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Review

Mechanism of Action of the Plateau-Adapted Gene PPARA in COPD

Honge Li[1], Wenhui Pei[1], Yunchao Wang[2], Yuhuan Zhang[1], Zhen Yang[1], Xinhua Wang[1,*]

[1]Institute of Public Health, Gansu University of Chinese Medicine, 730000 Lanzhou, Gansu, China
[2]Institute of Basic Medicine, Gansu University of Chinese Medicine, 730000 Lanzhou, Gansu, China
*Correspondence: wxh@gszy.edu.cn (Xinhua Wang)

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Abstract

Chronic obstructive pulmonary disease (COPD) is a complex respiratory disorder influenced by various factors and involving multiple genes. Respiratory dysfunction in COPD patients leads to hypoxia, resulting in limited oxygen uptake. Peroxisome proliferator-activated receptor alpha (*PPARA*) is a plateau-adapted gene that regulates respiratory function in populations adapted to high-altitude areas through multiple pathways. Interestingly, *PPARA* expression is higher in long-term inhabiting Tibetan populations that have adapted to the plateau environment. However, in patients with COPD, the expression of *PPARA* is downregulated, leading to dysregulation of the hypoxia-inducible factor pathway. Moreover, abnormal PPARA expression in lung epithelial cells triggers inflammatory responses, oxidative stress, and disrupted lipid metabolism, thereby exacerbating disease progression. Thus, this paper explored the mechanism underlying the role of plateau-adapted *PPARA* in COPD, providing essential theoretical insights into the treatment and prevention of COPD in high-altitude regions.

Keywords: *PPARA*; chronic obstructive pulmonary disease; plateau adaptation genes; inflammatory response; oxidative stress reaction; lipid metabolism

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive respiratory disease characterized by chronic airflow limitation and irreversible lung damage caused by an inflammatory response in the airways to harmful gases and particulate matter [1–3]. Common clinical symptoms include chronic or progressive dyspnea, chronic cough, sputum production, chest tightness, and fatigue [4]. Dyspnea, resulting from airflow limitation, is the main symptom of COPD and the primary reason why patients seek medical treatment [5]. The onset and progression of COPD are influenced by various factors, including long-term smoking, environmental factors, and genetics [6]. While treatment and prevention options for COPD are currently limited, numerous risk factors and molecular mechanisms relevant to the pathogenesis and management of the disease have been identified. In recent years, there has been a growing focus on exploring gene–environment interactions in COPD research.

Although peroxisome proliferator-activated receptor alpha (*PPARA*) has been in use for more than three decades since its discovery, its mechanism of action in lung tissue remains poorly investigated [7]. As a member of the transcription factor family, *PPARA* is widely expressed in various tissues, including the lung, heart, liver, kidney, testis, and adipose tissue, and is involved in diverse signaling pathways and metabolic responses [8]. In a mouse study, Yukio *et al.* [9] showed that the expression level of PPARA in the mouse lung is about 2–10 times that in the heart, liver, kidney, and testis, and about 0.5–1 times that in adipose tissue. However, at present, there are no precise data on the expression of *PPARA* in different organs in the human body. Yasushi *et al.* [10] used immunohistochemical methods to analyze PPARA protein expression in human lung tissue and other normal tissues. The results showed that PPARA is highly expressed in alveolar epithelial cells, vascular endothelial cells, and fibroblasts in human lungs. Recent genomic studies have revealed the presence of genes associated with plateau adaptation in high-altitude Tibetan populations, including endothelial persistent atrial standstill domain-containing protein 1, egl nine homolog 1, and *PPARA* [11]. In response to long-term hypoxic conditions, species residing in the plateau region have undergone adaptive evolution through natural selection, leading to the phenomenon known as plateau adaptation [12]. *PPARA*, as a key gene involved in plateau adaptation, exhibits higher expression levels in Tibetan populations that have long adapted to the plateau environment. However, recent studies by our team showed that PPARA expression is reduced in COPD patients at high altitudes (the findings are unpublished). Concurrently, Kanti *et al.* [13] found that *PPARA* expression is downregulated and the oxidative metabolism of fatty acids is reduced, resulting in the accumulation of fatty acids in lung tissue. Additionally, PPARA plays a role in the regulation of lung inflammation and oxidative stress [14,15]. Activation of *PPARA* effectively inhibits the expression of interleukin 8 (IL-8) and monocyte chemoattractant protein-1, which are inflammatory factors associated with oxidative stress, thus

reducing oxidative stress-induced injury and apoptosis, preserving lung function, and preventing the development of COPD [16]. Therefore, gaining an in-depth understanding of the regulatory mechanism of action of *PPARA* is crucial for slowing the progression of COPD and holds promise as a novel approach for COPD treatment.

2. Overview of COPD

COPD is a heterogeneous disease primarily characterized by persistent respiratory symptoms and airflow limitation, which encompass chronic bronchitis and emphysema [17]. While smoking is the primary cause, COPD can also be influenced by factors such as air pollution, occupational hazards, and exposure to biofuels. The age of onset and severity of COPD vary depending on its cause, and the progression of the disease, coupled with reduced physical activity, can impose a substantial financial burden on patients, as well as contribute to psychological conditions like anxiety and depression [18,19].

As a global health concern, the prevalence of COPD has increased by 15.6% between 2007 and 2017 [20], resulting in more than 30,000 deaths annually [21]. The healthcare costs associated with COPD exceed $400 million, making it a leading cause of morbidity, mortality, and healthcare utilization worldwide [22]. It is estimated that approximately 2.51 billion people worldwide are affected by COPD [17], and more than half of all COPD cases might go undiagnosed [23], highlighting the need for heightened awareness. In 2019, COPD ranked as the third most common cause of death globally [24]. With an increasing number of smokers and an aging population, the economic burden of COPD is projected to rise significantly in the coming decades, particularly in China [25]. Recent surveys indicate that COPD globally affects 25% of the population in China, representing a staggering 67% increase in prevalence among individuals aged 40 years and older and reaching epidemic proportions [26].

While a complete cure for COPD is not currently attainable with existing medical technology, disease progression can be mitigated through appropriate medical interventions and medications. These interventions include the use of oxygen therapy, respiratory therapy, and bronchodilators to alleviate symptoms such as dyspnea, coughing, and excessive sputum production. Additionally, lifestyle modifications such as smoking cessation, reducing exposure to air pollution and respiratory infections, and maintaining healthy living and dietary habits are essential. Despite the inability to achieve a complete cure, active treatment and management can enhance the quality of life and slow down the onset and progression of COPD.

3. *PPARA* and Plateau Adaptation

3.1 Overview of PPARA

The *PPARA* gene is located on chromosome 22q13-31 in humans and consists of eight exons, with a transcriptional sequence of 93,161 base pairs (bp) and a coding sequence of 36,997 bp. It also encompasses an intronic region spanning 56,164 bp. *PPARA* is a transcription factor that belongs to the nuclear receptor superfamily. The active form of PPARA is a dimer consisting of two identical subunits [27]. Ligands for PPARA are typically fatty acid derivatives, such as fatty acids and prostaglandins [28]. Binding of these ligands to PPARA induces conformational changes in the receptor that alter its transcriptional activity against target genes. After binding the ligand, PPARA enters the nucleus and binds to the PPAR response element (PPRE) in the promoter region of the target gene [29]. Binding of PPARA and PPRE induces chromosomal remodeling, leading to the transcriptional activation of target genes. The target genes of *PPARA* mainly include those involved in inflammation, fat metabolism, cell proliferation and differentiation [30]. By regulating the expression of these target genes, PPARA plays an important role in inflammation, metabolism, and cardiovascular health. Recent studies have revealed that *PPARA* is not only expressed in the liver but also in alveolar epithelial cells, alveolar macrophages, and bronchial epithelial cells [31]. Among these, alveolar epithelial cells primarily serve as the main source of *PPARA* mRNA. In patients with COPD, *PPARA* mRNA expression in respiratory mucous glands is markedly reduced. However, treatment with *PPARA* agonists leads to a significant upregulation of its expression, which is involved in pulmonary vascular remodeling, suggesting that PPARA plays a key role in the development and progression of abnormal lung function [32,33]. Furthermore, *PPARA* has been found in cultured vascular endothelial and smooth muscle cells, as well as in atherosclerotic lesions [34].

As a member of the nuclear receptor transcription factor family, PPARA is one of the isoforms of PPARs. PPARA typically forms heterodimers with retinoid X receptor (RXR), and together they bind to specific sites on the DNA, regulating the expression of genes involved in lipid metabolism and inflammatory responses [35]. Among its downstream target genes are carnitine palmitoyl transferase 1, acyl-CoA synthetase long-chain family member 1, medium-chain coenzyme A dehydrogenase, and other genes related to lipid metabolism. *PPARA* also regulates the expression of genes associated with the inflammatory response, including nitric oxide synthase 2, nuclear factor kappa B (NF-κB), and interleukin 6 (IL-6) [36–38].

Studies conducted on COPD patients have demonstrated that *PPARA* plays a crucial role in reducing oxidative stress and inflammation in the lungs. It achieves this by modulating the expression of transcription factors such as NF-κB, leading to the inhibition of the inflammatory response. Furthermore, PPARA helps to decrease the produc-

tion of reactive oxygen species (ROS), thereby protecting cells from oxidative stress. Additionally, it has been observed that increased *PPARA* expression is associated with the enhanced expression of *PPAR gamma* (*PPARG*), which may contribute to the prevention of cardiovascular diseases [39]. Hence, PPARA serves as a key regulator of lipid metabolism, inflammatory responses, and oxidative stress.

3.2 Role of PPARA in Plateau Acclimatization

Altitude acclimatization refers to the physiological and metabolic adaptations exhibited by organisms living at high altitudes for extended periods in response to unfavorable environmental conditions such as hypoxia, reduced oxygen delivery, and oxidative stress [40]. Certain populations, including Tibetans, Andeans, and Ethiopians, display unique advantages and adaptive differences. While these adaptations were initially thought to be primarily influenced by genetic factors, recent genomic studies have provided evidence highlighting the strong adaptive traits present in Tibetan populations [41]. Tibetans who have resided at high altitudes for prolonged durations have increased *PPARA* gene expression, which may play a critical role in maintaining altitude acclimatization by influencing various biological processes such as inflammation, oxidative stress, and lipid metabolism [42–44].

Ge *et al*. and Simonson *et al*. [45,46] showed that metabolic adaptation is related to the *PPARA* haplotype, which is the mechanism of high altitude adaptation in Tibetan people. Notably, PPARA is also a transcription factor that regulates fatty acid metabolism. A recent study showed that for certain single nucleotide polymorphisms in *PPARA*, favorable alleles for metabolic adaptation to hypobaric hypoxia are enriched in Sherpa highlanders that are associated with adaptive phenotypes in Sherpa Highlanders (e.g., reduced fatty acid oxidation capacity in skeletal muscle, increased oxygen utilization efficiency, and improved muscle energetics) to protect them from oxidative stress [47]. This genetic variation in *PPARA* in Sherpa Plateau people may be related to the establishment of appropriate metabolic levels at high altitudes to adapt to anoxic environments. In the anoxic environment at high altitudes, Sherpa Highlanders can achieve energy balance by prioritizing the use of glucose or glycogen over free fatty acids or lipids, despite low oxygen levels [48].

The *PPARA* gene acts as an important regulator of the hypoxia inducible factor (HIF) pathway and exerts a central role in energy metabolism within hypoxic environments [49]. However, the precise genetic mechanisms underlying these physiological and metabolic adaptations still require further exploration. A notable finding suggests that for each additional dominant haplotype of the *PPARA* gene, the hemoglobin concentration may decrease by approximately 1.7 g/dL [50]. This reduction is anticipated to alleviate complications associated with elevated hemoglobin levels, such as altitude erythrocytosis, which is triggered by the increase in hemoglobin levels at high altitudes. Consequently, the *PPARA* gene emerges as a crucial player in plateau adaptation. Although the genetic mechanisms driving these physiological and metabolic adaptations have yet to be fully understood, the current study suggests that involvement of the *PPARA* gene in a hypoxic plateau environment may help alleviate the dual hypoxia symptoms in COPD patients. The research group plans to delve deeper into investigating the relationship between *PPARA* and its genotype in plateau adaptation and the development of COPD.

3.3 PPARA is Involved in the HIF Pathway in COPD Patients

Genome-wide association studies have revealed genetic variations between populations residing in highland and plain regions [51]. As a consequence, genomic loci of highland populations have been subject to hundreds of generations of natural selection. The HIF family of transcription factors plays crucial roles in cellular and systemic adaptations, encompassing erythropoiesis, iron metabolism, vascular growth, and permeability [52]. Simultaneously, PPARA is linked to energy metabolism, particularly fatty acid β-oxidation in both mitochondria and peroxisomes under hypoxic conditions [53]. Suppression of *PPARA* function may elevate organ susceptibility to oxidative damage. Additionally, hypoxia-inducible factor-1α (HIF-1α), HIF-2α, and *PPARA* contribute to oxidative stress and metabolic disorders through HIF-mediated transcriptional regulatory mechanisms [54]. Hence, we propose the hypothesis of a potential association between the *PPARA* gene, adapted to plateau environments, and the HIF pathway.

HIF-1α constitutes a major pathway that responds to hypoxia or ischemia, particularly in the context of lung disease and tissue damage [55]. Within the lung tissue of COPD patients, the transcriptional pathway of HIF-1α often becomes dysregulated, leading to heightened inflammatory and oxidative damage responses [56]. Smoking and hypoxia are significant causative factors for COPD, with activation of HIF-1 playing a role [57]. HIF-1 is involved in the development of lung diseases such as asthma and emphysema through the regulation of several genes including *PPARA*, peroxisome *PPARG*, and *PPAR*, which are associated with oxidative stress, autophagy, and mitochondrial biosynthesis [58,59]. Studies have demonstrated the vital protective role of PPARA in COPD patients. By inhibiting the expression of HIF-1α, PPARA can alleviate hypoxia in COPD patients, thereby enhancing the expression of alveolar-associated proteins. This, in turn, increases the alveolar area and the partial pressure of oxygen in the lungs [60].

As a downstream target gene of the HIF pathway, *PPARA* plays a critical role in promoting erythropoiesis and angiogenesis, improving energy and oxygen utilization, and

mitigating hypoxic damage within the body through synergistic effects with HIF pathway-related genes such as prolyl hydroxylase domain (PHD) and HIF-2α [61]. Under normoxic conditions, the HIF-1α protein undergoes hydroxylation by PHD and subsequently undergoes degradation through the ubiquitin–proteasome pathway, leading to the termination of HIF-1α transcriptional activity. Under hypoxic conditions, PHD enzyme activity is inhibited, resulting in the accumulation and polymerization of HIF-1α and triggering a series of hypoxic physiological responses [62]. The inhibition of PHD also leads to the accumulation and polymerization of HIF-1α. Simultaneously, the inhibition of PHD can promote the accumulation and activity of HIF-2α, which translocates into the nucleus and upregulates the expression of *PPARA* and other downstream genes, aiding the body in adapting to the hypoxic environment and enhancing oxidative tolerance [63]. HIF-2α translocates to the nucleus and upregulates the expression of *PPARA* and other downstream genes. *PPARA*, as a specific gene regulated by HIF-2α, serves as an important indicator of oxidative stress and is mainly involved in metabolic physiological processes. While PHD is involved in glucose degradation and enzyme changes in the tricarboxylic acid cycle, enhancing anaerobic metabolism under hypoxic conditions [64]. HIF-2α participates in and regulates the transcription of enzymes related to metabolic pathways, boosts the expression of protease mRNA, sustains adenosine 5'-triphosphate production, and regulates intracellular oxygen homeostasis (Fig. 1). Based on these findings, we hypothesized that *PPARA*, as a downstream gene of the HIF pathway, plays an important role in maintaining cell homeostasis and alleviating hypoxic damage, thereby reducing the risk of COPD.

4. Mechanism of Action of *PPARA* in COPD

4.1 PPARA is Involved in the Inflammatory Response

Inflammatory response is a significant characteristic in COPD patients, and sustained activation of NF-κB is considered a key mechanism in the lung's inflammatory response [65]. NF-κB is a multifunctional nuclear transcription factor that forms trimers in the cytoplasm with the inhibitor of NF-κB (IκB) when inactive. IκB masks the nuclear localization signal of NF-κB. Upon stimulation, IκB is phosphorylated by the IκB kinase complex, leading to the degradation of IκB and subsequent release of NF-κB. NF-κB translocates into the nucleus, binds to specific sites in the DNA, and regulates gene transcription [66]. The current study revealed that NF-κB regulates the expression of pro-inflammatory cellular genes through the classical pathway. Due to the pro-inflammatory effects of NF-κB, excessive or inappropriate activation is considered detrimental to the organism.

In COPD patients, the persistent inflammatory response leads to excessive activation of NF-κB. Studies have demonstrated that *PPAR*α exerts anti-inflammatory activity by inhibiting NF-κB signaling [67]. The endogenous ligand of *PPARA,* cytochrome P450 (CYP450), inhibits Toll-like receptor (TLR) signaling, and CYP450 lipid mediators activate the nuclear receptor and transcription factor PPARA, which can influence other transcription factors through protein interactions within the regulatory networks [68]. Upon TLR stimulation, activation of PPARA can modify its phosphorylation and nuclear translocation, thereby inhibiting NF-κB p65 activity [69]. Evidence indicates that the CYP450–*PPARA* axis acts on inflammatory signaling, where CYP450 lipid metabolites inhibit the inflammatory transcriptional response to TLR in macrophages, and increased production of CYP450 metabolites reduces the induction of pro-inflammatory genes in cells isolated from bronchoalveolar lavage fluid or whole lung lysates [70]. When *PPARA* binds to an exogenous ligand (WY14643, pirinixic acid), the heterodimer formed by PPARA binding to the RXR, a retinoid derivative, interacts with the transcriptional co-activator, RRAR, initiating the transcription of downstream target genes [35,71]. Activation of PPARA can promote the polarization of macrophages towards the anti-inflammatory M2 phenotype, and this transition leads to changes in macrophage morphology and motor capacity. Anti-inflammatory M2 phenotype macrophages have a higher phagocytosis and migration capacity, helping to clear tissue debris and inflammatory factors, thereby promoting tissue repair and inflammation resolution [72]. This regulatory mechanism plays a crucial role in inflammation (Fig. 2). NF-κB regulates the transcription of various cytokines, chemokines, inflammation-associated proteins, and immune receptors upon binding to target genes in the nucleus, and is involved in the progression of COPD. In this paper, we hypothesized that *PPARA* may mediate the transcription of multiple chemokines and inflammatory factors through the NF-κB pathway, thereby reducing the risk of COPD. Building upon this hypothesis, activation of PPARA could be a potential therapeutic approach for managing the inflammatory response in COPD.

4.2 PPARA is Involved in Oxidative Stress and Mitochondrial Dysfunction

Oxidative stress and mitochondrial dysfunction are widely recognized as common pathophysiological phenomena in patients with COPD. These abnormalities lead to cellular damage in the lungs, exacerbation of the inflammatory response, and disease progression, which manifest as small airway fibrosis and emphysema [73]. Vascular remodeling is a key pathogenic mechanism in COPD, and angiotensin II (Ang II) plays a significant role in both vascular remodeling and the generation of oxidative stress-induced processes [74,75]. Research has indicated that mitochondrial respiration is a major source of reactive oxygen species (ROS), and excessive ROS levels can lead to mitochondrial dysfunction and damage [76]. ROS and Ang II alter the structural and physiological integrity of pulmonary

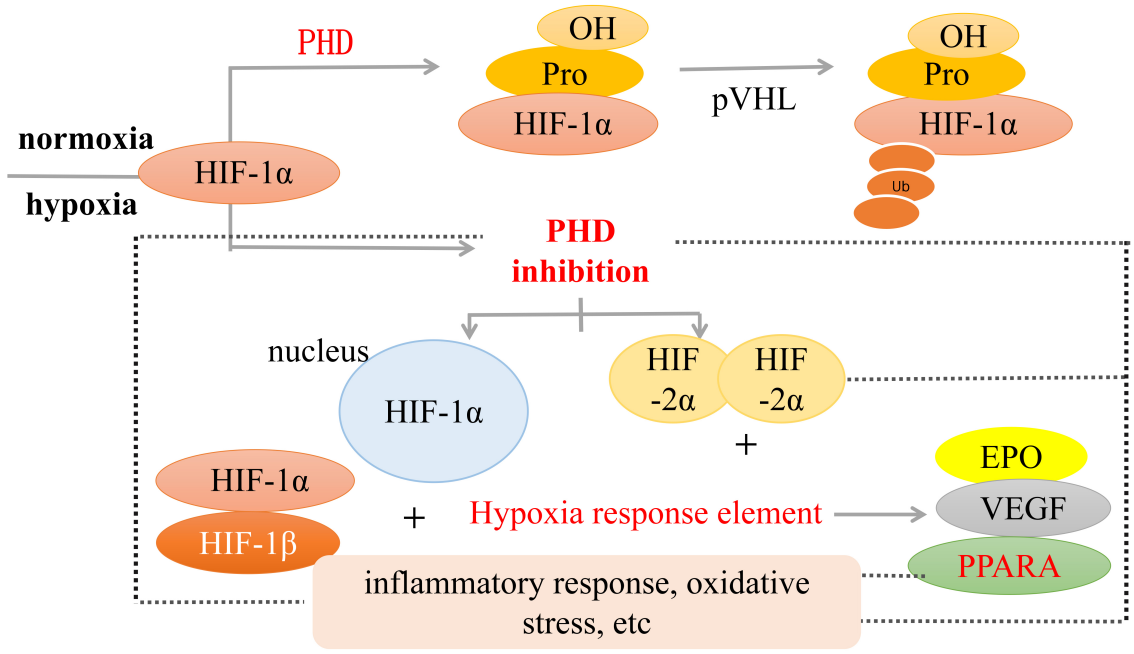

Fig. 1. Schematic diagram of *PPARA* involvement in COPD mechanisms. In normal oxygen, HIF-1α protein is hydroxylated by PHD and subsequently degraded by ubiquitin–proteasome pathway, resulting in termination of HIF-1α transcriptional activity. Under hypoxia, the PHD enzyme activity is inhibited, leading to the accumulation of HIF-1α and promoting the polymerization with HIF-1β, while promoting the accumulation and enhancement of HIF-2α activity. HIF-1α, HIF-1β, HIF-2α translocate into the nucleus, help the body adapt to the hypoxia environment, upregulate the expression of downstream HIF genes (*EPO*, *VEGF*, *PPARA*), enhance oxidation tolerance, and jointly participate in inflammation, oxidative stress, and other reactions. Abbreviations: COPD, chronic obstructive pulmonary disease; PHD, prolyl hydroxylase domain; pVHL, von Hippel–Lindau protein; HIF-1α, hypoxia-inducible factor-1α; HIF-2α, hypoxia-inducible factor-2α; HIF-1β, hypoxia-inducible factor-1β; *EPO*, erythropoietin; *VEGF*, vascular endothelial growth factor; *PPARA*, peroxisome proliferator-activated receptor alpha.

artery vascular smooth muscle cells [77]. Ang II activates the nicotinamide adenine dinucleotide phosphate oxidase (NOX) system through its binding to the angiotensin II type 1 receptor (AT1), resulting in the generation of ROS through the reduction of oxygen to superoxide anions [78]. Additionally, Ang II increases the activity of CYP450 enzymes in the mitochondrial membrane, disrupts the respiratory chain complex, and impairs the electron transport system and oxidative stress regulation. Ang II also affects calcium and potassium channels in mitochondria, leading to excessive ROS production and triggering oxidative stress [79]. PPARA deficiency in vascular smooth muscle cells significantly exacerbates Ang II-induced vascular remodeling and oxidative stress, along with increased mitochondrial oxidant production [80]. Conversely, activation of *PPARA* through WY14643, a *PPARA* agonist, enhances its transcriptional activity, thereby regulating the expression of antioxidant enzymes and genes related to ROS scavenging. This activation of PPARA promotes mitochondrial function recovery and helps maintain a balance between ROS production and scavenging in mitochondria. Therefore, the activation of the PPARA pathway by WY14643 can reduce mitochondrial ROS production and alleviate Ang II-induced oxidative stress and inflammation (Fig. 3).

Activation of *PPARA* leads to increased expression of peroxisome proliferator-activated receptor-γ coactlvator-1α (PGC-1α) [81]. As a transcriptional coactivator, PGC-1α promotes mitochondrial biogenesis and functional regulation under the biological action of *PPARA,* alleviates lung inflammation and cell damage by inhibiting the apoptosis process of mitochondrial pathway, and promotes lung rehabilitation, thus improving patients' conditions [82]. Furthermore, the inhibition of *PPARA* function may increase susceptibility to oxidative damage, suggesting that *PPARA* can help mitigate oxidative damage to some extent [83]. As a result, it can facilitate adaptation to high-altitude environments and reduce the detrimental effects of hypoxia on the organism. The authors of the study propose that *PPARA,* through metabolic regulation, can aid in the adaptation of the population to high-altitude environments, potentially reducing the impact of oxidative stress induced by hypoxic stimuli on COPD patients.

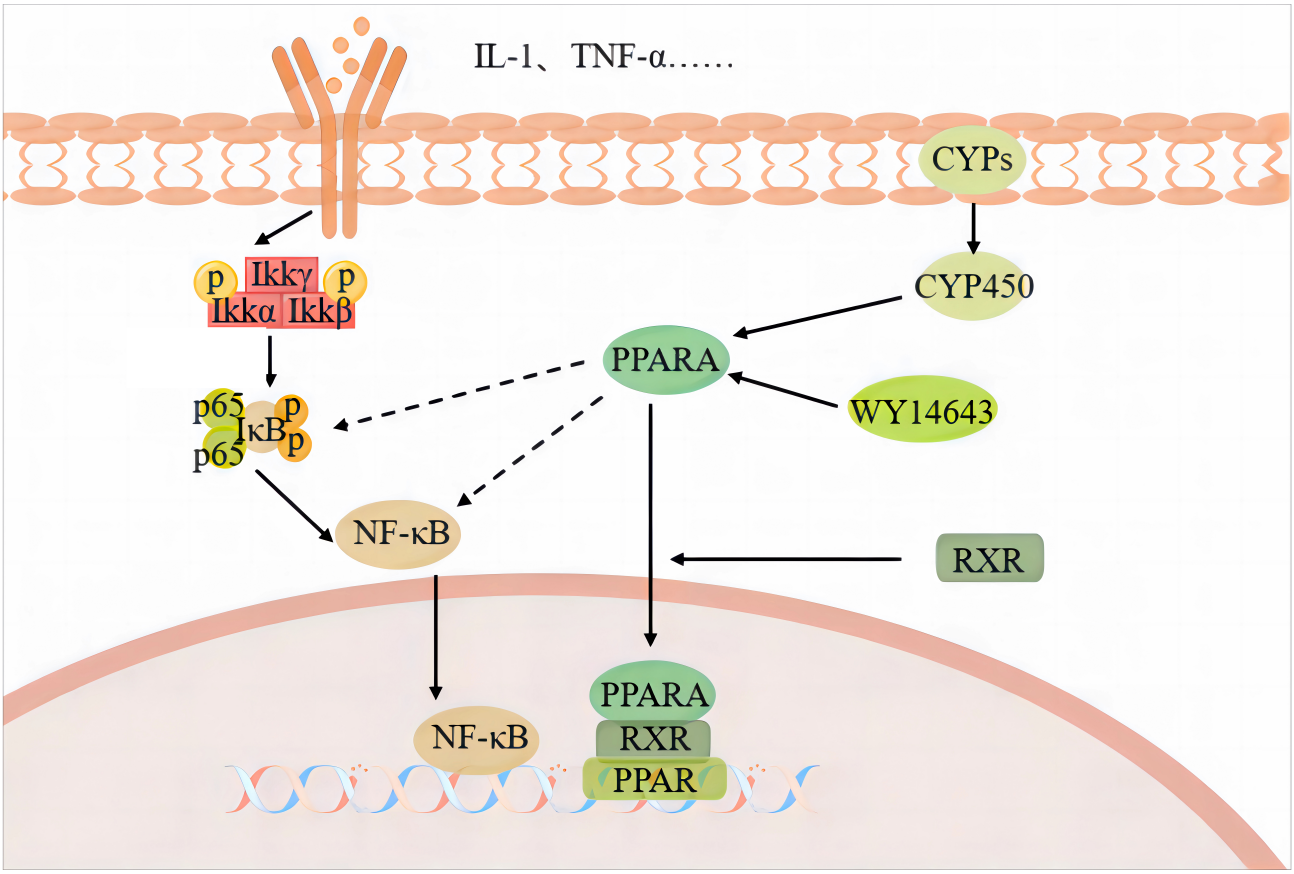

Fig. 2. Schematic diagram of *PPARA* involvement in the mechanism of inflammatory response in COPD. Under the stimulation of inflammatory factors, NF-κB regulates the expression of proinflammatory cell genes through a classical pathway. CYP450 inhibits TLR signaling pathways, and CYP450 lipid mediators activate nuclear receptors and the transcription factor PPARA. Activation of PPARA in response to TLR alters its phosphorylation and nuclear translocation, impeding the activity of NF-κB p65. When *PPARA* binds to WY14643, *PPARA* binds to RXR to form a heterodimer that interacts with transcriptional coactivator *RRAR* to initiate transcription of downstream target genes. Abbreviations: IL-1, interleukin-1; TNF-α, tumor necrosis factor-α; CYPs, cytochrome P450 proteins; CYP450, cytochrome P450; WY14643, pirinixic acid; *PPARA,* peroxisome proliferator-activated receptor alpha; TLR, tolllike receptor; RXR, retinoid X receptor; NF-κB, nuclear factor kappa B; *PPAR*, peroxisome proliferator-activated receptor.

4.3 PPARA is Involved in Lipid Metabolism

PPARA is a transcriptional regulator known for its crucial role in fatty acid metabolism, exerting anti-inflammatory and anti-oxidative stress effects [31]. It regulates all three major fatty acid metabolic pathways *in vivo* [84]. *PPARA* has been implicated in various metabolic disorders, including non-alcoholicfatty liver disease, acute liver injury, type 2 diabetes, gestational diabetes mellitus, and coronary heart disease [85–89]. Studies have reported an increase in *PPARA* expression following acute exposure to high altitudes. This leads to the stimulation of gluconeogenesis in the liver, resulting in elevated blood glucose levels to ensure the energy supply and metabolic homeostasis necessary for adaptation to the plateau environment [90,91]. Under prolonged hypoxia, *PPARA* plays a transcriptional regulatory role, reducing aerobic glucose oxidation in mitochondria while enhancing glycolysis. This adaptive response improves oxygen utilization and maintains sufficient oxygen and energy supply [49]. When PPARA binds to its ligands, such as saturated and unsaturated fatty acids and fatty acid metabolites, a cascade of metabolic reactions is triggered, leading to the suppression of glucose metabolism and enhancement of lipid metabolism (Fig. 4). Alveolar epithelial cells normally utilize fatty acids for carbon dioxide and oxygen exchange and cellular energy supply. However, abnormal lipid metabolism in the lung tissues of COPD patients disrupts fatty acid homeostasis, triggering cellular inflammatory responses and apoptosis, thereby exacerbating respiratory disease development [92]. As a protective factor against hypoxia, *PPARA* promotes fatty acid oxidation in the lungs, orchestrates the expression of various lipid metabolism-related genes, and preserves lipid homeostasis in lung tissues.

PPARA plays an important role in mitochondrial fatty acid β-oxidation as a lung surface active substance. Iron death is an iron-dependent cell death involving iron accu-

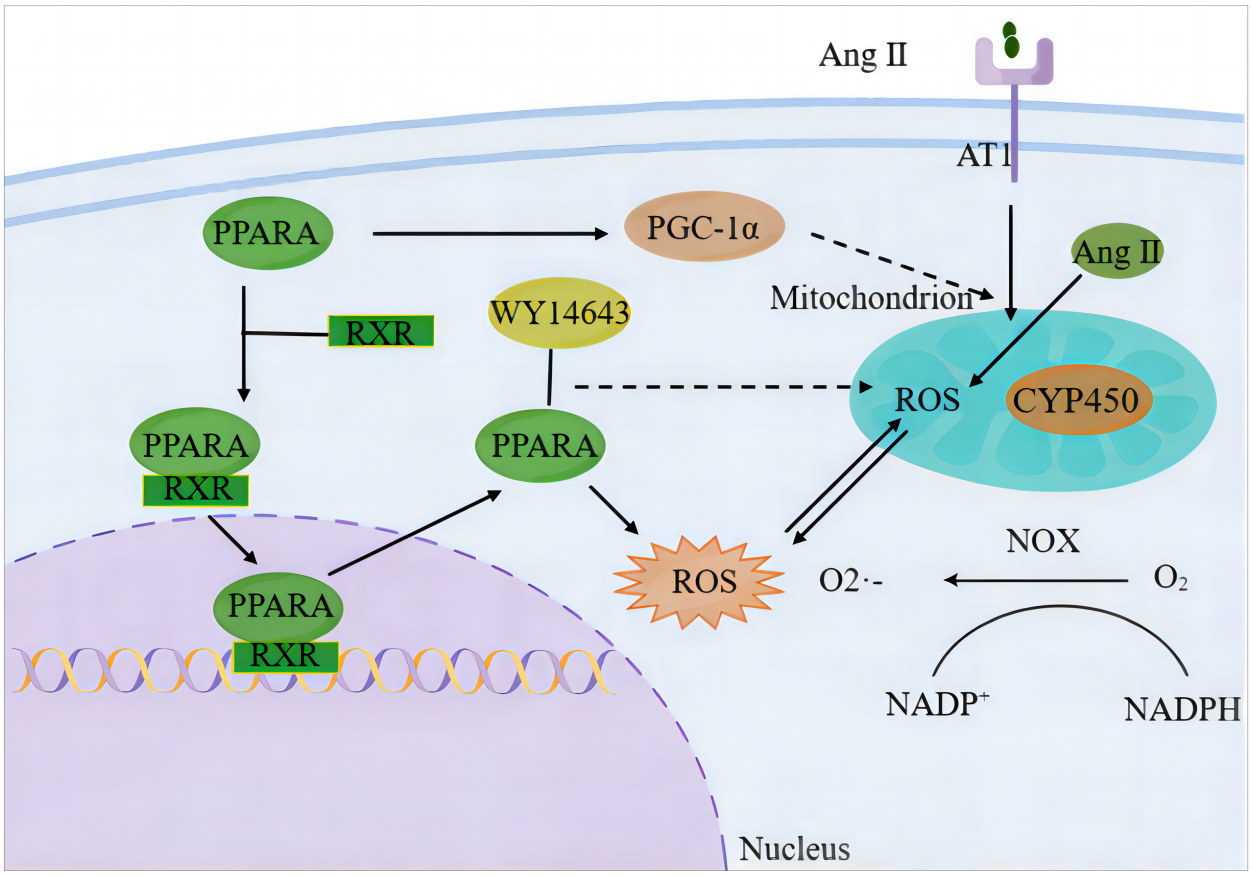

Fig. 3. Schematic diagram of *PPARA* involvement in oxidative stress and mitochondrial dysfunction mechanisms. Mitochondrial respiration is the main source of ROS. Ang II activates NOX by binding to AT1 and produces ROS by reducing oxygen to superoxide anions. In addition, Ang II increases the activity of the CYP450 enzyme in the mitochondrial membrane, leading to excess ROS production and triggering oxidative stress. In contrast, activation of *PPARA* by WY14643 leads to the increased expression of PGC-1α, which regulates the expression of genes associated with antioxidant enzymes and ROS clearance. Under the biological action of *PPARA,* it promotes the biogenesis and functional regulation of mitochondria, alleviates lung inflammation and cell damage by inhibiting the apoptotic process of mitochondrial pathway. Abbreviations: Ang II, Angiotensin II; AT1, angiotensin II type 1 receptor; PGC-1α, peroxisome proliferator-activated receptor-γ coactivator-1α; ROS, reactive oxygen species; NOX, nicotinamide adenine dinucleotide phosphate oxidase system; $NADP^+$, nicotinamide adenine dinucleotide phosphate; NADPH, nicotinamide adenine dinucleotide phosphate; O_2, oxygen; CYP450, cytochrome P450; WY14643, pirinixic acid; *PPARA,* peroxisome proliferator-activated receptor alpha; RXR, retinoid X receptor.

mulation and lipid peroxidation. The onset and progression of COPD are associated with iron death through induction of genetic deletion of glutathione peroxidase 4 (*GPX4*). *GPX4*, an important regulator of lipid peroxidation, has been identified as a central regulator of iron death, acting by inhibiting the production of lipid peroxidation. Inactivation of *GPX4* by glutathione depletion triggers iron death through lipid peroxidation accumulation of ROS production, suggesting a protective role for *GPX4* as a molecular target in iron death-related diseases. *PPARA* directly stimulates the expression of target genes by binding to the PPRE in the initiation region of target genes. Upon ligand-induced activation, *PPARA* regulates the expression of genes involved in lipid metabolism and peroxisome proliferation PPARA alters lipid metabolism through multiple mechanisms that promote the transfer of fatty acids into mitochondria. *PPARA* was found to correlate with iron death, and PPARA activation decreased *GPX4* expression, resulting in a subsequent decrease in transferrin expression. Furthermore, *PPARA* deficiency was sufficient to promote iron overload-induced death *in vivo*, suggesting that PPARA provides protection against iron death during iron accumulation.

PPARA plays a crucial role in mitochondrial fatty acid β-oxidation, serving as a vital component of lung surfactant [93]. Iron death is a form of iron-dependent cell death characterized by iron accumulation and lipid peroxidation [94]. The onset and progression of COPD have been associated with iron death due to the induction of *GPX4* genetic deletion [95]. *GPX4*, which serves as a central regulator of lipid

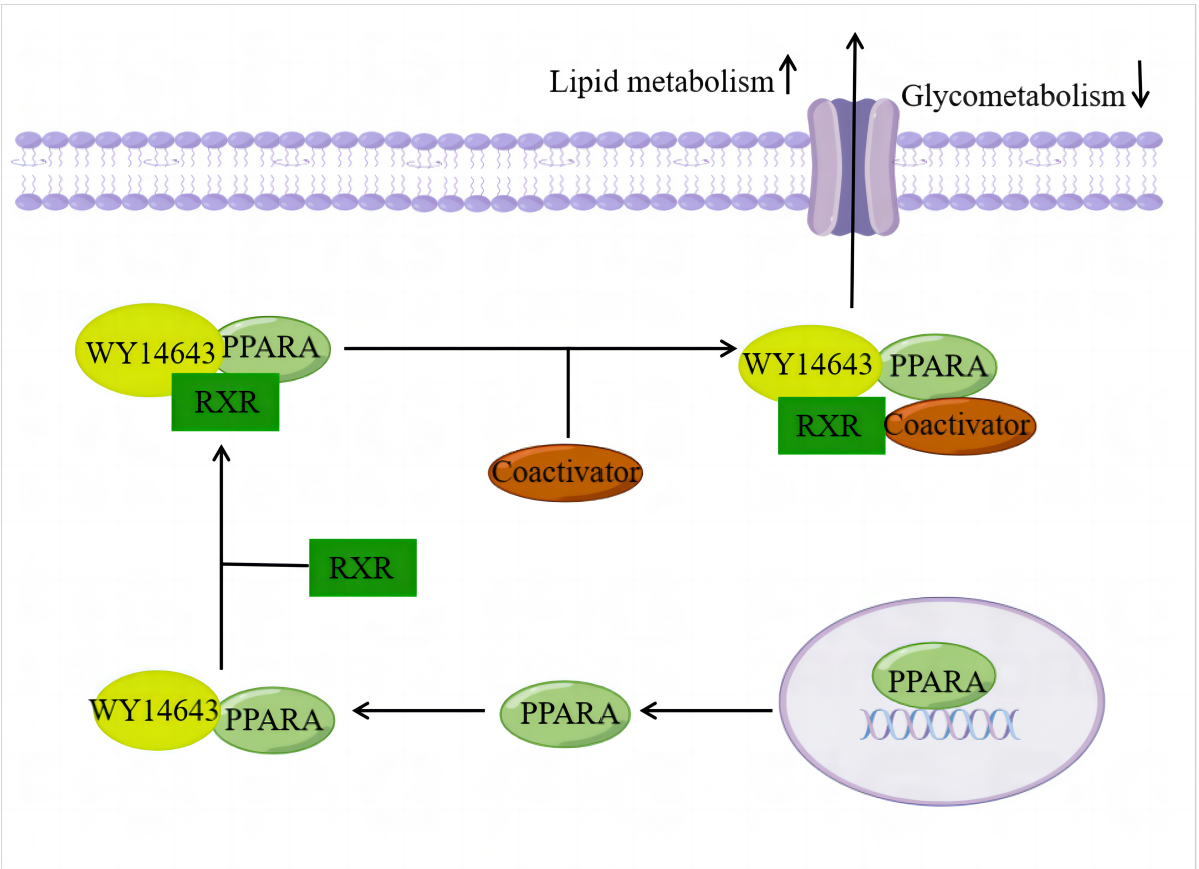

Fig. 4. Schematic diagram of *PPARA* involvement in metabolic mechanisms. When PPARA binds to ligand WY14643 (e.g., saturated and unsaturated fatty acids, fatty acid metabolites), it triggers a cascade of metabolic reactions that bind to RXR, resulting in inhibited glucose metabolism and enhanced lipid metabolism under the action of coactivators. Abbreviations: WY14643, pirinixic acid; *PPARA*, peroxisome proliferator-activated receptor alpha; RXR, retinoid X receptor.

peroxidation, inhibits the generation of lipid peroxides, thus playing a protective role in iron death-related diseases. Inactivation of *GPX4* through glutathione depletion triggers iron death by promoting the accumulation of lipid peroxidation and the production of ROS [96]. PPARA directly stimulates the expression of target genes by binding to the PPRE in the promoter region of these genes. Upon ligand-induced activation, PPARA regulates the expression of genes involved in lipid metabolism and peroxisome proliferation [97]. PPARA influences lipid metabolism through multiple mechanisms that enhance the transport of fatty acids into mitochondria. Interestingly, *PPARA* has been found to be associated with iron death, and its activation leads to reduced expression of *GPX4*, resulting in a subsequent decrease in transferrin expression [98]. Significantly, *PPARA* deficiency has been demonstrated to promote iron overload-induced cell death *in vivo*, highlighting the protective role of *PPARA* against iron-related cell death during iron accumulation.

5. Conclusions

Due to the unique environment of the plateau region, the population living in high altitude areas experiences prolonged exposure to low oxygen and low atmospheric pressure. This can lead to limited airflow and insufficient oxygenation in the lungs, further exacerbating airway and lung inflammation in COPD patients. As a member of the *PPAR* family, *PPARA* plays crucial roles in COPD by regulating inflammation, inhibiting oxidative stress, protecting lung cells, and modulating lipid metabolism. Studies have found that mutations in the susceptibility site of the high-altitude adaptation gene *PPARA* increase the risk of COPD, but few studies have explored the direct relationship between *PPARA* and COPD risk. However, a large number of studies have shown that the expression level of *PPARA* gene is high in inhabitants of the Tibetan Plateau. Moreover, *PPARA* has been shown to be associated with altitude diseases such as altitude headache, altitude pulmonary edema, and altitude polycythemia. Additionally, the antioxidant properties of *PPARA* also play a significant regulatory role in altitude adaptation. Further investigation into these mechanisms could help improve patient outcomes and prevent

and treat complications of COPD. Despite demonstrating potential in COPD treatment, the current understanding of the mechanism of action of *PPARA* in COPD remains relatively limited. Our research group focused on the role and clinical significance of *PPARA* in COPD. The downregulation of *PPARA* expression in COPD patients was found to be closely related to alveolar injury, inflammatory responses, and oxidative stress. At the same time, activation of *PPARA* can improve the lung function of patients and slow down the disease process, indicating that it is expected to become a new target for the treatment of COPD. To deepen the clinical significance of this study, future research directions will focus on the role of *PPARA* in the repair of alveolar damage in patients with COPD. Specifically, studying how *PPARA* promotes the regeneration of alveolar epithelial cells and repair of alveolar walls will lead to new ways to improve lung function. At the same time, the development of highly selective and highly active *PPARA* agonists is also a promising direction. By evaluating its safety and efficacy, it is expected to provide new therapeutic drugs for COPD patients. By further exploring the role of *PPARA* in COPD, we hope to provide more effective treatments for COPD patients and improve their quality of life. Future studies should focus on the multifaceted effects of *PPARA* in COPD to provide more evidence and support for clinical practice.

Author Contributions

ZY, XW, HL, YW, WP and YZ have made substantial contributions to conception, design and writing; and all authors been involved in drafting the manuscript or reviewing it critically for important intellectual content; and all authors given final approval of the version to be published. Each author have participated sufficiently in the work to take public responsibility for appropriate portions of the content; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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