

PPAR- γ : A master metabolic nuclear receptor

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Summary

Peroxisome proliferator-activated receptor- γ (PPAR- γ) is a member of metabolic nuclear receptors called PPARs, which regulate all facets of the fatty acid metabolism including transport, synthesis, storage, mobilization, activation and oxidation of fatty acids. Hence, this receptor could be a drug target for metabolic syndrome-related non-communicable diseases (NCD) like obesity, diabetes, cardiovascular disease and cancers. The PPAR- γ gene has different size and transcriptional variants in different species. The major transcriptional variants (PPAR- γ 1 and PPAR- γ 2) encode proteins with 475/477 and 505 amino acids, respectively. Transcriptional regulation of PPAR- γ is mainly due to combinatorial activity of several transcription factors, chromatin remodelers and non-coding RNA at its promoters and enhancers during energy-surplus state. The miR-130a/b could be a major miRNA regulating PPAR- γ transcripts at post-transcriptional levels. Its protein has a large ligand-binding pocket to bind a wide range of endogenous and exogenous natural (e.g., dietary lipids) and synthetic ligands (TZDs). Along with its obligate partner RXR, and other co-activators, it exerts its action by DNA binding at DR1 and DR2 repeats and also by chromatin remodeling at the promoters and enhancers of its target genes. It has important physiological roles in adipocyte differentiation, inflammation, insulin sensitivity and reproduction. By enhancing the transcription of genes related to lipid uptake, triglyceride synthesis and glucose metabolism, PPAR- γ sequesters the plasma-free fatty acids into adipose tissue and, thereby, it plays a greater role of promoting systemic insulin sensitivity. Hence, it is a key target for anti-diabetic drugs like TZDs. Due to many side effects for classical PPAR- γ -targeting drugs like TZDs, selective PPAR- γ modulators are gaining a great lot of attention. Future studies need to be carried out to understand its transcriptional and post-transcriptional regulation in non-adipose tissues adopting advanced “omics” approaches. Such studies will be helpful in designing selective PPAR- γ modulators with limited side effects.

Key words: Insulin sensitivity, Ligands, Non-communicable diseases, PPAR- γ , Transcriptional regulation

Introduction

In the contemporary scenario, the prevalence of non-communicable diseases (NCD) including obesity, diabetes, cardiovascular disease and cancers has been increasing. Among 57 million worldwide deaths in 2008, 37 million (67%) were mainly due to these NCD. It is projected that these NCD deaths will be further increased to 15% globally between 2010 and 2030 (WHO, 2008). These diseases result not only due to genetic changes but also to the huge effect of environmental factors including nutrition and sedentary lifestyles. In order to control these diseases, several pharmaceutical interventions are being practiced. One such intervention targets key metabolic nuclear receptors called peroxisome proliferator-activated receptors (PPARs), which comprise three subtypes viz., PPAR- α , PPAR- β (δ) and PPAR- γ . The PPARs were initially identified as mediators for compounds that stimulate peroxisome proliferation in the liver of rodents (Wahli, 2002). Later, they were found to play significant roles in carbohydrate and lipid metabolisms, cellular differentiation and cancers.

The PPAR- α , PPAR- β (δ) and PPAR- γ , especially, regulate all facets of the fatty acid metabolism including transport, synthesis, storage, mobilization, activation and oxidation of fatty acids (Kersten et al., 2000; Evans et al., 2004). The PPAR- α and PPAR- β (δ) mediate mainly fatty acid catabolic processes like β and ω oxidation of fatty acids in peripheral tissues. But the PPAR- γ facilitates transcription of genes required for the anabolic process viz., storage of triglycerides in adipose tissue, which is the center of the metabolic syndrome. Additionally, PPAR- γ 's dominant role in adipocyte differentiation, a key event imbalanced in obesity and its associated NCD, and insulin sensitivity through expression of adipokines make the PPAR- γ as a “master” gene of fat cell biology, energy homeostasis and, eventually, NCD. This review focuses on the PPAR- γ gene, its transcriptional regulation, tissue-specific expression, protein structure, agonists, mechanism of action, physiological roles and the associated NCD.

PPAR- γ gene

According to the human, animal and bird genomes available at www.ensembl.org, the *PPAR- γ* gene ranges from 20 kb to 147 kb from chicken to human (Table 1). A total of 15 exons and 15 transcription variants have been observed in the human *PPAR- γ* gene. These transcription variants encode proteins with different amino acids ranging from 40 to 505. However, two transcripts encoding the proteins with 477 and 505 amino acids are elaborately studied in humans. These were considered as PPAR- γ 1 and PPAR- γ 2, encoding 475 and 505 amino acid containing proteins, respectively, in other species. Some of the human transcripts are non-coding, and few of the transcripts

belong to a category of nonsense-mediated decay. Around 96 variations, including SNPs, somatic SNVs and indels, were identified in human *PPAR- γ* gene. Among them, 74 variations were found to be involved in different NCDs like insulin-independent diabetes, obesity, lipodystrophy and cancers (Database available at GenePhenotype option at www.ensembl.org). The involvement of these genetic variations in different diseases reinforces the subtle role of *PPAR- γ* genetics in NCD. But no phenotype description has been observed for the remaining 22 genetic variations by HGMD (Human Genome Mutation Database) annotation (www.ensembl.org). Apart from the variations, 7 paralogues are reported for the *PPAR- γ* gene in the human and animal genomes (Table 1).

Table 1. PPAR γ gene structure and variations in different species*

Species	Chr.	Gene size (Kb)	No. of transcript variants (TV)	Maximum number of exons	Paralogues	Protein size in amino acids (TV)
Primates						
Human	3	147	15	15	7	505 (TV1) 477 (TV2, TV3, TV4) 483 (TV5) 250 (TV6) 248 (TV7) 186 (TV8) 132 (TV9) 99 (TV10) 40 (TV11) Non-coding transcripts (TV12, TV13, TV14, TV15)
Chimpanzee	3	83	1	7	7	505
Farm animals						
Cattle	22	122	3	8	7	475 (TV1) 505 (TV2) 475(TV3)
Pig	13	72	1	7	8	504
Horse	16	107	1	7	7	474
Pet animals						
Dog	20	73	1	7	7	529
Cat	1	135	2	8	7	475 (TV1) 505(TV2)
Birds						
Chick	12	20	1	6	7	475
Duck	Scaffold 1	24	1	6	7	480
Laboratory animals						
Rat	4	124	2	8	8	475 (TV1) 505 (TV2)
Mouse	6	129	2	9	7	475 (TV1) 505 (TV2)

* The data in the table is based on the information available from different genomes at www.ensembl.org

Transcriptional regulation of *PPAR- γ* gene

A 1Kb sequence upstream of the human *PPAR- γ* gene was considered enough to be an effective promoter for its expression (Fajas et al., 1997). A hierarchical and combinatorial activity of several transcription factors, chromatin remodelers and non-coding RNA at the promoters leads to the expression of *PPAR- γ* 1 and γ 2 in adipose tissue, a primary tissue for *PPAR- γ* expression and a typical model for better understanding of *PPAR- γ* transcriptional regulation. These events in *PPAR- γ* transcriptional regulation were explained to a greater detail in a recent review (Eeckhoutte et al., 2012). Briefly, adipogenesis events are triggered by an imbalance between energy surplus and expenditure, commitment of mesenchymal stem cells into preadipocytes by the influence of wnt and BMP family members as well as mitotic clonal expansion of preadipocytes by differentiation inducers like IGF1, glucocorticoid and cyclic AMP. During these early differentiation events, especially at mitotic clonal expansion of preadipocytes, a cascade of transcription events happen to induce the expression of *PPAR- γ* and CCAAT/enhancer binding protein (C/EBP)- α , which eventually cause the expression of several genes required for adipocyte phenotype (Tang et al., 2003).

The *PPAR- γ* transcription is regulated by a transcriptional cascade of transcription factors and also by the epigenetic switches at chromatin remodeling. The cascade on transcriptional events include the expression of ecotropic viral integration site 1 (Evi1), C/EBP- β , C/EBP δ (Veh et al., 1995; Ishibashi et al., 2012), kruppel-like factors 5 and 15 (KLF5 and KLF15) (Mori et al., 2005; Oishi et al., 2005), nuclear family I (NFI) and nuclear factor E2-related factor 2 (Nrf2) (Pi et al., 2010; Waki et al., 2011). The Evi1-C/EBP- β complex induces low levels of *PPAR- γ* , specifically *PPAR- γ* 2, and C/EBP- α expression probably by removing the SMRT (silencing mediator of retinoic acid and thyroid hormone receptor) repression at their promoters (Ishibashi et al., 2012; Raghav et al., 2012). By positive feed-back mode, the *PPAR- γ* 2 and C/EBP- α regulate their expressions each other to high levels leading to adipocyte differentiation.

The epigenetic switches mainly involve histone activation and deactivation marks at the promoters of *PPAR- γ* . Histone activation and deactivation are generally represented by H3K27 acetylation and methylation, respectively (Tie et al., 2009; Mikkelsen et al., 2010). Additionally, demethylation of the promoter DNA (Fujiki et al., 2009) and H3K9me2 (Noer et al., 2009) also promote the *PPAR- γ* transcription during adipogenesis. Acetylation of H3K27 at enhancer regions within or near the *PPAR- γ*

gene is catalyzed by the transcriptional co-activators CREB-binding protein (CBP) and p300 (Tie et al., 2009). Once the activation switch is on, the transcription is induced. However, transcriptional elongation needs further chromatin remodeling such as binding of the nucleosome-remodeling complex switch/sucrose non-fermentable (SWI/SNF), which facilitates the release of stalled RNA polymerase II (Salma et al., 2004, Levin, 2011). The release of stalled RNA polymerase II finally results in trimethylation of H3K36 within the *PPAR γ* gene, which is a feature of actively transcribed genomic regions (Rao et al., 2005). The epigenetic regulation of *PPAR- γ* transcription is not only confined to the involvement of proteins but also long-non coding RNAs (lncRNA), which may act as a modular scaffold and fasten the protein factors for forming a chromatin modifying complex (Sun et al., 2013).

Post-transcriptional regulation of *PPAR- γ* gene

The important molecules with significant roles in post-transcriptional regulation are miRNAs, which are short non-coding RNAs around 22 nucleotides long. These non-coding RNAs usually make partial complementary base pairing with mRNAs and trigger their degradation processes and, eventually, repress their translation (Bartel, 2009). Two miRNAs, miR-27a/b and miR-130a/b, are considered to be regulating the *PPAR- γ* transcripts in adipocyte differentiation, a major event regulated by the *PPAR- γ* . Both these miRNAs can bind at 3'-UTR of the *PPAR- γ* transcripts. The miR-130a/b can also bind at coding region of the *PPAR- γ* transcripts (Karbiener et al., 2009; Kim et al., 2010; Lee et al., 2011). A negative correlation has been observed between miR-130a/b expression and *PPARG* in abdominal fat deposits in females (Lee et al., 2011). But such negative correlation could not be observed between the expressions of miR-27a/b and *PPAR- γ* in epididymal fats, obese mice and *in vitro* studies (Lin et al., 2009). These observations indicated that miR-130a/b could be the major miRNA that regulates *PPAR- γ* transcripts at post-transcriptional levels. As the *PPAR- γ* 5' and 3'UTRs are short, with 173 and 211 nucleotides, respectively, many miRNAs may not target *PPAR- γ* (Cheng et al., 2009; Wang et al., 2012). However, further studies are needed to explore further miRNAs that regulate *PPAR- γ* post-transcriptionally. Some miRNA indirectly control *PPAR- γ* expression by acting on its transcriptional factors like C/EBP α and C/EBP β mRNAs (Sun et al., 2009; Liu et al., 2011).

PPAR- γ protein

Although the human *PPAR- γ* gene expresses 15 transcriptional variants in different tissues, mainly two

transcripts have relatively higher consensus with the other species (Table 1). These transcripts encode proteins with 477 and 505 amino acids in human, and 475 and 505 amino acids in other species. As mentioned earlier, while explaining the PPAR- γ gene structure, these are named as PPAR- γ 1, and PPAR- γ 2. The human PPAR- γ 2 has an extra 28 N-terminal amino acids (30 in rat and mice) compared to PPAR- γ 1, and is generally expressed in adipose tissue. Like other nuclear receptors, the PPAR- γ isoforms have four important regions viz., N-terminal ligand independent transactivation domain (A/B region or AF1), a DNA binding domain (DBD), a hinge region and a C-terminal ligand binding and dimerization domain with a ligand-dependent transactivation domain (AF2) (Fig. 1) (Wahli, 2002; Savage, 2005; Chandra et al., 2008). Phosphorylation and ligand (endogenous or exogenous ligands) binding at AF1 and LBD regions, respectively, can replace co-repressors with co-activators. As the other nuclear factors, the DBD is folded in two zinc fingers, the LBD is organized into 12 helices and form a hydrophobic pocket for ligand binding like thyroid hormone and retinoic acid receptors (Bourguet et al., 1995; Wagner et al., 1995; Renaud et al., 1995; Chandra et al., 2008). The ligand-binding pocket in this domain of PPAR- γ is larger than the other nuclear receptors, and this property might have evolved to accommodate a wide spectrum of natural PPAR- γ ligands with low affinity (Wahli, 2002). Crystal structure of the intact PPAR- γ -RXR- α receptor complex revealed that LBD domain not only helps to bind other receptor segments but also modulates the DNA binding domain function depending on the organization of the complex (Chandra et al., 2008).

PPAR- γ ligands

Nearly 211 partial agonists for PPAR- γ have been reported in literature. In general, PPAR- γ has natural and synthetic ligands. The natural ligands could be exogenous or endogenous. The endogenous natural ligands are considered to be weak ligands because of their low concentrations in the body. Usually, the metabolic products of fatty acids, like oxidized unsaturated fatty acids, are better ligands for PPAR- γ than the non-oxidized unsaturated and saturated fatty acids. For instance, 12/15 lipoxygenase derived oxidized fatty acids [13-hydroxyoctadecadienoic acid (13-HODE), 12-HETE and 15-HETE] (Huang et al., 1999; Limor et al., 2008), LDL derived oxidized fatty acids [9-HODE, 13-HODE, 1-O-hexadecyl-2-Azelaoyl-sn-glycero-3-phosphocholine (AZ-PC)] (Davies et al., 2001) and arachidonic acid derived prostaglandins ([5-deoxy- Δ 12,14-prostaglandin J 2(PGJ2)] (Forman et al., 1997) are better natural endogenous ligands

to activate PPAR- γ . The natural exogenous PPAR- γ ligands are dietary compounds or nutraceuticals. Dietary lipids or oils rich in n-3 and n-6 lipids are the major source of natural exogenous ligands for PPAR- γ (Wolf, 1999; Kita and Arai, 2001; Siess and Tigyi, 2004; Barlic and Murthy, 2007; Uchida, 2007; Itoh and Yamamoto, 2008; Garelnabi et al., 2008; Fei et al., 2011). Specifically, more the metabolic products of fatty acids than the parent molecules might be mediating the response of PPAR- γ . For example, 13-HODE might be converted to 13-Ox-HODE prior to the binding of PPAR- γ . The crystal structures of PPAR- γ -bound fatty acids revealed that covalent binding and polar nature of lipids enhance the PPAR- γ activity. Hence, oxidized fatty acids are better ligands probably due to their polar nature. Moreover, oxidation or nitration of fatty acids can occur within diet or *in-vivo*. Additionally, the intestine can absorb oxidized lipids that can be incorporated into lipoproteins and tissues. Among dietary unsaturated fatty acids, isomers of linoleic acid called conjugated linoleic acids (CLA), which are present in dairy products, act as ligands for both PPAR- γ and PPAR- α with strong affinity to PPAR- α than PPAR- γ (Moya-Camarena, 1999; Belury et al., 2002). However, the protective aspects of CLA have been attributed to PPAR- γ activation in experimental colitis (Bassaganya-Riera and Hontecillas, 2010). A list of nutraceuticals with PPAR- γ agonistic activity was well presented in a latest review by Penumetcha and Santanam (2012). Briefly, the dietary isoflavones like genistein, daidzein, equol, biochanin A (Dang et al., 2003; Cho et al., 2010), and flavonoids such as psi-baptigenin and hesperidin (Salam et al., 2008) were considered to be potential PPAR- γ agonists. As fatty acid metabolites, the metabolites of isoflavones determine the agonistic activity for PPAR- γ and their associated transcription factors. Metabolism of dietary isoflavones is generally determined by the microbiome of the intestine. Hence, this microbiome also has a role to activate or deactivate PPAR- γ by exogenous ligands. One such example is the production of equol from daidzein (Penumetcha and Santanam, 2012).

Potent synthetic PPAR- γ ligands are thiazolidinediones (TZD). With the help of a TZD, known as pioglitazone, the PPAR- γ was discovered (Kliwer et al., 1992; Kletzien et al., 1992; Graves et al., 1992). The TZDs such as troglitazone (Rezulin), rosiglitazone (Avanda) and pioglitazone (Actos) have been used in the treatment of type-2 diabetes. But these drugs have other side effects like hepatotoxicity, edema and cardiovascular risk. Hence, troglitazone was banned from markets and others have some warnings (Peraza et al., 2006). Further

studies need to be conducted to find whether the TZD toxic effects are due to PPAR- γ activation or through other mechanisms. To prevent such toxic effects, new synthetic compounds, including non-TZD like PPAR- γ agonists, PPAR α/γ agonists, PPAR pan agonists, PPAR- γ antagonists and selective PPAR- γ modulating drugs (SPPAR γ M, e.g., F-MOC-L-leucine) are under trials. Overall, PPAR- γ has a wide gamut of ligands from endogenous natural ligands to exogenous synthetic ligands.

Tissue-specific expression of PPAR- γ and its mechanism of action

Among PPAR isotypes, PPAR- α and PPAR- β express at high levels in liver, heart, kidney and brown adipose tissue, where fatty acid oxidation is at a high rate. However, PPAR- γ is expressed mainly in adipose tissue, where it promotes fatty acid storage by promoting triglyceride formation, and also in insulin responsive tissues like skeletal muscle, heart and liver (Mukherjee et al., 1997). The PPAR- γ 2 isoform expression is essentially confined to adipose tissue. But the PPAR- γ 1 expression can occur at detectable levels in large intestine and haematopoietic cells, and at low levels in liver, skeletal muscle, pancreas and other tissues. All the three isotypes were detected in ovaries of several species such as rat (Komar et al., 2001), mouse (Minge et al., 2006), pig (Gasic et al., 1998), human (Wu et al., 2004; Froment et al., 2006), cow (Mohan et al., 2002) and buffaloes (Sharma et al., 2012).

In the absence of ligands, PPAR- γ acts as a transcriptional repressor because of its ability to complex with repressor proteins. Binding of a ligand at LBD region causes conformational changes that lead to release of repressors and hetero-dimerization of PPAR- γ to its obligate partner RXR- α and other transcriptional co-activators/co-repressors. The resultant complex, comprising PPAR- γ , RXR- α and other co-activators/co-repressors, causes chromatin remodeling at enhancers and promoters of the target genes, binds to the specific DNA sequence of those target gene promoters and finally fine tunes the transcription of target genes in different tissues (Vekatachalam et al., 2009; Eeckhoutte et al., 2012) (Fig. 2).

The specific DNA sequence of PPAR-RXR binding is called peroxisome proliferator response element (PPRE). A typical PPRE contains two hexamers (AGGTCA) separated by one nucleotide (direct repeat-1 or DR1 element) or two nucleotides (direct repeat-2 or DR-2 element) (Gervois et al., 1999; Fontaine et al., 2003; Kumar et al., 2004, 2009; Venkatachalam et al., 2009). This kind of DR1 and DR2 elements with minor variations including 0-5 nucleotide spacing between hexamers can

also be binding sites for other nuclear receptors such as HNF4, APR1 and RXR-RXR heterodimers. However, a seven nucleotide 5' flanking sequence [C(A/G)(A/G)A(A/T)CT] of the 1st hexamer of DR1 and DR2 elements is not only specific for PPAR-RXR binding but also imparts specificity to different PPAR isotypes. Based on these DNA binding principles, an inbuilt computational program, PPARESearch (<http://www.classicus.com/PPRE/>), has been developed to search the PPAREs in the given DNA sequence (Vekatachalam et al., 2009b). A genome-wide screening of PPRE elements based on 13bp sequence including PPRE and flanking sequence, and 15bp PPRE associated sequence (PCAMs) in 5000bp upstream of human 24,033 genes identified that 1085 and 1207 genes have PPRE and PCAMs, respectively. A total of 172 genes have both PPRE and PCAMs in their upstream sequences of 5000bp. These genes not only belong to the classical lipid and carbohydrate metabolism-related genes but also the genes involved in immune and stress responses, cell cycle control and development, chromatin remodeling and different signaling pathways including Wnt and MAPK (Lemay and Hwang, 2006).

Additional to the DNA binding, chromatin remodeling is a part of the PPAR- γ mechanism of action. The co-activators attached to PPAR- γ have enzymatic activities catalyzing histone acetylation and methylation at enhancers, where chromatin remodeling occurs at sequential stages through hierarchical binding of TFs and cofactors. For example, increased H3K9 acetylation and hypomethylation of cytosines at enhancers during adipogenesis (Nielsen et al., 2008; Lefterova et al., 2010; Sugii and Evans, 2011; Serandour et al., 2012). Among the methylation events, methylation of H4K20 by SET domain containing lysine methyl transferase 8 (Setd8) could be important for PPAR- γ action at its target gene promoters (Wakabayashi et al., 2009). During adipogenesis, the PPAR- γ also needs a mediator complex, which acts as a scaffold for recruitment of general transcription factor, RNA polymerase II and also chromatin remodelers such as chromatin helicase DNA-binding protein 1 (CHD1) (Lin et al., 2011). In a nutshell, PPAR- γ exerts its action by DNA binding and chromatin remodeling at promoters and enhancers of its target genes (Fig. 2).

Physiological roles of PPAR- γ

PPAR- γ has multifaceted physiological roles including overall lipid metabolism, adipogenesis, insulin signalling, immune response, bone and reproduction-related functions (Fig. 3) (Yessoufu and Wahli, 2010; Bionaz et al., 2013).

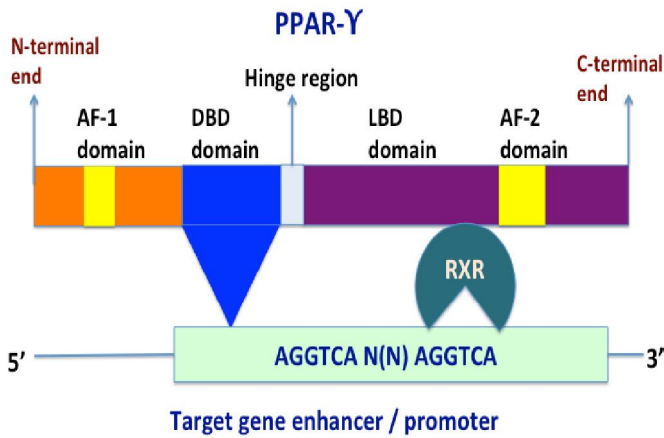


Fig. 1. Schematic representation of PPAR- γ protein. The picture is a modified version from Li et al. (2006) and Venkatachalam et al. (2009b). The functional domains are highlighted in different colors. AF-1: Activating factor 1; DBD: DNA binding domain; LBD: Ligand binding domain; AF-2: Activating factor 2; RXR: Retenoic acid X receptor.

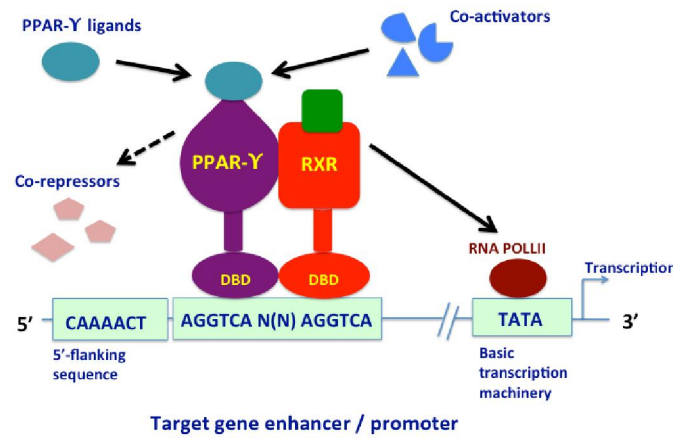


Fig. 2. Schematic representation of PPAR- γ mechanism of action. The picture is a modified version from Rumi et al. (2004) and Venkatachalam et al. (2009b). In an unbound state, PPAR- γ is attached with repressors. Ligand binding at ligand binding site on PPAR- γ causes conformational changes so that it can bind to its obligate partner, RXR and other co-activators with the replacement of co-repressors. The PPAR- γ /RXR/co-activators causes chromatin remodeling and binds to the specific sequences on DNA called DR1 or DR2 repeats. These events lead RNA-polymerase II to proceed with transcription of the target genes.

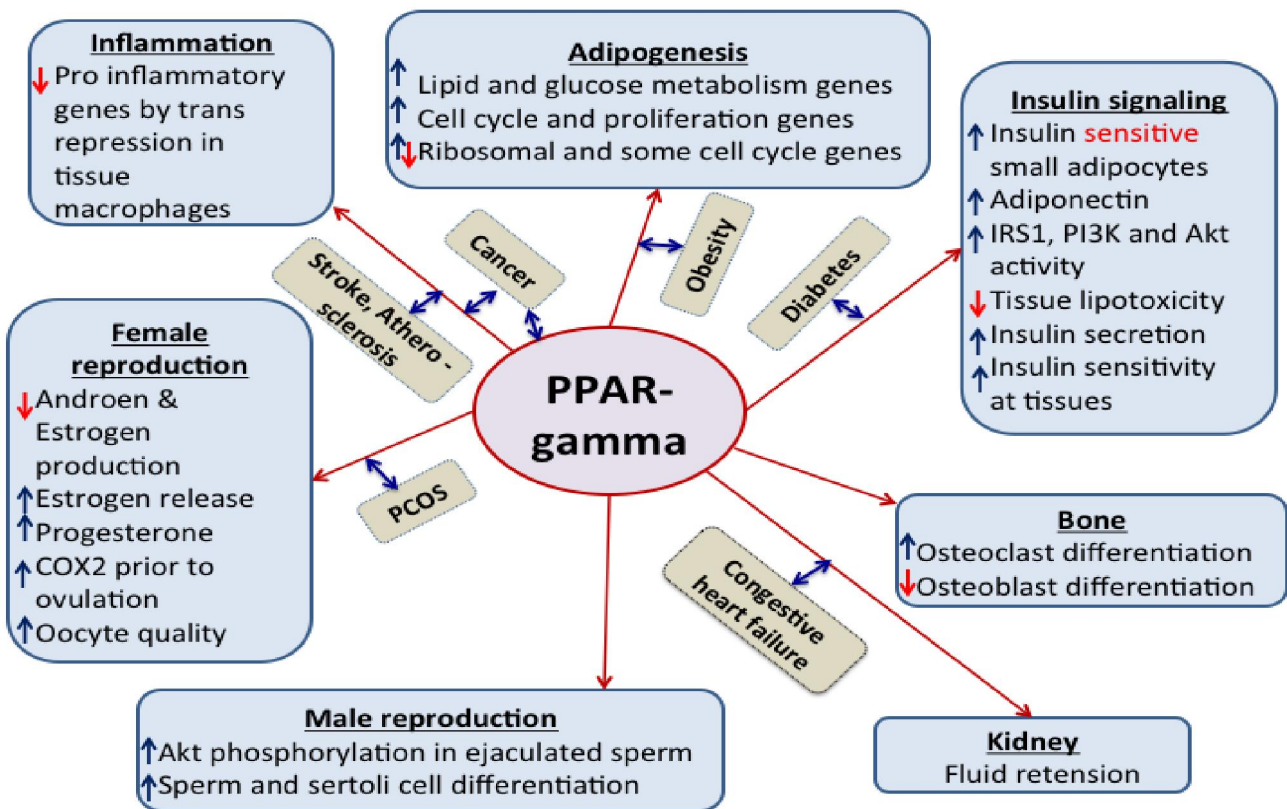


Fig. 3. PPAR- γ physiological roles and their associated non-communicable diseases (NCD). Arrows with bi-direction indicate the possible association of NCD with the physiological role. PCOS: Polycystic ovarian syndrome. Up-arrow indicates upregulation or increase. Down arrow indicates downregulation or decrease.

PPAR- γ and adipogenesis

Among aforementioned physiological roles, the well-studied and very important function of the PPAR- γ is adipocyte differentiation and lipid storage. An over-expression of PPAR- γ isoforms in adipose tissue is sufficient for its differentiation even though low levels of C/EBP- α , another important adipose tissue differentiation transcription factor (Lazar, 2002). Consequently, PPAR- γ is considered as a “master regulator” for adipocyte differentiation (Rosen et al., 2002). Genome-wide profiling by Chip-seq identified five different gene clusters being regulated by PPAR- γ at different time points during adipogenesis. The genes in cell cycle and proliferation were down-regulated, and some cell cycle and ribosomal genes were transiently down-regulated and later up-regulated during adipocyte differentiation. However, all the lipid and glucose metabolism genes were up-regulated during adipocyte differentiation process (Nielsen et al., 2008). As PPAR- γ promotes lipid deposition, it up-regulates the genes involved in plasma lipid uptake (lipoprotein lipase, CD36, fatty acid transport protein and aquaporin) and triacyl glycerol synthesis (acyl-CoA-synthase, glycerol kinase, GLUT4 for glucose uptake and phosphoenol pyruvate carboxy kinase). Additionally, PPAR- γ also up-regulates the perilipin and, thus, regulates lipolysis as well (Savage, 2005).

PPAR- γ and inflammation

PPAR- γ shows anti-inflammatory effects by reducing the transcription of the genes for production of pro-inflammatory cytokines in macrophages and T-lymphocytes, and also by promoting the expression of anti-inflammatory genes in the innate immune system (Haung and Glass, 2010). The inhibition of pro-inflammatory genes was found to be due to its trans-repression of NF- κ B targeted genes. The trans-repression mechanism consists of ligand-dependent sumoylation of the PPAR- γ ligand-binding domain. Such sumoylation targets PPAR- γ to nuclear receptor co-repressor (NcoR)/histone deacetylase (HDAC3) complexes on the inflammatory gene promoters. These events prevent the recruitment of the ubiquitylation/19S proteasome complex machinery, which mediates the signal-dependent removal of corepressor complexes needed for activation of genes. Consequently, the NCoR/HDAC3/PPAR- γ complex cannot be cleared from the NF- κ B targeted gene promoters and, thus, these inflammatory genes could be under repression (Pascual et al., 2005). Such trans-repression of inflammatory genes (e.g., TNF- α , IL1- β) by PPAR- γ occurs especially in tissue macrophages and endothelial cells located in

different tissues like adipose tissue, liver, vascular walls, intestine, mammary gland, skeletal muscle and cardiac muscle (Wahli and Michalik, 2012). It was observed that the deletion of PPAR- γ in hematopoietic and endothelial cells (ECs) in female mice to produce milk containing inflammatory lipids, which could be generated by the increased expression of 12-lipoxygenase and epoxide hydrolase. Such milk caused inflammation, alopecia, and growth retardation in the nursing pups (Wan et al., 2007). Based on this study, maternal PPAR- γ can protect the pups by inhibiting the production of inflammatory lipids in the milk.

PPAR- γ and insulin signalling

Activation of PPAR- γ in different tissues causes increasing insulin sensitivity and reduces insulin resistance and, thereby, improves glucose utilization. This effect is because of the concerted action of different events at cellular, molecular, systemic and tissue levels. At cellular levels, PPAR- γ activation promotes the synthesis of small insulin sensitive adipocytes (Leonardini et al., 2009). Additionally, PPAR- γ in adipocytes modulates the synthesis and release of adipokines, especially increased adiponectin (Hu et al., 1996), and reduced insulin-resistance genes like TNF- α and resistin (Steppan et al., 2001). Adiponectin enhances insulin activity by suppression of gluconeogenesis, regulation of fatty acid metabolism (Berg et al., 2001; Yamaguchi et al., 2001; Awazawa et al., 2009) and modulating the calcium signalling in skeletal muscles by activation of AMP-activated kinase (AMPK) and PPAR- α through AdipoR1 and AdipoR2 receptors (Yamaguchi et al., 2002, 2007; Iwabu et al., 2010). Additionally, adiponectin directly stimulates insulin sensitivity in liver by up-regulating insulin receptor substrate 2 (IRS-2) through activation of signal transducer and activator of transcription -3 (STAT3), which could be due to transient production of IL-6 from macrophages by NF- κ B mediated activity of adiponectin through its unknown receptors (Awazawa et al., 2011). Further, PPAR- γ affects the insulin-signaling cascade by directly modulating the expression or phosphorylation of specific signaling molecules. These modulating effects vary for different insulin signaling molecules based on the PPAR- γ ligand and the type of tissue. For example, TZDs troglitazone increases IRS1, PI3K and AKT activities, and rosiglitazone increases PKC ζ activity but not Akt activity in skeletal muscle. Similarly, another PPAR- γ ligand, metformin, increased PKC ζ and AMPK activities but not IRS1, PI3K and AKT activities in skeletal muscle. Similarly, increased and changed activities of Akt were observed by troglitazone and metformin in adipose tissue.

At systemic level, by increasing expression of several genes as explained in the above section of adipogenesis, PPAR- γ decreases plasma free fatty acids but increases their uptake and storage in adipose tissue. Specifically, fat deposition by PPAR- γ occurs at subcutaneous adipose tissue rather than other tissues like liver and skeletal muscle, where free fatty acids cause lipotoxicity and insulin resistance. The reduction of plasma free fatty acids, thereby lowering lipotoxicity, improves the insulin secretion from pancreatic β -islets (Bays et al., 2004). Overall, PPAR- γ activation enhances insulin sensitivity at multi-levels in body systems.

PPAR- γ and bone functions

The PPAR- γ promotes osteoclast differentiation and bone resorption (Wahli, 2008). Additionally, it favors adipogenesis and reduces osteoblast differentiation from bone marrow progenitor cells (Akune et al., 2004; Cock et al., 2004). Deletion of PPAR- γ from osteoclast progenitor cells increases bone density and extra-medullary hematopoiesis, which leads to a clinical syndrome called osteopetrosis (Yessoufou and Wahli, 2010).

PPAR- γ and reproduction

Many studies of PPAR- γ have been focused more on female reproductive processes than the male reproduction events. PPAR- γ has either direct or systemic effects on ovarian follicular growth, oocyte quality, corpus luteum function and placental establishment. PPAR- γ expression was observed in the ovary of several species including human (Lambe and Tugwood, 1996; Mu et al., 2000), rat (Braissant et al., 1996; Komer et al., 2001), mouse (Cui et al., 2002), cow (Sundvold et al., 1997; Lohrke et al., 1998), pig (Schoppee et al., 2002), sheep (Froment et al., 2003) and buffalo (Sharma et al., 2012; Sharma and Singh, 2012). Its expression varies in different ovarian cells such as thecal cells, granulosa cells, oocytes, luteal cells and ovarian macrophages. Although thecal cells have low to negative expression (Komer et al., 2001), granulosa cells have higher expression from primary to preovulatory follicle, followed by low expression after LH surge (Gasic et al., 1998). In ovarian macrophages, its expression is high along with follicular growth, followed by transient low expression during ovulation and regains high expression during luteal phase (Minge et al., 2006). In luteal cells, its expression was low at early luteal stages with high progesterone levels, and high at later stages, where progesterone levels came down (Komar and Curry, 2003). Its expression was moderate in bovine oocytes but yet to be identified in human oocytes (Mohan et al., 2002).

The local dynamic expressions of PPAR- γ in the ovary indicated its direct role in follicular growth. Such direct role could be due to species- and stage-specific modulation of key steroidogenic gene expressions (stAR, 3 β -HSD, steroid 17 α -hydroxylase, P450 aromatase) and eventual ovarian hormone synthesis and secretion at different stages of follicular growth (Steinkampf et al., 1987; Doody et al., 1990; Krasnow et al., 1990; Duncan et al., 1999; Arlt et al., 2001; Gasic et al., 2001; Mu et al., 2001; Yanase et al., 2001; Veldhuis et al., 2002; Coffler et al., 2003; Fan et al., 2005; Minge et al., 2006; Miller et al., 2007; Seto-Young et al., 2007; Kempna et al., 2007). Overall, PPAR- γ , with its external ligands TZDs, decreased LH- and insulin-stimulated androgen production in porcine thecal cells and human ovarian mixed cells. Such property has been exploited to reduce androgen synthesis during the treatment of PCOS patients by TZDs (Romualdi et al., 2003; Baillargeon et al., 2004). Although, PPAR- γ down-regulates aromatase expression (Yanase et al., 2001; Mu et al., 2001; Fan et al., 2005; Sharma and Singh, 2012) and, thus, decreases the synthesis of estradiol, it enhances the secretion of estradiol in granulosa cell culture (Komer et al., 2001). Progesterone secretion has been shown to be increased by PPAR- γ ligands in bovine, ovine, and rodent granulosa and porcine thecal cell cultures (Komer et al., 2001; Schoppee et al., 2002; Froment et al., 2003), but the secretion decreased in porcine granulosa cells (Gasic et al., 1998). In addition to the roles on expression of genes encoding steroid hormones, PPAR- γ , along with its endogenous ligands viz., prostaglandin metabolites, plays another important direct potential role such as the promotion of COX2 expression, an important event prior to the ovulation (Tsafriri, 1995; Armstrong, 1981; Dennefors et al., 1983; Evans et al., 1983; Pontsler et al., 2002).

The systemic effects of PPAR- γ on female reproduction could be through enhancement of ovarian- (Seto-Young et al., 2007) and peripheral insulin sensitivity, modulation of adipokines (leptin and adiponectin) production, enhancement of lipid uptake by CD36 and SCARB1, and suppression of chronic inflammation (Minge et al., 2008). Increased insulin sensitivity reduces insulin sensitive androgen production as well as deleterious effects of high glucose on oocyte (Hashimoto et al., 2000; Colton et al., 2002). Adiponectin would play a role during ovulation by induction of COX2 and prostaglandin E synthase expression in granulosa cells (Ledoux et al., 2006). Leptin, down-regulated by PPAR- γ , can influence gonadotropin and steroid secretion, oocyte quality and developmental potential (Ryan et al., 2002; Swain et al., 2004).

Few studies have been performed on PPAR- γ in relation to male reproduction. Functional PPAR- γ transcript and protein were identified in human sperm, and its physiological role was attributed to sperm capacitation, acrosome reaction and motility through increased Akt phosphorylation that can influence glucose and lipid metabolism (Aquila et al., 2006). This study reinforces the sperm as a mobile endocrine unit without systemic regulation. In addition to ejaculated spermatozoa, PPAR- γ can play a role during spermatogenesis by regulating the genes involved in lipid metabolism during differentiation of spermatozoa and Sertoli cells (Thomas et al., 2011). Further, extensive research is needed to pinpoint the local and systemic effects of PPAR- γ in male reproductive processes.

PPAR- γ and non-communicable diseases (NCD)

Addressing the detailed role of PPAR- γ in NCDs is beyond the scope of this review. However, an attempt is made here-in to provide a glimpse of PPAR- γ 's role in NCD.

Obesity

Obesity is a multi-factorial disease including a factor, high fat diet, which enhances plasma free fatty acids levels. As discussed earlier free fatty acids, specifically polyunsaturated fatty acids, the natural endogenous ligands of PPAR- γ , induce transcription of PPAR- γ target genes. At this point, PPAR- γ acts as a double-edged sword to promote the differentiation of progenitor fat cells into either white or brown adipose tissues. If progenitor fat cells are differentiated into white adipose tissue, it may lead to further accumulation of fat due to the transcription of triacylglycerol biosynthesis genes by PPAR- γ , and conversion of small adipocytes into large adipocytes that are resistant to insulin. These events, at physiological activation of PPAR- γ , lead to increased body weight gain or obesity and insulin resistance (<http://www.hhmi.org/biointeractive/ppar-gamma-activation-fat-cell>). If progenitor fat cells are differentiated into brown adipose tissue the energy is converted to heat, and obesity can be prevented (Rajakumari et al., 2013). The differentiation of progenitor fat cells into white or brown adipose tissue could be determined by the chromatin remodeling and epigenetic modification by a protein switch called B-cell factor 2 (Ebf2) at target genes for PPAR- γ binding. The Ebf2 promotes PPAR- γ binding at target genes (e.g., *PRDM16*) promoting brown adipose tissue differentiation (Rajakumari et al., 2013). As PPAR- γ generally stimulates fatty acid uptake and fat deposition in white adipose tissue, it seems logical that antagonism against PPAR- γ and its

partner RXR could be a potential strategy for obesity management. This strategy of PPAR- γ / RXR antagonism by their inhibitors was identified to be successful in ameliorating diet-induced obesity and insulin resistance by decreasing the fat accumulation in white adipose tissue, skeletal muscle and liver. Moreover, such inhibitors promoting PPAR- γ / RXR antagonism potentiate leptin's effects such as increased fatty acid combustion and energy dissipation (Yamauchi et al., 2001).

Diabetes

PPAR- γ was discovered based on its ligands' (TZDs) beneficial effects such as increasing insulin sensitivity in type II diabetes, which develops during insulin resistance, and also in pancreatic β -cell failure. The molecular events of PPAR- γ in insulin signaling have been explained *vide supra*. Briefly, PPAR- γ activation leads to the sequestration of plasma free fatty acids and glucose into the fat of white adipose tissue rather than non-adipose tissues. Such events cause insulin sensitivity and glucose uptake. Additionally, PPAR- γ can directly stimulate the glucose sensing apparatus in liver and pancreatic cells by increasing the expression of GLUT2 and β -glucokinase (Kim and Ann, 2004). Therefore, PPAR- γ ligands have been used as antidiabetic drugs. However, due to the side-effects, including weight gain, edema, anemia, pulmonary edema and congestive cardiac failure, by classical PPAR- γ ligands, TZDs, selective PPAR- γ modulators (e.g., metaglidase/halofenate, PA-082, and the angiotensin receptor antagonists) have been developed (Zhang et al., 2007; Bermudez et al., 2010). These selective PPAR- γ modulators bind to the ligand-binding pocket of PPAR- γ in different manners, which lead to different receptor conformations, different cofactor recruitments and differential expression. Hence, these selective PPAR- γ modulators can show limited side effects apart from their positive anti-diabetic effects (Zhang et al., 2007).

Cardiovascular diseases

One of the risk factors for cardiovascular diseases such as coronary heart disease, atherosclerosis and stroke is a metabolic syndrome, which is due to a core trio of insulin resistance, dyslipidemia and hypertension (Bishop-Bailey, 2000; Eckel et al., 2005; Shaw et al., 2005). Being a key metabolic nuclear receptor, PPAR- γ is a key molecule to link the metabolic syndrome with cardiovascular diseases. In addition to the systemic metabolic regulation like improving insulin sensitivity, preventing dyslipidemia and reducing hypertension through anti-inflammatory actions, PPAR- γ has direct effects on cardiovascular-related tissues like heart, endothelium,

vascular smooth muscle, kidney and macrophages (Braissant et al., 1996; Fajas et al., 1997; Vidal-Puig et al., 1997; Bishop-Bailey, 2000; Akiyama et al., 2002; Rangwala and Lazar, 2002). Over-expression of PPAR- γ in heart leads to dilated cardiomyopathy by increased uptake of fatty acids and unaltered glucose uptake in mice (Son et al., 2007). Similarly, PPAR- γ over-activation by TZDs in kidney collecting tubules causes increased sodium and water reabsorption, edema and heart failure (Kiss-Toth and Roszer, 2008). Besides these deleterious effects on cardiovascular system, PPAR- γ has much beneficial effects like reduction of atherosclerosis and stroke. By inhibiting the vascular inflammation, an important factor for atherosclerosis, PPAR- γ can prevent atherosclerosis. Specifically, PPAR- γ inhibits pro-inflammatory cytokine production and promotes cholesterol efflux from macrophages at atherosclerotic regions (Jiang et al., 1998; Ricote et al., 1998; Chawla et al., 2001). PPAR- γ weakens the post-ischemic inflammation and damage by increasing the catalase, decreasing NADP-oxidase levels, reducing reactive oxygen species and eventually lessening the post-ischemic degradation of Bcl-2, Bcl-xL and Akt (anti-apoptosis) (Culman et al., 2007; Fong et al., 2010). Moreover, PPAR- γ protects cerebrovascular endothelium at ischemic stroke through KLF-11 co-activator and transcriptional suppression of the pro-apoptotic microRNA-15 (miR-15a) (Yin et al., 2013). These roles reinforce that PPAR- γ is a potential drug target for ischemic stroke.

Cancer

PPAR- γ was found to be over-expressed in many human tumors (Krishnan et al., 2007). Overexpression of PPAR- γ and its ligand-mediated activation have protective functions in several cancers including colon (Takano et al., 2008), thyroid (Ohta et al., 2001; Chen et al., 2006), lung (Panigrahy et al., 2002), liver (Shen et al., 2012) and prostate (Annecotte et al., 2007) cancers. The tumor suppression is mediated by inhibiting the growth, inflammation, angiogenesis, cell proliferation and migration, and promoting the cell adhesion and differentiation (Koeffler, 2003; Grommes et al., 2004). These events are mediated through cross talk among several molecular pathways influenced by ligand-activated PPAR- γ . For instance, PPAR- γ activated by thiazolidinediones caused cell cycle arrest and decreased cell proliferation by down-regulation of cyclin E1 (Komatsu et al., 2008) and up-regulation of cyclin kinase inhibitor P21 (Lyles et al., 2009). Similarly, PPAR- γ inhibited cell migration by increasing the expression of cell adhesion molecules such as E-cadherins and spleen tyrosine kinase (Shen et al., 2012).

Based on these observations, PPAR- γ can be considered as one of the key targets for cancer therapy and their agonists can be tried in cancer treatment.

Conclusions and future directions

The PPAR- γ gene has species-specific variation regarding its size and the transcriptional variants. Many genetic variations in the human gene have been associated with several metabolic diseases including NCD. Major transcriptional variants encoding 475/477 and 505 amino acids are considered as PPAR- γ 1 and PPAR- γ 2. The expression of PPAR- γ 2 is confined to adipose tissue but PPAR- γ 1 expression is widespread and occurs in non-adipose tissues as well. Transcriptional regulation of PPAR- γ has been well studied during adipogenesis. The regulation is mainly due to hierarchical and combinatorial activity of several transcription factors, chromatin remodelers and non-coding RNA at the PPAR- γ promoters during energy-surplus state. The miR-130a/b could be a major miRNA that can regulate PPAR- γ transcripts at post-transcriptional levels. Like all other nuclear receptors, PPAR- γ also contains AF1, DBD, hinge region and LBD domain with large ligand-binding pocket to bind a wide range of endogenous and exogenous natural (e.g., dietary lipids) and synthetic (TZDs) ligands. Along with its obligate partner RXR and other co-activators, PPAR- γ exerts its action by DNA binding at DR1 and DR2 repeats and also by chromatin remodeling at the promoters and enhancers of its target genes. By enhancing the transcription of genes related to lipid uptake, triglyceride synthesis and glucose metabolism, PPAR- γ sequesters the plasma free fatty acids into adipose tissue, thereby playing a great role of promoting systemic insulin sensitivity. Hence, it is a key target for anti-diabetic drugs like TZDs. It has important physiological roles in adipocyte differentiation, inflammation, insulin sensitivity, ovarian follicular steroidogenesis and ovulation, sperm capacitation, differentiation of sperm and Sertolicells, osteoclast differentiation and fluid retention. As a key metabolic regulator, PPAR- γ could be a drug target for metabolic syndrome or NCDs like obesity, diabetes, cardiovascular disease and cancers. In view of many side effects of classical PPAR- γ targeting drugs like TZDs, selective PPAR- γ modulators have been developed to reduce side effects.

Transcriptional and post-transcriptional regulation of PPAR- γ has been well studied in the adipose tissue compared to non-adipose tissues. Hence, future studies have to be considered to understand its transcriptional and

post-transcriptional regulation in non-adipose tissues by using advanced “omics” approaches. Such studies will be helpful for designing selective PPAR- γ modulators with limited side effects. Moreover, such studies will also lead to explore the unknown physiological roles of PPAR- γ in non-adipose tissues. Similarly, global profiling studies in

different species need to be performed to identify the novel targets of PPAR- γ . Such novel targets could be more efficient drug targets for reducing the global burden of NCDs. Additionally, studies need to be extended to explore more natural and selective PPAR- γ modulators with minimal side effects.

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