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Invited review

PPARγ signaling and emerging opportunities for improved therapeutics

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ABSTRACT

Peroxisome proliferator-activated receptor gamma (PPARγ) is a ligand-activated nuclear receptor that regulates glucose and lipid metabolism, endothelial function and inflammation. Rosiglitazone (RGZ) and other thiazolidinedione (TZD) synthetic ligands of PPARγ are insulin sensitizers that have been used for the treatment of type 2 diabetes. However, undesirable side effects including weight gain, fluid retention, bone loss, congestive heart failure, and a possible increased risk of myocardial infarction and bladder cancer, have limited the use of TZDs. Therefore, there is a need to better understand PPARγ signaling and to develop safer and more effective PPARγ-directed therapeutics. In addition to PPARγ itself, many PPARγ ligands including TZDs bind to and activate G protein-coupled receptor 40 (GPR40), also known as free fatty acid receptor 1. GPR40 signaling activates stress kinase pathways that ultimately regulate downstream PPARγ responses. Recent studies in human endothelial cells have demonstrated that RGZ activation of GPR40 is essential to the optimal propagation of PPARγ genomic signaling. RGZ/GPR40/p38 MAPK signaling induces and activates PPARγ co-activator-1α, and recruits E1A binding protein p300 to the promoters of target genes, markedly enhancing PPARγ-dependent transcription. Therefore in endothelium, GPR40 and PPARγ function as an integrated signaling pathway. However, GPR40 can also activate ERK1/2, a proinflammatory kinase that directly phosphorylates and inactivates PPARγ. Thus the role of GPR40 in PPARγ signaling may have important implications for drug development. Ligands that strongly activate PPARγ, but do not bind to or activate GPR40 may be safer than currently approved PPARγ agonists. Alternatively, biased GPR40 agonists might be sought that activate both p38 MAPK and PPARγ, but not ERK1/2, avoiding its harmful effects on PPARγ signaling, insulin resistance and inflammation. Such next generation drugs might be useful in treating not only type 2 diabetes, but also diverse chronic and acute forms of vascular inflammation such as atherosclerosis and septic shock.

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Abbreviations: PPARγ, peroxisome proliferator-activated receptor gamma; TZD, thiazolidinedione; T2DM, type 2 diabetes mellitus; RGZ, rosiglitazone; 15d-PGJ$_2$, 15-deoxy-D^{12,14}-prostanglandin J$_2$; PGC-1α, PPARγ co-activator-1α; RXR, retinoid X receptor; PPRE, peroxisome proliferator response element; NO, nitric oxide; EP300, E1A binding protein p300; PTM, post-translational modification; BAT, brown adipose tissue; SAT, subcutaneous white adipose tissue; VAT, visceral white adipose tissue; GPR40, G protein-coupled receptor 40; FFA, free fatty acid.

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1. Introduction

1.1. Peroxisome proliferator-activated receptor gamma (PPARγ) as a target for treating type 2 diabetes and thiazolidinediones (TZDs)

In 2010, an estimated 257 million people worldwide had type 2 diabetes mellitus (T2DM) and the number is projected to rise to 395 million by 2030 [1]. TZDs, commonly called glitazones, have been widely used to treat this disease [2]. The anti-diabetic effects of TZDs were originally discovered in 1982 [3]. Ciglitazone was the first TZD shown to normalize hyperglycemia, hyperinsulinemia, and hypertriglyceridemia in mouse models of T2DM [4]. Later, troglitazone [5] and pioglitazone [6] were also shown to decrease insulin resistance by increasing insulin-stimulated glucose utilization and reducing hepatic glucose production. Rosiglitazone (RGZ), synthesized in 1988, was a more selective and potent insulin sensitizer than ciglitazone in rodent models [7,8]. In 1997, troglitazone was the first TZD approved for clinical use, but was soon withdrawn worldwide because of liver toxicity [9]. The U.S. Food and Drug Administration subsequently approved RGZ and pioglitazone in 1999 for the treatment of T2DM [10]. RGZ was later withdrawn in Europe and its use restricted in the United States due to an increased risk of myocardial infarction [11,12]. Pioglitazone does not appear to share this risk, but otherwise has the same adverse profile common to TZDs and has been associated with bladder cancer [13,14].

Named for its activation by fibrates and other peroxisome proliferators [15], peroxisome proliferator-activated receptor α (PPARα/NR1C1) was first identified in 1990. Two other genes belonging to the same family, PPARβ/δ (NR1C2) and PPARγ (NR1C3), were cloned in Xenopus two years later [16]. Human homologues of three PPAR isoforms, α [17], β [18] and γ [19], were soon identified. PPARγ has two isoforms, PPARγ1 and PPARγ2, with the latter harboring an additional 30 amino acids at its N-terminus [20]. PPARγ1 is expressed in many tissues including leukocytes and endothelial cells, while PPARγ2 is normally restricted to adipose tissue, but can be induced elsewhere [20,21]. In 1994, PPARγ was found to be a major adipogenic transcription factor in mice [22]. Long after the anti-diabetic effects of TZDs were discovered in 1982 [3], PPARγ was identified as the receptor target of TZDs in 1995 [23,24]. As noted above, this was less than two years before the first TZD was approved for clinical use [9,25,26]. Besides synthetic TZDs, the endogenous arachidonate 15-deoxy-$D^{12,14}$ - prostanglandin J_2 (15d-PGJ_2) and related metabolites also activate PPARγ and induce adipogenesis [24], but at concentrations above that found in cells [27]. In addition some unsaturated fatty acids activate PPARγ, such as the dietary polyunsaturated eicosapentanoic acid, linolenic acids, linoleic acid, and oxidized low-density lipoprotein [28]. Therefore, PPARγ may under some circumstances function as a general fatty acid sensor, with affinity K_D values of 2–50 μM [29]. Also two linoleic acid oxidation products detected in significant amounts in oxidized low-density lipoprotein particles, 9-HODE and 13-HODE, were previously identified as endogenous ligands and activators of PPARγ [30].

As noted above, TZDs including RGZ and pioglitazone have been associated with a number of adverse effects. These include weight gain [31], fluid retention [31,32], and reduction in bone mineral density [33]. Besides these class effects, RGZ has been associated with excess myocardial infarctions and pioglitazone with bladder cancer. These undesirable, "off-target" effects of TZDs have driven research to better understand PPARγ signaling and to develop new agents with improved efficacy and safety. TZD-induced weight gain has recently been linked to activation of PPARγ in the brain, rather than in adipose tissue [34,35]. Intraventricular TZD administration or overexpression of PPARγ in the brain of normal rats promote sustained increases in feeding and body weight [34]. Conversely, mice with selected ablation of brain PPARγ consumed less food and gained less weight than controls in response to TZD treatment during high-fat feeding. These mice also showed increased physical activity and energy expenditure [35]. TZD-induced fluid retention and peripheral edema has been attributed to increased sodium and water reabsorption in the distal collecting ducts of the kidney. Collecting duct-specific knockout of PPARγ blocked TZD-associated increases in plasma volume and body weight [36]. How TZDs exert this action remains unclear, as findings about the role of epithelial sodium channels in this phenomenon are contradictory [36,37]. Besides weight gain, fluid retention associated with TZDs may also contribute to adverse cardiovascular events, such as congestive heart failure [20]. Consistent with reductions in bone mineral density and a higher rate of fractures, TZDs caused bone loss in rodents by inhibiting osteoblastogenesis (bone formation) and enhancing osteoclastogenesis (bone resorption). TZDs were proposed to exert these effects through PPARγ-dependent induction of c-fos, β-catenin, and ERRα [38–40].

1.2. PPARγ as a therapeutic target in atherosclerosis, pulmonary arterial hypertension, adult respiratory distress syndrome, and septic shock

The direct binding of TZDs and other ligands to PPARγ activates two distinct signaling pathways. *Cis*-activation drives transcription through agonist-dependent conformational changes in the activation function 2 (AF-2) domain of PPARγ, recruitment of co-activators such as PPARγ co-activator-1α (PGC-1α), PPARγ dimerization with the retinoid X receptor (RXR) [41], and the binding of this complex to peroxisome proliferator response elements (PPREs) in the promoters of target genes. This signaling pathway is closely linked to the essential roles of PPARγ in adipogenesis and glucose homeostasis. Alternatively, ligand-bound PPARγ has also been shown to suppress inflammation *via* a mechanism called *trans*-repression. *trans*-repression is independent of DNA binding by PPARγ as demonstrated by the PPARγ C126A/E127A mutant, which remains capable of repressing lipopolysaccharide-induced genes while being rendered incapable of *cis*-activation [42]. This