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Review Article

The Myofibroblast: TGFβ-1, A Conductor which Plays a Key Role in Fibrosis by Regulating the Balance between PPARγ and the Canonical WNT Pathway

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Abstract. Myofibroblasts are non-muscular contractile cells that occur physiologically in organs such as in stem villi of the human placenta during normal pregnancies. They have the ability to contract and relax in response to changes in the volume of the intervillous chamber. Myofibroblasts are also found in many pathological states, and are involved in wound healing and fibrosis processes in several organs such as liver, lung, kidney, and heart. During fibrosis, the contractile phenomenon is a relaxation-free mechanism, associated with the synthesis of collagen in the extracellular matrix (ECM), which leads to irreversible fibrosis, tissue retraction and finally apoptosis of the myofibroblasts. The molecular motor of myofibroblasts is the non-muscle myosin type II (NMII). Differentiation of fibroblasts into myofibroblast is largely regulated by the Transforming Growth Factor-β1 (TGF-β1). This system regulates the canonical WNT/β-catenin pathway in a positive manner and PPARγ in a negative manner. WNT/β-catenin promotes fibrosis while PPARγ prevents fibrosis. This review focuses on the contractile properties of myofibroblasts and on the TGF-β1 conductor which regulates the antagonism between PPARγ and the canonical WNT/β-catenin pathway.

Keywords: Transforming Growth Factor-β1; PPARγ; canonical WNT/β-catenin; Hippo/YAP/TAZ; Smad; myofibroblast; fibrosis; myosin.

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1. Introduction

Gabbiani et al. first discovered the presence of modified fibroblasts or myofibroblasts in the wound granulation tissue of healing skin [1]. They demonstrated that modified fibroblasts present contractile properties, share certain analogies with smooth muscles, and play a role in wound contraction. In fact, as early as 1916, it was shown that the process of contraction was the most important factor in the healing of a wound [2]. Wound contraction due to the active retraction of the granulation tissue is induced by contractile non-muscle cells, known as myofibroblasts [3, 4]. The transforming growth factor β1 (TGF-β1) interacts with a complex system, i.e., the canonical WNT/β-catenin and peroxisome proliferator activated receptor gamma (PPARγ). These two pathways generally operate in an opposing manner in numerous

pathological states [5]. Then, either the PPARγ expression is upregulated while the WNT/β-catenin pathway is downregulated, or vice versa. Myofibroblast differentiation is regulated by TGF-β1, that stimulates canonical WNT signaling and represses PPARγ [6, 7]. Fibroblasts and myofibroblasts are key effectors involved in the development of fibrosis through an excessive deposition of collagen and inappropriate extracellular matrix (ECM). In response to TGF-β1, resident fibroblasts transdifferentiate into contractile myofibroblasts which express α-smooth muscle actin (α-SMA) and synthesize extracellular matrix proteins, particularly collagen. This review will focus on the homeostasis and the contractile properties of myofibroblasts in normal and pathological tissues, particularly in fibrotic processes. The review will be largely based on the opposing regulatory role of TGF-β1 with respect to both the PPARγ pathway and the canonical WNT/β-catenin signaling.

2. The Myofibroblast

2.1. General

The main ultrastructural characterization of the contractile myofibroblast is the presence of actin filament bundles containing α-SMA, peripheral focal adhesions and gap junctions connecting myofibroblasts in the granulation tissue [8]. Soon after a wound is sustained, local fibroblasts known as proto-myofibroblasts migrate towards the wound core. These proto-myofibroblasts evolve into differentiated myofibroblasts containing α-SMA, responsible for wound retraction [9]. Proto-myofibroblasts synthesize ECM containing type I and type III collagen and ED-A fibronectin, that is essential for the myofibroblast differentiation [10]. After wound closure, myofibroblasts disappear through apoptosis [11].

The origins of myofibroblasts are multiple [12, 13]. Mesenchymal stem cells (MSC), fibroblasts, proto-myofibroblasts or differentiated myofibroblasts can be found in normal tissues such as occurring in lung alveolar septa, uterine submucosa, lymph nodes, spleen, adrenal capsule, periodontal ligament, intestinal crypts and bone marrow stroma. Generally, differentiation of fibroblasts into myofibroblasts occurs during skin repair processes after injury, or during fibrosis in the liver, skin, kidney, heart and lung. In granulation tissue, myofibroblasts have been shown to induce the deposition, retraction, and remodeling of the ECM, thereby promoting wound healing [14]. However, aberrant wound healing results in increased proliferation and attenuated apoptosis of myofibroblasts. Myofibroblast differentiation can be triggered by multiple cellular pathways [15, 16]. Growth factors are generally stored in the ECM and are activated and released by means of mechanical stress or proteolytic cleavage. They then bind membrane receptors. This leads to activation of intracellular complexes that migrate to the nucleus and thereby promote or repress the transcription of target genes that impact on fibrotic disorders.

Myofibroblasts have been reported in numerous fibrotic diseases, such as systemic sclerosis (SSc), glumerulosclerosis, idiopathic pulmonary fibrosis, liver cirrhosis, and heart failure and repair after myocardial infarction [17]. They are also reported in stromal reaction to epithelial cancers [18], retinal detachment [19] and human anterior capsular cataract [20]. Chronic injury leads to prolonged activation of fibroblasts [21] which differentiate toward myofibroblasts. Myofibroblasts can persist after wound closure resulting in hypertrophic scar, especially after burn injuries [22]. Precursors of myofibroblasts can be smooth muscle cells in coronary

atheromatous plaque [23], perisinusoidal cells in liver [24], keratocytes in eyes [17], pericytes in kidneys [25], and bone marrow-derived fibrocytes [26]. Non fibroblastic cell lineages [27–29] can differentiate into myofibroblasts through the processes of epithelial-mesenchymal transition [30] and endothelial-mesenchymal transition [31]. MSCs are myofibroblast precursors in several pathological states [32]. An important particular case is the presence of myofibroblasts in normal human placenta, a tissue in which the population of contractile myofibroblasts is dominant in placental stem villi [33]. In normal human placenta, the differentiation of fibroblast into myofibroblast occurs within the stem villi from the peripheral part of the villi towards its central part [34]. The differentiation of fibroblasts into myofibroblasts results from a complex process involving both physical and chemical factors. Among these factors are the increased stiffness of the tissue [9, 35] and TGF-β1 with ED-A fibronectin [10, 36]. TGF-β1 promotes the synthesis of α-SMA which leads to differentiated myofibroblasts. Incorporation of α-SMA into stress fibers significantly increases the contractile properties of myofibroblasts [37]. ECM allows the transmission of force generated by α-SMA and the molecular motor myosin through focal adhesions containing transmembrane integrins [38]. In ECM, TGF-β1 is liberated by an integrin-dependent mechanically induced process [22]. In addtion, TGF-β1 becomes more available with the increased stiffness of ECM [39, 40].

2.2. The myofibroblast: A contractile cell containing the non-muscle NMII myosin

There are two kinds of contractile cells, contractile muscle cells and contractile non-muscle cells. All contractile cells work by means of a molecular motor that is coupled with α-SMA. The molecular motor is the type II muscle myosin (MII) in muscle cells (smooth muscles and sarcomeric muscles) and the type II non-muscle myosin (NMII) in non-muscle contractile cells [41]. NMIIs are involved in the generation of cell polarity, cell migration and cell-cell adhesion. In myofibroblasts, the molecular motor is the non-muscle myosin II (NMII). NMII predominates in myofibroblasts located in the extravascular part of the normal human placental stem villi (NM II type A) [42, 43]. Myofibroblasts are also present in several pathological tissues such as in cancers (mammary carcinoma, epithelial cells in cancerous mammary glands), and fibrotic lesions (Dupuytrens nodules, hypertrophic scars) [44].

Like MII, NMII contains three pairs of chains. There are two heavy chains of 230 kDa, two 20 kDa regulatory light chains (RLCs) which regulate the NMII activity and two 17 kDa essential light chains (ELCs) which stabilize the heavy chain structure. Two systems regulate the NMII activity: first, the calcium-calmoduline-myosin light chain kinase (MLCK); second, the Rho/ROCK/myosin light chain phosphatase [9, 45, 46]. NMII binds with actin through the head domain of the heavy chain. The ATPase site is also located on the myosin head. Myosin filaments link actin filaments together in thick bundles such as stress fibers. Importantly, NMII molecules assemble into bipolar filaments. This allows the sliding of the myosin molecules along the actin filaments. A tilt of the myosin head enables a conformational change that moves actin filaments in an anti-parallel manner. The crossbridge (CB) actin-myosin cycle of NMII is broadly similar to that observed in smooth and striated muscle myosin. An ATP molecule binds the NMII-ATPase site on the myosin head. This allows the dissociation of actin from the NMII head. ATP is then hydrolysed and subsequently, NMII binds with actin. Then, the power stroke

occurs with a tilt of the NMII head, which generates a CB single force (order of magnitude: pico Newton) and a displacement of a few nanometers. ADP is then released from the actin-NMII complex. A new ATP molecule dissociates actin from the myosin head, and a new CB cycle begins.

The main characteristic of NMII is that it is extremely slow. Kinetics of contractile NMII are dramatically slow [47, 48]. Compared with striated or smooth muscles, the values for the CB detachment constant, the CB attachment constant, the catalytic constant, and the myosin ATPase activity are particularly low. However, the NMII CB unitary force is of the same order of magnitude when compared with MII. From a thermodynamic point of view, the thermodynamic force, the thermodynamic flow, and the entropy production rate are extremely low [49]. This explains why this stationary contractile system operates as a near-equilibrium system. The low isometric tension reported in placental stem villi [43, 50, 51] can be partly explained by the low placental myosin content [52–54]. The extremely slow shortening velocity can be accounted for by the very low placental myosin ATPase activity [48, 52, 54].

In myofibroblasts of human placenta, the actin-myosin apparatus functions as in smooth muscles. The contraction phase is induced by either an electrical field or the addition of KCl in the experimental bath. Relaxation is induced by either 2,3-butanedione monoxime (BDM), a quasi-specific inhibitor of NMII or isosorbide dinitrate (ISDN), a donor of NO [43]. Numerous contraction-relaxation cycles can ensue. In the human placenta, changes in the volume of the intervillous chamber alter the length of the placental stem villi. Due to the Starling phenomenon observed in placental stem villi, contraction of myofibroblasts modifies the distal resistance of the umbilical artery which regulates the umbilical blood flow. In pathological processes such as wound healing or fibrotic processes, myofibroblasts generate a phenomenon of contraction-retraction with no relaxation and the pathological tissue undergoes an irreversible retraction, evolving towards fibrosis favored by the synthesis of collagen [1, 55].

Within myofibroblasts, three main systems play a major regulatory role in the genesis of tissue fibrosis. These are PPARγ, the canonical Wingless/Int (WNT)/β-catenin signaling, and the Transforming Growth Factor (TGF-β), where the latter represses the first and activates the second. TGF-β, WNT, and more recently the yes-associated protein 1 (YAP)/transcriptional coactivator and PDZ-binding motif (TAZ) have been shown to interfere in the pathophysiology of fibrosis. These pathways share the molecular mechanism of cytosolic/nuclear regulation of their transcriptional activators.

3. Regulation of Fibrosis in Myofibroblast

3.1. TGF-β1 [56]

TGF-βs are three structurally similar proteins, i.e., TGF-β1, TGF-β2 and TGF-β3. TGF-β receptors are transmembrane proteins and include Type I (TβRI) and Type II (TβRII) receptors (Figures 1 and 2). TGF-β1 binds TβR2 but does not bind TβR1. TGF-β1 is secreted and deposited into ECM as a large latent complex that consists of latent TGF-β1 binding protein bound with a small latency complex. TGF-β1 is secreted as a monomeric form which is an inactive latent complex [15]. The monomeric form is a competitive inhibitor of the active dimeric form [57].

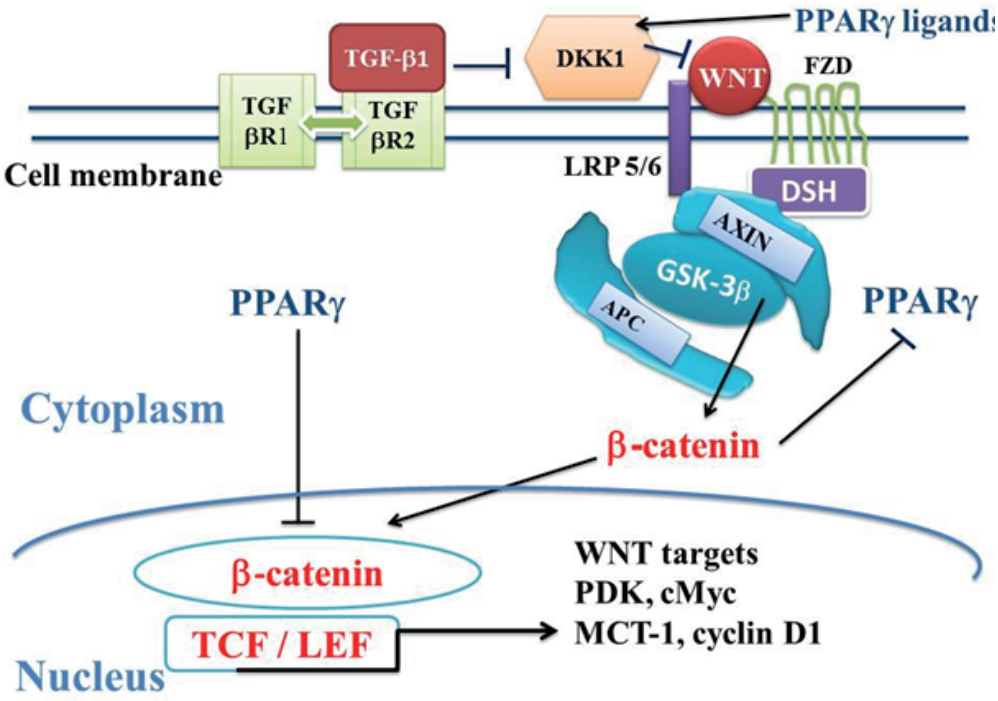

Figure 1: **Schema of TGF-β1 effects on the balance between the canonical WNT/β-catenin pathway and PPARγ.** In the presence of the WNT ligands, WNT receptor binds both FZD and LRP5/6 receptors to initiate LRP phosphorylation and DSH-mediated Frizzled internalization. This leads to dissociation of the AXIN/APC/GSK-3 β destruction complex. Phosphorylation of β-catenin is inhibited which inhibits its degradation in the proteasome. Thus, β-catenin accumulates in the cytosol and then translocates to the nucleus to bind TCF-LEF co-transcription factors. This induces the WNT-response gene transcription (PDK, MCT-1, MYC, and CYCLIN D1). PPARγ inhibits the β-catenin/TCF-LEF-induced activation of WNT target genes. TGF-β also enhances WNT signaling through the inhibition of DKK1. PPARγ activates DKK1. Abbreviations: adenomatous polyposis coli (APC); Dickkopf-1 (DKK1); Dishevelled (DSH); Frizzled (FZD); glycogen synthase kinase-3β (GSK-3β); lactate dehydrogenase (LDH); low-density lipoprotein receptor-related protein 5/6 (LRP5/6); monocarboxylate lactate transporter-1 (MCT-1); peroxisome proliferator-activated receptor gamma (PPARγ); pyruvate dehydrogenase kinase (PDK); T-cell factor/lymphoid enhancer factor (TCF/LEF); Transforming Growth Factor (TGF).

Active TGF-β1 dimer reacts with its receptor complex to stimulate phosphorylation and activation of the SMAD pathway that transmits information to the nucleus [58]. Integrins $\alpha_v\beta5$ and $\alpha_v\beta6$ activate TGF-β1. Moreover, TGF-β1 activates the Smad pathway and non-Smad pathways such as MAPK, Rho, PI3K-AKT, MAP kinases p38 and JNK, TGF-β activated kinase (TAK1), and focal adhesion kinase [59, 60]. Moreover, CTGF, platelet-derived growth factor (PDGF), IL-4, IL-6, IL-8, and IL-13 impact on TGF-β1 and contribute to fibrosis [61].

Many fibrotic disorders are characterized by upregulation of TGF-β1. Thus, TGF-β1 is upregulated in glomerular and tubulointerstitial diseases [62], in type II diabetes [63], in lungs [64], in bronchoalveolar lavage from patients with SSc [65] and in hypertrophic and restrictive cardiomyopathy [66].

3.2. The Smad pathway

The Smad pathway helps understand the link between TGF-β1, canonical WNT and PPARγ (Figure 2). In myofibroblast activation, the canonical Smad pathway regulates the intracellular

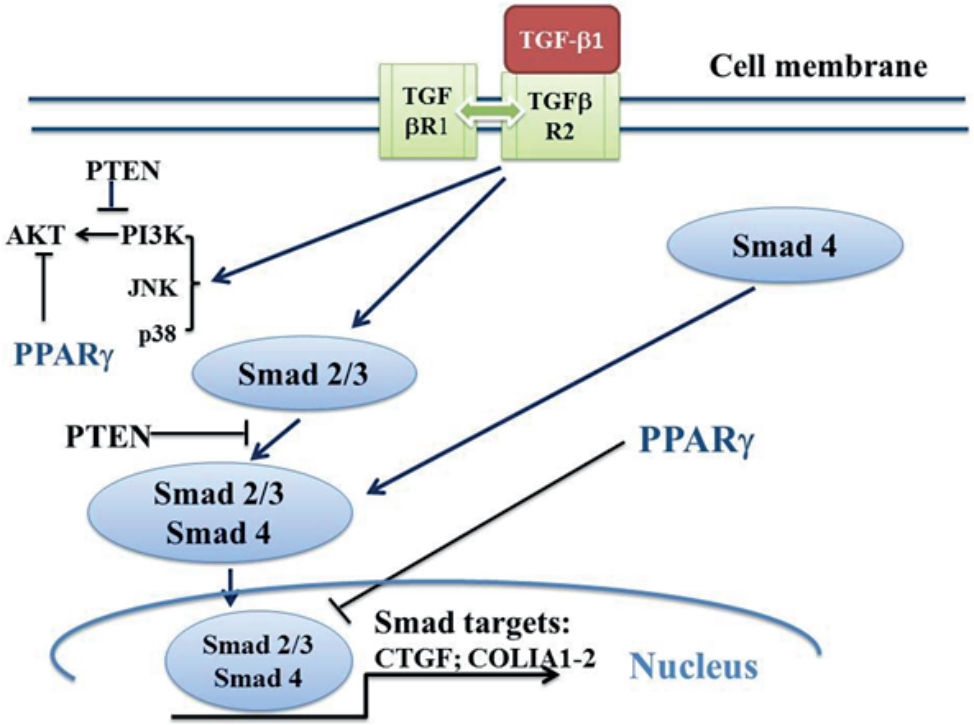

Figure 2: **Schema of TGF-β1/Smad pathway and PPARγ.** TGF-β1 has several effects on the Smad pathway. TGF-β1 binds type 2 TGF-β receptor (TGF-βRII) which recruits type 1 TGF-β receptors (TGF-βRI). This leads to a heterotetramer that phosphorylates Smad2/Smad3, which then binds to Smad4. The Smad 2-3-4 complex then translocates to the nucleus, where it interacts with various transcription factors to regulate the transcription of target genes (CTGF, COL1A1, and COL1A2). Other non-Smad pathways can occur through PI3K-AKT, p38, and JNK. PTEN inhibits PI3K-AKT and interferes with PPARγ.

TGF-β1 signaling. TGF-β1 binds TGF-βR2 that recruits TGF-βR1. This forms an heterotetramer that phosphorylates Smad 2 and Smad 3 which bind Smad 4. This complex translocates to the nucleus and then binds the Smad binding element (SBE) DNA sequences (Figure 2). This leads to the recruitment of coactivators such as histone acetyltransferase p300, and transcription of target genes [67]. TGF-β induces association of SMAD3 with both SMAD4 and the corepressors E2F4 and p107.

3.3. The canonical WNT/β-catenin pathway (Figure 1)

The canonical WNT/β-catenin pathway plays an important role in metabolism, embryonic development, cell fate, and epithelial-mesenchymal transition (EMT) [68]. Activation of the canonical WNT signaling increases the levels of β-catenin in the nucleus and/or cytoplasm (Figure 1). In the presence of canonical WNT ligands, the canonical WNT receptor is linked with Frizzled (FZD) and LDL receptor-related protein 5/6 (LRP5/6). FZD is linked to Dishevelled (DSH). This disrupts the destruction complex and prevents β-catenin degradation in the proteasome. The destruction complex consists of tumor suppressor adenomatous polyposis coli (APC), AXIN and glycogen synthase kinase-3 (GSK-3β). β-catenin translocates to the nucleus and associates with the transcription factor T-cell/lymphoid enhancer (TCF/LEF). This activates numerous β-catenin target genes (cMyc, cyclin D, Cox 2, AXIN, PDK, MTC-1) [69, 70]. In the absence of WNT ligands, the destruction complex phosphorylates β-catenin that is degraded in

the proteasome. A dysfunction of the WNT signaling has been reported in numerous diseases such as cancers [71–73]. Activation of the WNT/β-catenin pathway is upregulated in liver, skin, lung, kidney, and heart, presenting fibrosis [74–76, 79].

3.4. PPARγ

3.4.1. General

PPARγ is a pleiotropic ligand-dependent transcriptional factor that belongs to the nuclear hormone receptor superfamily [80]. PPARγ heterodimerizes with the retinoid X receptor and binds PPAR response elements (PPRE) that present repeats of the AGGTCA sequence [81]. PPARγ activated by ligands bind co-activators (p300/CBP and p160). PPARγ is expressed in numerous cell types, such as adipose tissues, muscles, brain, and immune cells. PPARγ activates the expression of many genes and regulates glucose homeostasis, insulin sensitivity, lipid metabolism, innate immune responses, cell fate and inflammation, and connective tissue homeostasis [82–85]. PPARγ is also present in fibroblasts [86]. Two isoforms of PPARγ are expressed. PPARγ1 is present in macrophages, epithelial cells, endothelial cells, and vascular smooth muscle cells. PPARγ2 is mainly expressed in adipose tissue to regulate adipogenesis.

PPARγ is activated by natural agents such as 15d- prostaglandin J2 (15d-PGJ2), lysophosphatidic acid, and nitrolinoleic acid. PPARγ can also be activated by synthetic ligands including thiazolidinediones (TZDs) and oleanic acid derivatives such as triterpenoids (2-cyano-3,12-dioxoolean-1,9-dien-28-oic-acid (CDDO)). TZDs improve insulin sensitivity in peripheral tissues [87] and ameliorate glucose tolerance and insulin sensitivity in type 2 diabetic patients [88]. TZDs act on the promoters of glucose transporter (GLUT-2) and glucokinase (GK) in pancreatic β-cells and liver. In addition, PPARγ interacts in connective tissue regulation, mesenchymal cell activation, differentiation and cell survival creating a link between metabolism and fibrogenesis [6]. Abnormalities of PPARγ are observed in several pathological states such as cancers, diabetes, obesity, atherosclerosis and all sclerosis diseases. Some TZDs have been used for treating type 2 diabetes. However, side effects induced by certain TZDs have been reported [89]. Benefits induced by TZDs are offset by the possibility for fluid retention, congestive heart failure, weight gain, and bone loss. It appears most important to develop newer classes of molecules that reduce or eliminate adverse effects due to TZD therapy. PPARγ also plays an important role in regulating cardiovascular rhythms by controlling circadian variations of blood pressure and heart rate through BMAL1 [90, 91].

PPARγ plays a key role in fibrotic processes and particularly in skin injury. When the skin is disrupted due to injury, resident fibroblasts become subjected to a mechanical tension. This stress, combined with the release of TGF-β1 from immune cells and platelets at the wound site, induces fibroblast migration from the dermis of the normal adjacent skin near the site of the injury [92]. Fibroblasts then differentiate into myofibroblasts. By antagonizing the TGF-β1 pathway, PPARγ plays a key role in suppressing tissue fibrosis. PPARγ agonists inhibit TGF-β-induced collagen deposition and myofibroblast differentiation [93–95]. Excessive scarring and/or chronic wounds represent a major clinical problem during tissue injury. Fibrosis can

be countered by activation of PPARγ that binds to specific DNA response elements to regulate gene transcription and control various cellular functions [96]. PPARγ agonists exert antifibrotic activity *in vitro* and in a bleomycin-induced murine model of pulmonary fibrosis [94, 97, 98]. PPARγ activation dedifferentiates myofibroblasts, increases collagen uptake by alveolar macrophages, and reverses established fibrosis in a murine model [98]. TGF-β downregulates PPARγ expression in various systems via the SMAD pathway [98–100]. Expression of PPARγ is decreased in lung tissue and lung fibroblasts from human idiopathic pulmonary fibrosis. Moreover, knockdown or knockout of PPARγ expression in isolated human and mouse lung fibroblasts induces a profibrotic phenotype [98]. Human fibroblasts treated with PPARγ agonists blocked TGF-β signaling. Knockdown of either SMAD3 or SMAD4 suppresses the effects of TGF-β on PPARγ mRNA and protein expression [7]. The discovery of new drugs to control the rate of the fibro-proliferative phase is of major clinical interest. PPARγ may be useful in preventing excessive scarring. At the moment, it remains to be clarified whether PPARγ agonists actually induce beneficial effects on cutaneous tissue repair in humans.

3.4.2. PPARγ modulators

Several cytokines, chemokines, or intracellular pathways result in a decrease PPARγ expression. These include TFG-β1, the canonical WNT/β-catenin pathway, TNF-α, interleukin (IL)-1β, IFN-γ, IL-13, the Connective Tissue Growth Factor (CTGF), leptin, and lysophosphatidic acid (LPA) [101–103]. The transcription factor COUP II is a canonical WNT target that suppresses PPARγ [104]. Hypoxia inhibits PPAR [105, 106]. Conversely, other molecules increase PPARγ expression. Therse include adiponectin, TZDs, L-carnitine, statins, eplerenone, and irbesartan [107]. Adiponectin increases PPARγ 2 expression and inhibits LPS-induced NF-kappaB activation and IL-6 production in adipocytes [108]. Other transcription factors regulate PPARγ in a positive manner, such as C/EBPs, EBF proteins, NF-E2 related factor 2 (Nrf2), and the bile acid receptor farnesoid X receptor (FXR) which interferes with the canonical WNT pathway [6, 109–111].

3.5. The YAP and TAZ pathway

YAP and TAZ are transcriptional co-activators from the Hippo core kinase complex [112]. The Hippo signaling regulates organ size, tissue regeneration, and stem cell self-renewal. The Hippo complex is made up of several components such as serine/threonine-protein kinases (MST1/2), MOB kinase activator 1 (MOB1), salvador (SAV), and serine/threonine-protein kinases (LATS1/2). When the Hippo kinase complex is activated, YAP and TAZ become phosphorylated and create a phosphodegron. Both YAP and TAZ can be either sequestered in the cytoplasm by 14-3-3 proteins or degraded by β-TrCP. The Hippo activity induces phosphorylation of YAP and modifies the level of β-catenin in the nucleus.

F-actin polymerization inhibits the activity of MST1/2 and this leads to inactivation of the Hippo complex. Both YAP and TAZ are then released and can translocate to the nucleus where they associate with transcription factors such as Runt-related transcription factor (RUNX) and TEA domain family member (TEAD) to activate gene transcription. YAP and TAZ have been

found to be involved in myofibroblast activation and to induce fibrosis. In biopsies from idiopathic pulmonary fibrosis, both YAP and TAZ levels have been found to be elevated, and to induce fibroblast activation and fibrosis. In mouse lung and liver fibroblasts, YAP and TAZ knockdown diminishes pro-collagen, αSMA, and plasminogen activator inhibitor 1 that are associated with myofibroblast differentiation [113, 114].

4. Interplays among the above Regulators

4.1. Crosstalk between PPARγ, the canonical WNT and TGF-β1 (Figures 1 and 2)

The link between TGF-β1, canonical WNT/β-catenin and PPARγ has been established [6, 7, 107]. TGF-β1 has been shown to activate the canonical WNT signaling, and to inhibit PPARγ. Conversely, PPARγ inhibits the TGF-β1/WNT/β-catenin pathway. PPARγ ligands repress TGF-β1-induced myofibroblast differentiation by targeting the PI3K/AKT pathway [115]. TGF-β1 represents an important regulator of fibrosis and a key therapeutic target in fibrosis diseases [116, 117]. TGF-β1 plays a central role in pathogenesis of fibrotic diseases [15, 118]. Fibrosis involves TGF-β-induced downregulation of PPARγ expression and activity [98–100]. PPARγ activation is able to block TGF-β-induced fibrosis and can actually reverse established pulmonary fibrosis in mice [98]. TGF-β1 induces differentiation of human lung fibroblasts to myofibroblasts. Fibrosis is inhibited by blocking TGF-β1 via PPARγ agonists [119]. PPARγ induces protection from excessive fibrogenesis [117]. In the eye, PPARγ ligands (15-deoxy-delta12,14-prostaglandin J2, troglitazone, and rosiglitazone) have been shown to suppress corneal myofibroblasts [120].

Importantly, the antagonism between PPARγ and TGF-β1 would partly explain the fibrogenesis. TGF-β1 upregulation promotes the fibroblast-myofibroblast transdifferentiation and negatively regulates the expression of PPARγ. TGF-β1 inhibits PPARγ expression [7] in both fibroblasts [100] and hepatic stellate cells [121]. Conversely, PPARγ agonists directly disrupt the TGF-β1 signaling and synthesis [6, 122]. PPARγ ligands (15d-PGJ2 and troglitazone) prevent expression and synthesis of collagen in fibroblasts stimulated by TGF-β1 [93, 122–124]. Troglitazone, 15d-PGJ2 and CDDO prevent α-SMA expression [93, 124]. PPARγ agonists inhibit the TGF-β1-induced CTGF expression [125, 126]. In bleomycin-induced lung fibrosis, the absence of WNT signaling through LRP5 diminishes TGF-β1 and attenuates the fibrosis [127]. TGF-β also enhances WNT signaling through the inhibition of Dickkopf-1 (DKK1) [128] (Figure 2). Although DDK1 diminished TGF-β-induced fibrosis, the reduced expression of DKK1 enhances the stability and nuclear accumulation of β-catenin in both epithelial cells and fibroblasts which favored fibrosis.

PPARγ ligands disrupt both the Smad-dependent and Smad-independent TGF-β1 pathways. Inhibition of PPARγ expression favors the canonical Smad 2/3 signaling. The human PPARγ promoter possesses two Smad binding elements [121].

PPARγ agonists can abrogate TGF-β1-induced fibrosis independently of the Smad pathway (Figure 2) [93, 94, 122]. Thus, rosiglitazone does not diminish Smad2 phosphorylation. Moreover, in lung fibroblasts, PTEN inhibits myofibroblast transdifferentiation, and the expression of both collagen and α-SMA [129]. PTEN decreases the PI3'-OH kinase (PI3K)-AKT pathway [130]. PI3K generates phosphatidylinositol-3,4,5-triphosphate (PIP3) from PIP2. AKT is

activated by PIP3. PTEN is a PIP3-phosphatase and its activity is the opposite to that of PIK3. In mouse fibroblast, 15d-PGJ2 inhibits the TGF-β1 transcription through PTEN-mediated p70 ribosomal S6 kinase-1 inhibition [131]. PPARγ ligands repress TGF-β1-induced myofibroblast differentiation by targeting the PI3K/AKT pathway [115].

The canonical WNT signaling is negatively regulated by PPARγ ligands. Activation of the canonical WNT/β-catenin pathway appears to be a key mechanism in fibrosis [132, 133]. Importantly in adipocytes, TZDs activate DKK1 that is an inhibitor of the canonical WNT pathway (Figure 2), and block fibroblast differentiation [134]. GW11929, a non-TZD PPARγ agonist inhibits the transcription of β-catenin [135]. The inhibitory effects induced by the canonical WNT signaling on PPARγ have been shown to be the mechanism that results in the anti-adipogenic effect [136]. The WNT signaling activates osteoblastogenesis of mesenchymal precursors by inhibiting PPARγ and CCAAT/enhancer-binding protein α [137]. Thus, activation of the WNT/β-catenin signaling and inhibition of GSK-3β induce activation of fibroblast and fibrosis [79, 138]. Inhibition of PPARγ induced by WNT ligands can also operate through non-canonical pathways [136, 139]. The non-canonical WNT pathway via CaMKII-TAK1-TAB2-NLK represses PPARγ transactivation. WNT-5a, a non-canonical WNT ligand, activates nemo-like kinase (NLK), leading to the formation of a co-repressor complex that inactivates the PPARγ function [140].

4.2. Crosstalk between Smad/TGF-β1 and the canonical WNT/PPARγ pathways in fibrosis

In the PPARγ promoter, the SMAD3-SMAD4 complex binds both to a TGF-β inhibitory element (TIE) and to canonical SMAD-binding elements (SBEs) [98]. TIE and SBEs independently mediate a partial repression of the PPARγ transcription, within the same promoter. The presence of two functional SBEs within the PPARγ promoter suggests that TGF-β-activated SMADs can repress PPARγ directly at the transcriptional level [98]. TGF-β upregulates expression of TβR1 and phosphorylation of SMAD2/3, simultaneously with a decrease in PPARγ transcription. TGF-β mediates suppression of PPARγ gene transcription through a SMAD-E2F4-p107 complex [7].

The Smad pathway partly explains the anti-fibrotic effects of PPARγ ligands. PPARγ, by inhibiting the TGF-β1 signaling helps to control fibrosis. Thus, aberrant PPARγ downregulation participate to the development of fibrosis in skin, lung, pancreas, heart, and liver [100]. PPARγ agonists prevent the TGF-β1/Smad 3 signaling in the human hepatic stellate cell [141]. Ligand-activated PPARγ suppresses the Smad-dependent collagen production by targeting the p300 transcriptional coactivator [123]. Triterpenoid improves fibrosis [124]. In fibroblast culture, CDDO prevents fibrosis induced by TGF-β1 through the suppression of Smad transcription and the inhibition of the AKT pathway [124]. Troglitazone, ciglitazone, and 15d-PGJ2 result in an overexpression of the hepatocyte growth factor (HGF) which induces the TG-interacting factor (TGIF), a Smad transcriptional co-repressor, and suppress the TGF-β1-induced fibrosis [142, 143]. Differentiation of human circulating fibrocytes are mediated by TGF-β1 and PPARγ [144]. Thus, troglitazone blocks the TGF-β1-induced SAPK/JNK pathway which decreases the Smad2 signaling and impairs differentiation into myofibroblast. PPARγ ligands inhibit the TGF-β1-induced Erg1 signaling [145]. In mouse, adiponectin prevents fibrosis in liver [146, 147].

PPARγ-induced tensin homologue PTEN [131] induces anti-fibrotic effects in lung fibrosis and SSc [129, 148]. PTEN prevents the collagen production and myofibroblast differentiation [149]. PPARγ suppresses the TGF-β1 induced EMT in alveolar epithelial cells and in tumor metastasis without abrogation of the Smad pathway [150, 151]. In PPARγ-deficient mice, Smad3 phosphorylation is increased as is the expression of both α-SMA and type 1 collagen [152]. WNT3a promotes myofibroblast differentiation by upregulating TGF-β1. This occurs through Smad2 in a β-catenin-dependent manner [153]. Interestingly, it has recently been demonstrated that aerobic glycolysis is induced in response to TGF-β1 [154]. TGF-β-induced downregulation of PPARγ is mediated by a SMAD-dependent pathway, i.e., SMAD3/4 co-transfection diminishes the PPARγ promoter activity [99, 100, 106].

4.3. Concerted actions of TGF-β, WNT, Smads and YAP/TAZ pathways in fibrosis

There is a complex crosstalk in the differentiation of myofibroblasts. During skin wound healing in mice, both YAP and TAZ are increased during injury and translocated to the nucleus. TGF-β1 has been found to be increased in skin wound healing, suggesting a link between activation of YAP and TAZ and the production of TGF-β1 [155]. YAP and TAZ also modulate the expression of certain components of the TGF-β1 pathway such as Smad2. A crosstalk has been established between YAP/TAZ and TGF-β. In epithelial cells, TAZ has been found to interact with Smad2/4 and Smad3/4 [156]. TAZ binds Smad2/3 and increases the nuclear transfer of Smad2/3 and the transcription of the *PAI1* and *SMAD7* target genes. In addition, in mesothelioma cells, YAP has been shown to bind Smad3 [157]. In the cytoplasm, TAZ appears to be linked to WNT pathway through the interaction of TAZ and β-catenin [158]. In WNT-on state signaling, release of β-catenin from the destruction complex impairs TAZ degradation and leads to accumulation of β-catenin and TAZ. This function of TAZ is independent of its role as a mediator of the Hippo signaling. In WNT-off state, cytoplasmic YAP/TAZ specifically binds AXIN [159]. WNT3a activation induces the dissociation of YAP/TAZ from the destruction complex. YAP/TAZ translocates to the nucleus, and activates the transcription of TEAD target genes.

5. PPARγ and Fibrosis: Synthesis [6, 7, 107]

5.1. General

Myofibroblasts play a key-role in fibrosis [160]. PPARγ has been shown to be a negative regulator of profibrotic signal-induced collagen synthesis and to blunt fibrosis in various pathological circumstances [6, 7, 93, 98, 100, 103, 122–124, 161–163]. PPARγ ligands diminish fibrotic effects. Thus, in cultured lung and skin fibroblasts, in hepatic stellate cells and in mesangial cells, PPARγ ligands (15d-PGJ2 and rosiglitazone) diminish the fibroblast-myofibroblast differentiation, the synthesis of collagen, fibronectin and TGF-β1 [93, 94, 164–166]. PPARγ ligands abrogate the epithelial-mesenchymal transition of alveoar epithelial cells induced by TGF-β1 [150]. In numerous animal models of fibrosis, PPARγ ligands decrease fibrosis in several organs such as heart [167, 168], lung [97, 169], liver [170, 171] and kidney [172, 173]. The PPARγ

ligands 15d-PGJ2 and rosiglitazone diminish lung fibrosis induced by bleomycin [174]. In asthma, PPARγ agonists decrease lung inflammation [175].

Regulation of the connective tissue homeostasis is a relatively newly discovered function of PPARγ, particularly in tissue repair and fibrosis. Generally, an inverse relationship is observed between PPARγ expression and fibrosis. In human fibrotic diseases, PPARγ expression is diminished such as in lung [176], liver [164], kidney [165] and scarring alopecia [177]. In several human fibrotic diseases, reduced PPARγ expression and/or activity precede fibrosis suggesting a causal role for fibrosis [6, 107]. In mice suffering from bleomycin-induced systemic sclerosis (SSc), expression of PPARγ is decreased in cutaneous tissue and the TZD rosiglitazone abrogates bleomycin-induced scleroderma and blocks profibrotic responses through PPARγ [122]. PPARγ deficient fibroblasts present an increase in TGF-β1, type 1 collagen, and α-SMA [152, 178].

5.2. Lung fibrosis

Lung fibrosis is oberved in numerous respiratory diseases, such as SSc, idiopathic interstitial pneumonia, sarcoidosis, asthma, and chronic obstructive pulmonary disease. There is an excessive production of collagen and the presence of fibroblasts that differentiate into myofibroblasts [179, 180]. Expression of PPARγ is reduced in lung fibroblasts of SSc patients [100, 181] and is deficient in alveolar macrophages of patients with pulmonary sarcoidosis [176]. PPARγ ligands repress the fibroblast-myofibroblast transdifferentiation induced by TGF-β1 [94, 97, 182, 183]. Furthermore, they reduce the expression of fibronectin [182] and type 1 collagen induced by TGF-β1 [94, 97]. PPARγ expression is decreased in lung fibroblasts stimulated by TGF-β1 [100, 184]. Overexpression of PPARγ suppresses the inhibition of its own transcriptional activity induced by TGF-β1 [162]. TZDs can inhibit lung fibrosis induced by bleomycin [97, 169, 174, 185].

5.3. Idiopathic pulmonary fibrosis (IPF) [98]

IPF is a progressive, fatal disease characterized by patchy areas of lung fibrosis [186]. TGF-β interferes in the pathophysiology of IPF and PPARγ is down-regulated in IPF patients. In isolated human and mouse lung fibroblasts, PPARγ knockdown or knockout expression induces a profibrotic phenotype. Conversely treating human fibroblasts with nitrated fatty acids (NFAs) which are PPARγ endogenous agonists [187] up-regulates PPARγ and blocks the TGF-β signaling. Moreover, NFAs convert TGF-β to inactive monomers, stimulate the collagen degradation by alveolar macrophages, and induce the dedifferentiation of myofibroblasts. IPF is reversed by NFAs by dedifferentiation of myofibroblasts and induction of collagen uptake by alveolar macrophages [98].

5.4. Chronic obstructive pulmonary disease (COPD) [163]

In lung tissue and epithelial cells of patients suffering from COPD, a progressive inflammatory disease, PPARγ is down-regulated. Cigarette smoking represents the main risk factor for COPD. Exposing airway epithelial cells to cigarette smoke extract (CSE) down-regulates PPARγ and

activates NF-κB. Moreover, CSE inhibits the glucocorticoid receptor (GR-α). Treating epithelial cells with PPARγ agonists suppresses CSE-induced increase of inflammatory cytokines, and reverses activation of NF-κB by promoting direct inhibitory binding of PPARγ to NF-κB. In pulmonary epithelial cells, down-regulation of PPARγ by cigarette smoke promotes inflammatory processes and diminishes glucocorticoid responsiveness, which favors the COPD pathogenesis [163].

5.5. Skin fibrosis

PPARγ is involved in the complex mechanism of wound repair. PPARγ is expressed at low levels in normal dermal fibroblasts [93, 122]. PPARγ agonists inhibit TGF-β1 and matrix production in human dermal fibroblasts [95]. PPARγ is upregulated in the terminal phase of wound repair [188] and PPARγ ligands suppress fibroblast migration and wound closure induced by TGF-β1. In the bleomycin-induced skin fibrosis model, PPARγ agonists diminish skin fibrosis [122, 124]. Upregulation of the fibrogenic genes COLIA1 and COLIA2 is reduced by PPARγ agonists which also reduce the α-SMA fibroblast number [122]. PPARγ supresses fibrosis particularly by antagonizing the TGF-β1 pathway, and loss of PPAR γ promotes fibrosis in skin [152, 189]. PPARγ agonists help minimize the abnormal synthesis of collagen in fibrotic tissues.

5.6. Systemic sclerosis (SSc)

SSc induces multiple tissue fibrosis in skin, lung, esophagus, and pulmonary arteries that lead to pulmonary hypertension [190]. PPARγ expression is reduced in SSc lung [100, 181]. In SSc, fibroblasts synthesize excessive collagen and profibrotic molecules such as integrins, receptors for TGF-β1 and αSMA [191, 192]. PPARγ expression is diminished in SSc skin fibroblast [100, 193, 194]. TGF-β1, CTGF, and certain interleukins help inhibit PPARγ expression in fibrotic processes [28]. In SSc, the downregulation of PPARγ expression is inversely related to the upregulation of the TGF-β1 pathway and the plasminogen activator inhibitor-1 (PAI-1) which is a TGF-β1 regulated gene [100]. In SSc fibroblasts, rosiglitazone diminishes the expression of both α-SMA and type1 collagen and their ability to contract the collagen matrix [194]. Non-TZD agonists such as CDDO and synthetic cannabinoid ajulemic diminish collagen synthesis in SSc fibroblasts [124, 193]. Adiponectin, a PPARγ transcriptional target, induces potent anti-fibrotic effects [195, 196]. In SSc patients, serum level of adiponectin is diminished and is inversely correlated with skin fibrosis [161, 197, 198]. In SSc fibroblasts, adiponectin abolishes the expression of α-SMA and type1 collagen even after TGF-β1 stimulation [195].

5.7. Pulmonary arterial hypertension (PAH)

PPARγ is a key regulator of lung vascular homeostasis and its reduced expression and function induce PAH [199, 200]. PAH can occur as a devastating complication of SSc, and may also occur in severe emphysema, chronic cigarette smoking, and chronic obstructive pulmonary disease (COPD). In transgenic mice, pulmonary vessel PPARγ knockout induces PAH and right ventricular hypertrophy [201, 202].

6. Conclusions and the Directions of Future Research

Many pathways directly or indirectly regulate the differentiation of fibroblasts into myofibroblasts. Moreover, myofibroblasts play an essential role in cellular fibrosis of numerous organs such as kidney, heart, lung, and liver as well as in wound healing. The canonical WNT/β-catenin signaling and PPARγ act in an opposing manner, by respectively promoting and diminishing fibrosis. TGF-β1 pathway controls the differentiation of fibroblasts into myofibroblasts and acts as a conductor by upregulating the canonical WNT and downregulating PPARγ. Significant progress has been made in understanding the cellular and molecular mechanisms responsible for tissue fibrosis. However, as far as the human clinical research is concerned, no therapeutics have so far been able to regress or even to stop fibrosis. Numerous assays have used antagonist antibodies or small molecules acting on the TGF-β, canonical WNT, Smads and YAP/TAZ cascades. While some therapeutic efficacy has been observed in animal models [203], most human trials have either been non-conclusive or caused serious adverse effects. However, a few human trials have been encouraging, particularly in scleroderma [204]. Numerous studies have addressed this subject [205–212]. The generally inadequate results with regard to the effective control of tissue fibrosis may be partly due to the extraordinary complex interplay between the different signaling pathways such as TGF-β, canonical WNT/β-catenin, Smads, and Hippo/YAP/TAZ, which can act in a partially opposing manner. PKC-δ inhibitors and angiotensin inhibitors also present anti-profibrotic effects and may become effective therapies for fibrotic diseases in the future [116]. Finally, PPAR gamma agonists are likely to interrupt or prevent the profibrotic effects of TGF-β, myofibroblast differentiation, and excess collagen production.

Author Contributions

YL, OS, VC, and AV have contributed equally to this review.

Competing Interests

The authors declare no competing interests.

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