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Review Article

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Transcription factors in abnormal metabolism and inflammatory of NAFLD

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Abstract

Non-Alcoholic Fatty Liver Disease (NAFLD) affects 25% of the adult population worldwide and is a major contributor to cirrhosis and hepatocellular carcinoma (HCC). In recent years, there is a growing number of research support the idea that NAFLD is not just a disease that is limited to the hepatocytes, but is associated with several extrahepatic manifestations. NAFLD is characterized by substantial heterogeneity of disease phenotypes and complex pathogenesis, and has no approved therapy. Numerous transcription factors control energy metabolism, inflammatory response and inter-organ crosstalk. This review provides an overview of the evidence linking transcription factors to NAFLD and discuss possible therapeutic strategies.

Keywords: Non-Alcoholic Fatty Liver Disease (NAFLD); Transcription factors; Obesity; Therapeutic strategies.

Introduction

With the epidemic of obesity and metabolic syndrome, NAFLD has emerged as a major public health problem with an estimated global prevalence of 25% [1]. NAFLD is a spectrum of chronic liver disease, and this disease progression ranges from excessive cytoplasmic retention of triglyceride in hepatocytes and steatosis, to hepatic triglyceride accumulation accompanied by inflammation and hepatocyte injury (Nonalcoholic Steatohepatitis (NASH)) and finally to severe fibrosis and cirrhosis in livers and/or HCC [2]. The excessive accumulation of lipids in hepatocytes is the central and initial step of nutrition-overload liver injury, and promotes the occurrence of lipotoxicity, oxidative and Endoplasmic Reticulum (ER) stress, metabolic inflammation, hepatocyte ballooning, apoptosis and cell death in different liver cells mainly including Liver Sinusoidal Endothelial Cells (LSECs), Hepatic Stellate Cells (HSCs), Kupffer Cells (KCs) and infiltration of immune cells [3]. The progression of NAFL to NASH and liver fibrosis is complex, multifactorial and heterogeneous; none of the drugs to date have been approved by the

Food and Drug Administration (FDA) for treating NAFLD.

Drugs are currently being developed for a variety of targets, including transcription factors, which have been a focus of research due to their diverse mechanisms of action. Transcription factors activate or inhibit transcription through direct or indirect binding to specific DNA target sequences within gene regulatory regions. The intricacy of their regulatory networks is increased by the multifaceted cross-talk between numerous transcription factors and their interactions with target genes across multiple tissues, cellular contexts, and temporal settings [4]. Notably, transcription factors are emerged as integrators of metabolic homeostasis, inflammatory and immune response, apoptosis, and fibrogenesis signaling networks, which have been linked the pathogenesis and progression of NAFL to NASH. Therefore, transcriptional factors may become an appropriate therapeutic target for hepatic steatosis and fibrosis in NAFLD. For example, Farnesoid X Receptor (FXR) has become one of the most promising drug targets for both steatosis and fibrogenic processes in the liver [5], and potent semi-synthetic bile acid FXR activators (such as obeticholic acid) have been developed for the treatment of NASH [6]. The peroxisome proliferator-activated receptors (PPARs), act as lipid sensors, are also important modulators of metabolic and inflammatory pathways in hepatic and extrahepatic tissues and are future therapeutic targets for NASH [7].

NAFLD is a heterogeneous condition and its exact aetiology is not completely understood, which urgently needs effective treatment strategies. Overall, the progression of NAFL to NASH or even HCC involves the development of steatosis, liver injury, inflammation and fibrosis. Transcription factors participate in the onset and progression of NAFLD and they also accompany by its evolution towards more debilitating conditions. Here, we describe the transcription landscape and mechanisms during NAFLD (such as lipotoxicity, oxidative stress, inflammation and fibrosis development) and summarize recent studies on the role of transcription factors in NAFLD and its transition to NASH. Finally, we wrap up by providing a summary of the therapies, targeting transcription factors, that are currently under development and possible future therapeutic options to combat liver diseases.

Pathogenesis of NAFLD

With the dramatic changes in living standards over the past few decades, NAFLD has become the most prevalent liver disease in the world [8]. However, the development of NAFLD and its progression to NASH remains elusive because of complex etiopathogenetic mechanisms. According to the current "multiple-hits" hypothesis, the first hit is the development of hepatic steatosis via accumulation of triglycerides in hepatocytes, the second hit includes exposure to oxidative stress, inflammatory cascades and fibrogenesis. Multiple parallel hits also contain multiple risk factors involving multiple cell types and multiple organs [9]. Thus, new pharmaceutical targets are a great unmet need for an increasingly NAFLD population and demand a comprehensive understanding of the pathophysiology of the disease.

Transcription factors in steatosis

Hepatic steatosis is caused by the accumulation of intracellular lipids within the cytoplasm of liver hepatocytes [10]. A considerable number of transcription factors may be contributed to the progression of hepatic steatosis, including FXR, PPARs, sterol regulatory element-binding protein-1c (SREBP-1c), carbohydrate response element-binding protein (ChREBP), forkhead Box O1 (FOXO1), liver X receptors (LXRs), hypoxia-inducible-factor 2alpha (HIF2α), CCAAT/enhancer-binding proteinα (C/EBPα) etc.

FXR, a receptor for bile acids, serves as a regulator in of energy metabolism in liver [11], and regulates glucose and lipid metabolism. The activation of FXR reduces lipotoxicity (by inactivating the de novo lipogenesis mediated by SREBP-1c) and increases mitochondrial β-oxidation and cholesterol excretion [12]. Previous studies demonstrated that activation of FXR decreased hepatic triglycerides through bile-acid-dependent decreases in intestinal lipid absorption or selective changes in lipogenesis [13]. LXRs (LXRα and LXRβ), a member of the nuclear receptor family of transcription factors, plays an important role in the transcriptional control of cholesterol homeostasis. Compared to ob/ob mice, LXRαβ-deficient-ob/ob mice show reduced hepatic steatosis and improved insulin sensitivity, but remain obese [14]. PPARs, a group of nuclear regulatory factors, consists of three isotypes-α, β/δ and γ. Constitutive mitochondrial β-oxidation activity was reduced in the livers of mice lacking PPARα [15]; while PPARα activation enhances hepatic FA β-oxidation and ameliorates fatty liver [16]. In diet-induced and genetically obese mouse models, over-expression of PPARβ/δ improves liver steatosis through phosphorylating lipogenic enzyme Acetyl-Coa Carboxylase (ACC) and Adenosine Monophosphate-Activated Protein Kinase (AMPK) [17,18]. Although PPARγ is highly expressed in adipose tissue and macrophages, ectopic expression of PPARγ in hepatocytes up-regulates several proteins associated with lipid uptake, triacylglycerol storage, and formation of lipid droplets, then aggravates hepatosteatosis [15]. Bettina König *et al*. clarified that PPARα/γ reduced the synthesis of fatty acids and triacylglycerols by inhibiting SREBP-1 activation [19]. SREBP-1c belongs to the family of SREBP transcription factors (SREBP-1a, SREBP-1c and SREBP-2), functionally responsible for controlling the synthesis and transport of cholesterol and fatty acids in the liver and the whole body [20]. Overactivation of SREBP1c is observed in models of diet-induced obesity, leptin-deficient ob/ob mice and db/db mice [21]. However, deficiency of SREBP1c only partially ameliorates hepatosteatosis [22]. ChREBP, highly expressed in the liver, intestine and adipose tissue [23], is involved in the processes of hepatic glycolysis, fatty acid synthesis, β oxidation of fatty acids [23,24]. Notably, ChREBP is the only transcription factor that can transduce glucose-dependent glycolysis and lipogenic signals, and is considered to be the main regulator of liver disease [24]. FOXO1 widely expressed in all tissue types, is one of the most important transcriptional effectors in the insulin and insulin-like growth factor 1 (IGF-1) signaling pathway [25]. FOXO1 plays a dual role in NAFLD. Hepatic steatosis is exacerbated by overexpression of FOXO1 in the liver, which causes an increase in gluconeogenesis and TG production and a decrease of fatty acid oxidation [26]. In addition, dephosphorylation and nuclear translocation of FOXO1 effectively relieve lipid accumulation in liver cells and thereby prevent NAFLD [27]. HIF2α is one of the four subunits that make up transcription factors activated by hypoxia [28]. Cen Xie *et al*. proved that activation of intestinal

HIF2α contributes to hepatic steatosis in obesity [29]. Moreover, the knockdown of HIF2α can suppress triglyceride accumulation and ameliorate steatosis in the liver [30]. C/EBPα is a key regulator of hepatocyte function [31]. Bobby Guillory *et al*. demonstrated that the inhibition of activation of C/EBPα can prevent hepatic steatosis [32]. It has also been illustrated that CEBP-α improves CCl_4-induced hepatic fibrosis in mice by promoting apoptosis of hepatic stellate cells [33].

Inflammation

NASH is characterized by hepatic lipid accumulation and inflammatory cell infiltration, which tend to develop into fibrosis, cirrhosis [34]. Hepatic inflammation and apoptosis depend on a variety of factors, including changes in systemic metabolism (for example, obesity, diabetes, non-alcoholic fatty liver disease), alcoholic hepatitis and so on [35]. Disproportionately inflammation can induce massive loss of hepatocytes, exacerbating the severity of various liver diseases. In severe cases, it can cause irreversible liver damage, fibrosis and carcinogenesis. Liver-resident cells like Kupffer cells, sinusoidal endothelial cells, and various immune cell subsets recruited in response to injury emit pro-inflammatory signals, leading to liver steatosis, inflammation, injury and fibrosis [36]. In this part of the review, we summarize the transcription factors associated with liver inflammation and apoptosis, for instance, Signal Transducer And Activator of Transcription (STAT), basic leucine zipper ATF-like transcription factor (BATF), HNF1 homeobox A (HNF1α, TCF-1), nuclear factor, IL-3 regulated (NFIL3, E4BP4), forkhead box P1 (FOXP1).

T cells and B cells

In the progression of inflammatory changes and hepatocellular damage in NASH, T cells exhibit heterogeneity and are composed of multiple differentially active subsets. Compared to healthy controls, Th1, Th17 cells are increased in NASH patients and mice [37]. The expression of Th1-related cytokines IFN-γ, IL-12 and TNF-α is elevated after ConA induced in choline-deficient-diet-fed mice; which is associated with STAT4 and T-bet activation [38]. However, conflicting results have emerged on the function of Th17 in animal models of NASH. Notably, recombinant IL-17A treatment can mimic NASH pathologic character and increase the expression of PPARγ [39]. Activator protein-1 (AP-1) transcription factor JunB and BATF are required for Th17 cells development [40]. Damasceno LEA *et al*. showed that the pyruvate kinase M2 (PKM2) translocated into the nucleus and interacts with STAT3, and mediated the differentiation of Th17 cells [41]. Treg cells play an important role in maintaining homeostasis. Adoptive transfer of Tregs can attenuate high fat diet (HFD)-induced hepatic inflammation [42]. Moreover, pioglitazone, the agonist of PPARγ, ameliorates liver pathology of NASH through strengthening Treg functionality [43]. Furthermore, the transcription factors TCF-1 [44], NFIL3/E4BP4 [45], FOXP1 [46] are essential for the development and function of Tregs, however HIF-1α or HIF-2α merely affects the function of Tregs [47]. Nevertheless, studies indicates that HIF-1α enhances Th17 cells development by glycolysis pathway, while diminishes Tregs differentiation via degrading Foxp3 [48,49]. IL-15 induced low activity of the FOXO1 in liver $CXCR6^+$ $CD8^+$ T cells in NASH mice and in patients with NASH [50]. The oxidative environment of obesity increases STAT1 and STAT3 signaling, which promotes T cell recruitment and NASH or drives HCC, respectively [51]. NF-κB1 deficiency accelerates MCD (methionine/choline-deficient) diet-induced NASH progression by favoring IL-15 production and NKT cell recruitment [52].

B lymphocytes can exacerbate inflammatory diseases through secreting pro-inflammatory cytokines, controlling nearby immune cells, and differentiating into autoreactive antibody-secreting cells [53]. Aberrant accumulation of B cells in the livers of NASH patients leads to high levels of lobular inflammation and fibrosis [54]. Activated pro-inflammatory B cells accumulate in the liver during NASH and impair insulin sensitivity and inflammation via MyD88/NF-κB signaling [55]. Bregs, the strong producers of IL-10 and IL-35, may against NASH via suppressing inflammation [56]. Additionally, FOXD3 suppresses the production of Breg cells by directly binding the IL-10 promoter [57]; and transcription factor c-Maf is indispensable for IL-10 expression in Bregs [58].

Macrophages

Liver macrophages, consist of tissue-resident Kupffer cells and recruited monocyte-derived macrophages from the systemic circulation, play a central role for in the development and progression of NAFLD and NASH [59].

Activating PPARα/γ shows effect of anti-inflammatory effects in NAFLD and NASH [60]. Kupffer cells aggravate NASH by IL-1β-dependent suppression of PPARα [61]. PPARα regulates inflammation by increasing the expression of leukotriene B_4 (LTB_4)- a catabolic enzyme that inhibits extracellular LTB_4- mediated inflammation, thereby preventing NF-κB-mediated the increase in the expression of IL-6 and IL-12. PPARγ inhibits NF-κB-mediated macrophages survival and iNOS up-regulation. Activation of NF-κB in macrophages can aggravate the progression of NASH, which in turn induces pro-inflammatory cytokines and lipid metabolism disorders [62]. Microphthalmia/Transcription Factor E (MiT-TFE) is a key regulator of Autophagy-Lysosomal Pathway (ALP), involved in cellular energy homeostasis and metabolic processes [63]. Activating the TFEB-mediated ALP improves hepatic steatosis and insulin resistance in NAFLD [64]. Further, activation of MiT/TFE transcription factors in Kupffer cells in murine and human NASH drives the occurrence of inflammation and fibrosis [65]. HIF-1α of hepatocytes induces steatosis, while macrophage-specific HIF-1α contributes to liver inflammation and decreases autophagic flux in MCD-induced NASH [66].

LSECs

Liver Sinusoidal Endothelial Cells (LSECs), the gatekeepers of liver homeostasis, display anti-inflammatory and anti-fibrogenic properties under steady-state conditions. At the stage of NASH, capillarized LSECs release inflammatory mediators and cause the recruitment of inflammatory cells, thus promoting liver injury and inflammation [67]. Mechanistically, targeted silencing of the runt-related transcription factor (RUNX1) gene in LSECs decreases T cells and myeloid cells infiltration and reduces liver inflammation [68].

Fibrosis

Liver fibrosis is a dynamic process characterized excessive and reversible accumulation of components of the Extra Fiber Matrix (ECM) in the liver, and caused by Hepatitis B Virus (HBV) and HCV infection, alcohol consumption or NASH, parasitic infections (Schistosoma) [69]. Notably, a number of transcription factors contribute to the development of hepatic fibrosis.

HSCs

Hepatic Stellate Cells (HSCs) represent the dominant hepatic fibrogenic cell population during NASH. A large amount of literature indicates that PPARγ, FOXO1 are fundamental tran-

scription factors for controlling anabolic functions. In addition, PPARγ is reported to exert protective effects on hepatic fibrosis. The expression of PPARγ is decreased in HSCs during MCD-induced NASH [70]. Specific disruption of PPARγ in HSCs exacerbated inflammatory and fibrogenesis in the liver [71]. Inactivation of FOXO1 is more susceptible to liver fibrosis [72]. GATA binding protein (GATA) family is essential in the development of the liver diseases [73]. GATA4/6 mediates the inhibition of fibrosis signals in HSCs, and GATA4/6 knockdown is the main cause of HSCs fibrosis gene expression [74,75]. GATA2 and GATA3 can bind to a site around -2323 in PPARγ1 promoter, contribute to inhibition of PPARγ1 expression in HSCs and exacerbation of liver fibrosis [76].

FOXF1 expressed in HSCs is closely related to liver regeneration [77]. Kerstin Abshagen *et al*. reported that FOXF1 silence was able to inhibit the activation of HSCs, effectively improve liver damage and fibrosis in mouse liver [78]. Kruppel-like factor 6 (KLF6) is induced as an early gene during HSCs activation [79], and inhibits activation of HSCs by repressing fibrogenic genes and increasing apoptosis of activated HSCs [80]. Interferon Regulatory Factor 1 (IRF-1) and IRF-2 are associated with humans and mice HSCs activation and fibrosis regression [81]. IRF-1/2 protect against liver damage [82], and induce the apoptosis of HSCs during hepatic fibrosis [83]. ATF3 is over-expressed in mice and human fibrotic livers, which worsens liver fibrosis and plays a positive role in NASH by activating HSCs [84,85]. It is interesting to know that over-expressing ATF3 promotes the pro-fibrotic genes and stimulates the activation of HSCs, thus aggravating the liver fibrosis [84]. With the rise of various omics, researchers identify ETS1, ETS2, GATA4, GATA6, IRF1 and IRF2 transcription factors as the HSC lineage regulators in mouse and human by ChIP-seq [81].

Macrophages

Macrophages, particularly abundant in the liver, have emerged as central players in the development of liver fibrosis and regression. Macrophages are conventionally divided into a classical M1 'pro-inflammatory' phenotype and an alternatively activated 'wound healing' M2 phenotype, and play different roles in the fibrosis progression of NASH [86] KLF4, involved in cell growth, differentiation and proliferation [87], is reported to induce M2 polarization in liver macrophages and prevent hepatic fibrosis in NASH [88]. HNF4α, as a therapeutic target for the treatment of liver fibrosis, which has been verified related to the epithelial-to-mesenchymal transition [89]. It has also been reported that HNF4α protects against alcohol- and MCD diet induced liver injury through affecting macrophages infiltration and polarization [90,91]. The pan-PPAR agonist lanifibranor indirectly inhibits hepatic macrophage infiltration and pro-inflammatory macrophages activation, thereby reduces steatosis, inflammation and fibrosis in NAFLD mouse models [92]. X-box binding protein-1 (XBP1) is upregulated in liver tissues from patients with NASH. Specific macrophage XBP1 depletion inhibits hepatic fibrosis and ameliorates nutritional steatohepatitis in mice [93]. IRF5 has been reported as an important pro-inflammatory transcription factor during inflammatory diseases. Lacking IRF5 in macrophages leads to immunosuppressive and antiapoptotic properties, thus complete protection from hepatic fibrogenesis [94]. ATF6 is associated with the activation of macrophages and involved in fibrogenesis. Macrophages ATF6 knockdown suppresses the secretion of IL-1α and attenuated fibrosis in the liver [95]. PU.1 is indispensable to tissues fibrosis [96], and high expressed in hepatocytes and macrophages of obese mice and populations. blocking PU.1 ameliorates liver steatosis, inflammation and fibrosis in mice in NASH. Targeting PU.1 in macrophages inhibits liver steatosis, inflammation, and fibrosis in Diet-Induced Obese (DIO) and genetically obese (db/db) NASH mouse model [97]. As above, FOXO1 is a key transcription factor of metabolic homeostasis. Myeloid cell conditional FoxO1-knockout skews macrophage polarization from M1 to M2 phenotype, contributing to reduced hepatic inflammation, steatosis and fibrosis [98].

The intercellular crosstalk between liver macrophages and surrounding cells is critical in NASH fibration. Overexpression of PPARγ in macrophages inhibited the migration and activation of HSCs through reducing IL-1β and CCL2, paralleling with mitigatory inflammation and fibrosis [99]. NFATc4 activation enhances the macrophage-mediated inflammatory response and promotes hepatic inflammation and fibrosis during the progression of NASH by increasing the production and secretion of osteopontin (OPN) from hepatocytes [100].

Th2 cells

Fibrosis is associated with the accumulation of Th2 cells, in particular, IL-4 and IL-13 signaling activation. STAT3, STAT6, STAT5, GATA3 and NFATc1 are required for Th2 cells differentiation, development or Th2 cytokine production [101,102]. In addition, transcription factor c-Maf can promote IL-4 production in $CD4^+$ T cells [103]. Differently, SOX4 binds directly to GATA-3 or the promoter region of the gene encoding IL-5 to suppress Th2 differentiation and Th2 cells–mediated inflammation [104].

ILC2

Innate lymphoid cells (ILCs) are a recently identified family of lymphoid effector cells. More studies describe the prominent role of ILCs on fibrosis in the mucosal tissues, especially the gut and lung. However, Tamar Mchedlidze *et al*. demonstrated a pathogenic capacity of ILC2 in hepatic inflammation and fibrosis [105]. IL-33 is increased in human cirrhotic liver tissue or mice fibrosis liver tissue, leading to accumulation and activation of ILC2 in the liver. Transcription factor ETS1 is required for the appropriate expansion of ILC2 in response to IL-33 [106]. Activated hepatic ILC2 induces inflammation and fibrosis through producing IL-13. Bcl11b, previously considered a T-cell lineage identity transcription factor, acts directly upstream of the key ILC2 transcription factor Gfi1. In the absence of Bcl11b, ILC2 fails to produce IL-13 in response to IL-33 [107].

Modulation of transcription factors and candidate drugs for NASH

FXR

FXR antagonism in the intestine improves obesity, T2D, and NAFLD/NASH in rodents, whereas FXR activation in the liver improves steatosis, inflammation, and fibrosis [108]. Considering the inhibitory effects on lipogenesis and hepatic fibrosis, FXR agonists are being developed for NASH treatment [109]. FXR agonists have been shown to inhibit the hepatic fatty acid and triglyceride synthesis by down-regulating the expression of SREBP1c [110,111], and increase hepatic fatty acid oxidation by up-regulating the expression of Pyruvate Dehydrogenase Kinase (PDK4) [112]. As a promising target, FXR is widely used in clinical trials for the treatment of liver fibrosis. OCA was a potent FXR agonist in phase III clinical trials. However, OCA treatment for NASH-induced liver fibrosis has a very low response rate and caused side effects such as itching [113]. Based on available

preclinical data and clinical applications, oral intestinal FXR inhibitors appear to prioritize improving glucose and cholesterol metabolism, while liver-targeted FXR agonists will improve liver function and fibrosis [114,115]. It is unknown whether interference with the FXR signaling pathway may induce adverse effects in the long term.

PPARs

PPARs belong to non-steroid hormone receptors and have emerged as integrators of inflammatory and metabolic signaling networks. Pan-PPAR agonist lanifibranor improved all histological features of steatohepatitis in mice, including liver fibrosis [92]. In this phase 2b trial, lanifibranor decreased levels of liver enzyme, the majority of lipid, inflammatory, and fibrosis biomarkers (NCT03008070) [116]. Systemic PPARα knockout and liver-specific knockout aggravate hepatic steatosis and obesity induced by HFD diets [117]. Clinical intervention trials were conducted on fatty liver with fibrate drugs (clofibrate and fenofibrate) [118]. One of the studies observed a significant improvement in the distribution of lipids in patients with NAFLD after treatment with fenofibrate, and patients with ALT, AST serum levels decreased, but their liver pathology did not change [118]. In another study, patients treated with fenofibrate had positive changes in ALT, AST, GGT, bilirubin, triglycerides, and cholesterol or histology-graded steatosis, inflammation, or fibrosis, but some of them had side effects and withdrew [119]. In HFD-induced or obese mouse models, liver-specific knockout PPARγ was able to protect mice from fatty liver [120,121]. PPARγ agonists (rosiglitazone and pioglitazone) improve fatty liver disease in NASH. In patients with NASH, rosiglitazone improves steatosis and aminotransferase levels, but gains weight [122]. Pioglitazone administration resulted in metabolic and histological improvements in subjects with nonalcoholic steatohepatitis, despite no reduction in liver fibrosis and weight gaining [123]. In addition to agonists for specific subtypes, pharmacological double PPARα/γ agonists called glitazars, have been developed to improve insulin resistance, dyslipidemia [124], and fatty liver [125] in rodents. PPARα/γ agonists saroglitazar has been shown to significantly improve liver fat content, ALT, insulin resistance, and atherosclerotic dyslipidemia in patients with NAFLD/NASH, and has improved lipoprotein particle composition and size, reducing the variety of lipotoxic lipids [126]. However, some compounds of this class of drugs have also been shown to have side effects on cardiovascular and kidney diseases [127].

LXRs

LXRs includes two different isoforms: LXR-α and LXR-β [113]. They are involved in both hepatic cholesterol metabolism and liver inflammation and fibrosis. The expression of LXRs is associated with the degree of hepatic fat deposition in patients with NAFLD as well as liver inflammation and fibrosis [128]. LXRs exert anti-inflammatory effect [129], increase cholesterol efflux [130], and promote lipid production [131] and gluconeogenesis [132]. LXR-β is mainly expressed in hepatic stellate cells, and LXR-α activation of hepatocytes mainly activates lipid production and bile acid export. In addition, LXR-α agonism promotes re-differentiation of primary liver sinusoidal endothelial cells, which alleviate the liver inflammation and promote the regression of liver fibrosis [133]. Peng Huang *et al*. reported that LXRs inverse agonist SR9243 and SR9238 effectively reduced hepatic steatosis and inhibited liver fibrosis in NASH mouse model [134,135]. It is worth noting that LXR-α activation has serious side effects, for example, hyperlipidemia and hepatic steatosis [113]. Therefore, studies targeting LXRs regulation need to be focused on the regulation of LXR-β.

Conclusions and perspectives

Mutated or dysregulated transcription factors are the main drivers of NAFLD development. Transcription factor activity is altered in NAFLD via various direct mechanisms including abnormal gene expression or function due to gene amplification, mutation, genetic instability, epigenetics, or post-transcriptional modifications. The significance and aberrant activity of transcription factors in NAFLD processes indicate their potential as therapeutic targets. Considering the growing impact on world health, there generated intense interest in the treatment of NAFLD and NASH among patients, regulatory agencies, and the biotechnology and pharmaceutical industries. Although the number of clinical trials to date is limited, some of these approaches have yielded encouraging results and even conditionally approved novel therapies and many researches in transcription factors liver disease have been made in previous studies, but their long-term efficacy, tolerability and safety need to be further evaluated. More attention should be focused on and targeted transcription factors that improve lipid accumulation, fibrosis, and circulatory system homeostasis without significant disruption of circulatory system to further investigate and obtain effective targeted therapy for liver-related diseases.

A key question for the future therapeutic applications of these drugs is how to screen out highly specific drugs for NAFLD treatment. Therefore, there is still a long way to go to develop transcription factor drugs for clinical use. Targeting the gene regulatory activity of different transcription factors is an exciting field with great future potential. Continued understanding of the molecular mechanisms of transcription factor function will provide clues for achieving fine-tuning of specific transcription factor functions with drugs and may be applied to the treatment of diseases in the future.

Declarations

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