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Review Article

Therapeutic Role of Peroxisome Proliferator-Activated Receptors Gamma in the Treatment of Fibrosis

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Abstract

Peroxisome proliferator-activated receptors (PPARs) are nuclear transcription factors that regulate many physiological processes. Recent studies have implicated PPARs in the control of fibrosis. In particular, agonists of PPARγ have been found to have antifibrotic effects on a number of tissues including the lung, heart, and liver. This antifibrotic effect is related to the inhibition of TGF-β/ Smad signal transduction including other pathways that still remain unidentified. This review focuses on PPARγ and its mode of activation in relation to fibrosis.

Keywords: Peroxisome Proliferator-activated receptor (PPAR), Peroxisome Proliferator-activated Receptor γ Coactivator 1-α (PGC-1a), Protein Kinase A (PKA), Relaxin, Relaxin Family Peptide Receptor 1 (RXFP1), fibrosis.

1. Introduction

1.1 Peroxisome Proliferator Activated Receptors

The PPARs are members of the large steroid/retinoid nuclear receptor family. To date, three sub-forms of PPARs have been identified, including PPAR-α, β/δ, and γ [1-3]. PPARs, like other nuclear receptors, contain several structural and functional domains. They consist of an N-terminal activation domain, a DNA binding domain (DBD) that consists of 2 zinc finger-like domains. The first zinc finger specifically recognizes the PPAR response element. The second zinc finger helps in heterodimerization with the retinoid X receptor, as well as interaction with corepressors and coactivators. The C-terminal ligand-binding domain helps in nuclear localization and ligand binding leading to ligand dependent activation [4]. The DNA binding and ligand-binding domains have been well characterized. The DBD of three PPARs recognize the PPRE region in genes and ligand binding domain responds to different ligand.

Each of the PPAR isotypes is encoded by a separate gene. The wide spread physiological roles of the different PPARs is explained in part by their tissue expression pattern. PPARα is expressed in metabolically active, energy-requiring tissues, including heart, liver, skeletal muscle, and kidney [3, 5-8]. PPARβ/δ has a broader expression pattern, essentially expressed in all cell types and tissues suggesting a fundamental role in physiology [6, 9]. PPARγ exists in two isoforms. One of the isoforms has broad expression pattern, whereas the other one is expressed predominantly in adipose tissue [10-12].

All three PPAR isoforms have distinct as well as overlapping sets of endogenous and exogenous ligands. Endogenous ligands, probably generated by fatty acid metabolism, act as lipid sensors and regulate fatty acid metabolism, as well as other functions such as their role in inflammatory responses, vascular biology, cell differentiation and proliferation, and tissue repair [8, 13]. The distribution and abundance of circulating and cellular fatty acids depends on pathophysiological conditions [14-16].

1.2 PPARγ

PPARγ functions as a master transcriptional regulator of metabolism. It is required to induce adipogenesis [17]. Its activity has been shown to be regulated by binding of lipid metabolites, various vitamins, steroid & thyroid hormones, and thiazolidinediones [18]. PPARγ activation enhances regulation of adipocyte differentiation and the uptake and storage of fatty acid [8, 13, 19-21]. PPARγ exists in two isoforms (γ1 and γ2) [13]. The two distinct isoforms of PPARγ are created by alternate promoter usage and splicing of the 5' end exons of the gene [11, 19]. PPARγ2 has an additional 28 (human) amino acids at its amino terminus, creating a ligand-independent activation domain that makes isoform 2 a stronger transcriptional activator compared to isoform1 in all tissues expressing it [22]. PPARγ1 has a broad

expression pattern that extends to the brain, vascular cells, and few types of immune and inflammatory cells [10, 11]. Although PPARγ2 is predominantly expressed in adipose tissues, also liver and skeletal muscle expresses PPARγ2 at low levels [10, 12, 23]. PPARγ activation can be induced by its interaction with coactivators or release of repressors. The interactions of PPARγ with different regulatory molecules decide its gene-specific effects including its role as a key transcriptional regulator in inducing antifibrotic genes.

1.3 Mechanism of PPARγ activation

DNA binding of PPARγ requires its heterodimerization with the 9-cis retinoid X receptor (RXR) [24, 25]. The PPARγ-RXR complex binds to sequence specific promoter regions of DNA, known as PPREs. The preferred PPRE consists of two direct repeats, i.e. 5'-AGGTCA-3', separated by a single nucleotide. Several other nuclear transcription factors such as hepatocyte nuclear receptor-4 (HNF-4), chicken ovalbumin upstream promoter transcription factor (COUP-TF), apolipoprotein regulatory protein 1 (ARP-1), and retinoic acid receptor (RAR) dimers also bind to DR-1 elements. The differential preference in binding of various homodimers and heterodimers to PPRE is regulated by a sequence of the core motif and spacer nucleotide(s) [26]. The transcriptional activity of these receptors correlates with their relative *in vitro* affinity to the promoter that in turn depends on the specific arrangement of nucleotides in promoter [26, 27].

The heterodimeriztion of PPARγ with RXR and transcriptional activation on binding with PPRE is not only regulated by the binding of endogenous or exogenous ligands, but is also regulated by coactivators and corepressors. Many coactivators, such as PGC1α, pCAF, p300 and CBP modulate the activity of PPARγ [21, 28]. The ligand binding to PPAR causes a conformational change, to facilitate its interaction with these coactivators. The coactivators form a bridge between the nuclear receptors and the transcription initiation machinery. Some coactivators like PGC1α, p300 and CBP have histone acetylase activity [21, 28]. Upon forming the transcriptional complex, they disrupt the nucleosome complex and "open up" chromatin structure to initiate the transcriptional machinery at PPRE. Most of the coactivators require ligand binding to PPAR to form the complex, so as to start transcription initiation at PPRE. Similarily, PPARγ corepressors such as NCORs and SMRT have histone deacetylase activity to block the initiation of transcription. In the case of corepressors, ligand-binding causes a conformational change in the PPAR that allows the exchange of corepressors for coactivators [29].

1.4 PGC1α and pCAF: ligand-independent coactivators of PPARγ.

PPARγ activation can be ligand-dependent or ligand-independent. The activation of PPARγ involves not only ligand binding, but release of corepressors and/or recruitment of coactivators of PPARγ [30]. Ligand-induced PPARγ activation requires binding of an agonist that facilitates PPAR-RXR heterodimerization and then the docking of coactivators [31]. Ligand-independent docking is also known to be induced by PPARγ coactivators such as PGC1α and pCAF [32]. These coactivators bind to PPARγ in a ligand-independent manner, and activate PPARγ on a specific subset of promoters to selectively express PPARγ target genes. Expression of PGC1α has been shown to be induced by CREB [33]. Similarly, stimulation of p38 MAPK directly phosphorylates the PGC1α protein, resulting in its activation and stabilization [34]. Activated PGC1α interacts with the histone acetyltransferase complex to facilitate initation of transcription complex at the gene promoter [34, 35]. Similarily, pCAF also associates with other initation machinery having histone acetyl transferase activity. This indicating that these coactivator proteins play a direct role in transcriptional regulation [32].

2. PPARγ and fibrosis

Recent studies have implicated PPARγ in the control of fibrosis [36-38]. *In vitro and in vivo* studies show the potentially exciting role of PPARγ as novel therapies for fibrosis of organ systems prone to scarring. Treatment with PPARγ ligands, or forced expression of PPARγ, suppresses fibrosis in organs such as heart, liver, kidney, and lung [36, 39, 40]. PPARγ and its ligands, including the thiazolidinediones, have been studied for their potential antifibrotic role on hepatic fibrosis in rat, pulmonary and cardiac fibrosis in rats, and kidney fibrosis in mice and rats [39]. In studies of experimentally-induced liver fibrosis by carbon-tetrachloride, PPARγ agonists reduced profibrotic differentiation of fibroblasts in vitro and reduced organ scarring in animal models of fibrosis [38, 39]. Activation of cellular PPARγ receptors using either synthetic or natural PPARγ ligands blocks the induction of profibrotic responses *in* skin and lung fibroblasts with rosiglitazone and inhibited TGF-β-induced stimulation of collagen and fibronectin synthesis, myofibroblast differentiation, fibroblast migration. Rosiglitazone also induced differentiation of mesenchymal progenitor cells into adipocytes instead of fibroblasts. PPARγ ligands ameliorated carbon tetrachloride induced liver fibrosis in mice, attenuated cardiac fibrosis and diabetic renal fibrosis, and attenuated lung fibrosis, attenuated skin fibrosis in bleomycin injected animal model of scleroderma.

2.1 PPARγ and Liver Fibrosis

Hepatic Stellate Cells (HSC) are major mediators of the fibrotic process in liver during the wound healing process. HSC reside in the space of Disse between hepatocytes and the heapatic sinusoids [41]. In normal uninjured liver, HSC are quiescent cells that store vitamin A. As a result of injury, HSCs activate or transdifferentiate to a myofibroblast-like cell that is characterized by having a different phenotype and

properties, including loss of normal retinoid-storing capacity, changes in cellular morphology and cytoskeletal organization, enhanced cell migration, adhesion, contractibility and proliferation, expression of α-SMA and acquisition of fibrogenic properties [42-44]. The expression of matrix-degrading enzymes such as matrix metalloproteinases (MMP)-1 and MMP 13 that degrade fibrillar collagen and MMP2 and MMP9 that degrade basement membrane collagen is reduced. Simultaneously, expression of tissue inhibitors of metalloproteinases (TIMPs) is increased [45]. Hence chronic liver injury leads to overall changes in expression of enzymes involved in matrix degradation resulting to a state towards accumulation of collagen and hepatic fibrosis. Relaxin and activators of PPAR have been shown to prevent the activation of activated HSC, bringing them back to quiescent stage and thus preventing progressive hepatic fibrosis [46-48].

In hepatic stellate cells, treatment with PPARγ agonists reversed the myofibroblastic phenotype to the quiescent, lipid storing form [49]. In PPARγ knockout mice, the severity of liver fibrosis was increased, whereas the overexpression of PPARγ or treatment with its ligand reduced fibrotic markers such as alpha smooth muscle actin, collagen and TIMPs, and increased MMPs in liver [38, 50]. Most of the effects of PPARγ agonists were similar to those of relaxin[50-54]. Though PPARγ agonists reduce fibrosis and are effective in initial stage of fibrosis, their action seems ineffective on established rodent models of hepatic fibrosis [55]. A mechanism to restore sensitivity to PPARγ agonists would possibly provide a treatment in established fibrosis.

2.2 PPARγ and Lung Fibrosis

Lung fibrosis occurs in a many diseases, including systemic sclerosis. Fibrotic remodeling of lung could occur in asthma, and other obstructive pulmonary disease characterized by inflammatory cell infiltration such as macrophages and activation of myofibroblasts to deposit excessive collagen and change the lung architecture[56].

Reduced PPARγ expression was shown in lung fibroblasts suggesting that decreased PPARγ activity contribute to dysregulated immune response and fibrosis. Ligands of PPARγ downregulates lung fibroblasts activity, by inhibiting their proliferation and migration. PPARγ agonists effects TGF-β to inhibit lung fibroblast transdifferentiation and significantly reduced expression of collagen 1[57]. TGF-β have been shown to downregulate the expression of PPARγ through Smad3 signaling and this effect was overcome in Smad3 deficient fibroblasts. In vivo studies have shown that PPARγ agonists such as rosiglitazone are able to inhibit lung fibrosis [58]. The agonists were able to reduce inflammatory markers of fibrosis and improved lung architecture. In short, PPARγ agonists inhibited Smad3 dependent TGF-β pathway to reduce collagen accumulation in injured animal models[46].

2.3 PPARγ and Cardiac Fibrosis

Cardiac fibrosis is an outcome of different cardiovascular diseases resulting in abnormal accumulation of extracellular matrix in the myocardial interstitium. The matrix composition of collagens and elastic fibers is derived mainly from fibroblasts. In normal conditions, matrix maintains the normal structure and function of the heart but in diseased state matrix metalloproteinases decreases and inflammatory molecules such as cytokines and TGF-β increases to invade the tissue resulting in extracellular matrix deposition leading to cardiac fibrosis leading to arrhythmia and heart failure, and cardiac arrest[59].

Interestingly, PPARγ has been studied to have the function of antimyocardial fibrosis. Treatment with the PPARγ activators resulted in the reduction of ECM deposition and cardiac fibrosis, while PPARγ antagonist GW9662 reversed these changes[60]. PPARγ has a wide range of effects in regulating metabolism, reducing inflammation, inhibiting apoptosis and oxidative stress, and enhancing endothelial function. Though, the underlying effects have not yet been fully understood, all of these functions are helpful in preventing the cardiac function. Genetic mutation in PPARγ have shown to induce cardiac fibrosis and increased hypertension[61]. Similarly, decrease in mRNA and protein expression of PPARγ induced myocardial interstitial fibrosis and vice versa. The agonists induced activation of PPARγ to not only inhibit the expressions of TGF-β but also the phosphorylation of Smad2/3.

3.Conclusion

A number of different mechanisms have been implicated in the pathogenesis of progressive fibrogenic disorders. Novel therapeutic agents based on the paradigm of limiting excessive secretion of ECM, have produced promising results in pre-clinical disease models of fibrosis, trying to reverse the diseases state and restore normal architecture of effected organs and tissues. The nuclear hormone receptor PPARγ have emerged as a regulatory molecule of interest in the pathogenesis and treatment of fibrosis. PPARγ signaling have been implicated in initiating endogenous mechanism, to prevent excessive fibrogenesis following injury, and negatively regulate profibrotic signal-that would otherwise induce collagen synthesis. PPARγ signaling and identification of pharmacological targets as combinatorial targets might lead to novel therapeutic approaches to the treatment of fibrosis.

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