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EDITORIAL

Pathogenesis and research progress of nonalcoholic fatty liver disease/nonalcoholic steatohepatitis

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Abstract

In this editorial, we comment on the article by Mei *et al*. Nonalcoholic steatohepatitis (NASH) is a severe inflammatory subtype of nonalcoholic fatty liver disease (NAFLD) with pathological features including steatosis, hepatocellular damage, and varying degrees of fibrosis. With the epidemic of metabolic diseases and obesity, the prevalence of NAFLD in China has increased, and it is now similar to that in developed countries; thus, NAFLD has become a major chronic liver disease in China. Human epidemiological data suggest that estrogen has a protective effect on NASH in premenopausal women and that sex hormones influence the development of liver disease. This review focuses on the pathogenesis, treatment, and relationship between NASH and other diseases as well as on the relationship between NASH and sex hormone metabolism, with the aim of providing new strategies for the treatment of NASH.

Key Words: NASH; Hepatic steatosis; Sex hormone metabolism; The treatment for NASH

Core Tip: In this study, the modified Xiaoyao San (MXS) formula was found can alleviated inflammation and hepatic steatosis in nonalcoholic steatohepatitis (NASH) by suppressing male hormone metabolism and modulating inflammation/Lipid metabolism-related signaling and factors. It suggested that the regulation of sex hormone metabolism and associated signaling could be new avenues for mechanistic research on NASH and for early diagnosis and treatment. This study offers substantial evidence for the therapeutic potential of MXS in NASH and makes a valuable contribution to the development of new drugs for this condition.

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INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is one of the earliest manifestations of metabolic syndrome worldwide and is characterized by hepatic lipid accumulation[2,3]. In China, the incidence of NAFLD has reached 29.2% and is increasing annually[4]. Nonalcoholic steatohepatitis (NASH) is a severe nonalcoholic fatty liver disease characterized by inflammation and fat accumulation in the liver[5]. The mortality rate of NASH is predicted to double by 2030[6]. NASH is a progressive form of NAFLD, and approximately 20% of patients with NAFLD progress to NASH; however, the molecular mechanisms underlying the transition from NAFLD to NASH are complex and not fully understood[2,7]. NAFLD/NASH has become the leading cause of liver disease worldwide and can lead to liver fibrosis, cirrhosis and even hepatocellular carcinoma.

Sex dimorphism is associated not only with physical and behavioral differences between males and females but also with physiological differences that are reflected in organ metabolism[8]. Sex hormones are steroid hormones that mainly include estrogen, progesterone, and testosterone. Differences in sex hormone levels and the expression of sex hormone-specific genes are thought to contribute to certain liver diseases[9]. Studies have shown that androgens can protect against NAFLD, but other studies have shown that androgens can promote the occurrence and development of NAFLD [10-12]. Androgens have an important effect on lipid metabolism in the female liver. There are also many indications that hyperandrogenetic PCOS may indirectly increase the risk of NAFLD through obesity and insulin resistance (IR) and directly increase the risk of NAFLD through hepatotoxic effects[13].

At present, the clinical methods for detecting NAFLD mainly include biopsy, imaging, and biomarker testing, among which biopsy is still the gold standard for NAFLD detection; however, as an invasive detection method, it is not suitable for frequent detection[14,15]. Despite the high incidence and increasing impact on world health, only one drug, Rezdiffra, is currently licensed with FDA approval, and developing additional drugs has been a major challenge[16]. Therefore, exploring the pathogenesis of NAFLD at the molecular biology level and identifying effective targets that play key roles in NAFLD are important for addressing the major clinical problem of NASH.

PATHOGENIC FACTORS AND PROGRESSION OF NAFLD/NASH

Historically, the double whammy theory has been used to describe the progression from normal liver to hepatic steatosis and then to the gradual development of NASH[17]. The evolution of NASH is complex, and the initial pathological manifestation is hepatocyte steatosis (first hit); however, this is not sufficient to induce inflammation and fibrosis[18]. As the disease progresses, subsequent events, including oxidative stress, genetic variation, abnormal lipid metabolism, oxidative stress, altered immune responses and imbalances in the intestinal microflora, are necessary to exacerbate liver injury. This theory can be explained by impaired lipid metabolism, which promotes the accumulation of fatty acids in the liver, leading to hepatic steatosis[19]. Oxidative stress is the "second hit" that occurs due to increased oxidation of fatty acids, which leads to reactive oxygen species production, lipid peroxidation, DNA damage, mitochondrial dysfunction, and the release of proinflammatory cytokines that amplify inflammation, resulting in a second injury to the liver, leading to hepatocellular damage, inflammation, and fibrosis[20-22]. However, the "second hit" theory can no longer fully explain the complex pathogenesis of NASH, and currently, the pathological progression is considered to involve a "triple hit" process of steatosis, lipotoxicity, and inflammation. Over time, liver fibrosis can progress to more serious diseases, such as cirrhosis or even cancer, for which liver transplantation is the only treatment option[23].

NASH is the result of a combination of factors, including genetic variants, abnormal lipid metabolism, oxidative stress, altered immune and inflammatory responses, and imbalances in the gut microbiome[24]. While NAFLD usually occurs in the absence of excessive alcohol consumption, NAFLD is associated with an unhealthy diet and a lack of physical activity [23]. Currently, a high-fat diet is believed to lead to lipid deposition and then to the abnormal activation of the innate immune system of the liver, which is the main reason for the progression of NAFLD. At the cellular level, after lipotoxic stimulation, cells transmit signals to downstream adaptor proteins and kinases through pattern recognition receptors. After receiving signals, adaptor proteins and kinases further transmit signals to downstream effectors, eventually leading to a series of pathological changes, such as inflammation and fibrosis. During this process, important adaptor proteins

and kinases in the signaling center are finely regulated at multiple cellular levels, and if abnormally activated, they trigger a downstream signaling cascade that ultimately leads to cell damage or death[25]. In NAFLD, apoptosis signal-regulating kinase 1 (ASK1) can be phosphorylated by upstream kinases to form a dimer-activated form, activating downstream apoptotic and inflammatory pathways[26]. TAK1 can be modified by K63 ubiquitination to undergo conformational changes and activate the self-phosphorylation activation process[27].

Inflammatory and immune signaling pathways are involved in the pathogenesis of NASH, including *via* specific processes involving the activation of inflammatory factors; the release of hepatogenic signals; alterations in innate immune signals; changes in macrophages, T cells, platelets and neutrophils; and changes in the biology of cytokines, adipokines and chemokines. During the pathogenesis of NASH, a large number of free fatty acids bind to TLR4, activate important inflammatory pathways, including the NF-kB pathway, and trigger endoplasmic reticulum stress and inflammatory responses, ultimately leading to the production of cytokines such as tumour necrosis factor alpha (TNF-α) and interleukin (IL)-1β[28]. Cytokines are cell signaling molecules produced by a variety of cells in the body, and they are important mediators of inflammation-related diseases. Both lipid accumulation and inflammation occur in NAFLD. Cytokines may play a key role in the pathogenesis of NAFLD by stimulating liver inflammation, steatosis, apoptosis, and necrosis, as well as by inducing fibrosis[29]. Moreover, inflammasomes are activated, and different inflammasomes affect NASH *via* different mechanisms. Studies have shown that the pathogenesis of NASH is also associated with T-cell regeneration. In the livers of NASH patients, the numbers of T helper cell 17 (Thl7) cells and natural killer T cells are significantly increased, and Thl7 cells can promote inflammation in NASH patients through the secretion of IL-17[30].

NAFLD patients have different intestinal flora compositions in different periods, and the accumulation or depletion of some specific bacteria is closely related to the progression of the disease. Lipopolysaccharide (LPS) derived from the intestinal flora can circulate through the portal vein to the liver, thereby activating toll-like receptor 4 (TLR4) on Kupffer cells and hepatic stellate cells (HSCs) and initiating a series of inflammatory signaling pathways that cause liver damage and fibrosis[31]. Short-chain fatty acids (SCFAs), including acetate, propionate and butyrate, are produced by the intestinal flora through the fermentation of dietary fiber. SCFAs are volatile fatty acids that can regulate the pH value of the intestine, inhibit the breeding of harmful bacteria, protect the homeostasis of the intestinal environment, and have an important impact on the metabolism of different organs in the body. At present, SCFAs are considered indirect indicators for determining whether the structure of the intestinal microbiota is normal. Ethyl hydrochloric acid uses cholesterol as a substrate and participates in fat synthesis. Propionate increases gluconeogenesis and then decreases hunger and cholesterol synthesis[32,33]. Studies have shown that the ratio of acetate and propionate to butyrate in normal rats is 58:26:16, and in rats with NASH induced by a high-fat diet, the ratio of the three is 74:21:5, which shows that the bacterial metabolites of the NASH model also change[34]. Genetic factors are critical in NAFLD and NASH, and five potential susceptibility sites have been identified: glucokinase regulator, tribbles pseudokinase 1, transmembrane 6 superfamily member 2, apolipoprotein E, and patatin-like phospholipase domain-containing protein 3[35]. During the progressive phase of NAFLD, the increase in oxidative stress and the lack of antioxidant defense mechanisms have been extensively studied and are thought to contribute to liver damage and the development of NASH[3]. Given the complexity of NASH pathophysiology, it is feasible to engage multiple targets and pathways to improve the outcome of drug interventions (Figure 1).

TREATMENT FOR NASH

The treatment of NASH is challenging because the progression from steatosis to NASH and fibrosis can involve multiple molecular pathways in different patient subpopulations and at different stages of liver disease[36]. At present, lifestyle intervention is the most important and effective strategy for the prevention and control of NAFLD[2].

NONDRUG TREATMENT

Dietary habits may affect the development of NAFLD and NASH[37]. For example, resistant starch can reduce the levels of triglycerides (TGs), which can induce weight loss[38,39]. Excessive accumulation of TG is the main pathophysiological feature of NAFLD, suggesting that metabolic disorders involving TG or other lipids are related to the occurrence of NAFLD[37]. A low-fructose diet is preferable because dietary fructose intake is a risk factor for NASH, and a Mediterranean and low-calorie diet can reduce serum transaminase levels in patients with NAFLD[40]. Therefore, this type of diet, especially when low in saturated fat, should benefit cardiac metabolic diseases other than those of the liver[41]. Excessive caloric intake leads to obesity, and if there is purposeful weight loss, it plays a strong role in improving NAFLD. If it is difficult to achieve weight loss through diet or exercise, bariatric surgery can be an option. While lifestyle interventions have been shown to improve fatty liver disease in patients with NAFLD, liver fibrosis that progresses to advanced stages is unlikely to be cured by lifestyle changes alone, so medications specifically targeted to improve liver inflammation, fibrosis, and steatohepatitis are needed[42].

DRUG THERAPY

Although there are very few treatments for NASH, in March, the FDA approved Rezdiffra for treating liver fibrosis

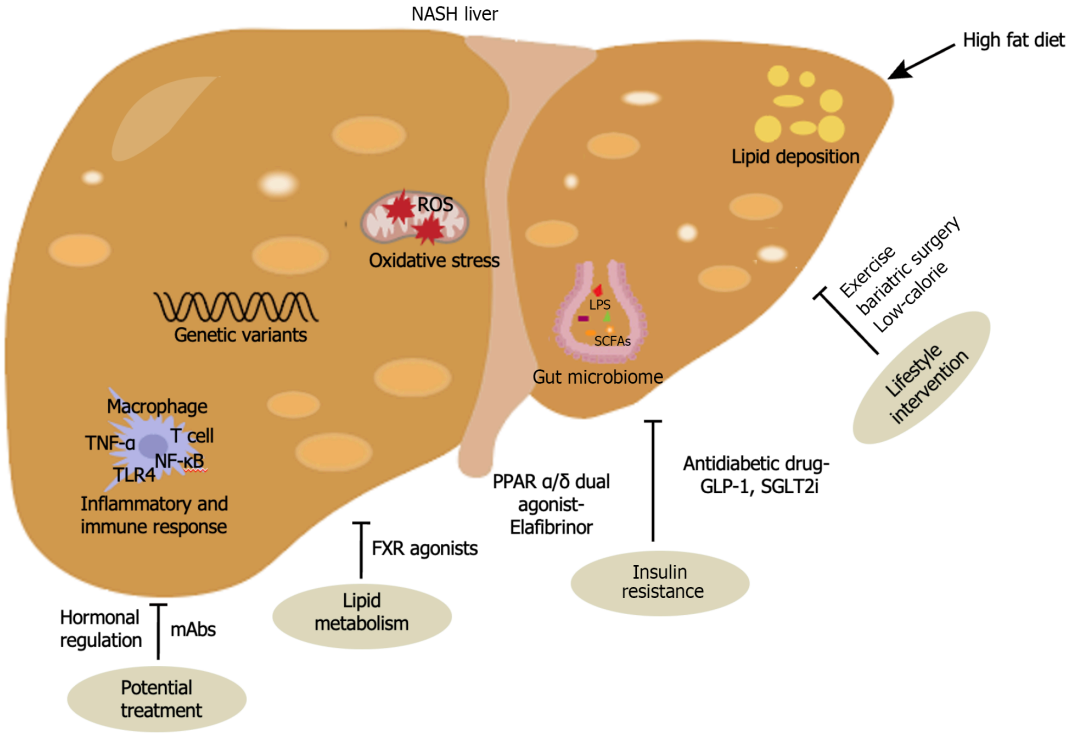

Figure 1 Pathogenic factors and treatment of non-alcoholic steatohepatitis. NASH: Non-alcoholic steatohepatitis; SCFSs: Short-chain fatty acids; LPS: Lipopolysaccharide; TNF-α: Tumor Necrosis Factor-α; TLR4: Toll-like receptor 4; NF-κB: Nuclear factor kappa-B; GLP-1: Glucagon-like peptide-1; SGLT2i: Sodium-glucose cotransporter 2 inhibitors; PPAR α/β: Peroxisome proliferator-activated receptors α/β; FXR: Farnesoid X receptor; mAbs: Monoclonal antibodies.

caused by nonalcoholic steatohepatitis in adults. The approval of Rezdiffra, a thyroid hormone beta receptor agonist, provides new directions for the development of drugs to treat NASH, offering a more comprehensive treatment approach [43]. However, patients should also pay attention to combining diet adjustment and strengthening exercise, but Rezdiffra cannot be used to treat patients with decompensated cirrhosis. For years, researchers have focused on targeting typical pathways involved in the progression of NASH, such as lipogenesis, oxidative stress, and inflammation[2]. Despite extensive efforts, these approaches have yet to yield any approved therapies.

In recent years, NASH therapeutics have been among most active areas of drug development, but a significant number of trials have not progressed from phase II to phase III, and most phase III trials have failed to reach their primary endpoints[44]. Although the exact pathogenesis of NASH is unclear, IR plays a key role in the development of NASH, and the prevalence of NASH is high in patients with type 2 diabetes; therefore, antidiabetic drugs are commonly used in the clinical treatment of patients with type 2 diabetes and NASH[45]. Glucagon-like peptide-1 (GLP-1) stimulates insulin secretion and suppresses the level of glucagon, and the GLP-1 agonist represented by liraglutide has been shown to improve the histological characterization of NASH[46,47]. SGLT2i is a novel oral hypoglycemic agent that inhibits renal reabsorption of glucose, thereby lowering blood glucose levels. Studies have shown that the addition of SGLT2i to common antidiabetic therapies in patients with type 2 diabetes mellitus can better reduce fat content and increase liver enzyme levels[48]. The peroxisome proliferator-activated receptor (PPAR) α/δ dual agonist Elafibrinor was shown to improve insulin resistance and liver inflammation, but the clinical phase III trial failed[49,50]. In addition, many drugs that target lipid metabolism, such as farnesoid X receptor (FXR) agonists, are under development. FXR agonists such as obeticholic acid (OCA/INT-747) have been shown to have significant lipid-lowering, anti-inflammatory, and antifibrotic effects in both mice and humans. However, it has not been approved by the FDA as a treatment for NASH, as it has been clinically shown to cause side effects such as an increase in serum LDL levels in patients[51]. Statins are common lipid-lowering drugs in clinical practice that can inhibit cholesterol synthesis[52].

While most clinical trials for NASH are based on a single drug treatment, the multiple complex mechanisms of the disease make it increasingly challenging to develop a single drug that can effectively treat most patients[53]. Therefore, combination therapy is an effective way to improve treatment efficiency, slow disease progression, and even reverse NASH. Combination therapy includes drugs from different classes, affecting multiple steps in the pathogenesis of NASH. Future combination therapies should include drugs that have been shown to be beneficial in terms of metabolism and complications as well as liver-directed therapy. For example, weight-loss drugs such as GLP1 receptor agonists and SGLT2 inhibitors have potential benefits in diabetes management and cardiovascular disease prevention, but combination therapy must be carefully weighed against the possible challenges of larger sample sizes and more types of side effects [54]. However, studies involving single drugs are still much more common than studies involving combination drugs and often focus more on their clinical course than most combinations do (Figure 1).

POTENTIAL TREATMENT

Although several drugs have multiple effects, most clinical results to date suggest that a single approach is unlikely to be a breakthrough treatment for NASH. One approach is to develop predictive biomarkers of response to a specific mechanism of action (MOA) at the time of investigational drug testing. Single-cell omics allows for the screening of novel therapeutic tools to assess on-target and off-target effects, immunophenotypes of different cell populations, and potential toxicology[55]. Another option is to use patient-derived pluripotent stem cells to generate organoids to test personalized responses to specific drugs[56]. Monoclonal antibodies have slowly begun to emerge as the preferred modality of drug treatment for the dominant drugs. However, it is inconclusive whether monoclonal antibodies have the same effect on disease progression in the treatment of metabolic disorders such as NASH. To date, only a few monoclonal antibody therapies have entered the clinical research stage, but the research has failed to live up to expectations. Some companies are using soloMER drugs to produce smaller antibody-like biologics for the treatment of advanced liver disease. This strategy offers the promise of further improving efficacy by combining biological and small-molecule drugs as a single targeted therapy.

Hormonal regulation of liver metabolism is a potential therapeutic target for the treatment of human liver disease and has been investigated in clinical trials[57]. Several studies have shown that there are sex differences in the occurrence of NAFLD, especially those related to estrogen[58,59]. Low serum levels are strongly associated with hepatic steatosis in men, suggesting that androgens protect against NAFLD[10,60]. However, other reports have shown the opposite result, with androgens contributing to the development of NAFLD[11,61]. Sex hormone-binding globulin (SHBG) is a liver factor that is produced mainly in the liver and is secreted into the blood, where it binds to circulating steroid hormones[62,63]. SHBG plays an important role in the development of NAFLD by regulating the production of fat in the liver[63]. In men, 44%-60% of testosterone binds to SHBG, whereas in women, 95% of circulating estrogen similarly binds to SHBG[64]. Therefore, SHBG can be used as a biomarker for NAFLD[8,65-67]. Another "star molecule" is formyl peptide receptor 2 (FPR2), which regulates inflammation in multiple organs. However, it is unclear whether and how FPR2 is involved in the pathophysiology of NAFLD. Most estrogen functions are mediated by its two nuclear receptors, ERα and Erβ[59]. In the liver, ERα and ERβ are expressed mainly in hepatocytes and activated hematopoietic stem cells, respectively[68,69]. Studies have shown that FPR2 is a downstream target of this gene and that estradiol stimulates estrogen expression[59]. Moreover, ERα knockout was found to induce steatosis in all mice, suggesting that ERα activation in fibrosis can be a sex-independent protective adaptation to liver injury, revealing estrogen receptors as potential drug targets for NAFLD management[70-72]. While hormone replacement therapy improves liver physiology and function in patients, it also carries risks. Therefore, while liver function can be enhanced, such therapy needs to be developed in a way that balances the benefits and risks, especially with long-term use[73] (Figure 1).

CONCLUSION

NAFLD has become a new challenge and major public health problem in the fields of liver disease and metabolism worldwide. Lifestyle intervention is an important basic treatment, and the regulation of glycolipid metabolism remains the focus in the treatment of NAFLD. I think that lifestyle modification and surgery are the best treatment strategies in the long run, but there are some drawbacks that cannot be ignored compared with some of the potential methods that are currently being explored. An unhealthy or irregular approach to weight loss that causes rapid weight loss can sometimes backfire. This can cause the body to break down fat too quickly, which can induce or exacerbate inflammatory infiltration or fibrosis of the liver. Bariatric surgery can be considered for patients with NASH who are not sensitive to behavior modification, effectively improving the quality of life and survival time of NASH patients. However, due to the safety issues faced by surgery, further research and verification are still needed.

Various novel metabolic drugs, such as PPAR agonists, FXR agonists and THRβ agonists, are also under development and are in clinical trials. However, clinical trials of most therapeutic agents have not been satisfactory, and liver histological endpoints have not been achieved. The reasons for NASH bottlenecks in the drug development process can be summarized as follows: First, target selection is a problem. On the one hand, there are multiple pathways involved from the sensing of lipotoxic stimuli to the final effect, and there are cross-interactions between signaling pathways. Thus, unless a critical component involved in the regulation of the signaling network is targeted, when the upstream drivers of the disease are still present, the other pathways remain active or even produce compensatory effects even though one pathway is inhibited[74]. On the other hand, many targets not only play key roles in the pathogenesis of NAFLD but also play important roles under normal physiological conditions. Therefore, approaches that interfere with the pathological process of NAFLD will also affect physiological function to varying degrees. Drug side effects often become one of the main obstacles in the translation of targets that have been verified in some animal experiments into clinical practice[75]. Second, there are unreasonable indicators for the observation of subjects. For example, the ASKI inhibitor selonsertib, the PPARα/δ agonist elafibranor, and the CCR2-CCR5 antagonist cenicriviroc, which were highly evaluated in early trials, ultimately failed in phase III trials[76]. Third, there is a lack of in-depth exploration of the complexity of disease pathogenesis. Failure of the pancaspase inhibitor emricasan is an example. The mechanism of action of emricasan involves the inhibition of hepatocyte apoptosis, which can improve liver function indicators in the short term but exacerbate liver fibrosis and hepatocyte balloon formation in the long term. Therefore, NAFLD/NASH therapy should be anchored to its underlying cause—lipotoxic stimulus—or have pleiotropic effects at different locations in the disease cascade[77]. To date, the use of pioglitazone, bariatric surgery, and GLP1 have successfully supported this idea[78]. An in-depth understanding of the pathogenesis of NAFLD and NASH will lead to more disease-related targets and is

expected to yield safer and more effective approaches for controlling these diseases.

FOOTNOTES

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