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Review

Peroxisome proliferator-activated receptor-γ cross-regulation of signaling events implicated in liver fibrogenesis

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ABSTRACT

Peroxisome proliferator-activated receptor-γ (PPARγ) is a nuclear receptor with transcriptional activity controlling multiple physical and pathological processes. Recently, PPARγ has been implicated in the pathogenesis of liver fibrosis. Its depleted expression has strong associations with the activation and transdifferentiation of hepatic stellate cells, the central event in liver fibrogenesis. Studies over the past decade demonstrate that PPARγ cross-regulates a number of signaling pathways mediated by growth factors and adipokines, and cellular events including apoptosis and senescence. These signaling and cellular events and their molecular interactions with PPARγ system are profoundly involved in liver fibrogenesis. We critically summarize these mechanistic insights into the PPARγ regulation in liver fibrogenesis based on the updated findings in this area. We conclude with a discussion of the impacts of these discoveries on the interpretation of liver fibrogenesis and their potential therapeutic implications. PPARγ activation could be a promising strategy for antifibrotic therapy.

Contents

Abbreviations: AdipoR, adiponectin receptor; AMPK, 5′-AMP-activated protein kinase; AP1, activator protein 1; C/EBP, CCAAT/enhancer binding protein; CHB, chronic hepatitis B; Cidea, mitochondrial cell death-inducing DNA fragmentation factor α-like effector A; CTGF, connective tissue growth factor; DR, death receptor; ECM, extracellular matrix; Egr-1, early growth response-1; ERK, extracellular signal-regulated kinase; HGF, hepatocyte growth factor; HSC, hepatic stellate cell; JAK2, Janus kinase 2; JNK, c-Jun N-terminal kinase; LXR-α, liver X receptor-α; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor-κB; NIK, NF-κB-inducing kinase; ObR, obese gene product receptor; PDGF, platelet-derived growth factor; PI3K, phosphatidylinositol-3-kinase; PPAR, peroxisome-proliferator activated receptor; PPRE, peroxisome proliferator response elements; RXR-α, retinoid X receptor-α; SA-β-gal, senescence-associated β-galactosidase; SIRT1, silent information regulator type 1; SMP30, senescence marker protein 30; SREBP-1c, sterol regulatory element-binding proteins-1c; STAT3, signal transducer and activator of transcription 3; TβR, transforming growth factor-β receptor; TGF-β, transforming growth factor-β; TLR, Toll-like receptor; TNF, tumor necrosis factor; TRAIL-R, TNF related apoptosis-inducing ligand receptor.

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1. Introduction

Peroxisome-proliferator activated receptors (PPARs) belong to the superfamily of nuclear hormone receptors. To date, four isoforms of PPARs have been identified, namely PPARα, β, γ and δ, which regulate transcription of a number of target genes controlling many important physiological processes [1]. There are two major forms of PPARγ, namely γ1 and γ2, resulting from alternate promoter usage and splicing [2]. PPARγ structurally comprises a central DNA-binding domain, a carboxy terminal ligand-binding domain and two transcription activation function motifs termed AF-1 and AF-2 [3]. The core of PPARγ ligand-binding site is a large Y-shaped cavity composed of 12 α-helices located at the C-terminal, which functions as a molecular switch and ligand binding to which is required for full agonist activity toward PPARγ [4]. In the absence of ligands, PPARγ interacts with the co-repressor proteins and inhibits gene expression. Upon binding to cognate ligands, PPARγ dissociates the co-repressor and translocates from cytoplasm to the nucleus where it recruits co-activator proteins and forms a heterodimer with retinoid X receptor-α (RXR-α). The multiprotein complex then binds to peroxisome proliferator response elements (PPRE), the specific DNA sequences in target gene promoter, leading to transcriptional activation [5]. Posttranslational modifications such as phosphorylation [6], sumoylation [7] or ubiquitination [8] may also modulate the transcription activity of PPARγ.

PPARγ is expressed in various tissues and cell types, mainly in adipose tissue, where it regulates adipocyte differentiation and glucose homestasis [9]. PPARγ activation by its endogenous ligands such as fatty acids initiates transcription of adipogenesis-associated target genes, such as *FABP4* (which encodes fatty acid-binding protein 4) and *CD36* (which encodes fatty acid translocase) [10]. Moreover, PPARγ plays a pivotal role in metabolic syndrome through genetic correlation with insulin resistance and type 2 diabetes mellitus, because it is a key regulator of insulin sensitivity and the drug target of synthetic thiazolidinedione agents against type 2 diabetes. PPARγ activation ameliorates hyperglycemia and dyslipidemia in diabetes due to its insulin sensitization capability [11].

Increasing understanding toward PPARγ biology demonstrates that this transcription factor has pleiotropic functions in various fundamental pathways with more wide-ranging pathophysiological implications. PPARγ is shown to be involved in circadian regulatory system [12] and bone marrow adipogenesis [13]. PPARγ is also implicated in cell-fate determination in a variety of cell types, for instance, ligand activation of PPARγ can result in growth inhibition or apoptosis in fibroblasts [14] and several kinds of cancer cells [15, 16]. Recently, much attention has been paid to the anti-inflammatory and protective effects of PPARγ during tissue repair program. PPARγ regulates gene transcriptions involved in the wound-healing process of many organs, and thereby ameliorates inflammation, oxidative stress, and matrix remolding in the injured tissue [17]. Mode for PPARγ-mediated gene transcription and the biological consequences are illustrated in Fig. 1. Furthermore, perhaps a breakthrough in understanding PPARγ pathophysiology over the past decade could be the recognition that PPARγ acts as a pivotal molecular in liver fibrogenesis. Its transcriptional dysfunction and interplay with a series of signaling events that are involved in fibrogenesis underlie the molecular pathogenesis of liver fibrosis [18]. Accumulating knowledge in this facet provides novel insights into the signal transduction-based pharmacological intervention of liver fibrosis, a widespread disorder for which effective therapies are still lack in current clinical context. In this review, we will first briefly describe the basic principles of liver fibrogenesis and the newly uncovered role of PPARγ in this pathology, and then critically discuss the updated findings on how PPARγ interacts with the primary signaling events implicated in liver fibrogenesis.

2. Role of PPARγ in liver fibrogenesis

Liver fibrogenesis is defined as a dynamic wound-healing process characterized by excessive production and deposition of extracellular matrix (ECM) mainly type I collagen in the liver. The ECM deposition distorts hepatic sinusoids and compromises hepatocyte function. It is well-established that activation of hepatic stellate cells (HSCs), a type of nonparenchymal cell resident in the space of Disse, is the central

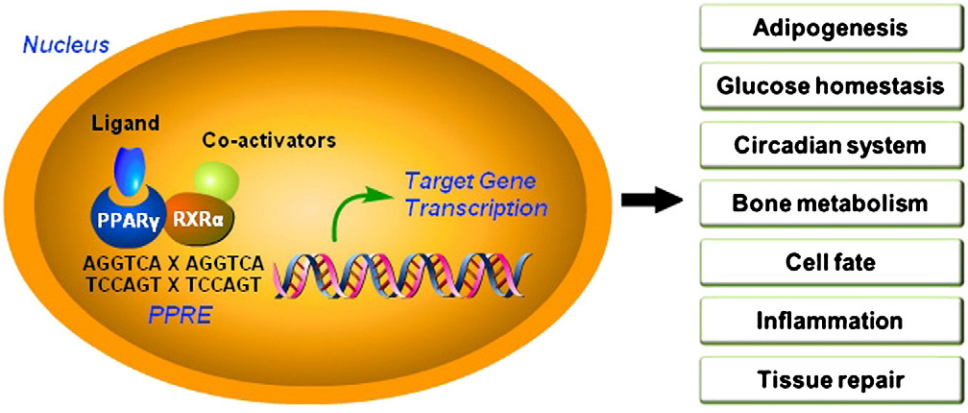

Fig. 1. This diagram represents the mode for PPARγ-mediated gene transcription and the biological outcomes. PPARγ activated by endogenous or exogenous ligands forms a multi-protein complex with RXRα and co-activators in the nucleus. The complex binds to the PPRE in the promoter region of target genes, which is a direct repeat of the hormone response element sequence AGGTCA separated by one base pair (indicated as X), and leads to transcriptional activation. The PPARγ transactivation has impacts upon a wide range of pathophysical processes including adipocyte differentiation, glucose homeostasis, circadian rhythm system, skeleton metabolism, cell-fate determination, inflammatory regulation, and tissue repair program. The anti-inflammatory properties and the beneficial effects in wound-healing process may imply the important role for PPARγ system in liver fibrosis therapy.