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The Mechanism of Action of Bile Acid Receptor TGR5 in NAFLD

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Abstract: With the global rise in obesity rates, the prevalence of non-alcoholic fatty liver disease (NAFLD) continues to increase annually, imposing a growing economic burden worldwide. Consequently, the prevention and treatment of NAFLD are becoming increasingly critical. Takeda G protein-coupled receptor 5 (TGR5) is a member of the G protein-coupled receptor (GPCR) family, widely expressed in human and animal tissues and organs. Increasing evidence indicates that the TGR5 signaling pathway participates in regulating glucose homeostasis, insulin resistance, lipid metabolism, suppressing inflammatory responses, and liver fibrosis, thereby influencing the development and progression of NAFLD. This paper primarily elucidates the mechanisms through which TGR5 exerts its anti-NAFLD effects and reviews research findings on TGR5 agonist-based treatments for NAFLD, aiming to provide insights for both basic and clinical research.

Keywords: NAFLD; TGR5; GLP-1; Metabolism; Inflammation; Liver Fibrosis; Gut Microbiota.

1. Introduction

Non-alcoholic fatty liver disease (NAFLD) refers to the condition where liver fat infiltration exceeds 5% of hepatocytes in patients consuming less than 20 grams of alcohol per day. It encompasses a spectrum of liver disorders including simple steatosis, non-alcoholic steatohepatitis (NASH), fibrosis, cirrhosis, and potentially hepatocellular carcinoma (HCC) [1]. The primary feature of NAFLD is excessive accumulation of fat within liver cells, excluding cases caused by alcohol or other known liver-damaging factors. With rising rates of diabetes and obesity, the prevalence of NAFLD has increased. Globally, it is estimated that 32% of individuals have NAFLD; prevalence is higher in males (40%) compared to females (26%)[2]. Recent studies indicate the highest prevalence in the Americas and Southeast Asia, exceeding 40%; in the Middle East and South America, it ranges from 36-44%; Western Europe has a prevalence of about 25%; East Asia about 30%; and Africa the lowest at approximately 15-20%[2, 3]. NAFLD is considered one of the leading causes of liver-related morbidity and mortality[4], with NASH being the third most common reason for liver transplantation; 5-25% of patients progress to cirrhosis and 13% to hepatocellular carcinoma, a leading cause of cancer-related deaths[5-11]. Recent research underscores the close association of metabolic dysfunction with the complex mechanisms underlying NAFLD, prompting international experts to propose renaming it metabolic-associated fatty liver disease[12].

The pathogenesis of NAFLD is complex, with understanding shifting from the "two-hit" theory to the "multiple-hit" theory[13, 14]. The initial hit involves intrahepatic triglyceride (TG) accumulation, governed primarily by four main regulatory mechanisms: increased uptake of free fatty acids (FFA), enhanced de novo lipogenesis, reduced fatty acid oxidation (FAO), and diminished hepatic export of triglycerides in very low-density lipoprotein form. Insulin resistance is considered the primary driver of lipid influx, while hyperinsulinemia and hyperglycemia further promote lipogenesis and inhibit fatty acid oxidation [14]. Lipid accumulation renders the liver vulnerable to additional hepatotoxic insults (the second hit), subsequently leading to disturbances in hepatic bile acid metabolism, inflammation, and fibrosis[13]. However, limitations of the two-hit theory have been highlighted as research progresses, including uncertainties about causality between the two hits and challenges in explaining the complexity of NAFLD. The "multiple-hit theory," encompassing insulin resistance, nutritional factors, stressors, inflammatory cytokines, obesity, type 2 diabetes, hormones, gut microbiota, and epigenetic factors, is increasingly recognized[15]. Currently, insulin resistance and hepatic FFA play pivotal roles in the pathogenesis of NAFLD[16]. It is evident that abnormalities in lipid and glucose metabolism, inflammatory immune responses, hepatic fibrosis, and alterations in gut microbiota are crucial factors contributing to NAFLD. However, the precise upstream mechanisms remain incompletely understood.

Takeda G protein-coupled receptor 5 (TGR5), also known as the bile acid receptor, can be activated by bile acids. It belongs to the family of G protein-coupled receptors (GPCRs) with seven transmembrane domains, encoded by a single-exon gene located on human chromosome 2q35 and mouse chromosome 1 (38.53 cM)[17]. TGR5 is widely expressed as a cell membrane receptor in human and animal tissues and organs including the brain, liver, heart, kidneys, small intestine, and nervous tissues, with highest expression levels of TGR5 mRNA observed in the placenta, lungs, and spleen [17] . In the liver, TGR5 expression is found in non-parenchymal cells such as Kupffer cells, sinusoidal endothelial cells, bile duct cells, and activated hepatic stellate cells, but not in hepatocytes[18].Upon binding with extracellular ligands, TGR5 transduces signals to intracellular downstream cascades through various signaling pathways, playing crucial roles in metabolic energy regulation, inflammatory responses, cancer intervention, and therapy[19]. Bile acids serve as endogenous agonists for TGR5, with taurochenodeoxycholic acid being the most potent, followed

by glycocholic acid, lithocholic acid, deoxycholic acid, ursodeoxycholic acid, and cholic acid [20, 21]. TGR5 receptors not only interact with bile acids to exert anti-inflammatory and immune-modulatory effects but are also activated by certain agonists, participating in physiological and pathological processes such as 4-phenylbutyric acid or 4-phenylpyridine-5-carboxamide compounds, and 6α-ethyl-23(S)-methylcholic acid (6-EMCA, INT-777) [22]. As a metabolic regulator, TGR5 is involved in energy expenditure, glucose metabolism, and organismal immunity[23]. The TGR5 agonist INT-777 promotes glucagon-like peptide-1 (GLP-1) secretion, controlling blood glucose levels, energy expenditure, and lipid metabolism[24]. Another TGR5 agonist, oleanolic acid, regulates blood glucose in obese mice, reduces serum insulin levels, and enhances glucose tolerance[25]. Previous studies have shown that TGR5 helps maintain blood glucose homeostasis, improves obesity, enhances intestinal microbiota, and regulates hypothalamic signaling pathways to suppress appetite[26]. Research indicates that TGR5 agonists effectively improve hepatic steatosis and insulin sensitivity in Western diet-fed mice, demonstrating potential therapeutic benefits for non-alcoholic fatty liver disease (NAFLD) or non-alcoholic steatohepatitis (NASH)[27]. This review explores the role of TGR5 in regulating glucose and lipid metabolism, liver fibrosis, inflammatory immune responses, and its impact on the development of NAFLD.

2. TGR5 Regulates Blood Glucose Homeostasis and Improves Insulin Resistance

The effect of TGR5 in maintaining glucose homeostasis and insulin sensitivity has been widely demonstrated. For instance, using the TGR5 agonist 6α-ethyl-23(S)-methyl-cholic acid (INT-777) enhances insulin sensitivity in obese mice [28], and 7-sulfate bile acid increases glucose tolerance in TGR5-dependent mice[29]. TGR5 in various tissues of the body participates in the regulation of glucose metabolism through different molecular mechanisms.

As a receptor for bile acids, activated TGR5 enhances insulin sensitivity by increasing intestinal insulin secretion, playing a crucial role in improving blood glucose levels and maintaining glucose stability[30].Studies indicate that bile acids can promote GLP-1 secretion by intestinal L cells, but this effect is absent in TGR5 knockout mice[31, 32]. Previous research by Katsuma et al[32]also showed that TGR5 activation promotes GLP-1 secretion in the mouse intestinal endocrine cell line STC-1. The role of TGR5 in glucose metabolism primarily involves the stimulation of intestinal insulin release by stimulating intestinal L cells to secrete GLP-1. GLP-1 belongs to the gut insulinotropic peptide family; previous studies[33] have shown that GLP-1 promotes insulin secretion, enhances pancreatic β-cell survival and proliferation, inhibits apoptosis, and effectively stimulates insulin secretion in type 2 diabetes patients while reducing blood sugar[34-36]. Early views suggested that after TGR5 activation, the increase in cAMP levels in intestinal L cells leads to increased mitochondrial oxidative phosphorylation, increased ATP/ADP ratio, closure of ATP-dependent potassium channels (KATP), opening of calcium channels, promotion of calcium influx, and release of GLP-1[28]. However, subsequent research[37] confirmed that GLP-1 secretion is indeed related to increased cAMP and intracellular calcium ions but is not related to ATP-dependent potassium channels. Experiments by Brighton et al[38]further validated that GLP-1 secretion is related to changes in cAMP and Ca2+ concentrations in L cells and explained that this effect is mainly mediated by TGR5 located on the outer basal side of L cell membranes. Goldspink et al. [39]found that TGR5 activation on intestinal L cells opens L-type calcium channels via the cAMP/PKA pathway, promoting calcium influx and triggering GLP-1 secretion. Experiments show that TGR5 is expressed on intestinal L cells and that TGR5 agonists effectively induce GLP-1 release [40].Some studies indicate that there is crosstalk stimulation between FXR and TGR5 to promote GLP-1 secretion[41]. The increase in GLP-1 secretion effectively regulates glucose levels, lipid metabolism, and inflammation[42], and plays an important role in maintaining glucose homeostasis and improving insulin resistance [43, 44].

In addition to indirectly stimulating insulin secretion through GLP-1 released via TGR5 mediation, activation of TGR5 present on pancreatic cells can directly increase insulin secretion, participating in the process of glucose metabolism. Early studies[45] suggested that insulin release depends on the Gαs/cAMP/Epac/Ca2+ pathway; that is, bile acids stimulate TGR5 on pancreatic β-cells, activate Gαs coupled with it, stimulate adenylate cyclase activity, increase intracellular cAMP, further activate cAMP-dependent Epac/PLC-ε pathways, increase intracellular Ca2+, and increase insulin secretion. However, other studies have described different signaling mechanisms. Vetorazzi et al[46]found that bile acids cholic acid and taurochenodeoxycholic acid increase insulin secretion via the cAMP/PKA pathway, and this pathway does not involve Ca2+ signaling or KATP channel activity. Research by Maczewsky et al[47]further verified the cAMP/PKA pathway but unlike previous studies, their results indicated that closure of KATP channels and activation of voltage-dependent calcium channels together increase Ca2+ and insulin secretion. For pancreatic β-cells, TGR5 receptors on their surface can promote β-cell proliferation via the PKA/CREB pathway and increase insulin secretion in a glucose-dependent manner[46]. For pancreatic α-cells, TGR5 can induce GLP-1 synthesis via the PKA/CREB pathway. Both glucagon-like peptide-1 (GLP-1) and glucagon originate from proglucagon via prohormone convertases 2 (PC2) and 1 (PC1) enzymes. Activation of TGR5 induces PC1 activation, transforming insulin synthesis in α-cells to GLP-1 synthesis, and improves β-cell function in a paracrine manner[48].

Bile acid TGR5 receptor signaling pathways regulate insulin resistance. Studies have found that specific deletion of TGR5 in mouse macrophages exacerbates high-fat diet-induced insulin resistance, and TGR5 activation reduces chemokine expression in macrophages through mTOR-dependent upregulation of C/EBPβ isoform LIP, thereby reducing ATM infiltration and improving obesity-induced insulin resistance[49]. The TGR5 agonist MN6 improves insulin resistance in skeletal muscle of DIO mice through the cAMP/PKA pathway, improving glucose and insulin tolerance, and enhancing glucose uptake in the skeletal muscle of DIO mice[50]. Skeletal muscle, as the largest glucose metabolic organ in the body, plays a critical role in glucose homeostasis, and decreased muscle mass is closely related to insulin resistance and the occurrence of type 2 diabetes[51, 52]. TGR5 is expressed in skeletal muscle and induces muscle cell differentiation, muscle hypertrophy in

mice, and increased muscle strength, thus TGR5 expression in skeletal muscle is important for blood glucose regulation[53].TGR5 in skeletal muscle not only stimulates protein synthesis and muscle hypertrophy via the known insulin-like growth factor-1 (IGF-1)/phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) pathway [54], but also effectively promotes mitochondrial biogenesis by enhancing PGC-1α expression[55]. Sasakis et al[56]xperiments showed that overexpression of TGR5 in skeletal muscle increases respiratory exchange rate and glycolytic flux and improves glucose clearance rate under a high-fat diet (HFD), suggesting that TGR5 in skeletal muscle improves glucose clearance rate by promoting glucose utilization, specifically by activating TGR5 through the cAMP/PKA pathway, which alters the activity of phosphofructokinase (PFK), promotes an increase in glycolysis, and promotes glucose uptake and metabolism in skeletal muscle[56, 57]. GLP-1 induced by TGR5 also improves insulin resistance in skeletal muscle. GLP-1 promotes glycogen synthesis gene glycogen synthase 1/2 (GYS 1/2) expression by promoting AMPK phosphorylation, and may also affect the translocation of glucose transporter 4 (GLUT 4) to the cell membrane[58, 59]. In addition, GLP-1 analogs promote autophagy by regulating Sestrin 2 (SESN 2) in skeletal muscle cells, promote GLUT 4 expression, and effectively increase glucose uptake[60].

2.1. TGR5 Regulates Lipid Metabolism

TGR5 plays an important role in lipid metabolism and is closely related to the development of NAFLD in patients. Using intestinal TGR5 agonist RDX8940 reduced liver weight, hepatic triglycerides, and cholesterol levels in NAFLD model mice[27]. Carino et al[61]found that the specific TGR5 agonist BAR501 alleviated liver damage in male NASH model mice, and TGR5 activation protects the liver by increasing mouse energy expenditure, promoting brown adipose tissue (BAT) function, and inducing whitening of periepididymal white adipose tissue (ep WAT). The specific mechanism involves TGR5 activation in adipose tissue, changes in intracellular cAMP concentration, drives the cAMP response element-binding protein (CREB) to aggregate on the cAMP response element (CRE) located in the Pgc-1α gene promoter, and regulates the expression of the Pgc-1α gene[61, 62]. This gene binds and activates multiple nuclear receptors and transcription factors, coordinates the expression of genes involved in glucose, fatty acid, and cholesterol homeostasis, promotes BAT function and ep WAT browning, and further reduces liver damage[63].

It has been shown that injecting bile acids into obese mice increases energy release in BAT, which is related to TGR5 receptor mediation, because TGR5 receptors are highly expressed in BAT mitochondria [25, 64]. After treatment with bile acids in BAT cells and human skeletal muscle cells, it was found that oxygen consumption, extracellular acidification rate, and cAMP-dependent type 2 iodothyronine deiodinase (D2) increased; D2, as the main heat-producing protein, can convert thyroxine 4 (T4) to active thyroxine 3 (T3), indicating that bile acids can increase D2 activity to promote thermogenesis. After feeding wild-type and TGR5-/- obese mice with natural TGR5 ligand oleanolic acid (OA) for 20 weeks, it was found that wild-type mice had increased glucose tolerance and cAMP content, and D2 expression was significantly higher than in TGR5-/- mice, with increased T3 levels[65], TGR5 receptor participates in energy metabolism via the cAMP-D2-T3 signaling pathway. Dietary supplementation with cholic acid and taurocholic acid can activate the TGR5-cAMP signaling pathway in thermogenic tissues such as brown adipose tissue, significantly reducing body weight in high-fat diet-fed mice[66, 67].

Activation of TGR5 promotes extracellular signal-regulated kinase (ERK) phosphorylation at serine 616, effectively activating dynamin-related protein 1 (DRP1) involved in mitochondrial fission, and increases mitochondrial fission factor (MFF) expression. MFF recruits DRP1 to mitochondria. Both the TGR5-MFF and TGR5-ERK-DRP1 pathways play important roles in mediating mitochondrial fission, effectively increasing mitochondrial number and heat production capacity in white adipose tissue (WAT) [68].Additionally, activated TGR5 promotes phosphorylation of cAMP response element-binding protein (CREB) via the cAMP-PKA pathway[69, 70]. CREB plays a crucial role in regulating the transcription and expression of peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC-1α), a key regulator of mitochondrial thermogenesis gene uncoupling protein 1 (UCP1)[71]. Furthermore, TGR5 can enhance mitochondrial mass and mitochondrial/nuclear DNA ratio (mtDNA/nDNA) through the CREB-PGC-1α signaling pathway, effectively improving mitochondrial function[72].

2.2. TGR5 Regulates Inflammation

Inflammation is a common pathological phenomenon involved in the development of many diseases, and chronic inflammation provides a favorable microenvironment for the occurrence and development of malignant tumors[73]. Activated as a bile acid receptor, TGR5 has anti-inflammatory properties and induces tolerance states in various systems to prevent chronic inflammation[74-78]. In the digestive system, TGR5 deficiency exacerbates steatosis and inflammation, thereby aggravating liver damage[79]. The anti-inflammatory effect of TGR5 in the enterohepatic circulation protects the host from excessive immune activation induced by antigens[80]. Macrophages exhibit two phenotypes, M1 and M2. Activation of M1 macrophages produces inflammatory factors such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), while the anti-inflammatory action of M2 macrophages involves increased secretion of anti-inflammatory cytokine interleukin-10 (IL-10) [81]. TGR5 activation promotes the transformation of macrophages from the pro-inflammatory M1 phenotype to the anti-inflammatory M2 phenotype [82]. In liver damage caused by chronic inflammation, TGR5 activation in Kupffer cells helps initiate FoxP3+ T-regulatory cells to maintain immune tolerance and protect the liver from additional damage [83]. Activation of TGR5 triggers Kupffer cells to transition from the pro-inflammatory and pro-fibrotic M1 phenotype to the anti-inflammatory and anti-fibrotic M2 phenotype (selective activation) [84, 85]. M2 macrophages produce high levels of anti-inflammatory cytokines such as IL-10 and transforming growth factor-beta (TGF-β), characterized by markers CD115, CD206, and CD163[86, 87].

TGR5 inhibits nuclear factor-kappa B (NF-κB) signaling transduction and activation of the NLRP3 inflammatory body [88], thereby reducing the expression of inflammatory cytokines such as TNF-α, IL-6, and IL-1β, and activating the NRF2/heme oxygenase-1 (HO-1) signaling pathway to suppress M1 macrophage polarization and reactive oxygen species (ROS) production. Research has found that activated TGR5 increases intracellular cAMP and calcium ion levels,

inhibits IκB phosphorylation, reduces p65 nuclear translocation, thus suppressing the NF-κB signaling pathway and reducing cytokine production[89]. Additionally, TGR5 also inhibits the NF-κB pathway by promoting interaction between IκBα and β-arrestin 2[90]. Furthermore, activation of the TGR5/PKA pathway promotes CREB phosphorylation [91], enhancing its competitive binding with NF-κB coactivator CREB-binding protein, thereby promoting secretion of IL-10 and TGF-β[86]. Signal transducer and activator of transcription 3 (STAT3) is also a key factor in inflammation and cancer, as TGR5 activation promotes STAT3 phosphorylation[92]. TGR5 increases intracellular cAMP expression in rat alveolar macrophages, thereby reducing macrophage phagocytic activity and inhibiting the production of pro-inflammatory cytokines induced by LPS[14]. Furthermore, TGR5 activation inhibits the expression of inflammatory mediators induced by endotoxin-activated Toll-like receptor 4 (TLR4) [93].

Increasingly, studies indicate that GLP-1 has anti-inflammatory effects [94].GLP-1 reduces the formation of inflammatory cytokines TNF-α, IL-6, and IL-1β, achieving anti-inflammatory effects[95].Moreover, GLP-1 analogs such as liraglutide effectively inhibit the NLRP3[96], inflammatory body, increasing Nrf2/HO-1 signaling pathway transduction. These actions help prevent oxidative damage and regulate inflammation, thereby achieving anti-inflammatory effects[97, 98]. Therefore, TGR5 can effectively inhibit inflammation through direct and indirect mechanisms.

2.3. TGR5 Regulates Liver Fibrosis

Liver fibrosis is a common pathological process in various chronic liver diseases, including viral hepatitis, autoimmune hepatitis, and NAFLD. Extracellular matrix deposition is a major pathological manifestation of liver fibrosis. Regardless of the triggering factors, liver injury causes changes in hepatic sinusoidal endothelial cells and hepatic stellate cells (HSCs), ultimately leading to the progression of liver fibrosis and microvascular dysfunction[99-102]. Persistent activation of HSCs leads to excessive deposition of extracellular matrix, replacing normal liver cells and disrupting the liver's inherent structure and function. This further progresses to bridging fibrosis and eventually develops into cirrhosis, and even liver failure [103]. Therefore, inhibiting the persistent activation of HSCs is one of the main measures for preventing and treating liver fibrosis. Activation of HSCs is regulated by multiple cytokines, among which platelet-derived growth factor-B (PDGF-B) is known as the most potent activator of HSCs, exerting strong chemotactic effects [104].In a study on the regulation of portal hypertension mediated by TGR5 through the inhibition of endothelin-1 (ET-1), Klindt et al. found that long-term treatment with lithocholic acid (LCA) significantly increased the mRNA expression levels of PDGFR-B in TGR5 knockout mice compared to WT mice[99]. Although these findings are insufficient to confirm the regulatory role of TGR5 on PDGFR-B in liver fibrosis, the absence of TGR5 disrupts bile acid balance and increases taurocholic acid (TCA). Conversely, TCA promotes cholesterol absorption, increases hepatic oxidative stress, and accelerates the progression of liver fibrosis [65, 99, 105]. Studies have shown that high doses of TGR5 agonist oleanolic acid (OA) affect bile acid metabolism and pose a risk of cholestatic liver injury, but OA at doses below the lowest toxic dose still exhibits anti-diabetic and anti-fibrotic effects [106, 107]. As an endogenous ligand of TGR5, lithocholic acid (LCA) can inhibit TGF-β activity, prevent M1 macrophage polarization, and mitigate liver fibrosis in mouse models following TGR5 activation[108]. It is noteworthy that although TGR5 is highly expressed in activated HSCs, its exact role in these cells remains unclear[109].

2.4. TGR5 Receptor and Gut Microbiota

In the intestines, the complex metabolism of bile acids is largely regulated by the gut microbiota. The gut microbiota plays a crucial role in bile acid metabolism by catalyzing a series of enzymatic reactions that convert primary bile acids into secondary bile acids[110]. Conversely, bile acids also influence the composition of the gut microbiota. Studies have shown that the size and composition of the bile acid pool appear to be important in regulating the ecological structure of the gut microbiota[110]. Bile acids have direct antimicrobial effects in the gut and also indirectly regulate host immune responses through receptors such as TGR5 and FXR. Furthermore, research has demonstrated that secondary bile acids derived from microbes serve as ligands for TGR5[110].Experimental studies have observed complex and significant changes in the gut microbiota composition in rats fed a diet high in cholic acid[110]. Moreover, it has been shown that the gut microbiota can enhance the secretion of glucagon-like peptide-1 (GLP-1) by stimulating the TGR5 signaling pathway, thereby improving glucose homeostasis[111].Research indicates that C57BL/6J mice recombinant with Bacteroides can increase serum insulin and GLP-1, suggesting that the gut microbiota can treat NAFLD through the TGR5/GLP-1 signaling pathway [112]. Research has shown that the gut microbiota can stimulate the secretion of glucagon-like peptides (GLP-1 and GLP-2) and the anorexigenic hormone peptide YY through activation of specific G protein-coupled receptors expressed on intestinal L cells, such as TGR5, GPR41, GPR43, and GPR119. These intestinal peptides control energy homeostasis, glucose metabolism, and metabolic inflammation[113].Changes in the gut microbiota affect the composition of the bile acid (BA) pool, leading to increased expression of TGR5. This induction catalyzes membrane-bound adenylate cyclase to convert ATP into the signaling molecule cAMP in the presence of Mg^{2+}, activating the TGR5-cAMP anti-inflammatory pathway to inhibit the NLRP3 inflammasome, thereby reducing the production of TLR4, TNF-α, and IL-6[114, 115]. Therefore, the metabolic balance between the gut microbiota and the BA-TGR5 pathway is crucial for the prevention and treatment of NAFLD.

2.5. TGR5 Agonist Therapy for NAFLD

TTGR5 is involved in the regulation of multiple cellular signaling pathways, and its agonists effectively alleviate inflammation, metabolic syndrome, and digestive system disorders[116, 117]. TGR5 agonists include natural compounds, semi-synthetic compounds, and synthetic ligands[118]. Furthermore, triterpenoid compounds such as ursolic acid, oleic acid, and ursodeoxycholic acid exhibit selective TGR5 agonist activity[119]. INT-1777 and BAR 501 are effective TGR5 agonists extensively studied for their therapeutic effects in animal models [120]. BAR 501 can reverse hepatic steatosis and fibrosis scores induced by HFD-β-fructose-β in NASH mouse models and shift macrophage polarization from an M1 to M2 phenotype[61]. Moreover, effective TGR5 agonist components have been discovered in

studies of food and traditional Chinese medicine, validated for improving glucose and lipid metabolism and preventing/treating NAFLD. Pure total flavonoids from citrus can ameliorate TGR5 deficiency symptoms in NASH mice and improve liver damage [121, 122]; active compounds like saponins from Panax notoginseng activate TGR5 and alleviate obesity and insulin resistance induced by a high-fat diet in mice[122]; berberine compounds improve hyperglycemia in mice through the colon TGR5-GLP pathway[123], providing new strategies for TGR5-based NAFLD treatment.

3. Prospects

With the global increase in obesity, the incidence of NAFLD is rising annually, imposing an increasingly heavy economic burden globally, making the prevention and treatment of NAFLD more important. Abnormal lipid and glucose metabolism, inflammatory responses, liver fibrosis, and changes in gut microbiota are significant factors contributing to NAFLD. TGR5 is a membrane receptor for bile acids widely distributed throughout the body with diverse functions. It regulates glucose homeostasis, insulin resistance, lipid regulation, inhibits inflammatory responses, and plays a regulatory role in liver fibrosis through complex signaling pathways, thereby influencing the occurrence and development of NAFLD. Activation of TGR5 stimulates the release of GLP-1 from enteroendocrine cells to maintain blood glucose stability. Activation of TGR5 improves insulin resistance through the cAMP/PKA pathway; it can increase energy metabolism through the TGR5/cAMP/D2/T3/UCP signaling pathway, thereby reducing fat deposition. TGR5 inhibits NF-kB signaling transduction and activation of the NLRP3 inflammasome, reducing the expression of inflammatory factors, thereby inhibiting inflammation, reducing liver cell damage, and slowing NAFLD progression. Activation of TGR5 alleviates liver fibrosis in mouse models. Changes in the gut microbiota enhance the secretion of glucagon-like peptide-1 (GLP-1) by stimulating the TGR5 signaling pathway, thereby improving glucose homeostasis. Increasing research suggests that the TGR5 signaling pathway may become a new therapeutic target for preventing and treating NAFLD. Current experimental studies demonstrate the effectiveness of TGR5-based NAFLD treatment. However, challenges such as the lack of clinically available TGR5 agonists remain, possibly due to adverse reactions associated with systemic TGR5 activation, such as inhibition of gallbladder emptying, itching, and reduced systemic vascular resistance [18]. Addressing these adverse reactions, studies propose increasing molecular weight or introducing large polar groups to effectively limit the impact of TGR5 agonists on the intestines while minimizing drug exposure in plasma and liver, thereby reducing gallbladder toxicity[124-126]. In recent studies, many traditional Chinese medicines have also been shown to effectively activate TGR5, suggesting potential avenues for further research on TGR5 agonists through exploration of traditional Chinese medicine.

4. Conclusion

The relationship between TGR5-mediated lipid and glucose metabolism, inflammatory responses, liver fibrosis, and changes in gut microbiota is closely related to the development of NAFLD. Activation of TGR5 plays a positive role in the prevention and treatment of NAFLD. Developing safe and effective TGR5 agonists, exploring appropriate usage ranges, is of significant importance for the prevention and treatment of NAFLD.

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