Original Article

miR-122-5p/KIF5B/AMPK/AKT regulatory network regulates the progression of NAFLD

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Abstract: Background: Nonalcoholic fatty liver disease (NAFLD) is a progressive liver disease, which may develop into end-stage liver disease and endanger human life. miR-122-5p may be related to the progression of NAFLD disease, but the specific regulation mechanism is still unknown. It is helpful for us to optimize the prevention or treatment strategy of NAFLD. Methods: Real-time PCR was applied to test miR-122-5p and KIF5B in serum, rat liver tissue induced by high fat diet (HFD), and primary hepatocytes exposed to oleic acid ester and palmitate (FFA) of NAFLD patients. The role of miR-122-5p on inflammatory factors (MCP-1, TNF-α, IL-10) and liver injury markers (AST, ALT) in vivo and in vitro was analyzed. Results: miR-122-5p and KIF5B were both highly expressed in NAFLD patients' serum, rat liver tissue and primary hepatocytes, while KIF5B was low expressed. miR-122-5p expression enhanced with the increase of HFD feeding time. The dual luciferase reporter gene assay system confirmed that there was a targeting relationship between miR-122-5p and KIF5B, indicating that KIF5B and protein level were evidently up-regulated in primary hepatocytes. Down-regulation of miR-122-5p was helpful to improve the liver weight/body weight ratio (liver index) level of rats, as well as the levels of triglyceride (TG), inflammatory factors and liver injury markers in liver tissues in vivo and in vitro. Phosphorylation of AMPK/AKT pathway-related proteins and fat metabolism-related factors in rat liver tissues and cells in primary hepatocytes were notably reduced, while down-regulation of miR-122-5p was helpful to restore activation of the pathway and increase the level of fat metabolism-related factors. Conclusion: Decrease of miR-122-5p can target and enhance KIF5B, which can be applied for treating NAFLD.

Keywords: miR-122-5p, KIF5B, non-alcoholic fatty liver disease, cell biology

Introduction

Non-alcoholic fatty liver (NAFLD) is a progressive liver disease with a wide range of lesions. It can be differentiated from invasive non-alcoholic fatty hepatitis (NASH) into liver cirrhosis or hepatocellular carcinoma (HCC), and the disease will rapidly deteriorate into the end-stage [1, 2]. According to NAFLD epidemiological data, its global prevalence rate is as high as 25%, and about 45% of NASH cases may progress to HCC [3, 4]. Although imaging or clinical symptoms can predict the development stage of NAFLD, the final diagnosis extremely depends on liver biopsy [5]. Individual metabolic problems are risk factors for NAFLD, including obesity, hyperglycemia, hyperlipidemia, and hypertension. Moreover, the association of metabolic problems with NAFLD is likely to be bi-directional [6]. In addition, NAFLD patients also have high risks of cardiovascular diseases [7]. Its pathogenesis involves inflammatory factors, inflammatory pathways and fatty acid metabolism abnormalities [8, 9]. At present, the treatment strategies of NAFLD include life intervention, drug treatment and surgical treatment. However, life intervention requires high self-discipline and long-term persistence of patients, and the side effects of surgical treatment are beyond imagination, so drug treatment is a relatively compromise choice [10, 11]. Therefore, we investigated new means for NAFLD from the molecular level, which may be beneficial to the control and prevention of NAFLD.

microRNA (miRNA) is a small molecule that participates in the progression of liver diseases,
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including NAFLD, at the post transcriptional level by regulating the cross target mRNA. It is also a non-invasive biological indicator to assist in the diagnosis of NAFLD severity [12, 13]. miR-101-3p has been pointed out by Meroni [14] that its down-regulation will probably aggravate the disease progression of NAFLD by promoting the transdifferentiation of hepatic stellate cells. The report of Ye [15] also indicated that the increase of miR-17, miR-122 and other indexes in plasma were helpful to explore the risk of NAFLD in patients with type 2 diabetes. miR-122-5p is a molecular index related to fatty liver metabolism and has been found to be abnormally enhanced in fatty liver individuals [16]. Kinesin family 5B (KIF5B) has been reported to have selective deletion in adipose tissue, which will aggravate obesity and metabolic disorders caused by high fat diet (HFD) [17]. HFD is also a common method for establishing NAFLD mouse model, which can simulate the histological and metabolic characteristics of human NASH with diffuse fibrosis but without cirrhosis [18]. In addition, AMPK/AKT pathway is a signal transduction pathway closely related to hyperlipidemia and hepatic steatosis. At present, it has been reported that the phosphorylation level of AMPK and AKT in NAFLD model is notably lower than that in healthy control group (CG), suggesting that this pathway may participate in the pathological process of NAFLD [19, 20].

We found that miR-122-5p and KIF5B have potential targets in the online website of target genes, and there are few studies on the regulation of the two in NAFLD at present. We presumed that miR-122-5p/KIF5B/AMPK/AKT regulatory network was existed to regulate disease progression of NAFLD, so we carried out the following verification.

Material and methods

Serum sample collection

Altogether 45 patients with NAFLD (NAFLD group) admitted to Tongji Hospital from November 2018 to November 2019 were selected, including 25 males and 20 females. They were aged 24-79 years, with an average of (58.79±6.87) years. During the same period, 40 healthy people were collected, including 22 males and 18 females. They were aged 22-78 years, with an average age of (57.64±6.48) years. The age and gender of the patients were comparable (P<0.05). Serum of two groups of subjects in fasting state in the morning was collected, frozen and stored for later use. Inclusion criteria: patients were confirmed as NAFLD for the first time [21]; patients have not been treated with NAFLD. Exclusion criteria: patients with other malignant tumors, severe renal dysfunction, and serious infectious diseases; patients have taken drugs that may affect this study in the past 6 months. All patients and their families have signed an informed consent form. The experiment has been approved by Ethics Committee.

Animal model

Male C57BL/6J mice (Cavens Lab Animal, Changzhou, China) were purchased, aged 9 weeks, adapted to the environment for research after 7 days, raised in a pathogen-free environment, with a 12 h day-night cycle at room temperature, and ate and drank at will. After starting the experiment, the mice were grouped into two groups on average. The control group (CG) (n=18) took a standard diet, which included 8% rice bran, 51% corn, 30% soybean powder, 3% bone meal, 1.3% multivitamins and 6.7% minerals. HFD group adopted a high-fat diet, which included 75% standard diet, 2% cholesterol, 15% lard and 8% egg yolk powder. At the 4th, 8th and 12th weeks (4 W, 8 W and 12 W) after eating, 6 mice in each group were executed respectively. Liver removed from mice was washed with phosphate buffer solution (PBS) (Kemin Biotechnology Co., Ltd., Shanghai, China, DXT-130-070-525) and stored in liquid nitrogen container for later use. All animal research was carried out with the approval of the Animal Protection Association and the use Committee.

Tail vein injection of lentivirus vector

Inhibitor was constructed on pLenti6.3/TO/V5 vector (Zeye Biotechnology Co., Ltd., Shanghai, China, ZY533-06) with a virus titer of 2×10^8 TU/ml. After 4 weeks, the HFD was grouped on average. The first group continued to maintain HFD (HFD group, n=6), and then the second group continued to maintain HFD, and 100 μl pLenti6.3/TO/V5 carrier (HFD+inhibitor group, n=6) was injected intravenously into the tail. The third group continued to maintain HFD, and
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NC of the same volume was injected, and the mice were executed 4 weeks later. Blood was collected for serum biochemical analysis before execution. The liver obtained from mice was rinsed with phosphate buffer (PBS) and stored in liquid nitrogen container for later use.

**Cell culture, modeling and transfection**

Primary hepatocytes [22, 23] were isolated from 10-week-old mice and cultivated in DMEM medium (Yaji Biotechnology) including 10% PBS and 50 mg/ml penicillin and streptomycin (Zeye Biotechnology) at 37°C. Primary hepatocytes were added with a mixture of FFA (oleate and palmitate, 2:1) (Shanghai Yuanye Bio-Technology Co., Ltd., China, S93193, B33594-20mg) at 1 mM to establish an in vitro fat overload model [24]. miR-122-5p over-expression sequence (mimics), miR-122-5p inhibition sequence (inhibitor) and miR negative control (NC) were respectively transfected into cells by using Lipofectamine™ 2000 kit (BioMag beads, Wuxi, China, 11668019).

**Real-time quantitative PCR**

Firstly, the total RNA was obtained using Trizol reagent (Shanghai Biological Technology Co., Ltd., enzyme research, Shanghai, China, 5007050), then 5 μg of total RNA (Chang Zhou Bei Yuan Xin Bio-Technology Co., LTD, Changzhou, China, BYX2622C) were obtained for reverse transcription of cDNA, and 1 μL of synthesized cDNA was applied for amplification after transcription. Amplification system: 1 μL cDNA, 0.4 μL upstream and downstream primers, 10 μL 2× TransScript® Tip Green qPCR SuperMix, 0.4 μL Passive Reference Dye (50×), and Nuclease-free Water was added to supplement to 20 μL. Conditions: initial denaturation at 94°C for 30 s, denaturation at 94°C for 5 s, and annealing at 55°C for 30 s, for a total of 40 cycles. β-Actin was applied as internal reference for mRNA, U6 for miRNA, and 2^{ΔΔCT} was applied for analyzing the data. The forward sequence of miR-122-5p: 5'-GG-GGTTGAGGATGTAAG-3', reverse sequence: 5'-ATTGGAAACGATAAAGATT-3'; forward sequence of KIF5B: 5'-GGAAACGCTTCCAGAATTTG-3'; reverse sequence: 5'-GGGGTGAGTGTGACAATG-3'; forward sequence of KIF5B: 5'-CAGTGCGTGTCGTGGAGT-3'; reverse sequence: 5'-GCACACAGACUGAGAGCA-3'; forward sequence of U6: 5'-TTCTCTTAAATGTCAGCGA-3'; the forward sequence of β-Actin: 5'-GCCGGGACCTGACTGACTAC-3', reverse sequence: 5'-TTCTCCTTAATGTCACGCGAT-3'; the forward sequence of U6: 5'-ATTGGAACGATACAGAGAAGATT-3', reverse sequence: 5'-GGAACGCTTCACGAATTTG-3'.

**Western blot**

RIPA was applied to extract total protein from cultured mouse liver tissue and each group of cells. BCA kit (Rongbai Biological, Shanghai, China, LCB004) was applied to test protein concentration, which was then adjusted to 4 μg/μL, and then 12% SDS-PAGE (Shanghai Ruichu Biotech Co., Ltd., Shanghai, China, R07016) was applied. After electrophoresis, the cells were transferred (Shanghai YuanMu Biological Technology Co. Ltd., Shanghai, China, YS-6154), dyed with Ponceau S working solution (Shanghai Xin Yu Biotech Co., Ltd, Shanghai, China, XY-0023), rinsed in PBST (Shanghai Yuanue Bio-Technology Co., Ltd., Shanghai, China, R20863) for 5 minutes, and sealed with 5% defatted milk powder (Shanghai Xin Yu Biotech Co., Ltd., Shanghai, China, SL1330-100 ml) for 2 hours. KIF5B, AMPK, AKT, CPT1, CPT2, SLC27A1, SLC27A4, ACBD3, β-Actin (Kemin Biotechnology Co., Ltd., Shanghai, China, bs-11026R, bs-33236M, bsm-52010R, ab107425, bs-10556R, bs-11535R, bs-11910R, bsm-33139M) with the dilution rate of 1:500, p-AMPK (Shanghai Yu Bo Biotech Co., Ltd., Shanghai, China, IC153948), and p-AKT (SHANGHAI ZZBIO CO., LTD., Shanghai, China, ZNB-F48643-0.4ML) were sealed at 4°C and incubated for 4 h overnight. The primary antibody was removed, horseradish peroxidase labeled goat anti-rabbit secondary antibody (Shanghai Xin Yu Biotech Co., Ltd, Shanghai, China, XY0650) with dilution ratio of 1:1000 was added and incubated for 2 h. The antibodies were obtained from Shanghai Kemin Biotechnology, cultivated at 37°C for 1 h, and rinsed with PBS, 5 min/time. Filter paper was used to absorb excess liquid on the membrane, ECL luminescence and development were performed to test the gray value. β-Actin was used as internal reference, and the relative expression level of protein = gray value of target protein band/gray value of β-actin protein band.

**Double luciferase report detection**

Targetscan7.2 was used to predict miR-122-5p downstream target genes. KIF5B 3'UTR-Wt, KIF5B 3'UTR-Mut, inhibitor and NC were transfected into primary hepatocytes by Lipo-jectamine™ 2000, and luciferase activity was
tested by double luciferase reporter (Qunji Biotech Co., Ltd., Shanghai, China, KA3784).

**MTT assay for detecting the cell activity**

Cells were obtained 24 hours after transfection, adjusted to $4 \times 10^3$ cells/well, and then moved on 96-well plates, cultivated at 37°C, added with 20 μL MTT solution (5 μmg/mL) (Yuanye Bio-Technology, R20227), cultivated for 4 hours at 37°C, added with 200 μL dimethyl sulfoxide per well, and then the OD value was tested at 450 nm wavelength using GeneQuant 1300 spectrophotometer (Binbio, Shanghai, China, 7415Naco).

**Flow cytometry for detecting the apoptosis**

Cells were treated with 0.25% trypsin, rinsed with PBS, mixed with 100 μL of binding buffer, made into suspension ($1 \times 10^6$ cells/mL). AnnexinV-FITC (10 μL) and PI (10 μL) were added and cultured in dark for 5 min. NovoCyt flow cytometer (Ranger instruments and equipment Co., Ltd., Shanghai, China) was applied for quantitative analysis.

**Determination of other indexes**

The triglyceride (TG) of liver tissue and primary hepatocytes was determined by extraction with a mixture of chloroform and methanol [25] and then by using colorimetric method. The determination was performed strictly according to the detection instructions of TG colorimetry kit (Shanghai Rongbai biological technology Co., Ltd., Shanghai, China, WD-0125). The collected blood samples and cell supernatants of mice were tested, and the concentrations of MCP-1, TNF-α, and IL-10 were detected by Boehringer Mannheim biochemical analyzer (Shanghai Lianshuo Biological Technology Co, Ltd., Shanghai, China).

**Statistical method**

GraphPad 6 was applied for data analysis. Independent sample t test was applied for pairwise comparison, one-way ANOVA for comparison among multiple groups, LSD-t test for post-event comparison, repeated measurement ANOVA for multi-time point expression, Bonferroni for back testing. The diagnostic role of miR-122-5p and KIF5B was visualized by ROC. Pearson test was applied to explore the correlation of miR-122-5p with KIF5B. P<0.05 means a statistical difference.

**Result**

**Increase of miR-122-5p in NAFLD**

The results of real-time quantitative PCR showed that miR-122-5p and KIF5B were significantly up-regulated in the serum of NAFLD patients (P<0.05). Pearson correlation coefficient was applied to explore the correlation of miR-122-5p with KIF5B. miR-122-5p had a negative correlation with KIF5B ($r=-0.666$, P<0.05). The ROC curve of diagnosis of NAFLD was visualized, and the AUC of diagnosis of NAFLD was 0.926 and 0.918 respectively (Figure 1).

**Obvious up-regulation of miR-122-5p in liver tissue of obese rats**

Compared with the control group mice with standard diet, miR-122-5p in the liver tissue of HFD rats was notably higher, and miR-122-5p showed an increasing trend with the increase of HFD feeding time, while mRNA expression and protein level of KIF5B in the liver tissue of HFD rats were notably higher (P<0.05) (Figure 2).

**A target control correlation of miR-122-5p with KIF5B**

A targeted binding site of KIF5B with miR-122-5p was found by Targetscan7.2. The activity of KIF5B 3'UTR-Wt luciferase was notably increased after down-regulating miR-122-5p (P<0.05), but KIF5B 3'UTR-Mut luciferase had no change (P>0.05). Western blot analysis revealed that KIF5B in the transfected inhibitor cells was notably enhanced (P<0.05) (Figure 3).

**miR-122-5p helps to improve NAFLD in obese mice**

miR-122-5p, TG and liver injury markers (AST, ALT) were notably increased in mice induced by HFD, while liver index decreased, and inflam-
Figure 1. Clinical value of miR-122-5p and KIF5B in NAFLD. A, B: Expression of miR-122-5p and KIF5B in NAFLD serum, miR-122-5p showed high expression and KIF5B showed low expression. C: miR-122-5p and KIF5B showed significant negative correlation ($r=-0.666$, $P<0.001$). D: ROC curves of miR-122-5p and KIF5B for diagnosis of NAFLD, with AUC of both not less than 0.900. Note: *** indicates the comparison between the two, $P<0.001$. 

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Inflammatory factors MCP-1, TNF-α, IL-10 were notably changed. When miR-122-5p was reduced in mice, the above indicators were improved to different degrees. With the exception of liver index, all results were statistically significant (P<0.05) (Figure 4).

miR-122-5p helps to improve NAFLD of fat overloaded hepatocytes

We found that under the intervention of FFA, miR-122-5p, TG, AST, ALT and the apoptosis level in primary hepatocytes were notably increased, the inflammatory factors MCP-1, TNF-α, IL-10 were notably changed, and the cell proliferation ability was notably reduced. However, when miR-122-5p was reduced in primary hepatocytes, the above results were reversed to varying degrees, and all results were statistically significant (P<0.05) (Figure 5).

miR-122-5p can mediate AMPK/AKT pathway and fat metabolism related genes to reduce FAA-induced NAFLD

We observed the effect of miR-122-5p on AMPK/AKT pathway, fatty acid β-oxidation
related genes CPT1, CPT2 and liver fatty acid transport related genes SLC27A1, SLC27A4, ACBD3, and we found that AMPK/Akt pathway was blocked in primary hepatocytes under FFA inducing, which was manifested by significant reduction in AMPK and AKT expression and phosphorylation levels. In addition, the expression of the above fat metabolism related genes was notably reduced, while the above result was notably improved after knocking down miR-122-5p in vitro expression, with statistical significance (P<0.05) (Figure 6).

Discussion

At present, we have collected a lot of research results and found that miR-122-5p may participate in the disease regulation of NAFLD. Tan [26] indicated that the dynamic up-regulation of miR-122-5p in NAFLD was the most significant, and the sensitivity for diagnosing NAFLD was as high as 93.4%. Zhao [27] pointed out that the down-regulation of miR-122-5p helped to inhibit macrophage activation and improved macrophage-related inflammatory reactions, thus inhibiting the progression of NASH. KIF5B is a driving protein, its specific down-regulation in adipose tissue of HFD mice will lead to an increase in liver TG level, and high TG level can often reflect the lipid accumulation in the liver laterally [28, 29]. Asano [30] showed that the lack of KIF5B aggravated the metabolic problems of the body, which may lead to NAFLD. However, we found that targeted regulation of miR-122-5p on KIF5B was helpful for NAFLD.

miR-122-5p was notably enhanced and KIF5B was reduced in serum of NAFLD patients, suggesting that miR-122-5p and KIF5B act in NAFLD disease. Then, the correlation results showed that there was an evident negative relationship between the two, suggesting that the two act in NAFLD disease. Furthermore, the possibility of both of them diagnosing NAFLD was explored. The results showed that the areas under the curve of miR-122-5p and KIF5B for diagnosis of NAFLD exceeded 0.900, indicating that both of them have great potential to serve as high-sensitive diagnostic indica-
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Figure 5. Effect of miR-122-5p on primary hepatocytes in vitro under FFA intervention. A: Expression of miR-122-5p in primary hepatocytes in vitro under FFA intervention. B: Down-regulation of miR-122-5p was helpful to improve the notably increased TG level. C: Down-regulation of miR-122-5p was helpful to improve notably changed levels of inflammatory factors. D: Down-regulation of miR-122-5p was helpful to improve notably enhanced AST and ALT levels. E: Down-regulation of miR-122-5p was helpful to improve notably reduced cell proliferation ability. F: Down-regulation of miR-122-5p was helpful to improve the notably enhanced level of apoptosis. G: Flow cytometry. Note: compared with the CG, *indicates that P<0.05, ** indicates that P<0.01; compared with FFA group, # indicates that P<0.05, ## indicates that P<0.01.
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diseases of NAFLD. We further verified it through in vitro and in vivo experiments and established NAFLD models with HFD and FFA respectively. The contents of miR-122-5p and KIF5B in rat liver tissues and primary hepatocytes were consistent with the previous result, which was miR-122-5p enhanced while KIF5B reduced. Interestingly, we found that miR-122-5p enhanced with HFD feeding time, indicating that miR-122-5p can predict the severity of NAFLD. We also verified the correlation of miR-122-5p with KIF5B through dual luciferase reporter gene assay and found the KIF5B 3'UTR-Wt luciferase activity was notably increased after knocking down miR-122-5p expression, but KIF5B 3'UTR-Mut luciferase activity had no change. KIF5B was notably reduced after transfection of mimics, but KIF5B was notably enhanced after transfection of inhibitor, indicating that there was a definite targeted regulatory correlation of miR-122-5p with KIF5B.

The disease severity of NAFLD is closely related to inflammation-related factors. The increase of TNF-α and the decrease of IL-10 were closely related to the promotion of the body's inflammatory environment on the process of steatosis [31]. Other studies have pointed out that the lack of MCP-1 was helpful to the improvement of NAFLD inflammatory environment [32]. Liver injury markers AST and ALT can assist in measuring the liver injury of NAFLD, and the decrease of ALT and AST is often related the improvement of inflammation and liver injury [33, 34]. Our rat model has abnormal high TG, AST and ALT induced by HFD, which indicates that the rat model has signs of fatty degeneration and liver function damage induced by HFD. The abnormal increase of pro-inflammatory factors MCP-1 and TNF-α and the abnormal decrease of anti-inflammatory factor IL-10 indicate that the rat body may be in an inflammatory environment. In addition, the liver index of rats also showed a slight decrease, indicating that the immune function of rats may be affected. However, when we reduced miR-122-5p, the above indicators were improved to some extent, indicating that miR-122-5p inhibitor may

Figure 6. Effect of miR-122-5p on AMPK/AKT pathway and genes related to fat metabolism. A, B: Down-regulation of miR-122-5p could reverse the expression and phosphorylation level of AMPK/AKT pathway related factors. C, D: Down-regulation of miR-122-5p was helpful to reverse the expression of notably reduced genes related to fat metabolism. E: Down-regulation of miR-122-5p was helpful to reverse the protein level of notably reduced fat metabolism related factors; protein graph. Note: compared with the CG, * indicates that P<0.05, ** indicates that P<0.01; compared with FFA group, # indicates that P<0.05, ## indicates that P<0.01.
restore the signs of NAFLD induced by HFD in rats. miR-122-5p inhibitor had the same results in primary rat hepatocytes, which once again confirmed the therapeutic feasibility of miR-122-5p for NAFLD models in vivo and in vitro.

At last, we also verified the role of miR-122-5p on AMPK/AKT pathway and fat metabolism related factors. AMPK/AKT pathway mediates the production of NAFLD inflammatory cytokines. AMPK is amp-activated protein kinase, which acts in the regulatory pathway of metabolic diseases including NAFLD, while AKT is an inflammatory response protein kinase in NAFLD [35-37]. Our research showed that FFA induced phosphorylation levels of AMPK/AKT pathway related factors AMPK and AKT are notably reduced, while the above phosphorylation levels are restored after reducing miR-122-5p, suggesting that miR-122-5p inhibitor is helpful to restore activation of AMPK/AKT pathway. CPT1 and CPT2, as fatty acid β-oxidation correlated genes, and SLC27A1, SLC27A4, ACBD3, as liver fatty acid transport related genes, have important regulatory effects in NAFLD fat metabolism [24]. Our research results showed that the above fat metabolism-related factors are notably reduced under FFA intervention, and the above results are reversed to varying degrees after knocking down miR-122-5p, indicating that miR-122-5p can mediate the above fat metabolism-related factors to exert NAFLD resistance. Furthermore, the effect of miR-122-5p on the progression of NAFLD may be related to its regulation of AMPK/AKT pathway and fat metabolism related factors.

There are still some shortcomings in this study. First, we can supplement the diagnostic value of miR-122-5p and KIF5B for different severity or different NAFLD phenotypes. Secondly, we can increase NAFLD serum samples to improve the accuracy of research results. Furthermore, we can also study miR-122-5p on insulin sensitivity in NAFLD patients.

To sum up, the existence of miR-122-5p/KIF5B regulatory network mediates the disease regulation of NAFLD, and down-regulation of miR-122-5p and targeted regulation of KIF5B help to improve NAFLD.

Disclosure of conflict of interest

None.

References


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