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EDITORIAL

Role of long non-coding RNAs in non-alcoholic fatty liver disease

Anju Mullath, Murali Krishna

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Abstract

Non-alcoholic fatty liver disease (NAFLD) is emerging as a common cause of chronic liver disease in children and adults. NAFLD can progress to steatohepatitis and potentially even hepatocellular carcinoma. Early identification of patients at risk for progressive disease is crucial for managing NAFLD. Recent studies have identified long noncoding RNAs (lncRNAs), circular RNAs, and microRNAs as playing important roles in the pathogenesis of NAFLD. These noncoding RNAs are involved in modulating several metabolic pathways such as hepatic glucose and lipid metabolism, oxidative stress, and even carcinogenesis. Elevated levels of lncARSR and lncRNA nuclear-enriched abundant transcript 1 have been found in patients with NAFLD. In addition, lncRNAs such as PRYP4-3 and RP11-128N14.5 can distinguish patients with NAFLD from healthy indi-viduals. Increased MEG3 expression has been observed in both NAFLD and non-alcoholic steatohepatitis, suggesting that it may help predict patients at risk for disease progression. With advances in transcriptomics, we may discover additional targets to help in the identification and prognostication of NAFLD.

Key Words: Long noncoding RNA; Non-alcoholic fatty liver disease; Plasmacytoma variant translocation 1; Nuclear-enriched abundant transcript 1; Muscle- and adipose-associated long intergenic non-coding RNA; H19

Core Tip: Non-alcoholic fatty liver disease (NAFLD) is one of the most common liver ailments. Early diagnosis and treatment can help mitigate its impact on the liver. The role of long non-coding RNAs (lncRNAs) in the pathogenesis of NAFLD has been the subject of research for some time. LncRNAs such as plasmacytoma variant translocation 1, nuclear-enriched abundant transcript 1, muscle- and adipose-associated long intergenic non-coding RNA, and H19 have been shown to play important roles in the disease process of NAFLD.

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) has emerged as one of the most prevalent causes of chronic liver disease globally. However, a lack of awareness surrounding this seemingly benign condition exacerbates the issue. NAFLD frequently manifests as part of metabolic syndrome, which includes obesity and type 2 diabetes[1]. The spectrum of NAFLD encompasses non-alcoholic steatohepatitis, cirrhosis, and hepatocellular carcinoma.

Long non-coding RNAs (lncRNAs) are transcripts exceeding 200 nucleotides and are intricately involved in various functions such as post-transcriptional regulation and epigenetic modifications. Recent research has uncovered the role lncRNAs play in several disease processes. These molecules hold promise as agents for diagnosis and prognostication in the near future.

ROLE OF LNCRNA IN NAFLD

Among non-coding RNAs, lncRNAs are believed to play a crucial role in regulating hepatic gluconeogenesis, inflammation, hepatic regeneration, and fibrosis. Several candidates have been identified thus far, including plasmacytoma variant translocation 1 (PVT1), nuclear-enriched abundant transcript 1 (NEAT1), PRYP4.3, RP 11-128N14.5, HCG18, and MEG3[2]. In this editorial, we will delve into four promising markers that may potentially revolutionize the diagnosis and management of NAFLD in the future.

PVT1

LncRNA PVT1 has garnered significant attention in the context of NAFLD owing to its multifaceted roles in hepatic pathophysiology. Studies have elucidated its involvement in diverse biological processes, including hepatic lipid metabolism, inflammation, and fibrosis, all of which are central to the progression of NAFLD. The dysregulation of PVT1 has been implicated in exacerbating liver injury and fibrosis severity in patients with NAFLD[3]. Moreover, elevated PVT1 expression levels have been correlated with the presence of steatosis and the degree of liver inflammation in NAFLD cohorts[4]. PVT1 affects liver fat metabolism by reducing the levels of microRNA (miR)-20a-5p. Mir-20a-5p acts by suppressing the expression of CD36, which, in turn, reduces lipid accumulation by binding to the 3′-untranslated region[5]. CD36 plays a crucial role in regulating inflammation, fatty acid oxidation, and intracellular fatty acid homeostasis.

Emerging evidence suggests that PVT1 holds promise as a diagnostic and prognostic biomarker for NAFLD. Its overexpression in hepatic tissues and circulation has been proposed as a potential indicator of the onset and progression of NAFLD[6]. Additionally, aberrant expression of PVT1 has been associated with adverse clinical outcomes, including liver cirrhosis and hepatocellular carcinoma, further underscoring its significance in the pathogenesis of NAFLD[7].

Targeting PVT1 presents a novel therapeutic avenue for managing NAFLD. Inhibition of PVT1 expression has shown promise in ameliorating hepatic steatosis, inflammation, and fibrosis in preclinical models, suggesting its potential as a therapeutic target for NAFLD intervention[8].

NEAT1

LncRNA NEAT1 has emerged as a pivotal player in the pathogenesis of NAFLD. Dysregulation of NEAT1 has been implicated in various aspects of the progression of NAFLD, including hepatic lipid metabolism, inflammation, and fibrosis[9]. Studies have revealed elevated NEAT1 expression levels in the liver tissues and circulation of patients with NAFLD, suggesting its potential as a diagnostic biomarker for the disease[10].

Table 1 Various long non-coding RNAs implicated in non-alcoholic fatty liver disease

Gene	Principal functions	Upregulated/downregulated
Gm9795	Endoplasmic reticulum stress Promoting inflammatory response	Upregulated
Platr4	Promoting inflammatory response	Upregulated
HOTAIR	Promoting lipid accumulation	Upregulated
LncTNF	Promoting inflammation	Upregulated
Gm15622	Promoting lipid accumulation	Upregulated
LncHR1	Preventing the accumulation of fatty acids and triglyceride	Downregulated
SRD5A3-AS1	Promoting cell proliferation, steatosis, inflammation and fibrosis	Downregulated
Gm16551	Promoting de novo lipogenesis	Downregulated
AC012668	Promoting lipid accumulation	Downregulated
Mirt2	Promoting hepatic steatosis	Downregulated

NEAT1 exerts its effects through diverse mechanisms, including the regulation of gene expression, chromatin organization, and nuclear structure maintenance[11]. In NAFLD, NEAT1 has been shown to modulate key signaling pathways involved in lipid accumulation, hepatic steatosis, and inflammation, thereby contributing to the pathogenesis of the disease[12]. NEAT1 Levels were found to be increased in patients with NAFLD, and higher NEAT1 Levels correlated with reduced levels of miR-212-5p. This miRNA is known to inhibit the activity of fatty acid synthase, and its inhibition has been shown to result in triglyceride accumulation in mouse primary hepatocytes[13].

Furthermore, NEAT1 has been implicated in promoting hepatic fibrosis through its interaction with various proteins and miRNAs, highlighting its multifaceted role in the progression of NAFLD[14]. Given its intricate involvement in the pathophysiology of NAFLD, NEAT1 represents a promising therapeutic target for developing novel interventions aimed at mitigating disease progression and improving clinical outcomes.

MUSCLE- AND ADIPOSE-ASSOCIATED LONG INTERGENIC NON-CODING RNA (MAYA)

LncRNA MAYA has emerged as a novel regulator of metabolic disorders, including NAFLD. The expression of MAYA is dysregulated in patients with NAFLD, suggesting its potential role in disease pathogenesis[15]. Recent studies have implicated MAYA in modulating lipid metabolism, insulin sensitivity, and inflammation in hepatic tissues, thereby contributing to the development and progression and NAFLD[15]. MAYA regulates the Hippo signaling pathway, which, when activated, leads to the repression of downstream transcriptional co-activators YAP and TAZ. The Hippo signaling pathway also plays a role in liver fibrosis.

Additionally, MAYA has been proposed as a diagnostic biomarker for NAFLD owing to its differential expression patterns in liver tissues and circulation of patients with NAFLD compared to healthy controls[16]. Further elucidation of the molecular mechanisms and functional significance of MAYA may unveil novel therapeutic targets for NAFLD intervention.

H19

LncRNA H19 has garnered considerable attention in the realm of NAFLD owing to its regulatory roles in hepatic lipid metabolism and inflammation. H19 expression levels are dysregulated in patients with NAFLD, suggesting its involvement in disease pathogenesis[17]. Mechanistically, H19 has been implicated in modulating key signaling pathways related to lipid accumulation, hepatic steatosis, and inflammation in the liver[18]. H19 downregulates the expression of miR-130a, which further inhibits the expression of PPARγ, and promotes steatosis by upregulating the transcription factor MLXIPL (also known as ChREBP)[17]. Furthermore, aberrant H19 expression has been correlated with the severity of liver injury and fibrosis in NAFLD cohorts[19]. Given its potential as a diagnostic and prognostic biomarker, further investigation into the functional significance of H19 in the pathophysiology of NAFLD may unveil novel therapeutic targets for disease intervention.

Table 1 provides a brief overview of other lncRNAs that are upregulated or downregulated in NAFLD[2].

CONCLUSION

NAFLD is emerging as the leading liver ailment with far-reaching effects on patient morbidity and mortality. Early

markers for diagnosis and prognostication will help in design and implementation of appropriate steps to ameliorate the condition. LncRNAs can play an important role in both these aspects, and further research is required to improve our understanding of their functions and potential applications.

FOOTNOTES

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