Advances on PPARγ Research in the Emerging Era of Precision Medicine

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Abstract: Peroxisome proliferator-activated receptor gamma (PPARγ) is a member of the nuclear receptor superfamily that functions as a ligand-inducible transcription factor. It regulates glucose and lipid metabolism, immunity, and cellular growth and differentiation. Thiazolidinediones (TZDs) are potent insulin sensitizers that function by activating PPARs, with a high specificity for PPARγ. Due to their ability to preserve pancreatic beta cell function and reduce insulin resistance, TZDs have become one of the most prescribed classes of medications for type 2 diabetes (T2D) since their approval by the US Food and Drug Administration (FDA) and initial use in 1997. However, adverse effects, including weight gain, bone loss, fluid retention, congestive heart failure, and risk to bladder cancer, have weakened the benefits of TZDs in T2D therapies. Therefore, there is an urgent need to have a deeper understanding of regulatory mechanisms of PPARγ expression and activity so that novel classes of PPARγ-modulating therapeutics with fewer or weaker side effects can be developed.

Conclusion: This article systematically reviews PPARγ’s mechanisms of action and multilayer regulations. In addition, novel classes of therapeutics modulating PPARγ and new direction of research on genetic variants that affect PPARγ function and antidiabetic drug response are highlighted, which sheds light on PPARγ as a promising target for developing safer and precision medicine based therapeutic strategies.

Keywords: Peroxisome proliferator-activated receptor gamma, precision medicine, novel therapeutics, mechanism of action and regulation, thiazolidinedione, type 2 diabetes.

1. INTRODUCTION

The peroxisome proliferator-activated receptors (PPARs) belong to the nuclear receptor superfamily that functions as ligand-inducible transcription factors. There are three PPAR subtypes: PPARα (also known as NR1C1), PPARβ/δ (also known as NR1C2), and PPARγ (also known as NR1C3) (Table 1). PPARγ is expressed in white and brown adipose tissues, which is a metabolic master regulator of fatty acid storage and glucose metabolism [1, 2]. PPARγ has two major splicing isoforms, PPARγ1 and PPARγ2 (Fig. 1A). They exist due to the two N-terminal variants [3]. In comparison with PPARγ1, PPARγ2 contains an additional 30 amino acids in its N-terminal domain and it only expresses in adipose tissues under physiological conditions, while high-fat diets can also induce expression of PPARγ2 in other tissues [4]. PPARγ was identified as the receptor of thiazolidinediones (TZDs), a class of potent insulin sensitizers [5]. In addition to the glucose and lipid metabolisms, PPARγ is a key regulator in immunity, cellular growth, and differentiation [6, 7].

In this review, we systematically summarize PPARγ’s mechanisms of action and regulation, highlight novel classes of therapeutics modulating PPARγ, and discuss the new direction of research on genetic variants that affect PPARγ function and antidiabetic drug response. Through this review, we aim to provide new insights into the PPARγ as a promising target for developing safer and precision medicine based therapeutic strategies.

2. MECHANISMS OF ACTION OF PPARγ

Like other PPAR subtypes, PPARγ functions as an obligate heterodimer with retinoid X receptors (RXRs). Specifically, it binds a consensus element called the PPAR-responsive regulatory element (PPRE), a two-hexanucleotide direct repeat motif separated by a single nucleotide [8, 9]. PPARγ is comprised of an N-terminal transactivation domain containing the activation function (AF) 1 region, a DNA-binding domain (DBD) with a C4-type zinc finger structure, a hinge region, and a C-terminal ligand-binding domain (LBD) that contains a ligand-dependent transactivation re-
thetic antagonists of PPAR have been also identified, such as rosiglitazone, lobeglitazone, among others. They have been used to treat type 2 diabetes (T2D) by activating transcriptional activity of PPARγ. Thus, physiological ligands and their derivatives, such as 15-deoxy-D12,14-prostaglandin J2; 15-DEOXY-15-HETE; 15-hydroxyeicosatetraenoic acid; BADGE: bisphenol A diglycidyl ether; C/EBPs: CCAAT/enhancer-binding proteins; KLF5: Kruppel-like factor 5; NFI: nuclear factor I.

Table 1. PPAR subtypes, tissue distributions, and FDA-approved drugs targeting PPARs.

<table>
<thead>
<tr>
<th>Name</th>
<th>Tissue Distribution</th>
<th>FDA-approved Drugs</th>
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<tbody>
<tr>
<td>PPARα (NR1C1)</td>
<td>Mainly in liver and skeletal muscle, also in kidney, heart, adipose tissue, and intestinal mucosa</td>
<td>Indomethacin, Clofibrate, Fenofibrate, Gemfibrozil, Bezafibrate</td>
</tr>
<tr>
<td>PPARβ/δ (NR1C2)</td>
<td>Ubiquitous, especially in gastrointestinal tract, kidney, and skeletal muscle</td>
<td>Icosapent, Treprostinil, Sulindac, Bezafibrate</td>
</tr>
<tr>
<td>PPARγ (NR1C3)</td>
<td>Mainly in adipose tissues, also in intestine, liver, kidney, retin, and immunologic tissues</td>
<td>Icosapent, Mesalazine, Rosiglitazone, Nateglinide, Sulfasalazine, Telmisartan, Balsalazine, Ibuprofen, Glipizide, Pioglitazone, Mitiglizone, Bezafibrate, Indomethacin, Troglitazone (withdrawn)</td>
</tr>
</tbody>
</table>

region, AF2 (Fig. 1A) [2]. All these domains play important roles for PPARγ signaling cascades. Similar to the typical nuclear receptors, the N-terminal domain of PPARγ has transcriptional activity when it fuses to a heterologous DNA-binding domain. The C-terminal domain is responsible for dimerization with RXR, docking of coactivator proteins, and formation of ligand-binding pockets [2]. Ligand binding activates PPARγ by inducing a conformational change and promoting the dissociation of corepressors. The activated PPARγ/RXR heterodimer controls the rate of gene transcription by binding to PPREs that are located upstream of the target genes [10]. Meanwhile, PPARγ/RXR and other transcription factors, such as NF-κB, bind competitively to the coactivators. PPARγ can also repress the expression of NF-κB’s target genes through induction of IκBα expression [11, 12].

3. MULTILAYER REGULATIONS OF PPAR EXPRESSION AND ACTIVITY

Precise control of gene expression and activity plays fundamental roles in biological processes. The control on PPARγ is highly integrated and refined, which consists of multiple layers of regulations. A comprehensive understanding on regulatory mechanisms of PPARγ is critical for identifying the key regulators and developing novel PPARγ-modulating therapeutics.

3.1. Ligand Binding Regulation of PPARγ

The process of PPARγ activation is mediated by both natural and synthetic PPARγ ligands. Although fatty acid and their derivatives, such as 15-deoxy-D12,14-prostaglandin J2 [13] and 15-hydroxyeicosatetraenoic acid [14], can activate PPARγ by direct binding, it is difficult to identify specific endogenous ligands of PPARγ. Thus, physiological PPARγ ligands in vivo remain unidentified [15]. In contrast, synthetic PPARγ ligands, like TZDs, have been frequently studied and well defined [16]. TZDs represent a class of potent activators of PPARγ, including troglitazone, pioglitazone, rosiglitazone, lobeglitazone, among others. They have been used to treat type 2 diabetes (T2D) by activating transcriptional activity of PPARγ [17]. On the other hand, synthetic antagonists of PPARγ have been also identified, such as bisphenol A diglycidyl ether (BADGE), GW9662, and SR-202 [18-20].
3.2. Transcriptional Regulation of PPARγ

The expression of PPARγ is highly induced in adipocytes during adipogenesis, and this induction is regulated by a number of transcription factors [21]. Transcription factors, GAGA (GAGA-2 and 3), Kremen-like factor 2 (KLF2), and CCAAT/enhancer binding protein (C/EBP) homologous protein (CHOP) 10, are highly expressed in preadipocyte cell lines (e.g. 3T3-F442A and 3T3-L1), which can repress PPARγ expression and preadipocyte differentiation [22-24]. During the early stage of adipogenesis, expression of C/EBPβ and C/EBPδ are stimulated by adipogenic inducers. These inducers include isobutylmethylxanthine (IBMX), dexamethasone (DEX), and insulin. C/EBPβ and C/EBPδ further induce the expression of PPARγ and C/EBPα [25]. There have been several reports on positive cross-regulations between PPARγ and C/EBPα, which form a mutual activation loop [26]. There is an evidence showing that PPARγ and C/EBPα co-localize on PPARγ gene locus. This evidence indicates a positive self-feedback loop of PPARγ [21]. In addition, several transcription factors, including KLFs (KLF5, KLF9, and KLF15) [27-29], nuclear factor I (NFI) [30], early B-cell factors 1 (EBF1) [30], and sterol regulatory element-binding protein 1 (SREBP1) [31], are also required to induce expression of PPARγ in different stages of adipogenesis.

3.3. Post-transcriptional Regulation of PPARγ

MicroRNA (miRNA) is a family of small non-coding RNA molecules with approximately 21-22 nucleotides. The main functions of miRNAs include RNA silencing and post-transcriptional control of gene expression [32]. miRNA can regulate both protein-coding genes including transcription factor genes and also noncoding genes like long noncoding RNA (lncRNA) [33, 34]. miRNAs could trigger mRNA degradation and repress gene expression by binding to the complementary sequences in the 3’ prime untranslated region (UTR) or coding regions of the target mRNAs [26]. It has been reported that miRNAs play important roles in a number of biological processes related to metabolic disorders, such as adipocyte differentiation and lipid metabolism, by regulating the master regulators of adipogenesis and systemic insulin sensitivity, such as PPARγ [35]. For instance, four miRNAs, miR-23a [36], miR-27a [37], miR-139-5p [38], and mmu-let-7d-5p [39], are negative regulators of 3T3-L1 adipocyte differentiations, which inhibit cell differentiation and decrease adipogenesis by repressing the gene expression of PPARγ. Consistently, miRNAs, such as miR-27 [40], miR-33b [41], and miR-143 [40], were also identified to repress the preadipocyte differentiation and development in the in vivo studies using porcine models. Interestingly, miRNAs could be positive regulators in adipocyte differentiation too. Recent studies show that miR-20a [42] and miR-24 [43] are both able to increase PPARγ expression during 3T3-L1 adipogenesis, which indicates a complex miRNA-PPARγ-regulatory axis during adipogenesis. One possible mechanism of miRNA-induced PPARγ gene expression is that miRNAs bind to miRNA target sites and transactivate PPARγ promoters [44].

3.4. Epigenetic Regulation of PPARγ

A nucleosome is a basic unit of the chromatin structure, which contains a histone octamer of two copies of four core histones, including H2A, H2B, H3, and H4. The N-terminal tail of nucleosome is susceptible to various modifications that can alter nucleosome structure in a dynamic way and thus regulate gene expression [45]. It has been reported that H3K9ac and H3K27ac are both highly induced on the PPARγ gene locus in adipogenesis. Those histone acetylations are mediated by histone acetyltransferases, GCN5/PCAF and p300/CPB, respectively [46]. GCN5/PCAF and p300/CPB have been shown to be essential for PPARγ expression and adipogenesis [47, 48]. While histone acetylations are mostly marks of active enhancers, histone modifications can be either active or repressive marks. For example, H3K4 methyltransferases MLL3/MLL4 can upregulate PPARγ expression and promote adipogenesis by performing H3K4me1/2 to establish enhancers on gene loci that encode PPARγ [49]. In contrast to H3K4me1/2, H3K9 methyltransferase G9a-mediated H3K9me2 is a repressive mark of expression of PPARγ [50]. Furthermore, the ATP-dependent chromatin remodels regulates PPARγ expression. The condensed chromatin structure represses gene transcription by disallowing regulatory transcription machinery proteins, such as transcription factors and RNA polymerases, to access the core DNA regulatory regions [51]. Switch/sucrose non-fermentable (SWI/SNF), a chromatin remodeling complex, has been shown to disrupt the core architecture of chromatin and open up the transcription-binding domains of PPARγ for transcription factors (e.g. C/EBPα and PPARγ itself) [21].

3.5. Post-translational Modification of PPARγ

Post-translational modifications are also important regulators of PPARγ’s activity (Fig. 1A). Post-translational modifications typically refer to the modifications that occur on proteins after protein biosynthesis. These modifications cover phosphorylation, acetylation, sumoylation, ubiquitination, among others [52]. PPARγ has multiple phosphorylation sites, such as Ser112 (PPARγ2) and Ser273 (PPARγ2), which are phosphorylated by mitogen-activated protein kinases [9] and cyclin-dependent kinase 5 (CDK5) [53], respectively. The regulation of transcription factors by acetylation and deacetylation is another significant post-translational regulatory mechanism [54]. Not only can acetylation of a protein modify its activity but also crosstalk with other post-translational modifications for dynamic control of cellular signaling [55]. Lys268 and Lys393 are both evolutionarily conserved in the helix 2-helix 2’ region of PPARγ [56]. Additionally, sumoylation of the PPARγ2 AF1 region at Lys107 is associated with the suppression of its transactivation activity [57], whereas the sumoylation of PPARγ2 at Lys395 transrepresses NF-κB’s activity [58]. Finally, ubiquitination of PPARγ shows the signals for the proteasome-dependent degradation of PPARγ. Ubiquitination and degradation are functional in the ligand-dependent activation of PPARγ. The mutation, glutamic acid 499 to glutamine, in AF-2 region can abrogate both ligand-dependent activation and degradation of PPARγ2 [59].

4. NOVEL PPARγ-MODULATING THERAPEUTICS

Although TZDs can improve insulin sensitivity and glycemic control in the treatment of T2D, adverse effects including weight gain, fluid retention and edema, an increased risk of fracture, congestive heart failure, hepatoxicity, and risk to bladder cancer, have weaken the benefits and limited
the use of TZDs [60, 61]. For instance, Troglitazone (Rezulin) was withdrawn from the market due to adverse liver effects and the sale of pioglitazone (Actos) was suspended due to an elevated risk of bladder cancer [60]. In addition, rosiglitazone (Avandia) was under sale restrictions in the USA and withdrawn from the markets in Europe earlier due to an increased cardiovascular risk [62, 63]. These adverse effects have driven researchers to better understand the mechanisms underlying these adverse effects and to develop more efficacious and safer therapeutics, especially in the emerging precision medicine era (Table 2).

### 4.1. Elucidating Side Effects of TZDs

Weight gain is one well-known, substantial side effect led by TZDs. Increased subcutaneous adipose tissue or decreased visceral fat content may lead to weight gain with TZDs [64]. TZD-induced fluid retention can also contribute to weight gain through multiple mechanisms, including stimulating renal tubular sodium reabsorption, increasing sympathetic nervous system activity, and altering interstitial ion transport [65]. Moreover, it is also reported that the action of PPARγ in the central nervous system (CNS) contributes largely to the TZD-induced weight gain [66]. Electroacupuncture was identified to inhibit TZD-induce weight gain by increasing expression of leptin receptor and signal transducer and activator of transcription 3 and decreasing PPARγ expression in CNS [67].

Fluid retention with associated edema is another serious adverse effect led by TZDs, which is caused by increased sodium and water reabsorption in kidney [68]. The upregulated epithelial sodium channel in the collecting ducts was previously considered as a primary cause of this side effect. However, recent studies suggest that transporters in the proximal tubule may play more important roles in the pathogenesis of TZD-induced fluid retention [69]. Knockout of PPARγ in collecting duct has been shown to suppress the increase in plasma volume and body weight led by TZDs [70]. In addition to the impact on weight gain, TZDs-induced fluid retention may also contribute to congestive heart failure [71]. Interestingly, TZDs were also shown to exert vasculoprotective effects in a mouse hindlimb ischemia model [72] and to be more beneficial for the rats with congestive heart failure [73]. These findings are interesting, but require further studies to clarify the role of PPARγ on heart disease.

A higher rate of fractures with lower bone mineral density is the third reported major side effect of TZDs [74]. The risk of fractures is higher to the female patients and the patients taking TZDs for extended period [75]. TZD-induced fractures often occur on upper and lower limbs [60]. Animal model studies have showed that TZDs caused bone loss by simultaneously enhancing osteolastogenesis and inhibiting osteoblastogenesis [76]. These effects were exerted through PPARγ-dependent induction of c-fos, β-catenin, and ERRα [77].

An elevated risk of bladder cancer induced by pioglitazone exposure is another well-known side effect of TZDs. This risk has been reported in several studies using different cohorts [78, 79]. Bladder cancer is considered as the ninth most common cancer. Bladder cancer is primarily led by the continual accumulation of toxic chemicals in urine, such as tobacco smoke (2-Naphthylamine), pioglitazone, and formaldehyde [80]. However, the established link between pioglitazone and bladder cancer is still controversial. Some recent studies were not able to identify significant associations between pioglitazone and bladder cancer, and thus, additional longer-term studies are needed with less allocation bias [81, 82]. PPARγ agonists have also been associated with the increased incidence of subcutaneous sarcomas. A hypothetical mechanism has been proposed in a rodent carcinogenicity study [83]. Tumor promotion may rely on PPARγ activation. Accordingly, PPARγ agonists can promote tumor development by activating PPARγ, although they play no role in tumor initiation [84, 85].

### 4.2. Selective Agonists

Although full agonists of PPARγ could effectively improve insulin sensitivity, they may cause unwanted side effects due to the nonspecific transcriptional activation. Thus, PPARγ-based therapies have to be specific and tailored modulation of PPARγ. This will reduce unwanted side effects while still producing desired glycemic effects. Selective PPARγ agonists with specific targeting of tissues of interest are able to achieve agonism effect in specific tissues [86]. Thus, identification of selective PPARγ agonists is promising for the development of safer PPARγ-modulating therapeutics [87]. Over the past decade, a major investment to develop safer PPARγ agonists has led to novel, effective, selective PPARγ agonists [15]. For example, selective partial PPARγ agonists, INT131, GQ-16, MRL24 and F12016, can

<table>
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<tr>
<th>TZDs</th>
<th>Associated Adverse Effects</th>
<th>Novel Therapeutics with Reduced Adverse Effects</th>
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<tbody>
<tr>
<td>Troglitazone, Pioglitazone, Rosiglitazone, Lobeglitazone</td>
<td>Weight gain</td>
<td>SR1664, INT-131, GQ-16, MRL24, F12016</td>
</tr>
<tr>
<td>Pioglitazone, Rosiglitazone, Lobeglitazone</td>
<td>Fluid retention and edema</td>
<td>SR1664, INT-131, GQ-16</td>
</tr>
<tr>
<td>Pioglitazone, Rosiglitazone</td>
<td>Increased fracture risk</td>
<td>SR1664, F12016, Metformin combined with PPARγ agonists</td>
</tr>
<tr>
<td>Pioglitazone, Rosiglitazone</td>
<td>Heart failure</td>
<td>SR1664, INT-131, 3-(5-alkoxypyrimidin-2-yl) pyrimidin-4(3H)-one</td>
</tr>
<tr>
<td>Pioglitazone, Rosiglitazone</td>
<td>Bladder cancer</td>
<td>Metformin combined with PPARγ agonists</td>
</tr>
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</table>
block CDK5-induced PPARγ phosphorylation without the classical side effects (Fig. 2A-D) [88-90]. CDK5 is a protein kinase that can stimulate diabetogenic gene expression after being activated by pro-inflammatory cytokines in adipose tissues [91, 92]. CDK5-induced PPARγ phosphorylation contributes to the pathogenesis of insulin-resistance [93]. SR1664 is another recently identified ligand of PPARγ that inhibits CDK5-induced PPARγ phosphorylation, yet it still lacks classical agonism [94]. Unlike TZDs, SR1664 does not cause side effects, including weight gain, fluid retention, and bone loss (Fig. 2E).

4.3. Dual Agonists and Agonist-antagonist

A number of studies have been performed to develop agonists with combined therapeutic effects, aiming to obtain greater efficacy in the treatment of metabolic syndromes [95]. Simultaneous activation of two PPARs, PPARα and PPARγ, can induce angiogenesis by increasing production of vascular endothelial growth factor [96] and stimulate uptake and utilization of fatty acid synthase in adipose tissue, liver and skeletal [15]. Recently, SN159 was identified as a new PPARα/γ dual agonist that is a potential therapeutic agent against T2D by enhancing fatty acid oxidation and glucose utilization (Fig. 2F) [97]. In addition, Angiotensin II receptor antagonists are mainly used in the treatment of hypertension, diabetic nephropathy, and congestive heart failure by modulating the renin–angiotensin system [98]. 3-(5-alkoxypyrimidin-2-yl) pyrimidin-4(3H)-one structure has both angiotensin II receptor antagonist and PPARγ agonist activities (Fig. 2G). Such agents with dual effects can be used for T2D while minimizing the risk of heart failure [15].

4.4. Combinational Therapy

Combination therapy that simultaneously targets multiple defects in T2D brings more opportunities to improve glycemic control and reduce long-term micro- and macro-vascular complications in patients with T2D [99]. Metformin belongs to the biguanide class of anti-diabetic agents, which has an action that lowers blood glucose without increasing body weight (Fig. 2H) [100]. Metformin could promote osteoblast differentiation via transactivation of Runx2 that regulates bone development, maturation, and maintenance [101]. Moreover, metformin suppresses receptor activator of NF-κB ligand (RANKL) expression and induces expression of osteoprotegerin, which further inhibits osteoclast differentiation [102]. Therefore, the combination of metformin and PPARγ agonists is proposed to offset the bone loss effect by TZDs. Moreover, recent studies reported that diabetic patients treated with metformin might have less risk to develop cancer and their underlying molecular mechanisms were explored [103, 104]. In addition, PPARγ agonists can be combined with epigenetic modulators that can only epigenetically activate specific adipogenic gene promoters [45]. It may reduce the side effects of TZD led by targeting non-adipose cells.

4.5. Ligand-binding-independent Regulator of PPARγ

Ligand binding-independent regulation of PPARγ represents a promising way to reduce or eliminate TZD-induced side effects. C-peptide can stimulate PPARγ activity in a ligand binding-independent fashion that is mediated by phosphatidylinositol 3-kinase (Fig. 2I). Although GW9662, a PPARγ antagonist, can block PPARγ activation led by TZDs, it has no effect on PPARγ activation led by C-peptide [105]. Furthermore, the anti-diabetic and anti-inflammatory efficacy of abscisic acid (ABA), a plant hormone, is dependent on activation of PPARγ (Fig. 2J) [106]. However, ABA does not directly bind to PPARγ, indicating that there exists a ligand binding-independent mechanism of PPARγ activation [107]. Lanthionine Synthetase Component C-Like Protein 2 (LANCL2) is identified as the molecular target for immune modulatory and anti-inflammatory efficacy of ABA [107, 108]. LANCL2 is coupled to G(i) that can increase PPARγ activity by up-regulating adenylate cyclase, CAM and protein kinase A (PKA), providing a basis for the existence of a LANCL2/CAMP/PKA/PPARγ signaling axis [109].

5. PPARG AND PRECISION MEDICINE

Most current treatments may be effective on some patients but not for others because they are designed based on the average patient (so called "one size fits all" protocol). The aim of precision medicine is to replace such generalized approaches with personalized strategies that consider individual variability in multiple genetic, physiological, treatment, and ethnic factors, such as genes, environment, and lifestyle [110]. Precision medicine will allow health care system to predict more accurately on which patients could obtain maximum benefits by taking which treatment and prevention strategies, and at the right time [111]. In January 2015, a new Precision Medicine Initiative was announced by former President Obama to improve health and treat disease by employing more personalized approaches (http://www.whitehouse.gov/precision-medicine). The goal is to cure diseases like diabetes and cancer, and to make people healthier by giving them an access to their personalized information [112]. Massive amounts of electronic medical data in a longitudinal fashion, plus other genetic and genomic data, will offer unprecedented opportunity to develop personalized treatment strategies.

5.1. Precision Medicine and Heterogeneous Diseases

Responses to any treatment that targets heterogeneous conditions, such as diabetes and cancer, typically vary greatly between individuals or among subtypes of disease [113-116]. Many factors could affect the responses of different individuals to pharmacotherapy, including demographic characteristics, comorbidities, and genetic polymorphism in drugs’ receptor/target genes and molecules involved in signal transduction [113]. For example, patient’s responses to anti-hyperglycaemic drugs can be better predicted with genotype information of metabolomic markers [117]. Furthermore, the specificity of the disease, such as duration and pathophysiology of diseases, is another factor to cause the variability in the therapeutic response. Finally, the pharmacokinetic properties of therapeutics, such as mode of action may also contribute. A large number of agents with different mechanisms of action have been developed, which makes the patient-centered therapeutic approach possible [118]. Precision medicine requires that attributes of patients, diseases, and the therapeutics should be considered and integrated when designing the specific therapies [113]. In other words, it is to treat the patient with the disease, not the disease only.

5.2. Advances in PPARG-based Precision Medicine

Although some individuals respond well to anti-diabetic agents targeting PPARG, other patients experience reduced efficacy and even substantial side effects. Thus, those medications should be prescribed and taken with careful examination of the risk/benefit ratio. Individual genotype is valuable information for examinations of the risk/benefit ratio, because it can provide important insight on how genomic variations in the form of single nucleotide polymorphisms (SNPs) could affect efficacy and toxicity of drugs [113]. Pharmacogenetics and pharmacogenomics have been put at the forefront of precision medicine, which is the study of how genetic/genomic variations influence individual response to drugs [119] (Table 3). The Pro12Ala polymorphism in PPARG and amino acid variants (Thr934Thr and Gly482Ser) in PPARG1-alpha have been found to be associated with rosiglitazone-induced decreased fasting blood glucose and HbA1c [120]. The Pro12Ala polymorphism also contributes to the improved insulin sensitivity [121, 122]. Recent studies showed that Pro12Ala polymorphism is also associated with T2D patients’ response to pioglitazone [123-125]. In addition, variants in SLCO1B1 and PAX4 have been reported to be associated with improved responses to rosiglitazone [126, 127]. Earlier studies have demonstrated that PAX4 mutations could lead to maturity-onset diabetes of the young, type 9 [128] and PAX4 polymorphisms, rs2233580 and rs712701, can disrupt transcriptional regulation of target genes and reduce β-cell survival in high glucose condition [129]. Regarding side effects of TZDs, the aquaporin 2 rs296766 T allele and the SLC12A rs12904216 G allele are associated with edema induced by rosiglitazone [130].

SNPs affecting drug responses often reside in protein-coding exons, but a recent study reported the mechanism by which non-coding variants could also alter drug responses to rosiglitazone [136]. Non-coding variants typically alter the binding affinity of the transcription factor by changing the DNA of sequence in transcription factor binding sites [137]. The recent study shows that SNPs are highly enriched in binding sites for PPARγ at mouse strain-selective adipose tissue. Moreover, it has been demonstrated that genetically determined binding of PPARγ can regulate transcriptional effects of TZD drugs. The discovery that individual non-coding variation leads to differences in drug responses paves the way to predict how beneficial a particular treatment is for specific patient [138]. It also has broader implication for developing personalized therapeutics that target other DNA-binding proteins [139].

Due to the heterogeneity of diseases, there is also an urgent clinical need to better characterize the complexity of patient populations and based of which to define the spectrum of disease. Identification of disease subgroups, such as T2D, is one important PPARG-based precision medicine strategy. T2D subgroups are originally defined using traditional measures. Precision medicine-based approaches can identify subgroups of T2D with less biases and to generate...
Table 3. Summary of pharmacogenetic studies on PPARG.

<table>
<thead>
<tr>
<th>Pharmacogenetic Association</th>
<th>Genetic Variance</th>
<th>Reference</th>
</tr>
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<tbody>
<tr>
<td>Response to Rosiglitazone</td>
<td>PPARG1 p.Thr394Thr and p.Gly482Ser, PPARG2 p.Pro12Ala</td>
<td>[131]</td>
</tr>
<tr>
<td>Response to Pioglitazone</td>
<td>PPARG p.Pro12Ala</td>
<td>[132]</td>
</tr>
<tr>
<td>Response to Acarbose (women)</td>
<td>PPARG p.Pro12Ala</td>
<td>[133]</td>
</tr>
<tr>
<td>Response to Fluvastatin</td>
<td>PPARG 54,347 C &gt; T</td>
<td>[134]</td>
</tr>
<tr>
<td>Response to Troglitazone (women)</td>
<td>PPARG rs13073869, rs880663, rs4135263, rs1152003, rs6806708, rs13065455, rs13088205, rs13088214</td>
<td>[135]</td>
</tr>
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Fig. (3). PPARγ-based precision medicine strategy. A). Schematic diagram of PPAR γ-based precision medicine strategy: 1) Diagnosis based on phenotype; 2) Determination of genotype; 3) Precision diagnosis based on subtypes of diseases; 4) Classification of patients based on genotype and other data; 5) Personalized prescription and follow up. B). Genetic variations such as single nucleotide polymorphisms (SNPs) in the PPARγ binding motif can affect PPARγ binding and determine individual drug response (two SNPs highlighted in red).
new hypotheses regarding pathogenesis using data mining [111]. A recent study utilizes phenotype data extracted from high-dimensional electronic medical records and genotype data to characterize populations of T2D patients. Three distinct subgroups of T2D were identified by this study using topology-based patient-patient networks. It is a key step of applying precision medicine in T2D treatment [140].

Beyond the benefits to diabetes, beneficial effects of PPARγ agonists have been also identified in treating other diseases, such as bipolar depression [141], Alzheimer’s disease [142], and cancer [85, 143]. For example, it has been shown that PPARγ agonists can inhibit tumorigenesis by regulating cancer cell differentiation, proliferation, and apoptosis [144]. Those novel therapeutic indications on drug repositioning of PPARγ agonists will make applications of PPARγ-based precision medicine paradigm much broader.

CONCLUSION

PPARγ belongs to the nuclear receptor superfamily that functions as ligand-inducible transcription factors. It regulates glucose and lipid metabolism, immunity, and cellular growth and differentiation. A number of pharmacological treatments have been developed targeting PPARγ, some of which have been applied in clinic, such as TZDs. However, adverse effects have weakened the benefits of TZDs in T2D therapies, which have driven research to better understand the mechanisms underlying these adverse effects. Advances on high-throughput genomic technologies make us better understand the multifactorial etiology of diseases and mechanisms of action of therapeutics [145]. Precision medicine that aims to individualize therapeutic interventions will significantly improve our understanding on mechanisms underlying the therapeutic and adverse effects of treatments, and thus, speed up the development and clinical application of new PPARγ-based therapeutics with improved efficacy and safety (Fig. 3) [146]. The implementation of precision medicine relies on rich, longitudinal data and intelligent algorithms in clinical decision support, both of which will be in dramatic growth in the next a few years.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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