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Role of long non-coding RNAs in alcoholic liver diseases

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Abstract

Exploring long non-coding RNAs (lncRNAs) in liver diseases, particularly liver fibrosis, presents significant opportunities for augmenting our understanding and treatment of these conditions. The rapid advancement of high-throughput sequencing technologies has revealed the complex networks of lncRNAs, highlighting their crucial functions in liver fibrosis. Identifying dysregulated lncRNAs offers promising diagnostic and prognostic biomarkers, as well as potential therapeutic targets. Extracellular vesicles contribute to the relevance of lncRNAs by protecting them from degradation and maintaining their activity in circulation, as exemplified by the role of lncRNA H19 in liver fibrosis. LncRNAs are vital in liver pathology, influencing fibrosis and cirrhosis by modulating responses to liver injury from ethanol. They affect inflammation, oxidative stress, and apoptosis through interactions with pathways like NF-κB and microRNA networks. LncRNAs also control hepatic stellate cells, the production of extracellular matrix, and the activation of stem cells, which opens up new ways to treat fibrosis. Ethanol modulates lncRNA expression, impacting liver fibrosis and cirrhosis development. LncRNAs also influence hepatocellular carcinoma progression by affecting cell proliferation, immune response, and tumor growth. Despite these insights, the regulatory networks and molecular mechanisms of lncRNAs in liver disorders are not entirely understood. In this review, we focus on unraveling these complexities and identifying effective lncRNAs that could revolutionize liver disease treatment, offer novel diagnostic and therapeutic avenues, and improve patient outcomes.

Keywords

long non-coding RNAs, molecular pathways, inflammation, oxidative stress, apoptosis

Introduction

The human genome is mainly translated into RNA; however, only a tiny fraction (1–3%) of these transcripts are protein-coding genes. The remainder consists of a varied array of nonprotein-coding RNAs, including ribosomal RNA (rRNA), transfer RNA (tRNA), small nuclear RNA (snRNA), microRNAs (miRNAs), piwi-interacting RNAs (piRNAs), and small interfering RNAs (siRNAs). A comprehensive investigation of the human transcriptome has found around 60,000 long non-coding RNAs (lncRNAs), which make up roughly 70% of all expressed genes. The enormous ubiquity of lncRNAs in biological processes highlights their potential relevance to human health and disease [1, 2]. Although our understanding of lncRNAs, their characteristics, and categorization has evolved, it remains imperfect. LncRNAs, typically about 200 nucleotides in length, feature complex three-dimensional structures that interact with DNA, RNA, and proteins to regulate protein complexes, modulate gene expression, recruit histone modifiers to chromatin, inactivate chromosomes, and influence pluripotency and differentiation [2, 3].

Recent studies have increasingly highlighted the pivotal roles of lncRNAs in the initiation and progression of a wide range of human diseases. These transcripts are now recognized as key regulators of gene expression, influencing diverse cellular processes such as chromatin remodeling, transcriptional control, post-transcriptional regulation, and signal transduction. Dysregulation of lncRNAs has been implicated in various pathological conditions, including cancer, cardiovascular disorders, metabolic diseases, and neurodegenerative conditions [4]. Although extensive in vitro investigations have provided valuable mechanistic insights into lncRNA functions and molecular interactions, these experimental systems cannot fully recapitulate the complexity of physiological environments. Consequently, comprehensive in vivo characterization and functional annotation of lncRNAs remain limited [5]. The lack of robust in vivo evidence hampers a complete understanding of their biological relevance, tissue-specific functions, and contributions to disease pathogenesis. Addressing this knowledge gap through advanced in vivo models and integrative approaches is essential for translating lncRNA research into meaningful diagnostic and therapeutic applications [6]. In particular, the investigation of lncRNAs in human liver function and disorders has been restricted [7]. Identified disease-specific targeted genes and lncRNAs implicated in alcoholic hepatitis, providing new insights into molecular signatures of disease. Research into lncRNAs in liver fibrosis is expanding, with in vivo and ex vivo studies revealing that variations in lncRNA levels may greatly affect the severity of the liver disease, highlighting their potential as therapeutic targets. LncRNAs interact with miRNAs, regulating each other's expression via sequence-specific binding, and influence different biochemical processes, including the NF-κB signaling pathway. Although preclinical models have proven successful strategies for manipulating lncRNA expression, the therapeutic potential of lncRNA-based therapeutics will rely on additional research and technical improvements. LncRNAs high-throughput sequencing has enabled the identification of HCC-related lncRNA signatures. Machine learning methods, including support vector machines, random forests, LASSO regression, clustering algorithms, and deep learning, are widely applied to construct diagnostic and prognostic models. These approaches improve tumor classification, survival prediction, and molecular subtype stratification in HCC patients [8]. In this review, focusing mainly on fibrosis or cancer, this work emphasizes ethanol-specific mechanisms such as oxidative stress, DNA methylation, and acetaldehyde-induced epigenetic changes. It highlights their biomarker potential and therapeutic significance.

Ethanol-induced liver damage

Ethanol exposure triggers molecular events that lead to liver damage, with lncRNAs playing pivotal roles in mediating these effects. Ethanol influences the expression of lncRNAs, which in turn regulate pathways involved in inflammation, oxidative stress, and apoptosis. Mechanistic insights into lncRNAs in alcohol-related liver disease (ALD) should be expanded. For instance, lncRNA H19 drives hepatic stellate cells (HSCs) activation through the TGF-β/Smad pathway and by sequestering antifibrotic miRNAs [9]. They are closely involved in programmed cell death (PCD), including apoptosis, autophagy, necroptosis, and ferroptosis. LncRNAs can suppress or activate specific PCD pathways by modulating related proteins or acting as competitive endogenous RNAs. Their regulatory roles have been widely reported in cancers such

as non-small cell lung cancer and gastric cancer, highlighting important clinical implications [9]. These lncRNAs impact lipid metabolism and inflammatory responses, orchestrating the liver's response to chronic alcohol exposure. Ethanol consumption also alters DNA methylation, leading to alcohol-induced liver damage. Ethanol metabolism produces excess reactive oxygen species (ROS), and the decreased NAD^+ levels in alcohol-exposed hepatocytes hinder histone acetylation. Reduced histone acetylation damages the sirtuin-1 (SIRT1)-AMP kinase pathway, leading to fatty liver and advanced fibrogenesis [10]. Early diagnosis and the identification of appropriate biomarkers are crucial for developing better treatment guidelines for ALD.

Chronic alcohol consumption leads to significant changes in sinusoidal endothelial cells, which are critical for maintaining liver function. In both in vitro and in vivo experiments, chronic alcohol consumption has been shown to damage these cells, causing early defenestration and compromising the basement membrane. Excessive alcohol consumption disrupts fluid and molecule circulation, as well as immune cell migration, promoting liver tissue fibrosis [11]. Sinusoidal endothelial cells play a critical role in clearing hyaluronic acid (HA). Chronic alcohol exposure upregulates circulating HA levels, contributing to liver damage. Elevated HA levels are linked to cellular damage, particularly sinusoidal endothelial functions that regulate alcoholic hepatic injury [12]. In vivo studies have shown that sinusoidal endothelial cell-specific STAT3 knockout mice exhibit reduced alcoholic liver injury during chronic ethanol consumption, as inhibiting STAT3 in these cells decreases hepatic inflammation [13, 14]. Furthermore, HSCs are key non-parenchymal cells that maintain liver homeostasis in their quiescent state. Upon acute or chronic injury, HSCs become activated and contribute to the progression of liver diseases, including liver fibrosis, cirrhosis, and hepatocellular carcinoma (HCC). In fatty liver diseases such as nonalcoholic fatty liver disease and ALD, activated HSCs regulate inflammation, fibrosis, tumor progression, angiogenesis, immunosuppression, and chemoresistance, highlighting their central role in disease progression. Chronic alcohol consumption induces sinusoidal endothelial cell damage, which is an initial step in the progression of ALD and chronic alcoholic cirrhosis. This process includes the stimulation of HSCs and the restoration of sinusoidal endothelial function. Understanding the intricate molecular mechanisms by which ethanol induces liver damage, particularly through lncRNA roles, is essential for developing targeted therapeutic strategies [15].

Hepatic stellate cell activation

HSCs are crucial to the development of liver fibrosis, transitioning from a quiescent to an activated state in response to liver injury. LncRNAs play a crucial role in regulating HSC activation by influencing genes involved in extracellular matrix (ECM) production and fibrogenesis [16]. For instance, lncRNA GAS5 inhibits HSC activation by targeting the mTOR pathway, reducing ECM production. Conversely, lncRNA MEG3 is downregulated in liver fibrosis and its restoration inhibits HSC activation and suppresses fibrogenesis. These lncRNAs' dual roles in fibrosis highlight their potential as therapeutic targets [17]. Liver fibrosis is a major global liver disorder resulting from dysregulated tissue repair after chronic injury or inflammation and may progress to cirrhosis and liver failure if untreated. LncRNAs regulate gene expression and signaling pathways, with some promoting and others inhibiting fibrosis. They interact with epigenetic mechanisms such as methylation and acetylation and often function by competitively binding miRNAs, thereby influencing gene transcription and representing potential therapeutic targets [17].

Lipid peroxidation and oxidative stress produce high levels of ROS and inflammatory cytokines. Via the NLRP3 inflammasome, elevated ROS activates cytokines including TNF-α, IL-1β, and IL-6. Lipopolysaccharides (LPS) released from gut bacteria bind to the CD14/TLR4 complex, triggering inflammatory responses. TNF-α production and expression are crucial in the progression of ALD. The TNF-α-mediated NF-κB signaling pathway in hepatocytes exacerbates ALD. Oxidative stress results from an imbalance between pro- and antioxidant species [17]. ROS, mostly generated in liver mitochondria and the endoplasmic reticulum via the cytochrome P450 enzyme, contribute to various pathological conditions. Key element in cellular redox states, the CYP2E1 isoenzyme produces high ROS levels by redox-sensitive transcription factors like NF-κB, NRF2, AP-1, and EGR-1, modifying hepatocyte proteins, lipids, and DNA

[18]. ROS directly damages DNA and induces lipid peroxidation, creating carcinogens from exocyclic etheno-DNA adduction. Acetaldehyde, a poisonous and carcinogenic chemical produced by alcohol oxidation, reduces ATP generation and influences liver function by impairing mitochondrial activity [19]. Chronic alcohol consumption reduces glutathione levels and disrupts the expression of oxidative insult regulators like NRF2 and thioredoxin. Alcohol intake also affects LPS levels, activating the toll-like receptor-4 [20].

Fibrosis

Fibrosis, a wound healing process involving ECM accumulation, is influenced by lncRNA expression. Dysregulated lncRNAs have an impact on cellular integrity and ECM accumulation, both of which are critical in the progression of liver disease. LncRNAs like GAS5 and MEG3 play opposing roles in fibrogenesis, either inhibiting or promoting ECM production and HSC activation. Targeting these lncRNAs may provide therapeutic avenues for managing liver fibrosis [21]. Aberrant DNA methylation and histone changes play an important role in disease development. DNA methylation adds methyl groups to cytosine residues in CpG islands, while histone changes include modification, acetylation, phosphorylation, sumoylation, and ubiquitination. miRNAs have an effect on histone modifications and post-transcriptional gene expression, which affects chromatin shape and expression [22]. Dysregulated miRNAs are related to liver damage, cell death, regeneration, inflammation, and negative consequences. miR-34a has both pro- and anti-apoptotic actions and causes alcohol-induced hypomethylation in liver diseases by affecting the redox-sensitive enzyme SIRT1, which is critical in the course of ALD [23]. miR-217 inhibits SIRT1 expression, altering the SIRT1–lipin1 axis in liver cells [24]. SIRT6 has emerged as a potential therapeutic target for ALD, and inhibiting miR-217 is perhaps a treatment strategy [25].

Excessive alcohol intake causes hypermethylation of the miR-148a promoter, which influences liver cell differentiation. miR-155 inhibits the PPARα signaling pathway, impacting oxidative stress, lipid metabolism, inflammation, and fibrosis in response to alcohol [26]. Excessive alcohol intake causes hypermethylation of the miR-148a promoter, which influences liver cell differentiation. miR-155 inhibits the PPARα signaling pathway, impacting oxidative stress, lipid metabolism, inflammation, and fibrosis in response to alcohol. Studies were investigated miR-148a regulation by FoxO1 and its targeting of TXNIP in alcohol-induced hepatocyte pyroptosis in ALD, without involving miR-155 or NF-κB signaling. Similarly, molecular mechanisms and potential biomarkers in portal hypertension are related to ethanol-induced miR-155 modulation of NF-κB. These miR-155-mediated NF-κB activation in alcohol-related liver injury [26].

miR-21 targets the *BTG2* gene, which inhibits the activity of the transcription factor forkhead box M1 [27, 28]. Up-regulated miR-21 inhibits BTG2 during liver cell regeneration while targeting FASLG and DR5, hence reducing liver cell death. Polymorphisms in the *PNPLA3* gene are closely linked to ALD development. Understanding the miRNAs involved in *PNPLA3* is critical for creating therapeutic markers. Overexpression of miR-9 suppresses the *PNPLA3* gene and increases AMPK phosphorylation.

Cirrhosis of the liver

Alcoholic cirrhosis, an end-stage chronic liver disease, is characterized by extensive fibrosis and liver dysfunction. LncRNAs contribute to cirrhosis pathogenesis by regulating cell proliferation, apoptosis, and ECM remodeling. Dysregulated expression of lncRNAs, such as HOTAIR and lncRNA-p21, correlates with disease severity. These lncRNAs influence key transcription factors and signaling molecules, affecting cirrhosis progression. Additionally, lncRNAs serve as biomarkers for early cirrhosis detection, offering non-invasive diagnostic potential [29]. LncRNAs are widely transcribed across the genome and regulate gene expression through diverse molecular mechanisms. Advances in sequencing and computational biology have improved their functional annotation and classification. Although lncRNA research has expanded rapidly, relatively few studies focus on hepatic biology. Emerging evidence highlights their roles in liver physiology and diseases, particularly nonalcoholic fatty liver disease, underscoring their potential importance in understanding liver pathology and therapeutic development [29]. In hepatic injury, these

non-coding RNAs show higher regulation of let-7c-5p, suppressing alcoholic steatosis by stimulating intracellular proteins and immune target genes like *NLRC5* (NOD-like receptor family 5) [29]. LncRNAs (AK128652 and AK054921) in chronic alcoholic liver progression, comparing excessive alcohol drinkers to healthy controls. This detailed analysis, along with the Child-Pugh score, showed higher regulation of lncRNAs in cirrhosis cases and downregulation in controls. Fold expression changes (> 2 or < 2) in excessive drinkers were observed, with lncRNA AK128652 predominantly rising in alcoholic liver cirrhosis patients [30]. AK128652 as a biomarker is supported by only one report. Integrating multicenter data where available, or acknowledging such gaps, is essential. A summary table categorizing lncRNAs by stage, experimental validation, and molecular targets would improve clarity and evidence visualization. These lncRNAs are novel prognostic and diagnostic biomarkers for alcoholic liver cirrhosis [30].

Liquid biopsy has emerged as a promising non-invasive strategy for early cancer detection and monitoring. Among circulating biomarkers, exosomal miRNAs are particularly valuable due to their stability in bodily fluids and ability to reflect tumor dynamics. Exosomal miRNAs can aid in early diagnosis, prognosis, and assessment of therapeutic response across multiple malignancies, including breast cancer and lung cancer. Advancing sensitive detection technologies will enhance their clinical utility in cancer management [31]. Alcohol and tobacco exposure may modulate the expression of non-coding RNAs like miRNAs, HOTAIR, and metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) through the IL-6/STAT3 signaling pathway. ALD also regulates miRNA-21. In ALD, lncRNAs associated with epigenomics play an important role [32]. In chronically ethanol-fed mice, inhibition of SIRT1 contributes to liver progression through inflammation response, hepatic steatosis, and fibrosis. LncRNAs are highly regulated during liver fibrosis by targeting MALAT1, which is stable and highly integrated with histone deacetylase SIRT1, mediating its degradation [33]. Further exploration of MALAT1 function in chronic alcoholic liver injury or disease is needed. While many studies have reported the expression of lncRNAs in ALD, some mechanisms of action in chronic alcohol consumption remain to be understood.

Hepatocellular carcinoma

HCC is characterized by irregular cellular proliferation influenced by viral infections, hepatic regeneration signals, and hypoxia. LncRNAs modulate the cellular immune response and hepatic regeneration through redox signaling, playing significant roles in regulating the hepatic microenvironment and disease progression [34]. Dysregulation of lncRNAs can lead to liver inflammation, oxidative stress, alcoholic hepatitis, and HCC progression. The *H19* gene, which is highly expressed in lncRNA, arises from the maternal allele and plays a crucial role in genetic imprinting, cell growth, and development. Studies have demonstrated that the *H19* gene is reactive in adult tissue regeneration and tumorigenesis. Loss of genetic material at the *H19* locus results in higher expression in cancer and hepatic metastasis progression [35]. Exosome-derived lncRNAs, such as lncRNA-ATB, LINC00511, and LINC00853, are associated with prognosis in HCC patients, signifying their potential role as diagnostic biomarkers for early detection of HCC [36].

Additionally, lncRNAs like lncRNA ROR and lncRNA VLDLR are putative modulators of HCC responses to sorafenib, influencing extracellular vesicle-mediated signaling and disease progression [37]. The study of lncRNAs in ALD reveals their critical roles in regulating disease mechanisms. LncRNAs are involved in various aspects of ALD, including metabolic processes, immune responses, and oxidative stress. These processes are influenced by complex regulatory networks and interactions with other molecular entities [38]. Future research should focus on identifying and validating specific lncRNAs associated with ALD progression. Understanding their roles in the disease could lead to the development of new biomarkers for early diagnosis and targeted therapies [39]. Given the intricate nature of lncRNA interactions and their potential as therapeutic targets, ongoing investigation is essential to leverage these molecules for improved clinical management and treatment outcomes in ALD.

Future prospective

Future investigations into lncRNAs in liver fibrosis provide significant opportunities for enhancing diagnostic and therapeutic techniques. The increased knowledge of lncRNA activities and their connections with biological circuits highlights their potential as biomarkers for early disease identification and surveillance. Advances in high-throughput sequencing and analytics are poised to find novel lncRNAs and unravel their involvement in liver fibrosis, cirrhosis, and HCC. By merging lncRNA profiles with clinical data, we might develop tailored treatment options and improve patient outcomes. Furthermore, tailored medicines focused on altering lncRNA expression or activity could change current therapeutic procedures. *CRISPR/Cas9* gene editing technology provides a precise strategy for modulating lncRNA expression, showing promise in preclinical animals. Continued study into lncRNA functions in liver pathology, paired with technological developments, is anticipated to increase our knowledge of liver disease processes and open the door for innovative diagnostic and therapeutic treatments [40]. Recent breakthroughs in molecular biology and high-throughput sequencing have emphasized the dysregulation of lncRNAs in liver fibrosis, demonstrating their important role in disease progression. Despite this, the regulatory networks and molecular pathways involving lncRNAs in liver fibrosis remain incompletely understood. Future research should concentrate on finding lncRNAs with diagnostic and therapeutic potential for liver fibrosis and creating appropriate applications. Extracellular vesicles, which carry a variety of molecules, including lncRNAs, may mirror the characteristics of their source cells [41]. For instance, human adipose-derived stem cells (hASCs) promote liver repair partly through paracrine mechanisms. In rat models of acute liver failure, transplantation of hASC-derived extracellular vesicles significantly improved survival. Gene sequencing revealed increased human lncRNA H19 in recipient livers after EV treatment. Silencing H19 in hASCs reduced the therapeutic efficacy of their EVs, lowering survival rates. These findings suggest that lncRNA H19 is a key mediator of EV-based therapy and a potential target for treating liver failure [41].

Clinical translation of lncRNAs requires more discussion. Circulating lncRNAs in extracellular vesicles offer stable, non-invasive biomarkers, detectable via qPCR, RNA sequencing, or digital PCR. Therapeutically, delivery strategies such as lipid nanoparticles, polymer carriers, or exosome-mediated transport enable targeted inhibition or replacement. Emerging siRNA, long RNAs, including mRNAs and lncRNAs, circulate in serum within extracellular vesicles such as apoptotic bodies, microvesicles, and exosomes. In patients with colorectal cancer, exosomes contain the highest abundance of long RNAs. Analysis of 79 cancer-related transcripts showed strong diagnostic performance, with exosomal RNA outperforming total serum RNA. A combined signature of *KRTAP5-4*, *MAGEA3*, and *BCAR4* demonstrated high accuracy, highlighting exosomal long RNAs as promising non-invasive biomarkers for colorectal cancer detection [42]. Additionally, CRISPR/Cas9 technology has been efficiently applied to alter protein-coding genes and plays a crucial role in liver fibrosis development. In a rat model, CRISPR targeting RSPO4 revealed a decrease in liver damage and restoration of intestinal flora. The ability of specificity and adaptability of CRISPR/Cas9 represent methodological attributes of a genome-editing platform. These technological advantages pertain to targeted genetic manipulation rather than intrinsic pathogenic mechanisms. Therefore, CRISPR/Cas9-based editing strategies are conceptually and mechanistically distinct from miRNA-mediated regulatory processes in ALD [43]. Advances in nanomedicine—lipid nanoparticles, polymeric carriers, and exosome-based delivery—also warrant discussion as potential therapeutic avenues [43]. This technique, which has previously shown promise in treating numerous conditions, including cancer, may provide a fresh strategy for regulating liver fibrosis through precise lncRNA regulation.

Conclusions

In conclusion, the research on lncRNAs has considerably expanded our knowledge of their functions in liver disease progression, including fibrosis, cirrhosis, and HCC. LncRNAs appear to be important regulators of numerous molecular pathways, including disease progression, response to ethanol-induced damage, and cellular mechanisms such as inflammation and fibrosis. LncRNAs with translational relevance rather than restating general findings. H19 and MALAT1 promote inflammation and fibrosis, positioning them as

therapeutic targets, whereas GAS5 acts protectively. Circulating lncRNAs like AK128652 and AK054921 show biomarker potential but require multicenter validation. Their capacity to interact with DNA, RNA, and proteins underlines their potential as biomarkers for early diagnosis and targets for therapeutic treatments. As research continues, incorporating lncRNA profiles with clinical data will likely increase tailored treatment regimens and improve patient outcomes. The ongoing investigation of lncRNA activities and their interactions in liver pathology promises to uncover new insights and therapeutic pathways, eventually enhancing the management and treatment.

Abbreviations

ALD: alcohol-related liver disease

ECM: extracellular matrix

HA: hyaluronic acid

hASCs: human adipose-derived stem cells

HCC: hepatocellular carcinoma

HSCs: hepatic stellate cells

lncRNAs: long non-coding RNAs

LPS: lipopolysaccharides

MALAT1: metastasis-associated lung adenocarcinoma transcript 1

miRNAs: microRNAs

PCD: programmed cell death

ROS: reactive oxygen species

siRNAs: small interfering RNAs

SIRT1: sirtuin-1

Declarations

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Author contributions

SPK: Writing—original draft, Supervision, Conceptualization. KSN: Writing—original draft, Writing—review & editing, Conceptualization. PN: Writing—original draft, Writing—review & editing, Conceptualization. All authors read and approved the submitted version.

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The authors declare no conflict of interest.

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