PPARγ is a Gatekeeper for Extracellular Matrix and Vascular Cell Homeostasis: Beneficial Role in Pulmonary Hypertension and Renal / Cardiac / Pulmonary Fibrosis

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ABSTRACT:

Purpose of review

Pulmonary arterial hypertension (PAH) is characterized by pulmonary arterial endothelial cell (PAEC) dysfunction and apoptosis, pulmonary arterial smooth muscle cell (PASMC) proliferation, inflammation, vasoconstriction, and metabolic disturbances that include disrupted bone morphogenetic protein receptor (BMPR2)-peroxisome proliferator-activated receptor gamma (PPARγ) axis and DNA damage. Activation of PPARγ improves many of these mechanisms, although erroneous reports on potential adverse effects of thiazolidinedione(TZD)-class PPARγ agonists reduced their clinical use in the last decade. Here, we review recent findings in heart, lung and kidney research related to the pathobiology of vascular remodeling and tissue fibrosis, as well as potential therapeutic effects of the PPARγ agonist pioglitazone.

Recent Findings

Independent of its metabolic effects (improved insulin sensitivity and fatty acid handling), PPARγ activation rescues BMPR2 dysfunction, inhibits TGFβ/Smad3/CTGF and TGFβ/pSTAT3/pFoxO1 pathways and induces the PPARγ/apoE axis, inhibiting vascular remodeling. PPARγ activation dampens mtDNA damage via PPARγ/UBR5/ATM pathway, improves function of endothelial progenitor cells (EPC) and decrease renal fibrosis by repressing TGFβ/pSTAT3 and TGFβ/EGR1.

Summary

Pharmacological PPARγ activation improves many hallmarks of PAH, including dysfunction of BMPR2-PPARγ axis, PAEC, PASMC, EPC, mitochondria/metabolism, and inflammation. Recent randomized controlled trials, including IRIS, emphasize the beneficial effects of PPARγ agonists in PAH patients, leading to recent revival for clinical use.

Introduction

Progressive pulmonary arterial hypertension (PAH)[1] resulting from pulmonary vascular disease (PVD) has a 25-66% mortality within five years of diagnosis[2-6]. Based on very promising preclinical studies[7, 8], peroxisome proliferator-activated receptor γ (PPARγ) agonists have emerged since 2007[9] as promising novel, efficient agents for the treatment of PAH. Prostacyclin analogues[10], the most effective PAH drug class used clinically so far, and sildenafil[11], exert their anti-proliferative, beneficial effects in PAH via PPARγ activation. A decade ago, reports on potential adverse effects, and misinterpretations of early diabetes studies led to concerns whether PPARγ agonists of the thiazolidinedione(TZD)-class could be safely used in PAH patients. However, based on recent clinical trials, PPARγ agonists have undergone a recent revival for clinical use[8, 12].This article discusses recent preclinical and translational findings (**Tables 1 and 2**) on the pathobiology of pulmonary artery endothelial cells (PAEC) and smooth muscle cells (PASMC) in PAH and the related therapeutic mechanisms of the TZD-class PPARγ agonist pioglitazone.

PPARγ and its beneficial effects in Pulmonary Arterial Hypertension

Peroxisome proliferator-activated receptors (PPARs; α, β/δ, γ) are ligand-activated transcription factors of the nuclear receptor superfamily. The ubiquitously expressed PPARγ plays a pivotal role in adipogenesis, glucose metabolism, and in placental and cardiac development. The ligand activated PPARγ forms a heterodimer with the retinoid X receptor (RXR) to regulate target genes implicated in the pathogenesis of PAH, including adiponectin (APN), cytokines like IL-6 or CCL2/MCP-1, endothelin-1 (ET-1)[7, 13]. The anti-proliferative (SMC), anti-inflammatory, pro-angiogenic and pro-apoptotic effects of PPARγ agonists all attenuate PAH (**Fig. 1**). Further protective roles of PPARγ are linked to its control on metabolic homeostasis of endothelial cells and DNA stability[14**, 15]. Therefore, PPARγ

agonists have therapeutic potential in PAH and other cardiopulmonary diseases[7] that is independent on the presence of insulin resistance

Crosstalk between PPARγ and the members of TGFβ superfamily plays a pivotal role in pulmonary vascular homeostasis

Members of the transforming growth factor beta (TGFβ) receptor superfamily (eg. TGFBR1, or bone morphogenetic protein receptor 2, BMPR2) and their ligands play a pivotal role vascular homeostasis, so that any major imbalance can result in vascular remodeling and development of PAH. BMP2, the ligand of BMPR2, inhibits SMC growth. On the other hand, BMP2 promotes endothelial cell (EC) survival that in the early stages of PAH, might prevent endothelial injury and dysfunction [8, 13]. Recently, in a mouse Sugen-hypoxia (SuHx) PAH model, pulmonary endothelial cells were shown to undergo *endothelial-to-mesenchymal transition (EndMT)* to form highly proliferative SM-like cells with low BMPR2 expression, which contribute to vascular remodeling[16], while BMPR2 mutant rats develop spontaneous PAH[17*]. Loss-of-function mutations in the BMPR2 gene are frequently present in both hereditary PAH (HPAH, 70-75%,) and idiopathic PAH (IPAH, 15-20%) patients. The anti-proliferative BMP2/BMPR2-PPARγ-ApoE axis, firstly discovered in human PASMC[18], suggests that dysfunctional BMPR2 leads to impairment of endogenous PPARγ activity[18]. Endothelial cell-specific loss of BMPR2 or PPARγ decreased endothelial apelin expression, thus shortening PAEC survival and inducing PASMC proliferation[19]. Additionally, deletion of low-density lipoprotein receptor-related protein 1 (LRP1) in mouse VSMC leads to the induction of canonical TGFβ-Smad3-CTGF pathway with suppression of PPARγ and PAH development, whereas plexiform lesions from PAH patients depict decreased LRP1 expression [20*]. Thus, in patients with or without BMPR2 mutations, PPARγ activation might reverse the PAH phenotype. This theory is further supported by reports on reduced pulmonary BMPR2 expression observed even in the absence of BMPR2 mutations in IPAH or HPAH, and in connective tissue or congenital heart disease associated PAH[13]. Notably,

PAH patients depict reduced pulmonary expression of BMP2[21], PPARγ[22], and apolipoprotein-E (ApoE) mRNA[21]. In PAH-HPASMC, the S100A4-mediated activation of RAGE resulted in STAT3 phosphorylation and reduced the expression of both BMPR2 and PPARγ[23], while RAGE-inhibition restored the BMPR2/PPARγ axis[23].

We recently demonstrated PPARγ as link and key regulator of the functional antagonism between BMP2 and TGFβ1 in human and murine VSMC[24, 25]. We showed that TGFβ1-mediated STAT3 phosphorylation induces nuclear exit of phosphorylated FoxO1, and thus disinhibition of pro-proliferative genes through this novel *non-canonical TGFβ1-pSTAT3-pFoxO1 pathway*, in addition to canonical TGFβ-pSMad3-CTGF signaling[24]. In human PASMC, the PPARγ ligand pioglitazone inhibited both the novel non-canonical TGFβ1-pSTAT3-pFoxO1 pathway and the canonical TGFβ1-pSmad3/4 axis[24]. Importantly, pioglitazone reversed pulmonary vascular remodeling and PAH observed in mice overexpressing TGFβ[24]. Moreover, PPARγ inhibits hypoxia-induced HPASMC proliferation and enhances apoptosis of HPASMC by suppressing miR-21 and stimulating PDCD4[26].

Interplay of PPARγ and microRNAs in pulmonary vascular homeostasis

Several microRNA (miRNA) molecules (expressed in pulmonary vascular and cardiac cells) appear to play a major role in the pathogenesis of PAH [25, 27, 28], and some of them regulate PPARγ, and vice versa: The miR-130/-301 family promotes pulmonary hypertension via regulating miRNA networks at systems-level [29-31], revealing PPARγ as a direct target of the miR-130/-301 family. MiR-130a/-301b expression is induced in pulmonary arteries from IPAH patients compared to controls[24]. Additionally, TGFβ1 stimulation suppresses the BMP2/BMPR2-PPARγ axis through decreasing PPARγ-mRNA expression via miR-130a/-301b. Intriguingly, in HPASMC, BMP2 induces miR-331-5p that represses the platelet isoform of phosphofructokinase (PFKP), a rate-limiting enzyme of glycolysis[24]. We demonstrated PFKP to be much higher expressed in pulmonary arteries of IPAH patients vs. controls, and to induce HPASMC proliferation[24]. In contrast, activation of the

BMP2/BMPR2-PPARγ axis upregulates miR-148a (a suspected repressor of cell proliferation) and miR-331-5p, thereby inhibiting vascular SMC proliferation and glucose metabolism[24, 25]. Hence, activation of PPARγ can re-establish TGFβ1/BMP2 balance, by regulating canonical and non-canonical TGFβ1 pathways, modulating key miRNAs involved in cell proliferation, and glucose/lipid metabolism, ultimately sustaining vascular homeostasis (**Fig. 1**).

Inhibitory role of PPARγ on inflammation that drives PAH in normoxia and hypoxia

The observed pathological changes in PAH include alterations in inflammatory cytokines such as IL-1β, IL-6, CCL2(MCP-1)and activation of nuclear factor of activated T cells[32]. Transgenic mice overexpressing IL-6 develop pulmonary vasculopathy and phenotype resembling human PAH[13]. Perivascular and vascular wall lymphocyte/macrophage infiltration in PAH result in cytokine/chemokine release and extracellular matrix degradation[32], that enhance further recruitment of circulating immune cells, including neutrophils[32]. Activated neutrophils release neutrophil elastase (NE), that worsens vascular injury[33]. However, NE is also produced by other cells such as SMC in PAH[34].

Preclinical pharmacological activation of PPARγ suppressed inflammation in PAH models[35*, 36**]: pioglitazone dampened the perivascular accumulation of $CD3^+/CD45^-$ T-lymphocytes and vascular wall remodeling in SuHx rat lungs[36**], while FGF-21-mediated PPARγ upregulation attenuated IL-1 and IL-6 expression in hypoxia-induced pulmonary hypertensive rats[35*].

Hypoxia is a strong stimulus of inflammation in the heart[37] and lung[38]. Hypoxia leads to STAT3 activation and CCL2/MCP-1 induction in both mouse lungs and in human primary PAECs[38], and suppression of PPARγ in PASMC[39*] and the subsequent macrophage activation enhances PASMC proliferation[38]. Hypoxia suppresses pulmonary vascular PPARγ, as a key step that drives PASMC proliferation and PAH[39*]. Repression of PPARγ in human control PASMC cell culture resulted in mitochondrial fission, hyperpolarization,

increased oxidative stress, and a shift toward glycolysis and stimulation of PASMC proliferation similar to clinical PAH phenotype[39*].

PPARγ activation suppresses pro-inflammatory signals, such as STAT3[24] in PAH-relevant cells. Infiltrating monocytes polarize to a pro-inflammatory „M1" or anti-inflammatory „M2" phenotype, and both M1 and M2 participate in the pathomechanisms of pulmonary fibrosis and PH in animal models[40], whereas pioglitazone or metformin represented efficient treatment for PH[8, 41, 42] or pulmonary fibrosis[43, 44*]. In human PASMC, a non-canonical TGF-β pathway and/or loss of PPARγ activity, led to pro-inflammatory STAT3 phosphorylation and nuclear exit of the repressor FoxO1 (TGFβ1-pSTAT3-pFoxO1 axis)[24], however, it has unknown whether such an pro-inflammatory axis exist in macrophages in PAH and other cardiovascular diseases.

In lungs of rats with monocrotalin(MCT)-induced PAH, pioglitazone dampened pulmonary osteopontin mRNA expression and thus reduced macrophage infiltration, yet the macrophage phenotype (M1 vs. M2) was not characterized in this study[45]. Mesenchymal stem cell(MSC)-derived extracellular vesicles changed the macrophage phenotype from M1 to M2 and attenuated pulmonary vascular remodeling and fibrosis in a mouse model of bronchopulmonal dysplasia (BPD)[46]. However, most of the perivascular macrophages in lungs from PAH patients were recently identified as M2-type that were reported to have a strong proliferative effect on PASMC *in vitro*[47]. Thus, M2 macrophage infiltration is likely to play a pivotal role in vascular remodeling in PAH.

Beneficial role of PPARγ on endothelial cell homeostasis, DNA damage and repair

Pulmonary endothelium integrity is essential for a normal vascular homeostasis and lung function. Endothelial cell (EC) injury and subsequent apoptosis are causal for many vascular disorders including pulmonary hypertension[48]. Pulmonary artery endothelial cells (PAEC) depend on cellular respiration as energy source, therefore PAEC are sensitive to small changes in oxygen concentrations[13], either due to alveolar hypoxia (group 3 PH or high

altitude PH), hyperoxia in premature newborn infants, or congenital heart disease with systemic-to pulmonary shunts. However, in PAEC of PAH patients with BMPR2 mutation, a metabolic shift to increased glycolysis occurs even at normal oxygen concentrations[15]. Consequences are enhanced reactive oxygen species (ROS) production and dysfunctional handling of oxidative stress by decreased expression of superoxide dismutases (SOD)[49]. PPARγ was recently identified as key regulator that impedes endothelial cell dysfunction and oxidative stress during senescence[50**].

Cellular oxidative stress by ROS can damage genomic DNA[51], and many PAH patients have somatic DNA damage involving BMPR2 and Smad8 in PAEC and peripheral blood cells [51, 52]. ***Mitochondrial proteins*** can be either mitochondrial or nuclear encoded (NEMPs). Mitochondrial DNA (mtDNA) is more sensitive to oxidative damage than nuclear DNA as mitochondria lack several protective mechanisms[51], thereby contributing to PAH pathogenesis[15]. Exposure of PAEC exogenous oxidative stress caused mitochondrial dysfunction and subsequent apoptosis[51]. BMPR2 deletion in EC of mice led to upregulation of the p53-PPARγ co-activator 1α (PGC1α) axis and mitochondrial transcription factor A (TFAM, essential for mitochondrial DNA integrity), that induced mitochondrial fission and glycolysis. Under hypoxia, loss of BMPR2 resulted in significant downregulation of p53-PGC1α, while PGC1α depletion in PAECs by siRNA reduced TFAM and induced PAEC apoptosis[15]. In the same study, PAEC from PAH patients with BMPR2 mutation exhibited decreased p53, PGC1α and TFAM expression under hypoxia, confirming that reduced BMPR2-p53-PPARγ axis activity results in mtDNA damage in PAH[15].

Additionally, PPARγ promotes DNA repair in response to genotoxic stimuli via the E3 ubiquitin ligase UBR5 promoting ATM phosphorylation in EC[14**]. In addition, a disrupted non-canonical PPARγ-UBR5 pathway was found in PAEC obtained from PAH patients[14**]. Recently, Krüppel-like factor-2 (KLF2)-dependent repression of PPARγ was found to result in ROS accumulation in pulmonary lymphatic endothelial cells (LEC), either exposed to shear stress *in vitro*, or *in vivo* by inducing experimentally increased pulmonary blood flow and

hypertension in lambs[53]. These recent findings suggest that pharmacological PPARγ activation could prevent or reduce DNA damage in endothelial cells. Importantly, (supra-)physiological pioglitazone doses did not cause any toxicity in cultured human PA endothelial cells (controls, IPAH) or neonatal rat cardiomyocytes[36**]. Taken together, activation of PPARγ likely reduce endothelial cell DNA damage in PAH, and that the PPARγ agonist pioglitazone does not appear to be toxic either *in vivo* or *in vitro*.

Beneficial role of PPARγ on endothelial progenitor cells

Circulating bone marrow-derived endothelial progenitor cells (EPC) largely determine angiogenesis and vascular repair. Dysfunctional EPC with increased proliferation and migration capacity were shown to play a significant role in the pathogenesis of PAH with reduced capacity to form vascular structures[54]. Several lines of evidence suggest that EPC dysfunction might be related (at least in part) to PPARγ dysfunction: In mice with endothelial cell-specific PPARγ deletion ($Tie2CrePPAR\gamma^{flox/flox}$mice), markedly reduced EPC count was found in the blood, but not in the bone marrow[55]. In the same study, downregulation of PPARγ in human primary PAECs led to impaired cell migration[55]. Along these lines, pharmacological activation of PPARγ with pioglitazone reduced EPC apoptosis in mice[56] and rats[57]. Administration of BMPR2-augmented, functional EPC enhanced pulmonary BMPR2/Smad1/5/8 signaling, thereby reversing pulmonary vascular remodeling[58]. Based on the aforementioned findings, BMPR2- and/or PPARγ-augmented EPC likely have a remarkable therapeutic potential in PAH[58].

The role of PPARγ in renal, pulmonary and cardiac fibrosis

Tissue and organ fibrosis represents a major health care burden worldwide that is associated with high morbidity and mortality, so that there is a high demand for new therapies fighting fibroproliferative disorders. PPARγ agonists are among these emerging therapies: Improvement of albuminuria and nephropathy were observed in T2DM patients

treated with TZD-class PPARγ agonists[59]. Experimental studies show further evidence for antifibrotic effect of PPARγ agonists, independent of glycemic control (**Fig. 1**). For instance, PPARγ agonists attenuated renal TGFβ expression thus preventing interstitial fibrosis and inflammation in fibrotic mouse kidneys subjected to unilateral ureter obstruction (UUO)[60]. Elevated angiotensin-II levels also decrease PPARγ expression in kidney fibrosis, both *in vivo* and *in vitro*, while the angiotensin-II receptor blocker losartan exerts its renoprotective effects partly via the upregulation of PPARγ[61*]. We have recently demonstrated that long-term pioglitazone treatment repressed the activation of transcription factors STAT3 and EGR1 in the kidneys of TGFβ transgenic mice *in vivo*, thus preventing TGFβ induced renal fibrosis[62*]. Interestingly, the widely used antidiabetic drug metformin has been reported to reduce bleomycin-induced lung fibrosis[43] and αSMA expression[44*], partly via activation of PPARγ signaling[63].

Several experimental models prove the beneficial effect of pioglitazone to be independent of insulin sensitivity/insulin resistance, i.e. the SuHx rat with severe PAH and RV failure[36], the mouse with targeted deletion of PPARγ in cardiomyocytes and biventricular dysfunction[36]. In addition, we have shown that oral pioglitazone treatment of TGFβ transgenic mice significantly ameliorated the TGFβ induced cardiac hypertrophy[24]. None of these models present any insulin resistance or dyslipidemia. In SU5416/hypoxia rat model of PAH and RV overload, pioglitazone prevented cardiac interstitial collagen accumulation through induction of fatty acid oxidation and maintenance of mitochondrial function by normalizing altered regulatory functions of miR-197 and miR-146b[36**]. In a mouse model of streptozotocin induced diabetes, PPARγ activation decreased cardiac fibrosis and EMT via repressing ERK1/2[64*]. Furthermore, pioglitazone reduced EMT and LV fibrosis in aortic banding mouse model of cardiac pressure overload[65].

Revival of Pioglitazone – a PPARγ agonist of the TZD Class

Pioglitazone, a PPARγ agonist of the thiazolidinedione (TZD)-class, has better clinical side effect profile than rosiglitazone[12, 66, 67], and does not seem to induce heart failure in patients with prediabetes/insulin resistance: In the recent randomized controlled IRIS trial (n=3876 non-diabetic patients status post TIA/ischemic stroke, followed for 4.8 years)[66] patients had similar incidence for heart failure, irrespective of pioglitazone therapy. Incidence of bladder cancer (p=0.37) or total cancer incidence (p=0.29) was similar in pioglitazone vs placebo treated patients. Further post-analyses failed to find any evidence showing pioglitazone to be associated with an elevated rate of serious events like bladder cancer, heart failure, or other co-morbidities[68*]. Additional RCT data on the efficacy of pioglitazone in preventing cardiovascular events, potential adverse effects/toxicity, and its efficacy in preclinical PAH cell/animal models, have been reviewed in detail elsewhere[8]. Importantly, the TGF-β overexpressing mouse[24] is the 5th PAH animal model in which TZD-class PPARγ agonists improve or reverse PAH, bringing the preclinical rigor score to 9 (dicloroacetate: score 11; metformin: score 8), i.e. pioglitazone achieved the 2nd highest preclinical rigor score of 22 medications that were very critically reviewed by Prins and colleagues[69]. The rigor score evaluates the rigor of the preclinical data that support a certain medication could potentially be used in PAH[69]. Given the convincing recent clinical trial data on the lack of significant toxicity in high risk populations, we herewith propose the timely conduction of clinical studies in order to achieve “repurposing”[70] of pioglitazone for the treatment of clinical PAH[8].

Conclusion

Recent preclinical studies on thiazolidinedione-class PPARγ agonists unraveled several mechanisms that inhibit or reverse vascular remodeling in PAH, either dependent or independent on regulation of glucose or lipid metabolism. For instance, in human PASMC, PPARγ activation rescues BMPR2 dysfunction, inhibits canonical TGFβ/Smad3 and non-canonical TGFβ/pSTAT3/pFoxO1 pathways, induces a PPARγ/apoE axis. PPARγ activation

also reduces mitochondrial damage in PAEC via PPARγ/UBR5/ATM pathway and improves endothelial progenitor cell function. Additionally, pioglitazone ameliorate experimental renal and cardiac fibrosis by repressing TGFβ/pSTAT3 and TGFβ/EGR1 pathways, and ultimately epithelial-mesenchymal transition (EMT). Very recent randomized controlled trials show beneficial effects of pioglitazone treatment without significant toxicity in high risk patients with cardiovascular disease. Hence, we suggest the "repurposing" of pioglitazone for the treatment of PAH represent a promising strategy to combat this fatal disease.

Key points

- In preclinical models of PAH, PPARγ activation inhibits and reverses vascular remodeling, by the inhibition of TGFβ/Smad3 and TGFβ/pSTAT3/pFoxO1 pathways in SMC and reduction of endothelial cell mitochondrial damage.
- The thiazolidinedione-class PPARγ agonist pioglitazone improves renal and cardiac fibrosis by repressing pro-fibrotic TGFβ signaling pathways and EMT.
- The recent randomized controlled IRIS trial did not show any significant toxicity of pioglitazone treatment in high risk patients, and thus, pioglitazone should be considered for "repurposing" as PAH therapy.

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Conflicts of interest

G.H. holds a patent application (USPTO no. 1289344) and an investigational new drug application (IND no. 105,428) related to the use of PPARγ agonistic agents for the treatment of pulmonary hypertension. L.C., E.L, G.K and M.M. have reported no relevant conflicts of interest or relationships with industry.

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Figure titles and legends

Figure 1. Regulatory pathways that are controlled by PPARγ and crucial for pulmonary vascular remodeling and reverse remodeling in pulmonary arterial hypertension and in cardiac, renal, hepatic or pulmonary fibrosis.

The hallmarks of PAH include endothelial dysfunction, mitochondrial dysfunction and mtDNA damage, smooth muscle cell proliferation and resistance to apoptosis, pericyte migration, perivascular inflammation, and vasoconstriction. Endothelial progenitor cells, post-transcriptional miRNA pathways and disturbed glucose and lipid metabolism also play important roles in the pathogenesis and therapy of PAH. Moreover, PPARγ plays contributes to the pathophysiology of pulmonary, cardiac, hepatic and renal fibrosis affecting both metabolic and profibrotic intracellular pathways.

Abbreviations: BMPR2, bone morphogenetic receptor 2; TGFβ, transforming growth factor beta; CTGF, connective tissue growth facor; PPARγ, peroxisome proliferator-activated receptor gamma; APN, adiponectin; apoE, apoliprotein E; STAT3, signal transducer and activator of transcription 3; PDGFRβ, platelet-derived growth factor receptor beta; PI3K, phosphoinositide 3-kinase; HDL, high-density lipoprotein(s); ET-1, endothelin 1; FAO, fatty acid oxidation; NFkB, nuclear factor kappa-light-chain-enhancer of activated B cells; ; IL-1, interleukin 1; IL-6, interleukin 6; MCP-1, monocyte chemoacttractant protein 1; NADPH, dihydronicotinamide-adenine dinucleotide phosphate; ROS, reactive oxygen species; SMC, smooth muscle cell(s); PAEC, pulmonary arterial endothelial cell(s); miR (also abbreviated as miRNA), microRNA; LV, left ventricle; RV, right ventricle; EPC, endothelial progenitor cell(s); T2DM, type 2 diabetes mellitus; EGR1, early growth response factor-1; AP1, activator protein complex-1.

Table legends

Table 1. Recent translational and preclinical findings on the therapeutic mechanisms of pioglitazone on PASMC in PAH. Abbreviations: connective tissue growth factor (CTGF); monocrotaline (MCT); Sugen Hypoxia (SuHx); pulmonary artery (PA); pulmonary arterial hypertension (PAH); pulmonary artery smooth muscle cells (PASMC); transforming growth factor-β (TGFβ).

Table 2. Recent translational and preclinical findings on the therapeutic mechanisms of PPARγ on endothelial cells in PAH. Abbreviations: bone morphogenetic protein 2 (BMP2); cyclooxygenase (COX); endothelial cells (EC); endothelial progenitor cells (EPC); lymphatic endothelial cells (LEC); nicotinamide adenine dinucleotide phosphate ($NADP^+$); pulmonary artery endothelial cells (PAEC);pulmonary arterial hypertension (PAH); pulmonary microvascular endothelial cells (PMVEC); rho-associated, coiled-coil-containing protein kinase (ROCK); reactive oxygen species (ROS); ubiquitin protein ligase E3 component N-recognin 5 (UBR5).