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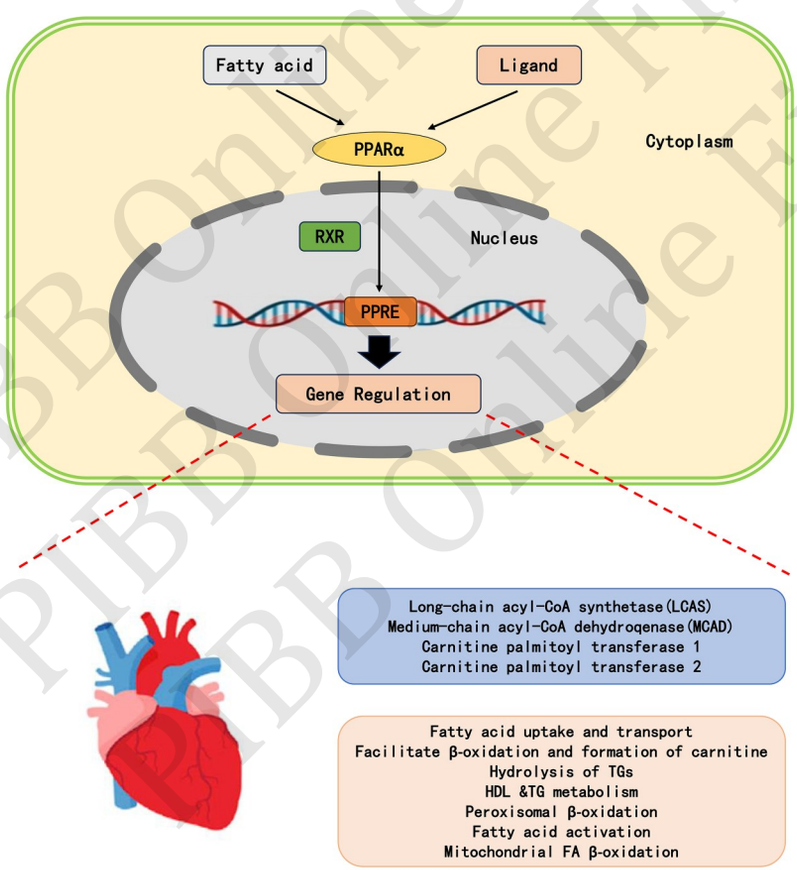
Targeting PPARα for The Treatment of Cardiovascular Diseases*

ZHANG Tong-Tong[1)], ZHANG Hao-Zhuo[1)], HE Li[2)], LIU Jia-Wei[1)], WU Jia-Zhen[1)], SU Wen-Hua[3)], DAN Ju-Hua[1)**]

([1)]*School of Basic Medical Sciences, Department of Medicine, Kunming University of Science and Technology, Kunming* 650500, China;
[2)]*Department of Ultrasound, Lijiang People's Hospital, Lijiang* 674100, China;
[3)]*School of Clinical Medicine, Department of Medicine, Kunming University of Science and Technology, Kunming* 650500, China)

Graphical abstract



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** Corresponding author.
Tel: 86-15812038761, E-mail: danjuhua@kust.edu.cn

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Abstract Cardiovascular disease (CVD) remains one of the leading causes of mortality among adults globally, with continuously rising morbidity and mortality rates. Metabolic disorders are closely linked to various cardiovascular diseases and play a critical role in their pathogenesis and progression, involving multifaceted mechanisms such as altered substrate utilization, mitochondrial structural and functional dysfunction, and impaired ATP synthesis and transport. In recent years, the potential role of peroxisome proliferator-activated receptors (PPARs) in cardiovascular diseases has garnered significant attention, particularly peroxisome proliferator-activated receptor alpha (PPARα), which is recognized as a highly promising therapeutic target for CVD. PPARα regulates cardiovascular physiological and pathological processes through fatty acid metabolism. As a ligand-activated receptor within the nuclear hormone receptor family, PPARα is highly expressed in multiple organs, including skeletal muscle, liver, intestine, kidney, and heart, where it governs the metabolism of diverse substrates. Functioning as a key transcription factor in maintaining metabolic homeostasis and catalyzing or regulating biochemical reactions, PPARα exerts its cardioprotective effects through multiple pathways: modulating lipid metabolism, participating in cardiac energy metabolism, enhancing insulin sensitivity, suppressing inflammatory responses, improving vascular endothelial function, and inhibiting smooth muscle cell proliferation and migration. These mechanisms collectively reduce the risk of cardiovascular disease development. Thus, PPARα plays a pivotal role in various pathological processes *via* mechanisms such as lipid metabolism regulation, anti-inflammatory actions, and anti-apoptotic effects. PPARα is activated by binding to natural or synthetic lipophilic ligands, including endogenous fatty acids and their derivatives (*e.g.*, linoleic acid, oleic acid, and arachidonic acid) as well as synthetic peroxisome proliferators. Upon ligand binding, PPARα activates the nuclear receptor retinoid X receptor (RXR), forming a PPARα -RXR heterodimer. This heterodimer, in conjunction with coactivators, undergoes further activation and subsequently binds to peroxisome proliferator response elements (PPREs), thereby regulating the transcription of target genes critical for lipid and glucose homeostasis. Key genes include fatty acid translocase (*FAT*/*CD36*), diacylglycerol acyltransferase (*DGAT*), carnitine palmitoyltransferase I (*CPT1*), and glucose transporter (*GLUT*), which are primarily involved in fatty acid uptake, storage, oxidation, and glucose utilization processes. Advancing research on PPARα as a therapeutic target for cardiovascular diseases has underscored its growing clinical significance. Currently, PPARα activators/agonists, such as fibrates (*e.g.*, fenofibrate and bezafibrate) and thiazolidinediones, have been extensively studied in clinical trials for CVD prevention. Traditional PPARα agonists, including fenofibrate and bezafibrate, are widely used in clinical practice to treat hypertriglyceridemia and low high-density lipoprotein cholesterol (HDL-C) levels. These fibrates enhance fatty acid metabolism in the liver and skeletal muscle by activating PPARα, and their cardioprotective effects have been validated in numerous clinical studies. Recent research highlights that fibrates improve insulin resistance, regulate lipid metabolism, correct energy metabolism imbalances, and inhibit the proliferation and migration of vascular smooth muscle and endothelial cells, thereby ameliorating pathological remodeling of the cardiovascular system and reducing blood pressure. Given the substantial attention to PPARα-targeted interventions in both basic research and clinical applications, activating PPARα may serve as a key therapeutic strategy for managing cardiovascular conditions such as myocardial hypertrophy, atherosclerosis, ischemic cardiomyopathy, myocardial infarction, diabetic cardiomyopathy, and heart failure. This review comprehensively examines the regulatory roles of PPARα in cardiovascular diseases and evaluates its clinical application value, aiming to provide a theoretical foundation for further development and utilization of PPARα-related therapies in CVD treatment.

Key words cardiovascular disease, PPARα, agonists, energy metabolism

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Cardiovascular disease (CVD) is one of the leading causes of death among adults worldwide, with its morbidity and mortality rates continuing to rise. It claims over 17 million lives annually, accounting for approximately 31% of global deaths. Extensive evidence demonstrates that CVD exerts a widespread impact globally and poses significant challenges to public health systems in countries across varying economic backgrounds. In China, the burden of CVD on national health is particularly severe, having remained the primary cause of death among urban residents for many consecutive years. This reality not only underscores the critical severity of CVD in China but also demands heightened efforts from the public health system to implement more effective prevention and treatment strategies to address this health crisis. According to the 2022 Report on Cardiovascular Health and Diseases in China, remarkable progress has been achieved over the past three decades in improving healthcare accessibility and service quality,

with some cardiovascular technologies reaching or approaching world-leading standards. These advancements indicate that China has made significant breakthroughs in tackling the challenges of CVD treatment. However, due to unhealthy lifestyles and accelerating trend of population aging, the incidence and mortality rates of CVD in China continue to rise, and a turning point in alleviating the disease burden remains elusive[1-2]. Therefore, to address this challenge effectively, in-depth research into CVD pathogenesis and the exploration of novel therapeutic strategies and targets are of paramount importance.

Metabolic disorders play a pivotal role in the onset and progression of cardiovascular diseases, involving alterations in substrate utilization, mitochondrial structural and functional impairments, and disruptions in ATP synthesis and transport, among other mechanisms[3-4]. Peroxisome proliferator-activated receptor α (PPARα), a ligand-activated receptor belonging to the nuclear hormone receptor family, is highly expressed in multiple organs, including skeletal muscle, liver, intestine, kidney, and heart, where it regulates the metabolism of diverse substrates[5]. As a key transcription factor critical for maintaining metabolic balance and catalyzing biochemical reactions, PPARα exerts cardioprotective effects by modulating lipid metabolism, participating in cardiac energy metabolism, enhancing insulin sensitivity[6-9], suppressing inflammatory responses, improving vascular endothelial function, and inhibiting smooth muscle cell proliferation and migration. These mechanisms collectively reduce the risk of cardiovascular diseases. Functioning as a transcriptional regulator, PPARα recognizes and binds to peroxisome proliferator response elements (PPREs) in the promoter regions of target genes, thereby governing processes such as fatty acid oxidation, mitochondrial β -oxidation, fatty acid uptake and transport, triglyceride (TG) catabolism, and gluconeogenesis, which ultimately influence intracellular lipid metabolism. Activation of PPARα not only promotes fatty acid oxidation for energy production but also regulates lipid synthesis, transport, and metabolism, playing a vital role in maintaining systemic energy balance and lipid homeostasis[10]. Furthermore, PPARα negatively modulates pro-inflammatory signaling pathways through both PPRE-binding-dependent and PPRE-binding-independent mechanisms, rendering it highly versatile and effective in suppressing inflammation[11]. Additionally, PPARα is pivotal in counteracting apoptosis by upregulating anti-apoptotic genes and downregulating pro-apoptotic genes, as well as by modulating mitochondrial energy supply to regulate apoptotic processes[12].

In summary, PPARα contributes to diverse pathological processes through mechanisms such as lipid metabolism regulation, anti-inflammatory actions, and anti-apoptotic effects, offering novel perspectives and potential therapeutic targets for related diseases. Consequently, PPARα may serve as a promising molecular target for treating various cardiovascular diseases and their complications. This review aims to elucidate the regulatory roles of PPARα in CVD and its clinical implications, providing a theoretical foundation for advancing the development and application of PPARα -targeted therapies in cardiovascular disease management.

1 Structure and function of PPARα

Peroxisome proliferator-activated receptors (PPARs) comprise 3 subtypes: PPARα (NR1C1), PPARβ/δ (NR1C2), and PPARγ (NR1C3). PPARα, a ligand-activated transcription factor within the nuclear receptor superfamily, was first identified in the 1990s[13]. As shown in Figure 1, in humans, the PPARα gene is located on chromosome 22, encodes a protein of 468 amino acids, and has a total length of approximately 93.2 kb[14]. PPARα is composed of 4 functional domains: A/B, C, D, and E/F. The N-terminal A/B domain contains a ligand-independent activation function (AF-1), which can activate gene transcription even in the absence of ligands. The C domain (DNA-binding domain, DBD) is a conserved region featuring two zinc finger structures that mediate the binding of PPARα to PPREs in the promoter regions of target genes. The D domain serves as a binding site for coregulators and contains a flexible hinge region that interacts with repression domains of corepressors. Notably, the corepressor-binding and coactivator-binding regions partially overlap, enabling dynamic interactions among PPARα, DNA, ligands, and associated proteins. The E/F domain (ligand-binding domain, LBD) binds various endogenous or exogenous lipophilic ligands with specificity. Additionally, the ligand-dependent

activation function (AF-2) within the E/F domain facilitates the recruitment of transcriptional coactivators during gene transcription[15].

PPARα can be activated by binding to natural or synthetic lipophilic ligands, including endogenous fatty acids and their derivatives (*e. g*., linoleic acid, oleic acid, and arachidonic acid) as well as synthetic peroxisome proliferators such as fibrate drugs[16]. Upon ligand binding, PPARα heterodimerizes with the retinoid X receptor (RXR), forming a PPARα -RXR complex[17]. Coactivators, such as nuclear receptor coactivator 1 (NCoA-1/SRC-1), interact with the activation function-2 (AF-2) of nuclear receptors *via* specific LXXLL motifs, stabilizing the active transcriptional complex and enhancing gene expression. The activated PPARα -RXR heterodimer binds to PPREs, regulating the transcription of key genes involved in lipid and glucose homeostasis. These target genes include fatty acid translocase (*FAT/CD36*), diacylglycerol acyltransferase (*DGAT*), carnitine palmitoyl transferase I (*CPT1*), and glucose transporters (*GLUT*), which collectively mediate fatty acid uptake, storage, fatty acid oxidation, and glucose oxidation[18-19]. Owing to its broad regulatory roles in metabolism, PPARα is highly expressed in metabolically active tissues and organs, such as the liver, skeletal muscle, brown adipose tissue, and vascular wall cells (including endothelial cells, smooth muscle cells, and macrophages). It is also present in mitochondria-rich tissues like the kidney, heart, and intestinal mucosa, reflecting its critical link to mitochondrial function. Beyond energy and lipid metabolism, PPARα has been implicated in endothelial function, immune responses, neurological processes, and cancer development. However, its regulatory role in the pathophysiology of the cardiovascular system is of particular interest to this review.

2 The regulatory role of PPARα in the pathogenesis of cardiovascular disease

The potential roles of PPARs in cardiovascular diseases have garnered increasing attention, particularly PPARα, which is recognized as a highly promising therapeutic target for CVD treatmen[20-21]. Extensive studies have demonstrated that PPARα plays a critical role in the pathogenesis, progression, and prevention of cardiovascular diseases. It regulates CVDs by modulating lipid and energy metabolism and suppressing inflammatory responses. With deepening research into the mechanisms of PPARα in CVDs, its functions and roles are being progressively elucidated. The advancement of studies targeting PPARα for CVD therapy has underscored its growing clinical significance. Currently, PPARα activators/agonists, such as fibrates and thiazolidinediones, have been widely used in clinical trials for cardiovascular disease prevention[22-23]. In the cardiovascular system, PPARα expressed by endothelial cells (ECs), vascular smooth muscle cells (VSMCs), and monocytes/macrophages plays a vital role in reducing TG levels by stimulating fatty acid oxidation[5, 24-26]. Therefore, activating PPARα may serve as a key therapeutic strategy for cardiovascular conditions such as cardiac hypertrophy, atherosclerosis, ischemic cardiomyopathy, myocardial infarction, diabetic cardiomyopathy, and heart failure. Below, we will review the research progress on PPARα in various types of cardiovascular diseases.

2.1 PPARα and cardiac hypertrophy

In the cardiovascular system, conditions such as hypertension, myocardial ischemia, myocardial infarction, and valvular diseases often induce myocardial hypertrophy (MH). Myocardial hypertrophy represents an adaptive compensatory remodeling of the heart in response to various injurious stimuli during the early stages of heart failure[27] and serves as both a major risk factor and a key pathophysiological mechanism underlying various cardiovascular diseases[28]. The transition from adaptive hypertrophy to maladaptive hypertrophy can lead to malignant arrhythmias, heart failure, and ultimately sudden cardiac death[29-30]. Energy metabolism imbalance is a hallmark of myocardial hypertrophy, and PPARα plays a critical role in myocardial energy metabolism by regulating fatty acid and glucose metabolism in cardiomyocytes, thereby influencing cellular function and adaptability.

Under the pathological conditions of myocardial hypertrophy, the mechanisms of PPARα are particularly complex, involving interactions among multiple signaling pathways and metabolic processes. Studies have shown that PPARα transcriptionally regulates key genes involved in fatty acid oxidation, such as carnitine palmitoyltransferase 1 (CPT1), carnitine palmitoyltransferase 2 (CPT2), long-chain acyl-CoA synthetase (ACSL), and medium-chain acyl-CoA dehydrogenase (MCAD), thereby modulating

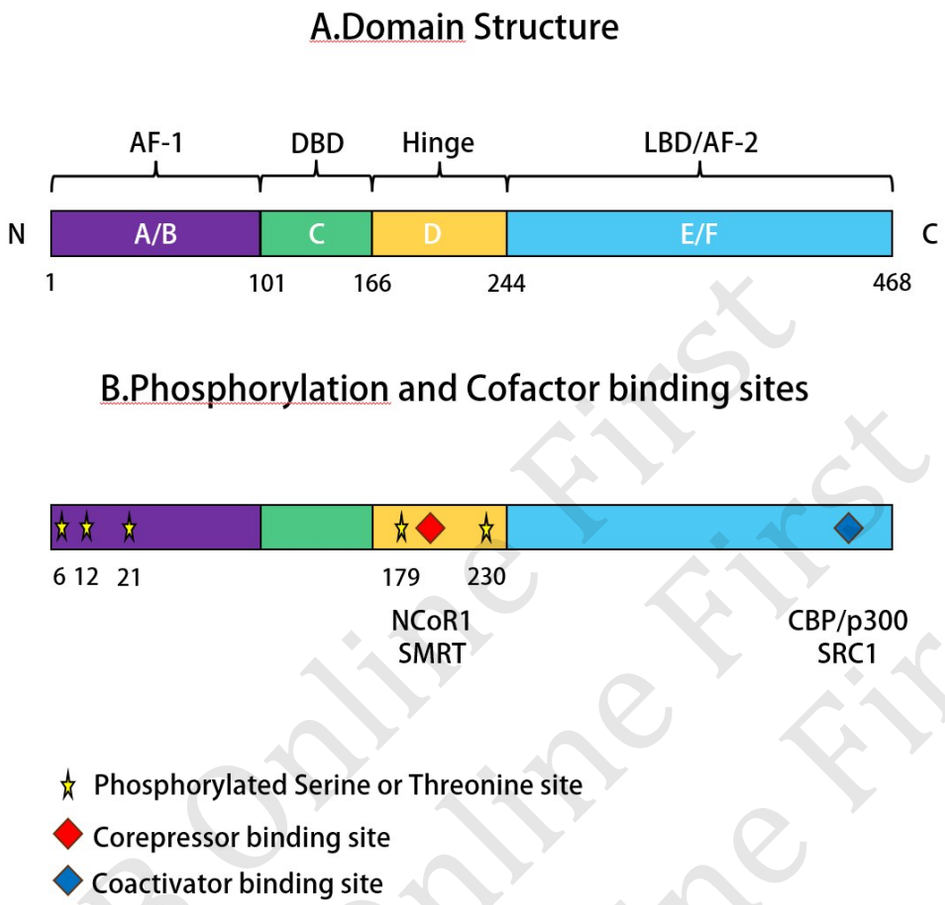

Fig. 1　Schematic representation of PPARα structure

Schematic representation of the structural domain （a） and phosphorylation and cofactor binding sites （b） of PPARα. PPARα：peroxisome proliferator-activated receptor α；AF-1：non-dependent ligand-activated functional region；DBD：DNA-binding domain；LBD/AF-2：ligand-binding domain or ligand-dependent activation functional region；NCoR1：nuclear receptor corepressor 1；SMRT：silencing mediator of retinoic acid and thyroid hormone；CBP/p300：CREB-binding protein；SRC1：steroid receptor coactivator 1. Phosphorylated serine or threonine sites are marked with yellow asterisks，corepressor binding sites are marked with red squares，and coactivator binding sites are marked with blue boxes.

fatty acid oxidation[31]. Research by Huang *et al.* [32] demonstrated that the extracellular regulated protein kinases 1/2 (ERK1/2)/PPARα/short-chain acyl-CoA dehydrogenase (SCAD) signaling pathway mediates cardiomyocyte hypertrophy. Activation of ERK1/2 reduces PPARα expression and activity, which suppresses the expression and activity of SCAD—a rate-limiting enzyme in fatty acid oxidation. This inhibition of myocardial fatty acid β-oxidation leads to reduced energy metabolism, decreased ATP levels, and exacerbation of cardiomyocyte hypertrophy. Studies have also indicated that knockdown of PPARα diminishes fatty acid oxidation, and PPARα deficiency exacerbates hypertrophic growth and cardiac dysfunction caused by chronic pressure overload[33]. Additionally, myocardial hypertrophy has been linked to the adenosine monophosphate-activated protein kinase (AMPK)/PPARα/SCAD signaling pathway. 5-Aminoimidazole-4-carboxamide ribonucleotide (AICAR) activates AMPK, thereby enhancing PPARα activity and upregulating SCAD expression. This promotes myocardial fatty acid oxidation, improves energy metabolism, and prevents cardiomyocyte hypertrophy[34]. Furthermore, the PPARα agonist fenofibrate has been shown to alleviate endothelin-1 (ET-1) or adrenaline-induced myocardial hypertrophy by activating PPARα-related signaling pathways[35]. Another study revealed that

PPARα inhibits the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR) signaling pathway, thereby suppressing cardiomyocyte hypertrophy[36]. Collectively, these findings highlight the inhibitory role of PPARα in myocardial hypertrophy and suggest that PPARα agonists may serve as potential therapeutic agents for this condition.

2.2 PPARα and atherosclerosis

Atherosclerosis (AS) is a vascular disease that poses a serious threat to cardiovascular and cerebrovascular health, with dysregulated lipid metabolism serving as a central factor in its initiation and progression. PPARα plays a pivotal regulatory role in multiple lipid metabolic processes. It mitigates atherosclerosis through transcriptional regulation by participating in macrophage-to-foam cell transformation, reducing blood lipids, exerting anti-inflammatory, anti-proliferative, and antioxidant effects, and improving endothelial cell vasodilation[37-40]. However, the precise regulatory role of PPARα in the development and progression of atherosclerosis remains controversial.

Research by Babaev *et al*.[41] demonstrated that bone marrow-specific knockout of PPARα leads to an expansion of atherosclerotic lesions. Macrophage-specific PPARα deficiency significantly increases oxidized low-density lipoprotein (LDL) uptake, abolishes PPARα -mediated activation of scavenger receptor class B type I (SR-BI), reduces ATP-binding cassette transporter A1 (ABCA1) protein levels, and accelerates inflammatory responses, thereby exacerbating vascular endothelial injury. This study suggests that PPARα suppression disrupts normal vascular function, highlighting PPARα's potential as a therapeutic target for atherosclerosis.

Currently, PPARα agonists are primarily used clinically to treat dyslipidemia. Studies indicate that the PPARα agonist fenofibrate effectively lowers LDL levels in hyperlipidemic patients. It achieves this by transcriptionally regulating high-density lipoprotein (HDL) apolipoprotein AI (ApoAI) and AII (ApoA II) *via* PPARα, thereby reducing hepatic LDL synthesis and release and improving lipid profiles[42]. Additionally, PPARα activation exerts anti-atherosclerotic effects by suppressing nuclear factor κB (NF-κB) and activator protein-1 (AP-1) pathways, attenuating inflammatory responses in vascular smooth muscle cells (VSMCs) and macrophages, and improving lipid metabolism[43]. However, PPARα agonists are associated with various side effects, such as unexpected hepatotoxicity linked to fibrates in atherosclerosis prevention, which may stem from their low selectivity for PPARα. Thus, while debates persist regarding the mechanisms and efficacy of PPARα -targeted drugs in atherosclerosis management, existing studies underscore PPARα's critical role in lipid regulation and key inflammatory pathways. Further in-depth research is needed to comprehensively elucidate PPARα's regulatory mechanisms, particularly how it integrates and controls the multifactorial processes of atherosclerosis, and how to optimize therapeutic outcomes by targeting PPARα.

2.3 PPARα and ischemic cardiomyopathy

Ischemic cardiomyopathy (ICM) imposes a substantial global health burden, affecting approximately 126 million individuals worldwide. Accounting for 1.72% of the global population, ICM contributes to nearly 9 million deaths annually[44] and stands as the most prevalent cause of heart failure globally. ICM is a cardiac condition caused by insufficient myocardial blood supply, characterized by localized or diffuse cardiac fibrosis[45]. This pathological alteration impairs both systolic and diastolic functions, leading to clinical manifestations such as cardiac dilation or stiffness, congestive heart failure, and arrhythmias. The etiology of ICM includes coronary artery stenosis, embolism, or diffuse small artery stenosis[46].

A hallmark of ICM is abnormal myocardial energy metabolism, marked by reduced oxidative catabolism in cardiomyocytes and decreased expression of fatty acid (FA) metabolism-related enzymes. These changes trigger cardiac metabolic remodeling, restrict mitochondrial FA oxidation, and result in diminished ATP (adenosine triphosphate) production alongside reduced PPARα expression[47]. Studies reveal that PPARα overexpression in myocardial tissue enhances the transcription of FA metabolism genes, whereas PPARα knockout downregulates PPARα -specific oxidative genes[48]. Under chronic ischemia and reduced oxygen supply, glucose becomes the primary substrate for myocardial energy metabolism—an adaptive compensatory mechanism. This suggests that ischemic and hypoxic conditions drive the heart to rely more heavily on glucose metabolism to meet energy demands. Thus,

PPARα plays a critical role in shifting cardiac energy substrates from FA to glucose, contributing to the pathogenesis and progression of ICM. Further research indicates that reduced PPARα expression during cardiac hypoxia represents an adaptive response. For instance, PPARα mRNA and protein levels significantly decline after 30 min of cardiac ischemia. If reperfusion occurs after 2 h, PPARα expression further decreases, accompanied by irreversible cardiac damage[49]. Restoring PPARα expression in ischemic myocardia enhances FA oxidation, improves contractile function, and reduces infarct size[50]. These findings underscore the intricate and phase-dependent regulatory role of PPARα in hypoxia, involving metabolic remodeling, energy adaptation, and cardioprotection to sustain cardiac function and survival under ischemic stress. Ravingerová *et al*.[51] demonstrated that pretreatment with PPARα agonists reduces myocardial infarct size in rats subjected to ischemia-reperfusion (I/R) injury. Cardiomyocyte apoptosis significantly contributes to cardiac dysfunction following global I/R injury induced by cardiac arrest and reperfusion. Recent *in vitro* studies further indicate that PPARα activation protects rat myocardium from I/R injury. Specifically, during hypothermic cardiac arrest and reperfusion, PPARα activation mitigates cardiomyocyte apoptosis and damage by reducing NF-κB nuclear translocation, inflammatory cytokine surges, myeloperoxidase (MPO) levels, and caspase-3 activation, while preserving cardiac contractility[52].

Research demonstrates that PPARα activation significantly enhances fatty acid oxidation rates in cardiomyocytes, improving myocardial energy metabolism and alleviating ischemic injury. Currently, multiple PPARα agonists, including bezafibrate and fenofibrate (fibrate drugs that act as natural PPARα ligands), are under investigation for ICM treatment. Clinical studies show that fibrates improve myocardial energy metabolism and exert cardioprotective effects by activating PPARα, thereby ameliorating symptoms and prognosis in ICM patients. With advancing insights into PPARα mechanisms and the development of novel agonists, PPARα holds promise as a therapeutic target for ICM, offering new hope for patients.

2.4 PPARα and myocardial infarction

Myocardial infarction (MI) occurs when sustained and severe myocardial ischemia caused by reduced or interrupted coronary blood flow leads to myocardial necrosis, typically under conditions of structural or functional coronary artery abnormalities[53]. In brief, MI is a necrotic process resulting from ischemia and hypoxia in cardiomyocytes due to coronary artery obstruction.

Following MI, the ventricle undergoes remodeling, characterized by pathological changes such as cardiomyocyte hypertrophy, myocardial fibrosis, and apoptosis. Studies indicate that MI induces insulin resistance in cardiomyocytes alongside reduced fatty acid oxidation[54]. Post-MI, decreased PPARα expression downregulates its downstream target genes, including CD36 and CPT1, ultimately impairing fatty acid transport into cells and mitochondria. This disrupts fatty acid β -oxidation, reduces energy production, and exacerbates ischemic injury, manifesting as enlarged infarct size, abnormal ventricular wall motion, and arrhythmias. Restoring PPARα expression promotes CD36 and CPT1 expression, thereby enhancing fatty acid oxidation[55-56] and ameliorating myocardial damage.

Building on these findings, multiple studies have explored the effects of PPARα activation in MI. One study revealed that testosterone upregulates PPARα expression, improving post-MI metabolic remodeling[57]. A recent investigation examined the therapeutic potential of ginsenoside Rb3 (GRb-3) in murine MI models. GRb-3, similar to fenofibrate, improved ejection fraction (EF) and fractional shortening (FS) while suppressing apoptosis. Notably, *in vitro* experiments using the PPARα inhibitor GW6471 attenuated GRb-3's effects on rat cardiomyocytes, suggesting that GRb-3's cardioprotective role is mediated *via* PPARα activation[58]. Therefore, PPARα activation protects post-infarct myocardium by alleviating metabolism imbalance, reducing infarct size, lowering arrhythmia incidence, and improving ventricular remodeling, ultimately enhancing cardiac function.

2.5 PPARα and diabetic cardiomyopathy

Diabetic cardiomyopathy (DCM), a major complication of diabetes, severely impacts the quality of life in diabetic patients. Characterized by myocardial lipid deposition, cardiomyocyte hypertrophy, myocardial fibrosis, and cardiac dysfunction, DCM can progress to heart failure and life-threatening arrhythmias if left untreated[59-61]. Recent studies highlight the pivotal role of PPARα in

the pathophysiology of DCM, offering novel insights into its understanding and treatment[62-63].

PPARα plays complex and paradoxical roles in metabolic regulation and cardiovascular diseases, particularly demonstrating bidirectional regulatory effects in dilated cardiomyopathy (DCM). Research suggests that altered myocardial PPARα expression in diabetic patients may correlate with disease severity[64]. In diabetic hearts, PPARα is typically downregulated, leading to impaired fatty acid utilization, lipid accumulation, and subsequent lipotoxicity due to lipid peroxidation, which exacerbates myocardial injury[65]. Drosatos *et al*. [66] demonstrated that lipid metabolism in the heart and other organs is significantly disrupted in insulin-deficient diabetes. During early-stage diabetes in mice, elevated plasma glucose levels reduce the expression of Krüppel-like factor 5 (KLF5), a zinc finger transcription factor, resulting in decreased PPARα levels, diminished fatty acid oxidation, reduced ATP production, and ultimately mild cardiac dysfunction. During the early stages of diabetes, PPARα expression may decline due to reduced KLF5 levels, as KLF5 serves as a positive regulator of PPARα transcription. KLF5 deficiency leads to diminished PPARα expression, consequently reducing fatty acid oxidation and ultimately exacerbating lipid accumulation in cardiomyocytes. This suggests a molecular mechanism whereby KLF5 directly binds to the PPARα promoter region to enhance its transcriptional activity. However, under diabetic conditions, activation of certain signaling pathways may suppress KLF5 function, thereby indirectly downregulating PPARα expression. In advanced diabetes, however, myocardial PPARα expression increases, likely as an adaptive response to excessive fatty acid uptake/oxidation and reduced glucose utilization, aiming to recalibrate energy metabolism and preserve cardiac function. Studies also reveal lipid deposition in cardiomyocytes of DCM patients. PPARα-overexpressing mouse models exhibit cardiac metabolic phenotypes resembling diabetic hearts, with enhanced fatty acid uptake and oxidation. Further investigations show that PPARα overexpression suppresses glucose oxidation by transcriptionally upregulating pyruvate dehydrogenase kinase 4 (PDK4) [59, 67]. Additionally, PPARα modulates cardiomyocyte metabolism by regulating insulin signaling. Overactivation of PPARα inhibits insulin receptor and substrate functions, exacerbating insulin resistance and metabolic dysregulation in cardiomyocytes[59, 68-69], thereby promoting intracellular lipid deposition and lipotoxicity, which contribute to myocardial damage and dysfunction[70]. These findings underscore the critical role of PPARα-driven lipid overload in DCM pathogenesis. Targeting PPARα, researchers are exploring therapeutic strategies for DCM. Preliminary studies indicate that PPARα agonists, such as fenofibrate, improve lipid metabolism and mitigate myocardial injury, demonstrating therapeutic potential. Recent work suggests that fenofibrate ameliorates structural abnormalities in diabetic hearts by modulating the PPARα/fibroblast growth factor 21 (FGF21)/sirtuin 1 (SIRT1) signaling axis[71]. However, clinical application of PPARα agonists faces challenges, including drug selectivity, dosage optimization, and safety concerns, necessitating further research. Based on the above findings, we hypothesize that the molecular mechanism may involve PPARα upregulation associated with activation of specific metabolic signals, such as dysregulated branched-chain amino acid (BCAA) metabolism. In diabetic myocardium, BCAA accumulation enhances PPARα-mediated fatty acid oxidation and lipid peroxidation, thereby exacerbating cardiomyocyte susceptibility to I/R injury. BCAA metabolites may promote PPARα transcription by inhibiting general control nonderepressible-2 (GCN2) and activating activating transcription factor-6 (ATF6), ultimately elevating PPARα expression levels.

In summary, PPARα plays a central role in the initiation and progression of DCM. Elucidating its regulatory mechanisms and developing PPARα-targeted therapies may yield novel treatments to improve clinical outcomes and quality of life for DCM patients.

2.6 PPARα and heart failure

Heart failure (HF) is a complex clinical syndrome marking the advanced stage of various cardiac diseases. It is characterized by impaired cardiac pump function, leading to inadequate blood supply to meet the body's metabolic demands[72-73]. HF is not an independent disease but rather the terminal phase of multiple cardiac conditions. As the end state of cardiovascular diseases, HF involves metabolic remodeling[74-75], wherein cardiomyocytes shift from primarily relying on fatty acids (FAs) as an energy

source to increased dependence on glucose. This metabolic shift may result in insufficient myocardial energy supply, further compromising cardiac function[76-77].

In HF, impaired myocardial FA utilization is a hallmark of cardiac metabolism, closely linked to mitochondrial dysfunction and disordered energy metabolism[78-79]. As shown in Figure 2, PPARα expression levels are downregulated in this pathological process. In HF, increased β3-adrenergic receptor expression reduces peroxisome proliferator-activated receptor γ coactivator-1α (PGC-1α) levels, further suppressing PPARα and its target genes involved in energy metabolism, mitochondrial biogenesis, and oxidative phosphorylation, ultimately disrupting glucose and lipid metabolism[80].

Research by Lam *et al*. [81] demonstrated that PPARα -deficient mice develop HF due to blocked cardiac FA oxidation. Conversely, Duerr *et al*. [82] found that PPARα overexpression in cardiomyocytes increases myocardial glycogen deposition, accelerates apoptosis, and impairs antioxidant capacity, leading to systolic dysfunction. These findings suggest that both deficiency and overexpression of PPARα can disrupt cardiac function. As HF progresses, FA and glucose oxidation rates decline, causing severe energy deficits that exacerbate HF progression, promote myocardial fibrosis, cardiac dysfunction, arrhythmias (*e.g*., atrial fibrillation), and even sudden cardiac death. Early activation of PPARα enhances FA oxidation, improves FA uptake and energy production, and alleviates myocardial remodeling, thereby delaying disease progression[83]. Liu *et al*. [84] revealed that fenofibrate modulates the PPARα/SIRT1/PGC-1α pathway, promoting FA oxidation gene transcription, correcting metabolic imbalances, attenuating atrial metabolic remodeling and fibro sis induced by atrial fibrillation, and preserving atrial structure. These studies highlight PPARα -targeted metabolic regulation as a promising strategy for HF treatment or ventricular remodeling reduction[76]. However, due to the multifactorial etiology and complexity of HF progression, the precise mechanisms by which PPARα regulates energy metabolism across HF stages require further exploration.

3　Clinical applications of PPARα agonists

Natural agonists of PPARα, such as fatty acids and leukotriene B4, along with synthetic agonists like fenofibrate, gemfibrozil, and various mono- , dual- , and pan-agonists—particularly fibrates—were initially developed to treat dyslipidemia. These agents

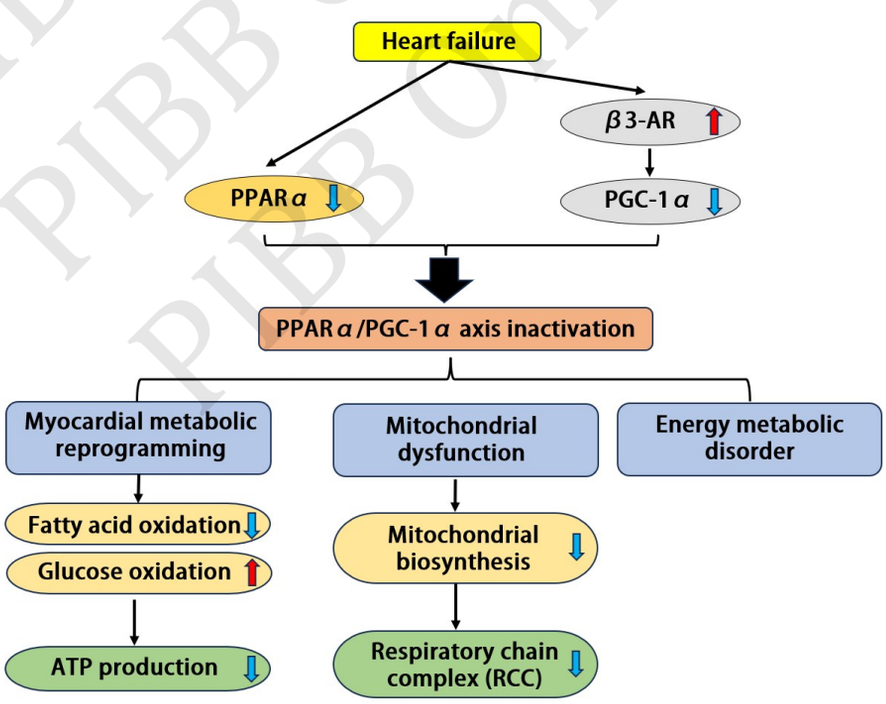

Fig. 2　Role of PPARα/PGC−1α in heart failure

PPARα: peroxisome proliferator-activated receptor α; PGC-1α: PPARγ coactivator-1α; β3-AR: β3-adrenergic receptor; ATP: adenosine triphosphate; ↑: enhanced; ↓: diminished.

exert cardioprotective effects by upregulating adiponectin expression, increasing HDL levels, enhancing lipoprotein activity, reducing triglycerides, and mildly lowering LDL cholesterol, thereby playing a significant role in cardiovascular disease prevention[40, 85-86].

Traditional PPARα agonists, including fenofibrate and bezafibrate, are widely used clinically to manage hypertriglyceridemia and low HDL cholesterol[20]. The clinical efficacy, safety profiles, and side effects of different PPARα agonists are summarized in Table 1. Fibrates, which activate PPARα receptors to enhance fatty acid metabolism in the liver and skeletal muscle, have demonstrated cardiovascular protective effects in multiple clinical trials. For example, the FIELD trial—a five-year randomized controlled study involving 9 795 patients with type 2 diabetes aged 50 – 75 years—showed through Cox proportional hazards model analysis that fenofibrate significantly reduces cardiovascular event risk[87]. Meanwhile, the Helsinki Heart Study, which enrolled 4 081 dyslipidemic male participants aged 40 – 55 years, confirmed *via* five-year follow-up and intention-to-treat analysis that gemfibrozil decreases coronary heart disease incidence[88]. These studies, with their distinct designs (*e. g*., diabetes-specific cohorts *vs.* male dyslipidemia populations), collectively indicate that fibrates substantially reduce cardiovascular event rates in patients with metabolic disorders or diabetes, further underscoring the therapeutic value of PPARα activation in cardiovascular disease management[89]. Fibrates activate PPARα to enhance fatty acid metabolism in the liver and skeletal muscle. Post hoc analyses of the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial[87] and the Helsinki Heart Study[88] demonstrated that fibrates reduce cardiovascular event rates in patients with diabetes or metabolic disorders[89]. Studies further indicate that fibrates help prevent coronary heart disease, particularly in individuals with elevated TG and low HDL cholesterol (HDL-C)[90]. Recent clinical research highlights that fibrates improve cardiovascular pathological remodeling by ameliorating insulin resistance, regulating lipid metabolism, correcting energy metabolism imbalances, and inhibiting vascular smooth muscle and endothelial cell proliferation/migration, while also lowering blood pressure. Large-scale clinical trials confirm that gemfibrozil treatment significantly reduces the incidence of non-fatal MI and coronary heart disease mortality[91]. The current clinical practice guidelines from the American Diabetes Association (ADA) recommend metformin as first-line pharmacotherapy for type 2 diabetes mellitus, while sulfonylureas, thiazolidinediones (TZDs), α -glucosidase inhibitors, benzoic acid derivatives such as meglitinides, glucagon-like peptide-1 receptor agonists, dipeptidyl peptidase-4 inhibitors, and sodium-glucose cotransporter-2 inhibitors serve as second-line therapeutic options. In clinical practice, combination therapy regimens are typically employed, utilizing medications with distinct mechanisms of action. This approach addresses multiple pathophysiological mechanisms underlying the progression of type 2 diabetes from various angles while concurrently managing other associated microvascular and macrovascular complications such as hyperlipidemia and hypertension. According to the latest ADA Standards of Care recommendations, when adding other agents to metformin-based therapy, clinicians should comprehensively consider patients' clinical characteristics, including the presence or risks of atherosclerotic cardiovascular disease, heart failure, chronic kidney disease, obesity, non-alcoholic fatty liver disease (NAFLD), or non-alcoholic steatohepatitis (NASH), while carefully weighing the risks of specific adverse drug reactions[92-93]. Studies have shown that the combination of metformin and peroxisome proliferator-activated receptor (PPAR) agonists offers novel insights into the management of type 2 diabetes through their complementary mechanisms of action[94]. This finding has opened a promising avenue for the clinical application of PPARα agonists, highlighting their significant potential in the treatment of cardiovascular diseases.

4 Discussion and conclusion

In the pathological progression of heart failure, PPARα plays a pivotal role and exhibits complex interactions with multiple metabolic pathways, such as AMPK and SIRT1. Notably, under heart failure conditions, the interaction between PPARα and SIRT1 suppresses the expression of fatty acid metabolism-related genes, leading to reduced fatty acid utilization. Under normal physiological conditions, PPARα forms a heterodimer complex with RXRα to promote the

Table 1 Clinical efficacy， safety， and side effects of different PPARα agonists

Name of drug	Class of drugs	Clinical effectiveness and efficacy	Side effects and safety
Fenofibrate [87，95-97]	Traditional non-selective agonist	Lipid-modulating effects： reduces TG and LDL-C levels while elevating HDL-C Cardiovascular protection： delays the progression of coronary atherosclerosis and lowers the incidence of cardiovascular events in diabetic patients Pleiotropic actions： improves endothelial function， exerts anti-inflammatory effects， and reduces plasma fibrinogen and thrombogenic precursors	Headache， gastrointestinal reactions （such as nausea， vomiting， and diarrhea）， abnormal liver function test results （*e.g.*， elevated AST and ALT levels）， cholelithiasis， pancreatitis， *etc.*
Gemfibrozil [88，91，98-100]	Traditional non-selective agonist	Lipid-lowering effects： reduces TG and LDL-C levels while increasing HDL-C levels CHD prevention and treatment： reduces the incidence of sudden cardiac death and MI	Gastrointestinal discomfort， musculoskeletal pain， cholelithiasis， rhabdomyolysis， *etc.*
Clofibrate [101-102]	Traditional non-selective agonist	Lipid-modulating effects： reduces TG and HDL-C levels， but demonstrates weaker efficacy compared to new-generation fibrates CHD prevention： lowers the incidence of CHD events， with risk reduction observed in primary prevention trials	Gastrointestinal reactions such as diarrhea and nausea， hepatotoxicity， cholelithiasis， *etc.*
Bezafibrate [103-104]	Traditional non-selective agonist	Lipid-modulating effects： reduces TG and LDL-C levels while increasing HDL-C CHD prevention and cardiovascular protection： lowers the incidence of CHD events and non-fatal MI， demonstrating broad cardioprotective benefits	Gastric discomfort， stomach pain， bloating， nausea， abnormal liver function， musculoskeletal pain， *etc.*
Pemafibrate [105-107]	Novel selective agonist	Improves lipid and glucose metabolism， demonstrating favorable efficacy and safety profiles， particularly in patients with renal impairment	Demonstrates a favorable safety profile with no clinically significant side effects observed

All of these drugs are used as traditional non-selective agonists. TG: triglyceride; DL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; CHD: coronary heart disease; MI: myocardial infarction; AST: aspartate aminotransferase; ALT: alanine aminotransferase.

transcription of fatty acid metabolism genes. However, in heart failure, the expression of SIRT1 is upregulated, which binds to PPARα, displaces RXRα, and forms a PPARα/SIRT1 heterodimer. This novel complex inhibits the expression of PPARα target genes, reduces fatty acid utilization, and may further exacerbate heart failure. This interaction constitutes one of the key mechanisms underlying cardiac metabolic reprogramming in heart failure. Relevant studies suggest that blocking the formation of the PPARα/SIRT1 heterodimer may provide a novel therapeutic avenue for treating heart failure[108]. In the context of heart failure, AMPK enhances cardiac function by regulating energy metabolism and maintaining mitochondrial stability. AMPK directly interacts with PGC-1α, a coactivator of PPARα, thereby promoting mitochondrial biogenesis or preserving their functional integrity. Additionally, AMPK indirectly modulates PPARα activity through SIRT1 activation. These mechanisms synergistically enhance fatty acid oxidation and energy production, improving energy supply during heart failure[109]. Although current research on direct interactions between AMPK and PPARα in heart failure remains limited, their specific relationship in this pathological context warrants further investigation. In summary, PPARα regulates fatty acid metabolism and energy production in heart failure through its interactions

with metabolic pathways such as SIRT1 and AMPK, exerting a profound impact on myocardial function and disease progression. These findings highlight novel potential therapeutic targets for heart failure treatment.

In cardiovascular diseases, the nuclear receptors PPARα, PPARγ, and PPARβ/δ collectively establish a multi-layered regulatory network through dynamic synergistic and antagonistic interactions. In terms of synergy, these receptors achieve functional complementarity via shared molecular mechanisms. First, PPARα and PPARγ form heterodimers with the retinoid X receptor (RXR), bind to PPREs, and cooperatively regulate the expression of lipid metabolism genes. For example, in the liver, PPARα activates fatty acid β-oxidation genes (*e.g.*, CPT1A), while PPARγ modulates bidirectional regulation of fatty acid synthesis/breakdown genes (*e. g.*, SCD1, FABP4), forming a "dual safeguard" for metabolic homeostasis[23, 110-112]. Second, they suppress the activity of pro-inflammatory transcription factors such as NF- κB, constructing an anti-inflammatory synergistic network: PPARα/γ competitively bind coactivators (*e. g.*, p300), whereas PPARβ/δ directly inhibits IKK complex activation, collectively blocking the release of inflammatory mediators like IL-6 and TNF- α[23-24, 113] Additionally, in. vascular protection, PPARα mitigates endothelial damage by reducing circulating lipid levels, PPARγ enhances vasodilation through eNOS phosphorylation, and PPARβ/δ promotes angiogenesis, together forming a three-dimensional protective barrier[5, 114].

Nevertheless, the antagonistic effects of PPARα, PPARγ, and PPARβ/δ are equally significant. At the transcriptional level, their competitive recruitment of coregulators (*e. g.*, PGC-1α) leads to reciprocal modulation of target gene expression. For instance, in adipose tissue, PPARγ promotes lipid storage (*via* aP2, CD36), while PPARα enhances lipolysis (*via* ATGL), creating metabolic antagonism. At the pathological level, excessive activation of PPARα may induce lipid overoxidation, thereby impairing PPARγ -mediated insulin-sensitizing effects, whereas PPARβ/δ's specific regulation of myocardial Ca^{2+} signaling may counteract the anti-hypertrophic effects of other subtypes. This dynamic equilibrium is particularly evident in pharmacotherapy. For example, combining fibrates (PPARα agonists) with TZDs (PPARγ agonists) may reduce therapeutic efficacy due to cross-pathway interference[16, 115-117].

PPARα and other nuclear receptors establish a regulatory hub through shared mechanisms. First, they collectively modulate the cAMP/PKA signaling axis: PPARα elevates cAMP levels by enhancing adenylate cyclase expression, PPARγ promotes the translocation of the PKA catalytic subunit, and PPARβ/δ inhibits phosphodiesterase activity, thereby synergistically regulating myocardial contraction and vascular tone. Second, they achieve long-term regulation *via* epigenetic mechanisms. For example, PPARγ recruits HDAC3 to remodel the chromatin structure of pro-fibrotic genes (*e.g.*, TGF-β1), while PPARα mediates DNA demethylation at the CPT1A gene promoter region. Finally, they form an interactive network with transcription factors such as NF- κB and AP-1. In atherosclerotic plaques, PPARs occupy enhancer regions of inflammatory genes, blocking the assembly of pro-inflammatory transcriptional complexes and establishing a dual epigenetic-transcriptional barrier[17, 118-120]. This finely tuned balance of synergy and antagonism provides critical targets for developing subtype-selective PPAR modulators.

PPARα, a pivotal member of the nuclear receptor family, plays a central role in regulating lipid metabolism, inflammatory responses, and energy homeostasis. Recent studies have revealed that PPARα activity is closely linked to the age-related progression and gender-specific differences observed in cardiovascular diseases, yet the underlying mechanisms remain to be fully elucidated. Therefore, the following sections will discuss age-related mechanisms, gender disparities, and future research directions in this field.

In age-related cardiovascular diseases, PPARα dysfunction exerts multidimensional impacts. First, metabolic remodeling in the aging myocardium is characterized by diminished fatty acid oxidation capacity and compensatory enhancement of glucose metabolism, a process closely linked to free fatty acid (FFA) accumulation and mitochondrial dysfunction in cardiac tissue. Studies demonstrate that the PPARα agonist fenofibrate restores fatty acid oxidation by upregulating the expression of fatty acid metabolism genes such as CPT1, while improving mitochondrial dysfunction and reducing reactive oxygen species (ROS) accumulation in aged hearts[121-122]. Second, in pressure overload-induced myocardial hypertrophy models, downregulated PPARα expression accelerates

hypertrophic progression by promoting phosphorylation of the Akt/GSK3β signaling pathway and nuclear translocation of the transcription factor NFATc4, both of which are reversed by fenofibrate intervention. Notably, PPARα -deficient mice exhibit exacerbated myocardial energy metabolism disorders in chronic heart failure models, whereas the traditional Chinese medicine compound Kanli Granules improves fatty acid metabolism *via* AMPK/PPARα pathway activation, suggesting PPARα as a potential therapeutic target for age-related heart failure[123-124]. Furthermore, reduced PPARα activity in aging individuals leads to mitochondrial dynamics imbalance (*e. g*., Drp1/Mfn1 dysregulation), exacerbating mitophagy and apoptosis. The agonist WY14643 alleviates sepsis-associated myocardial injury by enhancing mitochondrial fatty acid oxidation and suppressing the IL-6/STAT3/NF- κB inflammatory axis[125].

Regarding gender differences, current research suggests that estrogen may exert cardiovascular protective effects by upregulating PPARα expression, and the elevated cardiovascular risk in postmenopausal women may be associated with attenuation of this regulatory pathway. Clinical observations reveal that PPARα expression in peripheral blood lymphocytes of coronary artery disease (CAD) patients is negatively correlated with disease severity, with significantly lower expression levels in acute coronary syndrome (ACS) patients compared to controls. The higher prevalence in males may indicate an inhibitory effect of androgens on PPARα, though specific gender-dependent regulatory mechanisms require further validation. Current research limitations include the predominant use of male models in animal studies, resulting in gender data gaps, and the lack of clarity in clinical studies regarding age-gender interactive effects. For instance, elderly women may experience dual detrimental effects—declining estrogen levels and reduced PPARα activity—exacerbating cardiovascular metabolic abnormalities[125-129].

To further elucidate the underlying mechanisms, future research must address the following critical questions. First, decipher the synergistic regulatory mechanisms by which age and gender influence PPARα activity, integrating single-cell sequencing and other advanced technologies to map dynamic epigenetic modifications (*e. g*., DNA methylation) during aging. Second, refine PPARα -targeted therapeutic strategies by developing combination regimens—such as agonists paired with AMPK activators or mitochondrial protective agents—tailored to the metabolic hallmarks of elderly patients. Third, establish gender-specific animal models and clinical cohorts to dissect the signaling crosstalk between sex hormone receptors (*e. g*., estrogen receptor α, androgen receptor) and PPARα[33, 121, 130]. By leveraging multi-omics technologies and interdisciplinary collaboration, we can comprehensively delineate PPARα's regulatory panorama in cardiovascular diseases, thereby identifying novel precision therapeutic targets.

To overcome the limitations of traditional PPARα agonists, researchers are developing novel, highly selective agonists. Achieving specificity through pharmaceutical design and structural modifications is pivotal for enhancing efficacy and minimizing off-target effects. These next-generation agonists provide innovative approaches for treating metabolic and cardiovascular disorders. By optimizing molecular structures, they exhibit improved selectivity for PPARα while reducing

In summary, PPARα agonists exhibit pleiotropic effects in clinical applications, particularly in regulating energy metabolism, lipid metabolism, and inflammatory responses, offering novel therapeutic strategies for cardiovascular and metabolic diseases, as illustrated in Figure 3. Thus, in-depth research on PPARα and its agonists will provide broader therapeutic approaches and theoretical support for managing cardiovascular diseases and their complications. However, traditional PPARα agonists are associated with a range of adverse effects, including rhabdomyolysis, hepatotoxicity, cholelithiasis, cardiotoxicity, and gastrointestinal bleeding[23, 131-135]. These side effects are typically dose-dependent and exacerbated by the lack of tissue specificity, further limiting their clinical utility. Given the multi-organ risks (*e.g*., muscle, liver, heart) posed by traditional PPARα agonists, rigorous monitoring and timely adjustment of treatment regimens are essential. Concurrently, efforts to develop next-generation PPARα agonists with reduced toxicity and improved safety profiles are critical. In this context, designing PPARα agonists with higher potency, enhanced selectivity, and superior safety has become a key focus in the field.

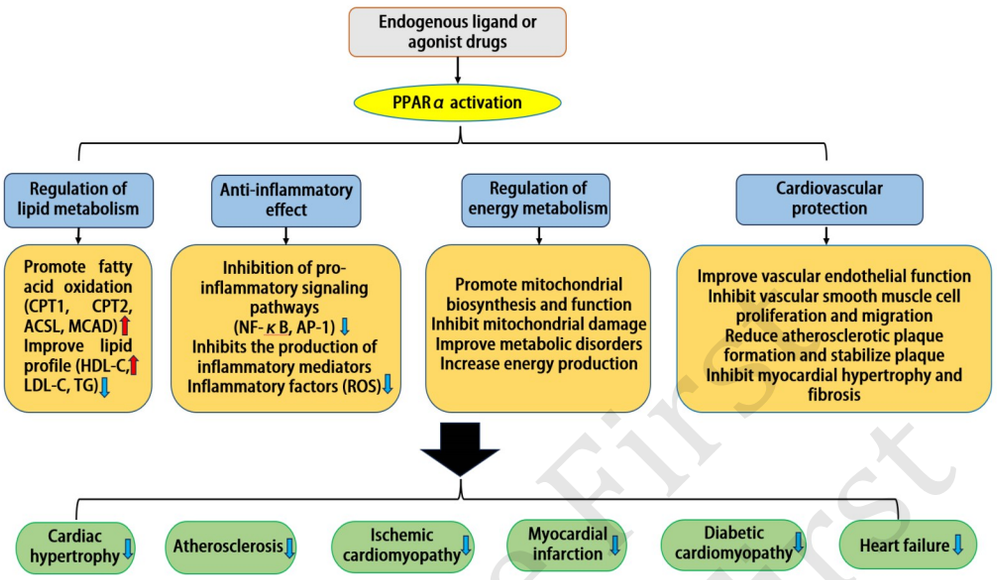

Fig. 3　Diagram of the pharmacological mechanism of PPARα

PPARα: peroxisome proliferator-activated receptor α; CPT1: carnitine palmitoyltransferase 1; CPT2: carnitine palmitoyltransferase 2; ACSL: long-chain acyl-CoA synthetase; MCAD: medium-chain acyl-CoA dehydrogenase; HDL-C: high-densty lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; TG: triglyceride; NF-κB: nuclear factor κB; AP-1: activator protein-1; ROS: reactive oxygen species; ↑: enhanced; ↓: diminished.

activation of other receptor subtypes, thereby lowering side effect risks. Several novel PPARα agonists have demonstrated potent lipid-lowering effects and favorable safety profiles in preclinical models[136-138]. Pemafibrate (Permaprost), a selective PPARα modulator, shows remarkable efficacy in managing dyslipidemia—either as monotherapy or as an adjunct to statins—significantly reducing triglyceride (TG) levels in patients with diabetes or hypertriglyceridemia[105-107]. It also exhibits anti-atherosclerotic effects in multiple murine models. Additionally, advancements in targeted drug delivery systems hold promise for enhancing therapeutic efficacy and reducing adverse effects. For instance, liposome-based delivery of the PPARα/γ dual agonist tesaglitazar enriches macrophage targeting while limiting hepatic and renal exposure in obesity models[139]. Newer PPARα agonists improve TG and HDL-C levels, along with TG-related parameters (*e.g.*, remnant cholesterol, apolipoprotein B), without elevating liver enzymes[140]. Although fibrates are often considered "secondary" options clinically, novel PPARα agonists may offer safer and more effective alternatives for treating hypertriglyceridemia, a prevalent clinical condition.

Therefore, further elucidation of PPARα's mechanisms is imperative. As research on PPARα's role in cardiovascular diseases deepens, accumulating evidence suggests that PPARα agonists may reduce cardiovascular adverse events in the future. However, prospective studies are needed to evaluate their long-term impact on cardiovascular outcomes.

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靶向过氧化物酶体增殖物激活受体α（PPARα）治疗心血管疾病*

张彤彤[1)]　张浩卓[1)]　和　丽[2)]　刘嘉伟[1)]　邬家贞[1)]　苏文华[3)]　旦菊花[1)**]

（[1)] 昆明理工大学医学部基础医学院，昆明 650500；

[2)] 丽江市人民医院超声科，丽江 674100；[3)] 昆明理工大学医学部临床医学院，昆明 650500）

摘要　心血管疾病（cardiovascular disease，CVD）是全球成年人死亡的主要原因之一，其发病率和病死率持续攀升，而代谢紊乱与多种心血管疾病密切相关。代谢紊乱在心血管疾病的发生发展过程中起到关键作用，其涉及底物利用的改变、线粒体结构和功能的障碍，以及ATP合成与运输的阻碍等多个方面。过氧化物酶体增殖物激活受体（peroxisome proliferators-activated receptors，PPARs）在心血管疾病中的潜在作用越来越引起人们的关注，特别是过氧化物酶体增殖物激活受体α（peroxisome proliferator-activated receptors α，PPARα），它被认为是心血管疾病治疗的一个极具潜力的靶点。PPARα通过脂肪酸代谢调控心血管生理与病理过程。PPARα作为核激素受体家族中的一种配体激活受体，在骨骼肌、肝脏、肠道、肾脏和心脏等多种器官中高度表达，能够调控多种底物的代谢。作为维持代谢平衡、催化和调节多种生化反应的关键转录因子，PPARα通过调节脂质代谢、参与心脏能量代谢、增加胰岛素敏感性、抑制炎症反应、改善血管内皮功能以及抑制平滑肌细胞增殖和迁移等多种方式，发挥其心血管保护作用，进而显著降低心血管疾病的发生风险。因此，PPARα通过调节脂质代谢、抗炎、抗凋亡等多种机制，在多种病理过程中发挥作用。PPARα可以通过结合天然或合成的脂溶性配体而被激活。这些配体包括内源性脂肪酸及其衍生物，如亚油酸、油酸和花生四烯酸，以及合成的过氧化物酶体增殖物。配体与PPARα结合后，激活了核受体视黄醛衍生物X受体（retinal dehyderivative X receptor，RXR），形成PPARα-RXR异二聚体。PPARα-RXR异二聚体在共激活因子的作用下进一步激活，活化后的复合物识别并结合PPRE，调控在脂质和葡萄糖稳态中起关键作用的靶基因转录，如脂肪酸转位酶（fatty acid translocase，FAT/CD36）、二酰甘油酰基转移酶（diacylglycerol acyltransferase，DGAT）、肉碱脂酰转移酶I（carnitine palmitoyl transferase，CPT1）和葡萄糖转运蛋白（glucose transporter，GLUT）等，这些基因主要参与脂肪酸的摄取、储存以及脂肪酸氧化和葡萄糖氧化的过程。PPARα作为心血管疾病治疗靶点的研究不断推进，使其在临床上的重要性日益凸显。目前，PPARα激活剂/激动剂，如贝特类和噻唑烷二酮类，已经广泛应用于大量预防心血管疾病的临床研究。传统的PPARα激动剂，例如非诺贝特和苯扎贝特，已经广泛应用于临床，主要用于治疗高甘油三酯血症和低高密度脂蛋白胆固醇血症。贝特类药物通过激活PPARα受体增强肝脏和骨骼肌的脂肪酸代谢能力，其心血管保护作用在多项临床研究中得到验证。最近的这些临床研究揭示，贝特类药物通过改善胰岛素抵抗、调节脂质代谢、纠正能量代谢紊乱、抑制血管平滑肌细胞和内皮细胞的增殖与迁移，从而改善心血管系统的病理重塑，同时还可以降低血压。干预PPARα在基础医学研究及临床应用中均受到诸多关注。因此，激活PPARα作为靶点可能是治疗心肌肥大、动脉粥样硬化、缺血性心肌病、心肌梗死、糖尿病心肌病以及心力衰竭等心血管疾病的关键策略之一。本文将对PPARα在心血管疾病中的调控作用及其临床应用价值进行综述，意在为进一步开发和利用PPARα相关药物治疗心血管疾病提供理论依据。

关键词　心血管疾病，PPARα，激动剂，能量代谢

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** 通讯联系人。

Tel：15812038761，E-mail：danjuhua@kust.edu.cn

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