhances adiponectin multimerization [18]. Rosiglitazone markedly repressed the transcription of another ER chaperone, ERp44, leading to decreased retention of adiponectin in the ER and elevated assembly and secretion of the HMW adiponectin complexes [30,31]. Taken together, these findings demonstrate that activation of PPARγ could enhance adiponectin levels and multimerization via post-transcription-dependent mechanisms involving ER chaperons such as Ero1-Lα, DsbA-L or ERp44 (Fig. 1) [18,29,30].

3. Up- and down-regulation of adiponectin levels by targeting PPARγ

While it is well established that adiponectin is regulated by PPARγ, much less is known on the signal pathways modulating PPARγ activity involved in the regulation of adiponectin expression, multimerization, and secretion. PPARγ has recently been found to undergo obesity-induced and protein kinase cdk5-mediated phosphorylation at Ser^{273} [20] (Fig. 2). Interestingly, this phosphorylation neither activates nor suppresses the adipogenic capacity

of PPARγ, but instead mediates obesity-induced down-regulation of a large number of genes including adiponectin in white adipose tissue [20]. The obesity-induced and cdk5-mediated PPARγ phosphorylation and adiponectin down-regulation *in vivo* is prevented by treating mice with TZDs or the PPARγ ligand MRL24, suggesting that inhibition of cdk5-meidated phosphorylation could be a mechanism by which TZDs enhance PPARγ action [20]. PPARγ has also been shown to be phosphorylated by ERK1/2 (extracellular signal–regulated kinases 1 and 2) at Ser^{82} [32] and Ser^{112} [33]. Phosphorylation at these sites has been shown to inhibit PPARγ transcriptional activity, but whether the phosphorylation has any effect on adiponectin gene expression remains to be clarified [32,34,35].

In addition to being regulated by phosphorylation, PPARγ activity is also modulated by nuclear factors such as retinoid acid receptors (RARs) and silencing mediator of retinoid and thyroid hormone receptors (SMRT) (Fig. 3). Retinoid X receptor (RXR) and retinoid acid receptor (RAR) play opposite roles in term of regulating PPARγ activity. In response to PPARγ agonist stimulation, RXR dimerizes with PPARγ to form a PPARγ/RXR heterodimer, which directly binds to the PPARγ-responsive element (PPRE) (–273/–285) in the adiponectin promoter to facilitate adiponectin gene transcription [15]. On the other hand, the transcriptional activity of PPARγ is negatively regulated by RARs [36], which are members of the ligand-dependent nuclear receptor families that compete with PPARγ in binding to the same heterodimer partner RXR. The PPARγ/RXR-stimulated adiponectin gene expression and adipogenesis are suppressed in mice by *in vivo* administration of retinaldehyde, a retinoic acid precursor derived from vitamin A that activates RAR/RXR signaling [37]. Adiponectin gene expression is also regulated by silencing mediator of retinoid and thyroid hormone receptors (SMRT), a nuclear corepressor that interacts with a subset of nuclear receptors (NRs), including RAR and PPARγ. The interaction, which is mediated via the receptor interacting domain 1 or 2 (RID1/2) in SMRT, represses the transcriptional activity of RAR or PPARγ, respectively [38].Knock-in the RID1 mutated form of SMRT in mice led to reduced PPARγ activity, accompanied with decreased adiponectin levels and enhanced diet-induced obesity [38] [39]. These findings suggest that retinoid acid may regulate adiponectin expression modulating the PPARγ/RXR complex formation.

4. Regulation of PPARγ activity by small molecules

A number of small native or chemically synthesized compounds, including sulfonylurea (SU), a class of oral hypoglycemic agents used in treating type 2 diabetes [40], resveratrol, a stilbenoid [41], metformin, an oral anti-diabetic drug in the biguanide class [42], cilostazol, a potent phosphodiesterase type III inhibitor [43], and puerarin, a major isoflavone glycoside from Kudzu root [44], have been shown to enhance adiponectin production. Cilostazol and puerarin activate PPARγ transcription, which may provide a mechanism to up-regulate adiponectin production [43,44]. SU, resveratrol and metformin, on the other hand, appear to promote adiponectin expression and multimerization through PPARγ-independent mechanisms.

SU agents are the most widely used oral hypoglycemic drugs that stimulate insulin secretion primarily by binding to the SU receptor on the plasma membrane of pancreatic β-cells. However, some studies have suggested that SU may also improve insulin resistance and its related disorders by up-regulation of adiponectin [40,45,46]. Two SU agents, glimepiride and glibenclamide, have been found to exert partial PPARγ agonist activity and potentiate PPARγ-mediated increase in adiponectin production [47]. In addition to a direct binding to PPARγ, these two SUs also recruit the PPARγ co-activator DRIP205 and subsequently dissociate PPARγ co-repressors such as the nuclear receptor corepressor and SMRT. There is also data showing that SUs could enhance adiponectin expression and insulin sensitivity

through inhibiting protein kinase A (PKA) via a PPARγ-independent mechanism [48]. Treating adipocytes with the PKA-selective activator forskolin significantly reduced adiponectin expression and secretion in adipocytes [48]. Additionally, Rp-cAMP, a diastereomer of cAMP that potently and selectively inhibits PKA activity by competitively binding to the regulatory subunit of PKA, further potentiated the stimulatory effect of rosiglitazone on adiponectin production [48]. One possible mechanism by which PKA inhibits adiponectin gene transcription is to activate CREB, a transcriptional repressor of adiponectin gene expression [49]. Consistent with this, adiponectin mRNA expression is also suppressed via β-adrenergic signaling-mediated activation of PKA [50], which could partly explain the role of β-adrenergic signaling in insulin resistance [51].

Resveratrol, a polyphenol originally found in different plant species such as grapes, has been shown to exert anti-diabetic activity *in vitro* and *in vivo* by improving mitochondria function and energy expenditure [23] [21]. Numerous studies have demonstrated that resveratrol enhances adiponectin levels, which could be one of the potential mechanisms by which resveratrol, improves insulin sensitivity. Resveratrol enhances adiponectin expression and improves insulin sensitivity in adipocytes and this effect is mediated by inhibition of inflammation [52] [53]. We have recently demonstrated that resveratrol enhances adiponectin cellular levels and multimerization by up-regulation of DsbA-L, which is mediated by the FOXO1 and AMPK signaling pathways [41]. Consistent with this finding, both FOXO1 and adiponectin mRNA expression are up-regulated by resveratrol treatment in human visceral adipocytes [54]. However, we found that while resveratrol treatment significantly enhanced the expression levels of DsbA-L, it had little effect on the mRNA levels of adiponectin [41] (Fig. 1). The exact reason for this discrepancy remains unknown but FOXO1 has been found to suppress PPARγ gene expression [41]. Since PPARγ positively regulates adiponectin gene expression and secretion, these findings suggest that the effects of FOXO1 on adiponectin biosynthesis may depend on cell content and upstream signal events.

Metformin is the first-line drug of choice for the treatment of 2 diabetes due to its potent anti-gluconeogenesis action and insulin sensitizing property. However, the mechanisms underlying metformin action remain to be established. Metformin activates AMP-dependent kinase (AMPK) and this property could play a key role in the inhibition of liver glucose production and promotion of glucose uptake and fatty acid oxidation in skeletal muscle [55,56]. Since AMPK plays an important role in resveratrol-stimulated adiponectin multimerization, it is conceivable that metformin may also promote adiponectin production by activation of AMPK. Consistent with this, six months of metformin therapy ameliorates insulin action in type 2 diabetes patients and leads to an increase of plasma adiponectin levels [42]. In addition, metformin has been found to up-regulate adiponectin expression and secretion from human subcutaneous adipose tissue (SAT) but not visceral adipose tissue (VAT), which provides evidence that metformin action on adiponectin production may be tissue specific [57]. However, there are studies showing that metformin has no effect on intracellular levels and secretion of adiponectin [58,59]. Further studies will be needed to address these controversies.

5. Summary

PPARγ is the major player regulating adiponectin expression, assembly and secretion. Two mechanisms, phosphorylation and interaction with other nuclear receptors such as SMRT and RARs, are shown to modulate PPARγ activity and its roles in regulating adiponectin gene activation. The cellular levels and multimerization of adiponectin could also be regulated by post-translational mechanisms via PPARγ-independent mechanisms, involving the FOXO1 and AMPK signaling pathways and DsbA-L. Understanding the mechanisms

regulating adiponectin multimerization and cellular levels and identification of novel molecules enhancing adiponectin expression and multimerization could be an effective therapeutic approach for the treatment of insulin resistance and its associated metabolic and cardiovascular diseases.

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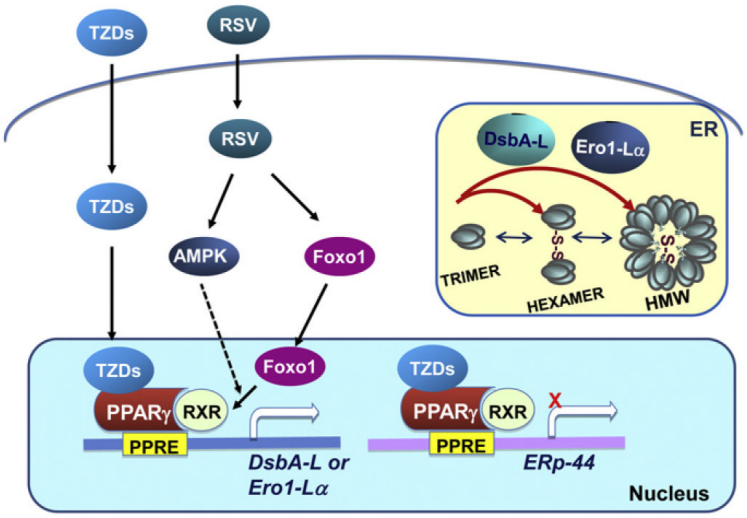

Fig. 1.

TZDs and resveratrol promote adiponectin multimerization through regulation of ER chaperones. TZD-activated PPARγ binds to the promoter of DsbA-L, Ero1-Lα or ERp44, leading to enhanced transcriptions of DsbA-L and Ero1-Lα, but repression of ERp44 transcription. Elevated cellular levels of DsbA-L and Ero1-Lα promote adiponectin multimerization in the ER. Resveratrol enhances adiponectin production and secretion mainly through increasing the expression levels of DsbA-L, which leads to elevated adiponectin multimerization and stability. Activation of AMPK or Foxo1 mediates the stimulatory effect of resveratrol on DsbA-L expression, but the underlying mechanism remains to be established.

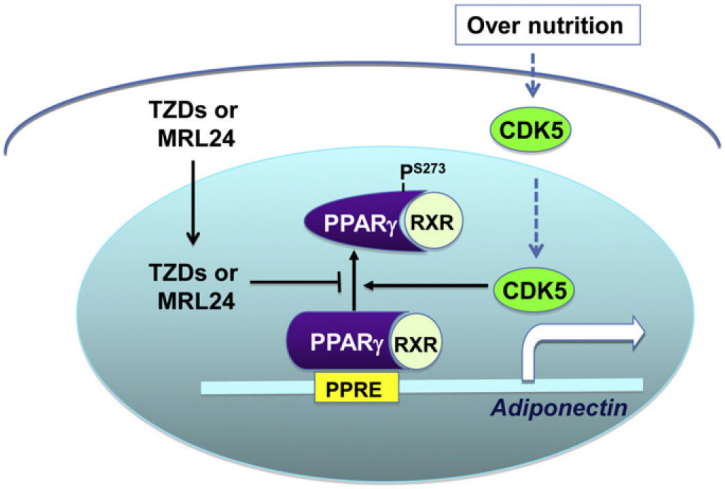

Fig. 2.

PPARγ transcriptional activity is regulated by phosphorylation. High fat diet induces CDK5 activation in mouse white fat tissue, leading to phosphorylation of PPARγ at Ser^{273}. Phosphorylation at this site reduces PPARγ transcriptional activity towards specific genes such as adiponectin. TZDs or MRL24 protects obesity-induced adiponectin down-regulation by suppressing CDK5-meidated PPARγ phosphorylation.

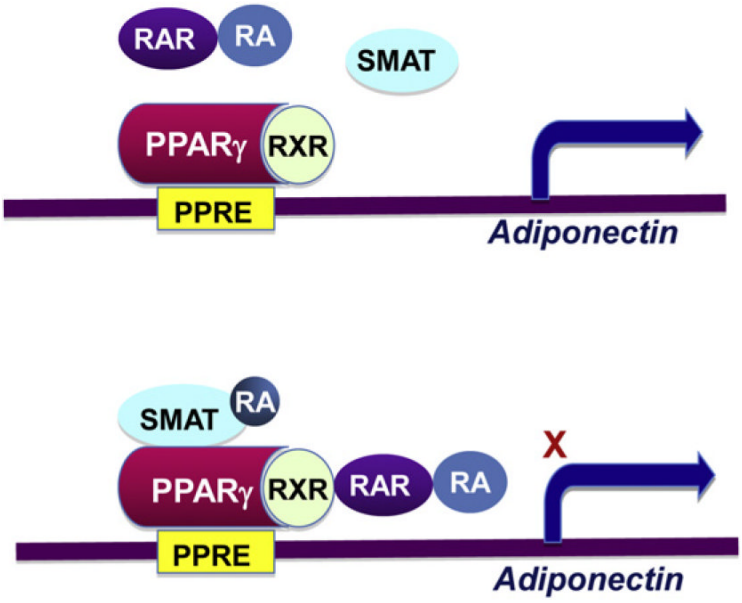

Fig. 3.

SMRT acts as a corepressor to regulate PPARγ activity and adiponectin transcription. The ligand-dependent nuclear corepressor SMRT interacts with RAR and PPARγ through receptor interacting domain 1 and 2 (RID1/2), respectively. The interaction of SMRT represses the transcriptional activity of RAR and PPARγ. Retinoid and thyroid hormone deficiency leads to dissociation of SMRT from PPARγ and subsequently activation of PPARγ and enhanced adiponectin transcription.