Research Progress of Peroxisome Proliferator-Activated Receptor in Non-Alcoholic Steatohepatitis

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Abstract. Non - alcoholic steatohepatitis represents a clinical - pathological syndrome. It is marked by the excessive buildup of fat within liver cells, which occurs due to diverse reasons and in the absence of a history of excessive alcohol intake. This condition leads to fatty degeneration and inflammation of liver cells, and may eventually progress to liver cirrhosis or even hepatocellular carcinoma. The incidence of non - alcoholic steatohepatitis has been on the rise annually and has emerged as a significant factor prompting liver transplantation. A large number of research findings indicate that the peroxisome proliferator - activated receptor (PPAR) is of great significance in the onset and development of non - alcoholic steatohepatitis. PPAR is a nuclear transcription factor that includes three subtypes: PPARα, PPARγ, and PPARβ. PPAR exerts multiple functions in the human body, including metabolic regulation, immune modulation, anti-inflammation, and therapy. Therefore, PPAR agonists can have therapeutic effects on non-alcoholic steatohepatitis by promoting hepatic lipid metabolism, reducing total cholesterol levels in the blood, and inhibiting inflammatory responses. Drugs such as fenofibrate and pioglitazone have been widely used in this regard. This article offers a comprehensive review of the research advancements regarding PPAR in non - alcoholic steatohepatitis. By doing so, it aims to lay a theoretical foundation for the exploration and development of novel medications designed to treat non - alcoholic steatohepatitis.

Keywords: NASH, PPAR, PPAR agonists.

1. Introduction

Fatty liver is a metabolic disorder. It occurs when, for various reasons, there is an over - metabolism of fat in the liver. Its main feature is an excessive build - up of lipids within liver cells. Fatty liver is classified into alcoholic fatty liver and non - alcoholic fatty liver (NAFLD), with NAFLD being more prevalent. NAFLD has the potential to progress to non - alcoholic steatohepatitis (NASH).In recent years, due to alterations in dietary patterns and other factors, the global incidence of non - alcoholic fatty liver has been increasing year by year. Research indicates that from 2016 to 2019, the prevalence of NAFLD in the general adult population rose from 25% in 2006 to 38%, with the number of affected individuals reaching 1.66 billion. Based on biopsy data from NAFLD research, the global prevalence of NASH is 5.27%, and among NAFLD patients, the prevalence of NASH is 16.02% [1]. NASH can give rise to hepatocellular carcinoma (HCC) and liver cirrhosis (LC) [2]. It has become the primary cause of liver cirrhosis, and the number of cases necessitating liver transplantation is surging rapidly. In the United States, it has become the disease with the fastest - growing demand for liver transplantation [3, 4]. Enhancing the treatment of NASH not only has the potential to decrease the incidence of diseases like hepatocellular carcinoma but also can improve patients' quality of life. Consequently, the urgent development of new therapeutic drugs is of great necessity.

NASH is a dynamic manifestation of NAFLD, and its pathogenesis involves multiple aspects, including lipid metabolism abnormalities, lipid peroxidation, and insulin resistance. The two-hit hypothesis is a widely accepted theory regarding the pathogenesis of NAFLD. During the first hit, excessive nutrient intake leads to insulin resistance in adipose tissue and skeletal muscle, causing a large amount of free fatty acids to be stored in the liver as triglycerides, resulting in excessive lipid accumulation in hepatocytes and triggering simple steatosis. During the second attack, oxidative

stress, increased inflammatory mediators, cell apoptosis, and mitochondrial dysfunction lead to liver cell damage, action the multiple pro-inflammatory damages of adipose tissue and the gastrointestinal tract, hepatic steatosis leads to the development of symptoms[5]. Inflammation triggers oxidative stress and endoplasmic reticulum (ER) stress, which are crucial elements contributing to hepatocellular damage during the advanced stage of liver disease [6]. When steatosis, ballooning degeneration, and lobular inflammation are identified in hepatocytes, a diagnosis of NASH can be established. Additionally, other histological alterations like portal inflammation, polymorphonuclear cell infiltration, Mallory - Denk bodies, apoptotic bodies, clear vacuolated nuclei, microvesicular fatty degeneration, and giant mitochondria might be present. However, these are not essential for the diagnosis [7]. As a result, the optimal therapeutic targets for NASH should be the molecules engaged in metabolism, inflammation, and liver fibrosis [8].Research findings have indicated that the peroxisome proliferator - activated receptor (PPAR) is significantly associated with oxidative stress, lipid metabolism, insulin resistance, as well as hepatocyte proliferation, differentiation, and apoptosis. Moreover, its agonist also exerts a therapeutic effect on non - alcoholic fatty liver disease [9].

2. Overview of PPAR

PPAR, or Peroxisome Proliferator - Activated Receptor, is a protein initially isolated from mouse liver in 1990. During their investigations, researchers found that PPAR acts as a common receptor for a group of compounds capable of triggering peroxisome proliferation. Consequently, it is commonly known as peroxisome proliferator - activated receptor (PPAR) [10]. PPAR is a significant component of the nuclear receptor (NR) superfamily. It is extensively expressed in diverse tissues and cells throughout the body and is involved in regulating numerous physiological processes, including fat metabolism, blood sugar homeostasis, and the inflammatory response [11]. PPAR consists of four functional domains: A/B, C, D, and E/F, each fulfilling a distinct function. The A/B domain is tasked with the phosphorylation of PPAR. The C domain, being the DNA - binding domain, is responsible for identifying specific DNA sequences, specifically peroxisome proliferator response elements (PPRE). The D domain functions as docking sites for various co - factors. The E domain, known as the ligand - binding domain, binds to specific ligands, such as long - chain polyunsaturated fatty acids and certain medications. These domains collaborate to enable the activation and regulatory functions of the receptor [12]. At present, three known subtypes of PPAR exist: PPARα, PPARβ, and PPARγ. Each subtype has its unique functions, yet there is also some overlap among them.

2.1. PPARα

PPARα is among the first - discovered members of the PPAR family. It is situated on the long arm of human chromosome 22, specifically in the q12 - q13.1 region. Spanning 93.2 kb, it encodes a polypeptide consisting of 468 amino acids.PPARα acts as a receptor for a variety of structurally diverse compounds. Its expression is predominantly observed in tissues such as the liver, myocardium, skeletal muscle, white adipose tissue, intestine, kidney, and pancreas. Moreover, it is also detected in endothelial cells, vascular smooth muscle cells, and other vascular - related cells [13]. Functionally, PPARα is engaged in the regulation of genes associated with substrate delivery, oxidation, and oxidative phosphorylation. This regulation has a direct impact on the uptake, transport, and β - and ω - oxidation processes of fatty acids. By promoting the breakdown of fatty acids, PPARα mitigates fat accumulation in the liver. Simultaneously, it boosts the oxidation rate of fatty acids within mitochondria and peroxisomes, thereby generating energy. These functions are crucial for maintaining lipid equilibrium and energy homeostasis in the body [10, 11, 14].

2.2. PPARβ

PPARβ is located on the p21.2-p21.11 of human chromosome 6, encoding 441 amino acids. It is a relatively conservative member of the nuclear receptor superfamily and is expressed at low levels in most tissue cells.11, but it not only has important physiological functions under normal

physiological conditions, but also plays a key role in the occurrence and development of various diseases. Current studies have found that PPARβ expression sites exist in various tissues and cells, but its expression level is relatively high in the brain, adipose tissue and skin, and it is also more distributed in inflammatory cells and hepatocytes[15]. PPARβ is involved in various biological processes such as fatty acid metabolism, glucose homeostasis, and skin wound healing, and has the action of promoting energy expenditure and cell proliferation.

2.3. PPARγ

PPARγ is located on human chromosome 3, and most scholars classify it into two subtypes, PPAR-γ1 and PPAR-γ2. It is noteworthy that PPAR-γ2 is expressed only in adipocytes. In contrast, PPARγ1 is expressed in the liver, skeletal muscle, intestine, immune cells, and brown adipose tissue. PPARγ was once considered an important regulator of glucose homeostasis and subcutaneous fat formation. Studies have shown that PPARγ also regulates adipocyte differentiation and lipid storage, oxidative stress, reduces inflammation, inhibits neuronal apoptosis, promotes cell proliferation, and also plays a key role in immune response and insulin sensitivity[16,17,18].

3. Role of PPAR in non-alcoholic steatohepatitis

3.1. Role of PPARα in non-alcoholic steatohepatitis

When PPARα is activated, it can promote the β-oxidation of fatty acids and energy metabolism, helping to reduce lipid accumulation in the liver. However, under certain conditions, such as insulin resistance, high-fat diet, or genetic factors, the function of PPARα may be impaired or suppressed. This leads to decreased fatty acid oxidation and excessive lipid accumulation in the liver, ultimately triggering the development of NASH[13].

Severe defects in PPARα signaling profoundly affect factorization in the mouse liver, an effect that is particularly important in the pathogenesis of NASH[19].The role of PPARα in adipocytes is to regulate lipid metabolism by modulating the expression levels of lipoprotein lipase (LPL), which plays a key role in transporting triglycerides from the blood into adipocytes for degradation. In the NAFLD mouse model lacking PPARα, a significant decrease in LPL levels in adipose tissue and an increase in low-density lipoprotein cholesterol (LDL-C) were observed[16] 18, which hinders the normal hydrolysis of lipoproteins and the transport of fatty acids. This lipid metabolism disorder will aggravate fat accumulation and inflammatory response in liver cells, ultimately promoting the occurrence and development of NASH[19].Mice with either systemic or conditional PPARα knockout in hepatocytes showed steatosis, weight gain, overexpression of genes involved in lipid synthesis, and increased liver inflammation under both control and high-fat diets[12].

The activity of PPARα is contingent upon the body's nutritional state. Yang's research revealed that the activity of PPARα follows a circadian rhythm and is correlated with the nutritional condition of mice. In the liver, PPARα is more active during fasting periods, with its activity peaking at night.PPARα plays a pivotal role in controlling the expression of multiple genes that contribute to maintaining systemic fatty acid homeostasis. This enables the liver to effectively utilize fatty acids and supply nutrients to other organs. Additionally, it regulates glucose metabolism by modulating the expression of genes involved in hepatic glycerol metabolism. Moreover, PPARα is involved in regulating amino acid metabolism in the liver through controlling the expression of enzymes related to amino acid transamination, deamination, and urea synthesis [14].Notably, when the diet contains an excessive amount of lipids, the expression of PPARα in the liver declines. In other words, PPARα has the ability to adjust the rates of fatty acid (FA) oxidation, lipogenesis, and ketone body synthesis based on the feeding and fasting states of the body [2].Once the PPARα/RXR complex dimerizes and translocates into the nucleus, it upregulates β - oxidation enzymes. Among these, carnitine palmitoyltransferase 1 (CPT - 1) is a crucial enzyme in the breakdown process. It transfers fatty acids to the mitochondrial matrix for subsequent metabolism [12]. Furthermore, PPARα induces the

expression of fatty acid binding protein 1 (FABP). This, in turn, inhibits the activation of hepatic stellate cells (HSCs), thereby contributing to the improvement of non - alcoholic steatohepatitis.

3.2. Action of PPARβ in NASH

PPARβ can promote lipid catabolism in various tissues and serves as a mediator of fatty acid oxidation and fat burning.

PPARβ activates thermogenic uncoupling enzymes in brown adipose tissue and muscle to prevent fat accumulation, thereby reducing the base of fatty degeneration[2]. PPARβ plays an important role in preventing fat accumulation, thereby reducing the likelihood of NASH occurrence from the source of the disease. At the same time, PPARβ plays moderating effect in fat metabolism by regulating the differentiation, maturation and function of adipocytes, such as regulating the expression of adipokines and inhibiting IL-6-induced STAT3 activation, thereby preventing IL-6-induced adipocyte insulin resistance and fat accumulation[5].

In particular, PPARβ can inhibit the activation of NF-κB, thereby downregulating the expression of adiponectin and adiponectin receptors, thereby inhibiting the expression of LPL and the differentiation of adipocytes, and these all play a certain role in the generation of NASH. Metabolically, PPARβ effectively regulates the lipid balance within hepatocytes by promoting the β-oxidation of fatty acids. It not only stimulates the uptake and utilization of fatty acids by mitochondria but also accelerates the catabolism of fats, thereby reducing lipid accumulation in liver cells. This regulatory action is critical for preventing steatosis in NASH[2]. PPARβ also has a regulatory action in inflammatory responses. It can directly action on the inflammatory signaling pathway, inhibit the production and release of inflammatory mediators (specific ones), thereby reducing the inflammatory response in NASH[1]. At the same time, in terms of oxidative stress affecting the causes of NASH, PPARβ also shows outstanding performance. PPARβ can activate the intracellular antioxidant system, eliminate harmful reactive oxygen species, and protect liver cells from oxidative damage. This antioxidant action not only helps maintain the normal function of liver cells, but also promotes the repair and regeneration of damaged cells, improving the further development of NASH[9]. In addition, PPARβ is also expressed in liver macrophages and hepatic stellate cells, indicating its potential role in inflammation and fibrosis. Hepatic PPARβ activation not only improves NASH through factorization related pathways, but also reduces hepatic steatosis through autophagy-mediated FA oxidation, thus forming a therapeutic action on NASH[2].

3.3. Role of PPARγ in NASH

In non - alcoholic steatohepatitis, the adipose tissue mainly consists of white fat. When activated, PPARγ affects the differentiation and function of white adipose tissue via multiple mechanisms. It is of great significance in the transformation process of white adipose tissue into brown adipose tissue. Brown adipose tissue has the capacity to generate heat. The activation of PPARγ can facilitate the conversion of white fat cells into brown fat cells, thus enhancing the body's heat production and energy consumption [2]. This process helps transfer fat from the liver, achieving a therapeutic effect on NASH.In white adipose tissue, the activation of PPARγ does not directly bind to triglycerides (TG). Instead, it typically forms a heterodimer with RXR (retinoid X receptor) and then binds to specific DNA sequences. This binding regulates the transcription of genes associated with fat metabolism [3].

Simultaneously, PPARγ is highly expressed in quiescent hepatic stellate cells. Here, it inhibits the activation of hepatic stellate cells during liver fibrosis and lessens the deposition of collagen in the liver fibrosis process. Consequently, PPARγ could potentially serve as a valuable target for treating liver fibrosis.Despite its role in alleviating liver fibrosis, PPARγ is also involved in lipogenesis. In hepatocytes, PPARγ prompts adipocyte protein 2 and cluster of differentiation (CD) 36 - mediated free fatty acid uptake, and promotes the activities of fatty acid synthase and acetyl - CoA carboxylase 1 [3]. Additionally, PPARγ has other functions in NASH - related processes, such as influencing insulin resistance, inflammation, oxidative stress, and endoplasmic reticulum (ER) stress [4].

4. PPAR agonists have therapeutic effects in NASH

4.1. Pharmacological action of PPARα agonists in NASH

PPARα agonists can have a therapeutic effect on NASH. Research has found that PPARα agonists can also be used to treat hyperlipidemia occurring concurrently with NASH. Among them, fibrates performed particularly well[5]. Several common PPARα agonists known to date include fenofibrate, bezafibrate, Wy-14643, and GW7647, and the latest research continues to discover new potential PPARα agonists[6].

4.1.1 Fenofibrate

Fenofibrate is a lipid-lowering drug widely used in clinical practice. Since its introduction, fenofibrate has shown significant effects in lowering blood lipids and reducing the risk of cardiovascular events, and has received widespread attention in the medical community[6]. As research progresses, their indications continue to expand, including hypertriglyceridemia, mixed hyperlipidemia, and more. At present, fenofibrate has become one of the important drugs for the treatment of hyperlipidemia[8,9]. Fenofibrate primarily works by increasing the activity of lipoprotein lipase, accelerating the catabolism of very low-density lipoprotein, thereby reducing plasma triglyceride and cholesterol levels. In the treatment of non-alcoholic steatohepatitis, fenofibrate can not only improve exceptions, but also reduce fatty degeneration of hepatocytes and inhibit inflammatory response[13]. In the study by Ali et al., 80 protein targets with significant interactions with fenofibrate and 95 genes related to NAFLD were identified based on the STITCH database screening. By conducting Venn diagram analysis, 11 key targets were pinpointed. These targets are LEP, SIRT1, ADIPOQ, PPARA, SREBF1, LDLR, GSTP1, VLDLR, SCARB1, MMP1, and APOC3. The Gene Ontology analysis of these 11 targets revealed that they are predominantly engaged in lipid metabolic processes. They are related to activities such as lipoprotein particle receptor activity, protein - lipid compound binding, and lipoprotein particle binding. Moreover, they are associated with entities like lipoprotein particles, plasma lipoprotein particles, and protein - lipid compounds.Researchers utilized the DISEASES database based on the STRING algorithm and the DisGeNET database based on the EnrichR algorithm for analysis. After this in - depth examination, they confirmed the connection of these 11 targets with NASH. The results indicated that their specificity for NASH is generally greater compared to other diseases, suggesting that these targets play a crucial role in the treatment of NASH [9].

4.1.2 Benzavapetine

The mechanism action of bezafibrate is similar to that of fenofibrate. It can also effectively lower blood lipids and promote β-oxidation of fatty acids and reduce fat accumulation in the liver through the activation of PPARα[6,7]. Some scholars have also compared bezafibrate and pemafibrate (also a PPARα agonist), showing that both, especially bezafibrate, can increase the patient's creatinine, but the duration of adverse effects caused is similar.

4.1.3 Other PPARα agonists

In addition to the above traditional PPARα agonists, recent studies have also discovered some new PPARα agonists [8]. For example, a compound called PEA has been confirmed to have PPARα agonistic activity. PEA is an endogenous fatty acid amide that has shown good anti-fatty liver effects in animal models. It activates PPARα, promotes the oxidative metabolism of fatty acids, reduces the synthesis and accumulation of liver fat, and inhibits inflammatory response and oxidative stress, which has positive significance for the treatment of fatty liver [9].

Recent studies have also discovered a dual agonist of PPARα/β named K-877. This drug not only activates PPARα but also activates PPARβ, thereby more comprehensively regulating fat metabolism and energy balance. In Yamashita's animal experiments, K-877 showed significant anti-fatty liver action, reducing hepatocyte fatty degeneration, improving liver function, and inhibiting liver inflammatory response [11].

4.1.4 Natural PPARα agonists

In addition to palmitic acid, some ingredients in traditional Chinese medicine can also be used as PPARα agonists, such as berberine in Coptis chinensis[13].

Therefore, some scholars have also studied the therapeutic effects of traditional Chinese medicine formulas on mice to illustrate the natural PPARα agonists contained in traditional Chinese medicine. Kwon et al. mixed salvia miltiorrhiza, kudzu root, astragalus, hawthorn, mulberry, and orientalis in a ratio of 1:1:2:2:2:2, extracted with distilled water, and administered to mice orally for ten weeks[15]. Lee mixed mulberry leaves, lemon balm leaves, and Artemisia capillaris leaves, extracted them with distilled water, and made a drug, which he fed to high-fat-fed mice for twelve weeks[16]. Both achieve the effect of increasing PPARα expression and reducing triglycerides in the body's circulation, which has a significant therapeutic effect on NASH.

4.1.5 Side effects of PPARα agonists

Some studies have shown that long-term use of PPARα agonists can increase the incidence of liver cancer in rodents, such as Wy-14,643. Although there are species differences between humans and mice, a large number of experiments are still needed to prove the reliability and low side effects of this agonist in treating human diseases. For example, in the experiment of Jennifer E Foreman et al., it was proved that long-term use of GW7647 had a low impact on the occurrence of liver cancer in mice[13].

Fenofibrate, as a PPARα agonist, is commonly used to lower blood lipids and treat non-alcoholic steatohepatitis. However, studies have found that gufilazia can cause patients to have a certain reaction to sepsis[15].

4.2. Pharmacological Effects of PPARβ Agonists in NASH

There are few studies on PPARβ agonists. GW501516[15] (also known as GW1516) is a specific agonist of PPARβ with an EC50 value of 1.1 nM, showing high potency and selectivity, and has shown improvement action on metabolic diseases in multiple animal models, including improving exercise endurance, improving blood lipid levels and lowering blood sugar[10]. The natural ligands associated with the activation of PPARβ-related pathways include the unsaturated fatty acids eicosapentaenoic acid (EPA) and prostacyclin[8].

4.3. Pharmacological role of PPARγ agonists in NASH

PPARγ agonists are mainly thiazolidinediones (TZDs), a class of insulin sensitizers widely used in clinical practice, primarily for the treatment of non-alcoholic steatohepatitis and diabetes caused by insulin resistance. Representative drugs include rosiglitazone, pioglitazone, and ciglitazone. These medications are capable of activating PPARγ nuclear receptors within tissues including fat, skeletal muscle, and the liver, which are sites where insulin exerts its effects. By doing so, they regulate the transcription of genes that respond to insulin, and in turn, govern the production, transportation, and utilization of blood glucose [13]. In terms of the treatment of fatty liver, there are also many clinical studies on the use of PPARs agonists in patients. For example Tan[12], et al. used rosiglitazone, fenofibrate and alogliptin in clinical trials to treat patients with fatty liver. The results showed that rosiglitazone and fenofibrate can reduce liver lipid deposition and improve liver fatty degeneration and inflammation[12].

At the same time, some nonsteroidal anti-inflammatory drugs, such as indomethacin and ibuprofen, have also been found to have PPARγ agonist action[15], but in a dose-dependent manner. In addition to 15-deoxyprostidine J2 and its derivatives, which have long been confirmed to be endogenous PPARγ natural agonists, a few oxidized polyunsaturated fatty acids and the traditional Chinese medicine ingredient rhamnolide have also been found to have PPARγ agonist activity[16].

4.4. PPAR Pan Agonists

In some clinical treatments, PPAR agonists have caused adverse reactions in patients and had a negative impact. Some PPAR agonists may induce other diseases while treating non-alcoholic steatohepatitis, or leave sequelae, or may cause the disease to worsen[14,18,19].

Dual or pan PPAR agonists can avoid the side effects of specific PPAR agonists through certain complementary effects. For example, the PPARα/γ dual agonist Tesaglitazar can improve exceptions and insulin resistance in patients with type 2 diabetes in a dose-dependent manner, and avoid non-alcoholic fatty liver disease caused by insulin resistance[14]. The PPARα/β dual agonist Elafibrinor, developed for the treatment of non-alcoholic steatohepatitis, has shown good tolerance and safety in clinical trials.

5. Conclusions

As living standards rise, the global incidence of metabolic syndromes like obesity and type 2 diabetes is on the increase, posing a substantial threat to human health. Fatty liver, a key manifestation of metabolic syndrome, frequently co - occurs with other symptoms or emerges as the end - result of them. Eventually, it can progress to diseases with alarmingly high mortality rates, such as hepatocellular carcinoma. Consequently, the study of fatty liver and its related derivative diseases holds great importance.PPAR is of crucial significance in the development of non - alcoholic steatohepatitis. It has a close association with liver lipid metabolism, cholesterol levels, and oxidative stress. Moreover, PPAR can address fatty liver through diverse mechanisms. It is hoped that more scholars will further explore the role and pharmacological mechanisms of PPARs and their agonists in non-alcoholic steatohepatitis, finding an optimal solution to balance drug treatment and drug side effects, in order to improve the development of new treatments for non-alcoholic steatohepatitis.

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