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Peroxisome proliferator-activated receptor γ : innate protection from excessive fibrogenesis and potential therapeutic target in systemic sclerosis

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Abstract

Purpose of review—Progressive organ fibrosis and pulmonary arterial hypertension (PAH) are the leading causes of death in patients with systemic sclerosis (SSc). However, the pathogenesis and the link between these two processes remain obscure. A better understanding of these events is needed in order to facilitate the discovery and development of effective therapies for SSc.

Recent findings—Recent reports provide evidence that the orphan receptor peroxisome proliferator-activated receptor γ (PPAR γ), better known for its pivotal role in metabolism, has potent effects on inflammation, fibrogenesis and vascular remodeling and is important in the pathogenesis of fibrosis and PAH, and as a potential therapeutic target in SSc. The studies discussed in this review indicate that ligands of PPAR γ potently modulate connective tissue turnover and suggest that aberrant expression or function of PPAR γ is associated with, and very likely contributes to, the progression of pathological fibrosis and vascular remodeling. These observations are of particularly relevance because FDA-approved drugs of the thiazolidinedione class currently used for the treatment of obesity-associated type 2 diabetes activate PPAR γ signaling. Moreover, novel PPAR γ ligands with selective activity are under development or in clinical trials for inflammatory diseases, asthma, Alzheimer disease and cancer.

Summary—Drugs targeting the PPAR γ pathway might be effective for the control of fibrosis as well as pathological vascular remodeling underlying PAH and, therefore, might have a therapeutic potential in SSc. A greater understanding of the mechanisms underlying the antifibrogenic and vascular remodeling activities of PPAR γ ligands will be necessary in order to advance these drugs into clinical use.

Keywords

fibroblast; fibrosis; fibrosis therapy; myofibroblast; pulmonary arterial hypertension; peroxisome proliferator-activated receptor γ ; scleroderma; transforming growth factor β

Introduction

It is thought that chemical, infectious, mechanical or autoimmune injury in a genetically susceptible host triggers persistent fibroblast activation and myofibroblast transdifferentiation that underlie pathological fibrosis. Injury can also cause transdifferentiation of epithelial cells into activated myofibroblasts through a process called epithelial–mesenchymal transition (EMT). Endothelial cells, preadipocytes and vascular pericytes can also trans-differentiate into myofibroblasts. These cellular transitions are regulated by a variety of factors, of which transforming growth factor β (TGF- β) and Wnt are most prominent. Activated myofibroblasts accumulate in the damaged tissue, where they engage in sustained matrix synthesis, resulting in excessive connective tissue accumulation and remodeling and buildup of intractable scar. Agents that block mesenchymal cell activation and transdifferentiation might be effective in controlling fibrosis.

The peroxisome proliferator-activated γ in physiology and disease

Peroxisome proliferator-activated receptor γ (PPAR γ) is an orphan receptor that belongs to the nuclear hormone receptor superfamily, members of which function as ligand-activated transcription factors that regulate a broad range of physiological responses [1^{*}]. The three distinct isoforms of PPAR (PPAR α , PPAR β/δ , PPAR γ) are encoded by three genes. PPAR γ itself exists in two isoforms, PPAR γ 1 and PPAR γ 2, which are the products of the same gene derived by differential transcription start site usage [2].

The expression level of PPAR γ in a given cell or tissue determines the intensity and duration of the cellular response to endogenous or synthetic PPAR γ ligands. In light of PPAR γ 's pleiotropic physiological roles, the level of PPAR γ expression could have an important modulating influence on a variety of homeostatic responses. Surprisingly, little is known regarding the factors that regulate the expression of PPAR γ . It is worth noting, however, that cytokines implicated in fibrosis generally suppress PPAR γ expression in mesenchymal effector cells (J. Wei, A.K. Ghosh, J.L. Sargent, *et al.*, submitted for publication). TGF- β is a potent inhibitor of PPAR γ expression in fibroblasts, but not in macrophages (J. Wei, A.K. Ghosh, J.L. Sargent, *et al.*, submitted for publication). Other inhibitors of PPAR γ expression include interleukin-13 (IL-13), Wnt, CCN2, leptin, lysophosphatidic acid (LPA) and hypoxia [3–6]. MicroRNA miR-27b is also a potent inhibitor of adipocyte differentiation via targeting PPAR γ . Moreover, cellular levels of PPAR γ are also regulated through proteasomal degradation. On the contrary, adiponectin, which is itself regulated by PPAR γ , enhances the expression of PPAR γ in the liver and adipose tissue. Serum adiponectin might therefore be a potential biomarker of the level of PPAR γ expression and progression of fibrosis in SSc (see below).

In unstimulated cells, the PPAR receptors reside in the cytoplasm as heterodimers complexed to their repressors. Upon activation by ligands, the PPARs undergo a conformational change allowing recruitment of retinoid X receptor (RXR) coactivators and the RXR–PPAR complex is then translocated into the nucleus, where it binds to conserved PPRE DNA elements in target gene promoters, resulting in induction, or less commonly repression, of transcription.

PPAR γ was originally identified in fat, but is now known to be widely expressed in immune cells such as macrophages, T and B lymphocytes, as well as platelets, epithelial and endothelial cells, smooth muscle cells and fibroblasts [7]. Tissues rich in PPAR γ include visceral and subcutaneous fat, along with colon, spleen, liver, skeletal muscle, bone marrow and lung [8]. Initial studies identified a pivotal role for PPAR γ in lipid metabolism and adipogenesis by inducing the expression of multiple target genes such as adiponectin and FABP4 [9]. It was subsequently shown that PPAR γ is important in regulation of glucose homeostasis. Recent attention has focused on the role of PPAR γ in inflammation, cell proliferation and apoptosis, and it is now clear that PPAR γ modulates diverse physiologic responses and is implicated in myriad disorders. Homozygous germline deletion of PPAR γ in the mouse results in embryonic lethality due to defective placental development [10]. Tissue-specific conditional deletion of PPAR γ is associated with substantial disorder, including spontaneous pulmonary hypertension in mice with loss of PPAR γ in the endothelium or vascular smooth muscle cells [11*,12]. The physiological importance of PPAR γ is further underlined by the range of human disorders that are associated with altered PPAR γ expression or function. Prominent examples include type 2 diabetes, lipodystrophy, the metabolic syndrome, as well as osteopenia, pulmonary hypertension, ulcerative colitis and inflammatory conditions. Recent studies indicate that SSc is also associated with altered PPAR γ biology. Allelic polymorphisms in the PPAR γ gene are associated with type 2 diabetes, obesity, asthma and cardiovascular disease, and dominant negative PPAR γ mutations cause lipodystrophy and diabetes [13].

Natural and synthetic ligands for peroxisome proliferator-activated receptor γ

The importance of PPAR γ became apparent in 1995, when it was identified as the cellular receptor for the thiazolidinedione class of antidiabetic drugs such as rosiglitazone and pioglitazone [14]. The antidiabetic efficacy of thiazolidinediones depends on induction of PPAR γ target genes mediating lipid and glucose metabolism [15]. Although the 'true' endogenous ligand for PPAR γ remains unknown [3], multiple naturally occurring compounds such as fatty acids, prostaglandin D-derived 15deoxy-12,14 prostaglandin J₂ (15d-PGJ₂) and LPA can activate PPAR γ in a variety of cell types [16]. It is very likely that there exist additional as-yet unidentified natural PPAR γ ligands that maintain basal or constitutive PPAR γ signaling. Synthetic ligands of PPAR γ include, in addition to thiazolidinediones, triterpenoid compounds derived from oleanic acid [17]. The clinical utility of thiazolidinediones is limited by side-effects including weight gain, fluid retention, osteopenia and bone fractures and, possibly, congestive heart failure [18]. The risk of cardiovascular events may also be increased in diabetic patients treated with thiazolidinediones, particularly in women, although a recent study [4] showed no increase. Strategies for safer insulin-sensitizer drugs involve the development of selective PPAR γ modulators (SPPARMs) with partial or gene-selective agonist activities or augmenting the expression of PPAR γ [19*]. A promising novel compound is CDDO, a stable orally active triterpenoid that has both PPAR γ -dependent and PPAR γ -independent biological activities while causing only modest adipogenic gene expression [20*]. CDDO inhibits cell

proliferation and inflammatory mediator synthesis and is currently used under the name bardoxolone in clinical trials for diabetic kidney disease and cancer.

Relevant biological functions of peroxisome proliferator-activated receptor γ

In addition to its importance in lipid and glucose metabolism, PPAR γ plays a role in controlling cell proliferation and differentiation. PPAR γ ligands have potent effects on bone metabolism, inflammation and tissue repair. Mice with conditional deletion of PPAR γ in adipose tissue develop lipoatrophy, and patients with dominant negative PPAR γ mutations develop lipodystrophy [21,22]. The disappearance of the subcutaneous adipose layer in these conditions resembles the subcutaneous changes observed in murine models of scleroderma [23]. Subcutaneous adipose tissue atrophy is also prominent in biopsies from patients with diffuse cutaneous SSc.

An important role for PPAR γ in broadly regulating inflammation and immunity is emerging. Rosiglitazone, by activating PPAR γ , caused potent inhibition of macrophage activation [24]. The anti-inflammatory effect of PPAR γ ligands is associated with reduced production of inflammatory mediators including IL-1, tumor necrosis factor α (TNF- α) and chemokines, but the precise molecular mechanisms underlying suppression remain to be fully elucidated. A recent study [25] reported that rosiglitazone attenuated the stimulation of CXCL10 secretion in explanted SSc fibroblasts. *In vivo*, PPAR γ ligands ameliorated allergic airway inflammation in a mouse model of asthma [26] and reduced the severity of disease manifestations in a mouse model of cystic fibrosis associated with inflammation [27]. Activation of PPAR γ also disrupts Toll-like receptor (TLR)-mediated innate immune responses [28]. The ability of PPAR γ to suppress inflammation and innate immunity has important therapeutic implications [29].

Peroxisome proliferator-activated receptor γ and fibrosis

Recent studies employing in-vitro and in-vivo approaches have revealed an entirely novel role for PPAR γ in fibrogenesis. This was initially recognized by Hazra *et al.* [30], who observed that ectopic PPAR γ expression in activated hepatic stellate cells induced a phenotypic switch of these cells to quiescence. The switch is associated with suppression of type I collagen gene expression. Moreover, activation of cellular PPAR γ receptors using either synthetic or natural PPAR γ ligands blocks the induction of profibrotic responses *in vitro*. For instance, treatment of normal skin and lung fibroblasts with PGJ₂ or rosiglitazone was found to abrogate TGF- β -induced stimulation of collagen and fibronectin synthesis, myofibroblast differentiation, fibroblast migration and the secretion of fibrotic growth factors such as TGF- β and CTGF [31,32]. Moreover, rosiglitazone attenuated the persistently activated phenotype of lesional skin fibroblasts explanted from patients with SSc [33]. Rosiglitazone also prevented differentiation of mesenchymal progenitor cells into fibroblasts and, instead, promoted their differentiation into adipocytes. These observations are entirely consistent with the well documented adipogenic potential of PPAR γ [34,35]. Remarkably, PPAR γ ligands also inhibited alveolar epithelial cells–mesenchymal transition induced by TGF- β , highlighting the regulation of cell differentiation as a fundamental

mechanism underlying the antifibrogenic activities of PPAR γ ligands [36]. In rodents, PPAR γ ligands ameliorated carbon tetrachloride or choline deficient diet-induced liver fibrosis. Rosiglitazone attenuated cardiac fibrosis and diabetic renal fibrosis and prevented chronic damage in a renal allograft model [37]. Troglitazone, an older PPAR γ ligand, attenuated lung fibrosis induced by intratracheal bleomycin installation, even when treatment was delayed [38]. In a mouse model of scleroderma induced by daily bleomycin injections, rosiglitazone both prevented and attenuated skin fibrosis [39]. It is likely that the striking protection from fibrosis afforded by PPAR γ ligands in these rodent models is due, at least in part, to their immunosuppressive effects as well as direct antifibrogenic effects. There is a suggestion that thiazolidinedione treatment of patients with type 2 diabetes delays and prevents the progression of chronic kidney disease [40].

How do peroxisome proliferator-activated receptor γ ligands block fibrogenic responses?

The molecular mechanisms underlying the antifibrotic effects of PPAR γ are the subject of intense investigation. In normal fibroblasts, ligand-activated PPAR γ blocks profibrotic signaling triggered by TGF- β and Wnt- β -catenin and interferes with downstream signal transduction [31,41]. In the case of TGF- β -mediated fibroblast activation, PPAR γ does not prevent Smad2/3 phosphorylation or nuclear accumulation, but, instead, prevents recruitment of the p300 to the transcriptional complex [42,43]. p300 is an obligate coactivator required for Smad-dependent collagen gene transcription. Because p300 acts via histone acetylation, the findings imply that PPAR γ ligands suppress fibrotic gene expression via epigenetic regulation. In contrast to fibroblasts, treatment of hepatic stellate cells with PPAR γ ligands was shown to block TGF- β -induced Smad3 phosphorylation, suggesting that the antagonistic effects of PPAR γ ligands on TGF- β signal transduction may involve distinct cell type-specific mechanisms [44]. Other studies showed that PPAR γ ligands stimulated hepatocyte growth factor (HGF), an endogenous antifibrotic agent that then mediates autocrine suppression of TGF- β -induced fibrogenic responses [45]. Finally, PPAR γ ligands have been shown to block the induction of Egr-1, an early-immediate transcription factor that plays a fundamental role in transducing fibrogenic activities triggered by TGF- β and other cytokines [39,46]. The antifibrotic effects triggered by PPAR γ ligands, including inhibition of fibroblast migration, adipocyte differentiation and myofibroblast transition, might also involve PPAR γ -independent pathways.

An alternate mechanism to account for the antifibrogenic effects of PPAR γ ligands has been proposed. This model involves PPAR γ -mediated stimulation of the tumor suppressor phosphatase and tensin homologue deleted on chromosome 10 (PTEN). PTEN abrogates the stimulation of collagen production and myofibroblasts differentiation in normal fibroblasts [47]. Studies have shown that the expression of PTEN is deficient in pulmonary fibrosis and in lesional SSc skin, and PTEN has been implicated as a causative agent in the progression of fibrosis [48,49]. Pharmacological stimulation of PTEN in these conditions using PPAR γ ligands may be a potential therapeutic approach in fibrosis [47].

Peroxisome proliferator-activated receptor γ expression in fibrosis

It was observed that in the resolution phase of wound healing, there is a switch from pro-inflammatory prostaglandin production to PGI_2 and $\text{PPAR}\gamma$ in the skin, suggesting that a physiologic role of $\text{PPAR}\gamma$ might be the negative regulation of matrix remodeling [50]. Indeed, an inverse relationship between fibrosis and $\text{PPAR}\gamma$ expression and function has been noted in multiple human fibrosing disorders as well as in rodent models of fibrosis. However, it is not immediately obvious whether fibrosis in these conditions is the cause of reduced $\text{PPAR}\gamma$, or the other way around, that is, reduced $\text{PPAR}\gamma$ causes fibrosis. Reduced $\text{PPAR}\gamma$ tissue levels have been found in fibrosis of the kidney [51], liver [52] and lungs [53], in SSc-associated pulmonary fibrosis (J. Wei, A.K. Ghosh, J.L. Sargent, *et al.*, submitted for publication), and associated with scarring alopecia in the scalp [54]. Fibroblasts explanted from lesional SSc skin show reduced $\text{PPAR}\gamma$ expression, although curiously they retain sensitivity to $\text{PPAR}\gamma$ ligand-induced suppression of collagen production and alpha smooth muscle actin expression [33]. Moreover, $\text{PPAR}\gamma$ in various tissues shows reduced expression with aging [55]. The development of skin fibrosis in bleomycin-induced scleroderma in the mouse is accompanied by a decline in cutaneous $\text{PPAR}\gamma$ levels [39]. Microarray-based transcriptional profiling in SSc showed reduced $\text{PPAR}\gamma$ expression and function in patient biopsies with a robust TGF- β -activated gene expression signature (J. Wei, A.K. Ghosh, J.L. Sargent, *et al.*, submitted for publication). These biopsies showed reduced expression of $\text{PPAR}\gamma$ target genes involved in adipogenesis and fat metabolism including *PGC1*, *PCK1* and *FABP2*. The same biopsies also showed reduced expression of *PTEN*. Moreover, there was a trend toward lower $\text{PPAR}\gamma$ expression in patients with more extensive skin involvement.

The existence of an inverse relationship between $\text{PPAR}\gamma$ expression levels and fibrogenesis indicates a potential physiologic function of $\text{PPAR}\gamma$ in affording protection from excessive fibrogenesis (Fig. 1). Consistent with this predicted homeostatic role for $\text{PPAR}\gamma$, inhibition of its expression or function is causally linked to the development of fibrosis in mouse models. For example, conditional knockout of the $\text{PPAR}\gamma$ gene targeted to follicular stem cells in the scalp is associated with scarring [54]. Fibroblast-specific deletion of $\text{PPAR}\gamma$ in the mouse resulted in enhanced sensitivity to the fibrogenic effects of bleomycin [56]. Mice harboring a dominant negative human $\text{PPAR}\gamma$ gene mutation develop exaggerated cardiac fibrosis when challenged with angiotensin II [57].

Reduced peroxisome proliferator-activated receptor γ expression and function in pulmonary arterial hypertension

Previous studies have noted reduced $\text{PPAR}\gamma$ expression in the lungs from patients with PAH [58]. Remarkably, in the mouse, targeted knockout of $\text{PPAR}\gamma$ in pulmonary vessels resulted in the spontaneous development of PAH, right ventricle hypertrophy and pulmonary vascular remodeling [11,12]. This was associated with marked upregulation of platelet-derived growth factor signaling in the blood vessels that could be abrogated by treatment with the tyrosine kinase inhibitor imatinib (Gleevec; Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, USA). Moreover, hypoxia-induced pulmonary hypertension in the mouse was attenuated by rosiglitazone [59]. Therefore, $\text{PPAR}\gamma$ appears to be important

for pulmonary vascular homeostasis, and reduced PPAR γ expression or function leads to PAH [60]. It is remarkable, therefore, that defective PPAR γ expression or function appears to be implicated in the pathogenesis of both fibrosis and PAH, two of the lethal complications of SSc, and, at least in experimental models, both of these PPAR γ -associated pathological processes could be ameliorated with PPAR γ ligands. These findings raise hope that pharmacological PPAR γ modulation might be an effective therapeutic strategy in SSc targeting both fibrotic and vascular disorders.

Conclusion

The multifunctional nuclear hormone receptor PPAR γ is beginning to emerge as a regulatory molecule of great interest in the pathogenesis and treatment of fibrosis in general and SSc in particular. Recent publications point to PPAR γ as a hitherto unsuspected nexus between metabolism and pathological fibrosis and vascular remodeling. Substantial evidence from several human diseases and animal models indicates that on the one hand, there exists a causal relationship between fibrosis and pulmonary vascular disease and reduced PPAR γ expression and function, and on the other hand, pharmacological targeting of PPAR γ might be able to prevent and even reverse fibrosis and vascular remodeling and pulmonary arterial hypertension (Fig. 1). Several PPAR γ ligands currently used in type 2 diabetes therapy are orally active and relatively well tolerated and could, therefore, be evaluated in patients with SSc. A precise understanding of the cellular mechanisms of action underlying the antifibrogenic and vascular remodeling activities of these PPAR γ ligands is needed. Moreover, it will be of great interest to investigate the genetic associations between PPAR γ gene polymorphisms and SSc and specific SSc disease phenotypes such as pulmonary fibrosis and pulmonary arterial hypertension.

Acknowledgments

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 709).

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Figure 1. Peroxisome proliferator-activated receptor γ signaling calibrates fibrogenic responses Under physiologic conditions, peroxisome proliferator-activated receptor γ (PPAR γ) shows a low level of constitutive activation, driven by natural ligands controlling fibrotic responses (left panel). Prolonged or recurrent fibrogenic stimulation due to injury (right panel) suppresses the expression of PPAR γ expression, reducing cellular responsiveness to natural endogenous PPAR γ ligands. This leads to unopposed stimulation of collagen synthesis and myofibroblast differentiation by fibrogenic stimuli such as TGF- β , resulting in progressive fibrosis.