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Long Non-Coding RNAs as Emerging Role in Prognosis of Alcohol Related Liver Disease

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Abstract

Chronic alcohol exposure significantly influences the prognosis and diagnosis of alcohol related liver disease (ALD), affecting gene expression and liver function. Hepatic proteins and non-coding RNAs are essential for many biological functions and disease progression. Regulatory processes associated with microRNAs and long non-coding RNAs (lncRNAs) are known enhanced by recent advances in RNA sequencing methods. This new importance of lncRNAs in hepatic disease progression encompasses their involvement in cellular growth, and regulation, necrosis, and the control of transcriptional factors. Regulation of cellular integrity and ECM accumulation are two of the many functions played by lncRNAs in hepatic fibrosis, a wound healing process characterized by the gradual formation of ECM during disease progression. In the context of hepatic disease progression, a multitude of lncRNAs actively participate in regulating cellular homeostasis, positioning them as potential therapeutic targets and valuable biomarkers in clinical practice. Acquiring insightful knowledge about the underlying biological processes and molecular mechanisms governing hepatic injuries is crucial for identifying specific and sensitive molecules that can facilitate hepatic regeneration. The studies are increasingly interested in understanding the function of lncRNAs in liver regeneration after long-term alcohol use. To better understand alcoholic liver disease clinically, this review seeks to clarify the predictive significance of lncRNAs regulatory factors in stimulating hepatic development and revitalization.

Keywords: Alcohol, Hepatic Cirrhosis, Long Non-Coding RNAs (lncRNAs), Regeneration, Steatohepatitis.

Introduction

Non-coding RNAs (ncRNAs) were formerly thought to be junk RNA or transcriptional noise, but they have now been identified across many cellular and pathological procedures, performing a critical part in complex regulatory networks that are growing in importance within cell interactions. The length of the nucleotides used to construct an RNA molecule determines whether it is a long non-coding RNA (lncRNA) or a short non-coding RNA. The former has 200 nucleotides or more, while the latter contains less than 200 (1). Most lncRNA species are transcribed by RNA polymerase II having 5` end m7G caps and 3` end poly(A) tails from the various genomic region, including introns and exons (2). Long non-coding RNAs (lncRNAs) largely engage in biological processes such replication, splicing, transcription, translation, chromatin structuring, proteins, as well as their alteration after translation (3). lncRNA regulates the gene activity and mediates the specific localization of targets by forming ribonucleoprotein complex. Decoy lncRNA is involved in the biological activity as chromatin modifiers, transcriptional factors and RNA binding proteins. Signaling long non-coding RNAs (lncRNAs) are often expressed during certain temporal phases and participate in activities confined inside specific sub-cellular structures. Scaffold lncRNA is also affects the molecular components of the complexes and enhanced the lncRNA elements and influences the activation of target specific genes. Accumulation of lncRNA can generate microRNAs (miRNAs, 2, 4).

Chronic alcohol consumption result in a subset of patients with ALD. Consumption of alcohol for a longterm leads to damage to sinusoidal endothelial cells in the basement membrane and early defenestration. Over alcohol intake may interrupt fluid, macro and micro molecule circulation in addition to immune cell migration which particularly promotes liver tissue fibrosis. Similarly, alcoholic and non-alcohol related liver

diseases are comprised of a series of pathogenic changes initiating from fatty liver to cirrhosis and finally hepatocellular carcinoma (HCC, Figure 1, 5, 6). The overconsumption of alcohol associated with severe alcohol-related liver injuries developed in medial age of patients who are taking excess alcohol. Several new concepts are elucidated for the significant role of lncRNAs in liver disease (7). Recently lncRNA is found to involve in alcohol related liver disorders and blood levels of AK128652, AK128400, and AK054921 were down-regulated these diseased patients (8).
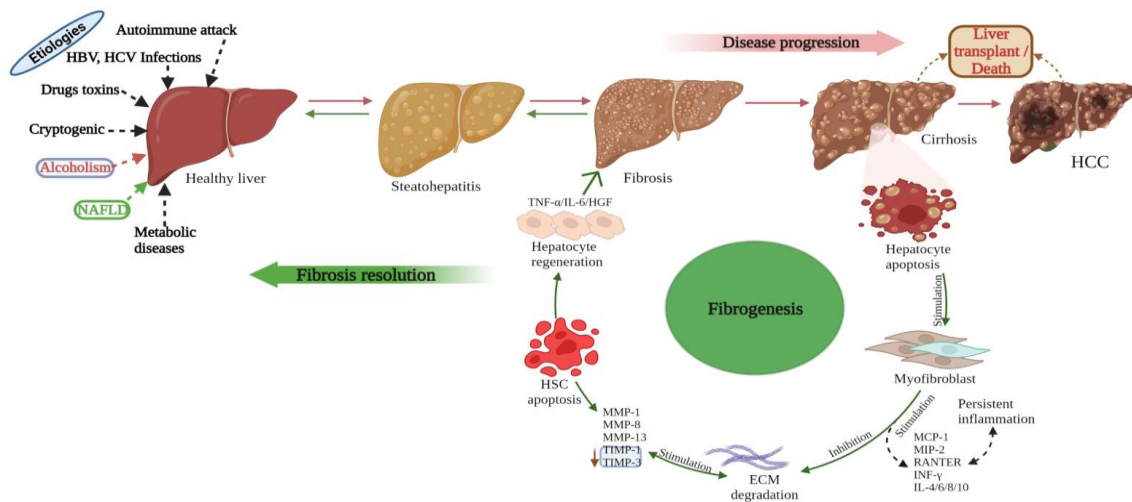
Hepatic fibrosis and alcohol-induced steatosis were shown in an animal model as a result of NEAT1, Gm5091, and MEG3 in contrast to lncRNAs role in alcoholic diseases including pro-inflammation and anti-fibrotic stage of HCCs progression (9, 10). These lncRNAs exhibit the prognostic biomarkers for alcohol-related liver cirrhosis and suggesting the essential function of lncRNAs as potential biomarkers in ALD (11). This mini-review is to highlight the regulation of lncRNAs in alcoholic liver disease which leads to progression of disease.

Figure 1: Schematic representation of liver disease and fibro-genesis progression

Role of lncRNA in hepatic stellate cell activation

lncRNA of Gm5091 strongly down-regulates hepatic stellate cells (HSCs) in mice with alcohol related fibrosis. A number of studies have found that downregulation of Gm5091 in cell migration, including desmin, collagen I production and HSC activation expression marker and α-smooth muscle actin. Following a bioinformatics analysis, it was shown that full Gm5091 may reduce miR-27b, miR-24, and miR-23b expression levels. Involvement of miR-27, miR-24 and miR-23 significantly regulates the activity of smad4 and TGF- β in HSC progression (12, 13). Overexpression of NEAT1 promotes the HSCs and cellular regulation observed in the hepatic fibrosis sample and NEAT1 has been considered as liver fibrotic marker. As per previous studies, miR-122 inhibits HSCs activation and induces some of the genes including TGF- β in liver fibrosis. It stimulates of kruppel-like factor-6 (KLF-6) is induced immediately during liver fibrosis, which induces the TGF-β RI and II in activated HSCs (14).

In addition, miR-122 has a particular target in NEAT1 and KLF6. NEAT1 competes for binding with miR-122 and affects the development of KLF6 in liver fibrosis. This shows that the NEAT1/KLF6/miR-122 axis triggers the activation (14, 15, Table 1). MALAT1 promoting the cell cycle, cell proliferation and HSCs activation by regulating miR-101b

These studies were conducted utilizing ethanol administration in vitro and in animals. The results demonstrated a down-regulation of let-7, a rise in fibrosis stage, and raised levels of the stem cell marker, lin28B. In a laboratory environment, HSCs received treatment with TGF-β or inflammatory chemicals such as LPS. It indicates lower levels of let-7 and higher expressions of Lin28A/B, migration, HMGA2, and mesenchymal markers (16, 17). Alcohol-related liver disease tissues have shown decreased let-7 levels. However, Elevated levels of Lin28A/B and HMGA2 imply the involvement of these variables in acute liver damage due to alcohol use. The results reveal a link between reduced activation of HSCs is related with let-7a and let-7b in ALD (17).

Table 1: The role of lncRNAs in alcohol-related liver disease

Long non-coding RNAs	*Loci*	Selected Targets	Biological function	Stage of marker
lncRNAs-Gm5091	*Chr 7*	miR-27b/ miR-24/ miR-23b	Immunoregulation, apoptosis	Hepatic fibrosis marker
miR-122	*18q21.31*	PPAR family of proteins	Proliferation, inflammation, and apoptosis	Potential biomarker for the liver disease
let-7	*22q13.31*	NOD-like receptor family CARD domain containing 5 (NLRC5)	Proliferation, fibrogenesis, and inflammation	Potential biomarker for therapeutic and diagnostic fibrosis marker
mir-let-7c		Pro-inflammatory cytokines	Apoptosis, Regulation of NLRC5	Therapeutic target for HCC
lncRNAs-MEG3	*14q32.3*	PPAR family of proteins/ Smoothened (SMO)	Tumor suppressor, anti-fibrosis	Novel potential therapeutic marker
miR-129-5P	*7q32.1*	Cytokine Signaling (SCOS)	Proliferation, inflammation, and apoptosis	Prognostic and diagnostic biomarker
AK128652 and AK054921		Collagen types	Pathogenesis of ALD	Potential biomarkers to predict the ALD progression
lncRNA-DSCR8	*21q22.13*	miR-485-5p/Frizzled-7 (FZD7)	Proliferation, cell cycle and apoptosis	Potential prognostic and therapeutic marker
lncRNA-SNHG5		MiR-26a-5p/glycogen synthase kinase-3 β (GSK3 β)	Proliferation, inflammation, and apoptosis	Prognostic and potential therapeutic marker
lncRNA-NEAT1	*11q13.1*	H3K27me3/miR-122/Kruppel-like factor 6	Proliferation, immunoregulator	Prognostic biomarker
miR-34a	*1p36.22*	Sirtuin 1	Cell migration, apoptosis, remodeling and regeneration	Therapeutic marker and diagnostic approach

Role of lncRNA in alcohol-related liver fibrosis

The particular lncRNAs are censorious to the transition from heavy drinkers without underlying alcohol associated liver disease. lncRNA are differentially expressed in alcohol drinkers with chronic liver disease. Some lncRNA have been involved in the pathophysiological mechanisms of hepatic fibrosis and producing cirrhosis via their roles as combining profibrotic and anti-fibrotic properties (18). Hepatic fibrosis damages liver tissues comprising hepatic cells (19).

lncRNA Gm5091 negatively regulates HSCs as well as liver fibrosis in mice and strongly downregulated during alcohol-induced liver fibrosis (20), which is stimulated by miR-27b/24/23b in alcoholic cirrhosis. Gm5091 increases the production of TGF-β regulating miR-23b/24/27b sponging progression of alcohol-related fibrosis (9, 12). Mainly, it is speculated that miR-27/24/23 might accelerate the occurrence of alcohol-related liver disease by encouraging the differentiation as well as multiplication of hepatic cells via the activation of smad4 and TGF-β signaling pathways. Gm5091 strongly regulates the regulation of reactive oxygen species (ROS) levels, and it exerts negative control over interleukin-1β release, cell migration, collagen I

expression, and activation markers of hepatic stellate cells, including desmin and α-SMA (9).

Ye et al. described action of NEAT1 and SOCS2 and elevated miR-129-5p able to minimize the hepatic fibrosis in mice with alcoholic steatohepatitis (21). The elimination of NEAT1 impedes hepatic fibrosis both in vitro and in vivo. Furthermore, the reduction of miR-129-5P, resulting in lower collagen I production in HSCs throughout the course of liver disease. NEAT1/miR-129-5p/SOCS2 axis controls hepatic fibrosis in alcohol induced steatohepatitis (21, 22). MALAT1 is negatively correlated with miR-101b levels in carbon tetrachloride treated mouse with liver fibrosis. MALAT1 has a function in regulating the association between miR-101b and Rac1 3'UTR, leading to the control of Rac1 expression and ultimately contributing to the advancement of liver fibrosis. The most recent studies have found that miR-let-7c-5p was raised in ethanol-fed mice and is down-regulated by MEG3 (23). In human liver disease, let-7 has a crucial function in hepatic steatosis and biliary diseases (17). A miR-let-7c-5p represents the obstructed alcohol-induced liver a fatty liver and cellular death in AML-12 cells (23). NLRC5 directly targets miR-let-7c-5p, and the amount it expresses is enhanced in mice exposed to ethanol. The let-7 plays an important function in alcohol-induced liver injury and reduction of let-7 leads to increased severity and progression of hepatic fibrosis (23). Chronic alcohol consumption may cause multi-cellular injury and this consistently leads to activation of mesenchymal progression. However let-7/lin28 signals have a link as tightly maintained in liver damage and progression of liver disease including ALD.

Role of lncRNA in alcoholic cirrhosis

Overconsumption of alcohol downregulates MEG3, This is a target of let-7c-5p in alcoholic hepatic damage and proven in both in-vitro and in-vivo settings. During hepatic damage, these non-coding RNAs have shown higher regulation of let-7c-5p involved in suppressing alcoholic steatosis by stimulating the intracellular proteins and immune target gene like NLRC5 (NOD-like receptor family 5, 23).

Yang et al. study identified specific lncRNAs AK128652 and AK054921 expression involved in regulation of ALD progression(8). In this detailed analysis of lncRNA along liver scoring compared cases with alcoholic and healthy controls, results have shown higher regulation of lncRNAs in cases and down-regulation in controls. They found the fold (>2 or <2) expression changes in excessive drinkers compared to controls (8). Among these, lncRNAs AK128652 was predominant increased in cases. These lncRNAs are novel prognostic and diagnostic biomarkers in liver diseases. Yang et al. found AK054921 and AK128652 as possible blood indicators in people with alcoholic liver cirrhosis (8, 24). Drinkers, tobacco exposure may modulate the expression of microRNAs, HOTAIR, and MALAT1 via IL-6/STAT3 signaling pathways. Moreover miRNA-21 regulates alcohol-related liver disease (18).

lncRNAs along with epigenomics plays a crucial role in the progression of alcoholic liver disease, and by inhibiting silent information regulation 1 (SIRT1) leading to inflammation, hepatic steatosis, fibrosis in chronic ethanol-fed mice(25, 26). Among lncRNAs, MALAT1 emerges as a target gene exhibiting heightened regulation in liver fibrosis. MALAT1 is notably stable and intricately linked with the histone deacetylase SIRT1, playing a role in mediating the degradation of SIRT1.

It needs to study the role of MALAT1 in chronic alcoholic liver disease. However, more studies have reported an expression of lncRNAs in alcohol-related liver disease, abnormal transcription of MALAT1, miR-101b, and Rac1 was identified in individuals with hepatic cirrhosis (27, 28).

Role of lncRNA in alcohol related Hepatocellular carcinoma

HCC is irregular cellular proliferation due to viral infections, hepatic regeneration signals, and hypoxic nature and nurture involvement. These factors may challenge irregular hepatic cellular proliferation and survival and opportunities for development of HCC (29, 30). Particularly, lncRNAs modulate the cellular immune response and hepatic regeneration by redox signaling. These signals may have a vital role in the regulation of hepatic microenvironment and hepatic disease progression. Regulation of lncRNAs may lead to liver inflammation, oxidative stress, alcohol-related hepatitis, and hepatic outgrowth, and it leads to progression of HCC (31, 32).

H19 stands out as one of the first discovered and described long non-coding RNAs. Its epigenetic

control incorporates a specific and complicated regulatory region with parent-of-origin-dependent differential methylation. Functionally, H19 plays a role in proper liver activities, including development. However, its dysregulation is connected with many liver illnesses such as type II diabetes mellitus, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, cholestatic liver fibrosis, HCC, and the advancement of hepatic metastasis (33).

Some of the exosome-derived lncRNAs in particular lncRNA-ATB, LINC00511, and LINC00853 were linked with development of HCC, thus signifying the potential role as diagnostic biomarkers for the early identification of HCC (34). lncRNAs like lncRNA ROR and lncRNA VLDLR were putative modulating HCC responses to sorafenib determined extracellular vesicles and mediated intracellular signaling to HCC progression. Elevated MALAT1 expression in hepatocellular carcinoma cells regulate the increased production of the oncogenic splicing factor SRSF1 and activates the mTOR pathway, resulting in higher cell proliferation and survival in HCC. Expression of MALAT1 regulates apoptosis, cell proliferation and autophagy of HCCs by downregulating miR-146a. miR-146a upregulates PI3K and modulate the expression of downstream Akt and mTOR. Hence, autophagy and apoptosis during development of HCCs can be inhibited by targeting PI3K/Akt/mTOR signaling pathway (35).

Currently, lncRNAs are potential diagnostic biomarkers identified from human fluids. A lnc-PCA3 identified from urine sample provided the sensitive and more specific marker for patients with prostate cancer but generally practices serum prostate-specific antigen (PSA), highlighting the non-invasive diagnostic technique (36). Similarly, increased expression of lncRNA-HULC associated with HCC determined in the blood sample of HCC patients using the traditional PCR method (37). Our idea is that human body fluids such as plasma, serum, and urine could contain a large number of lncRNAs. These compounds might possibly be detected utilizing quantitative RT-PCR or unbiased high-throughput methodologies and technologies like microarrays or deep RNA sequencing of the material (38). Exploring lncRNAs by comparative analysis in distinct cohorts of cancer patients and healthy persons within various human bodily fluids can disclose trustworthy new circulating lncRNAs, presenting potential biomarkers.

Role of lncRNAs and factors that induce liver regeneration

Long non-coding RNAs are target therapeutics for hepatic acute challenges and having dynamic response in the regrowth of liver. The hepatic is one of the visceral organs that may be capable of recovery after partial hepatectomy (i.e Surgery to remove all parts of the liver), regulates the hepatic growth factor related to greater rise of urokinase activity, loss of liver tissue which potentially regulates the EGFR and targeting the c-met pathway(39, 40). EGFR and c-met regulates the activation of hepatic cell proliferation by various signaling. Once hepatic regeneration completes which regulates the TGF-β by functional urokinase and HGF these are brought back to the liver initial stage (40).

In this stage several lncRNAs are involved in the pathway process such as lncRNA- LALR1. It has been found to suppress Axin 1 pathway which may activate the Wnt signaling and regulates the liver cell proliferation during hepatic regeneration. Recently, lncHand2 is highly regulated by NKX1-2 and activated c-met in hepatocellular to help hepatic regeneration (41). Persistent proliferative cell signaling, arising from the dysregulation of lncRNAs, is implicated in the development of HCC. Specifically, lncRNA-SNHG5 and lncRNA-DSCR8 display heightened regulation owing to Wnt signaling, leading to hepatic tumor formation. lncRNA-NEAT1 and lncRNA-EGFR which are capable of regulating the activation of EGFR and c-Met pathway, that leads progression of liver disease (31, 42, Figure 2). Possibly, long non-coding RNAs are activated when there is no liver tissue injury or when the inhibitory effect of the quiescent signal TGF-β fails. This TGF-β may favorably regulate lncRNAs like ATB, thereby contributing to hepatocellular carcinoma metastasis an important regulatory mechanism in liver regeneration (31).
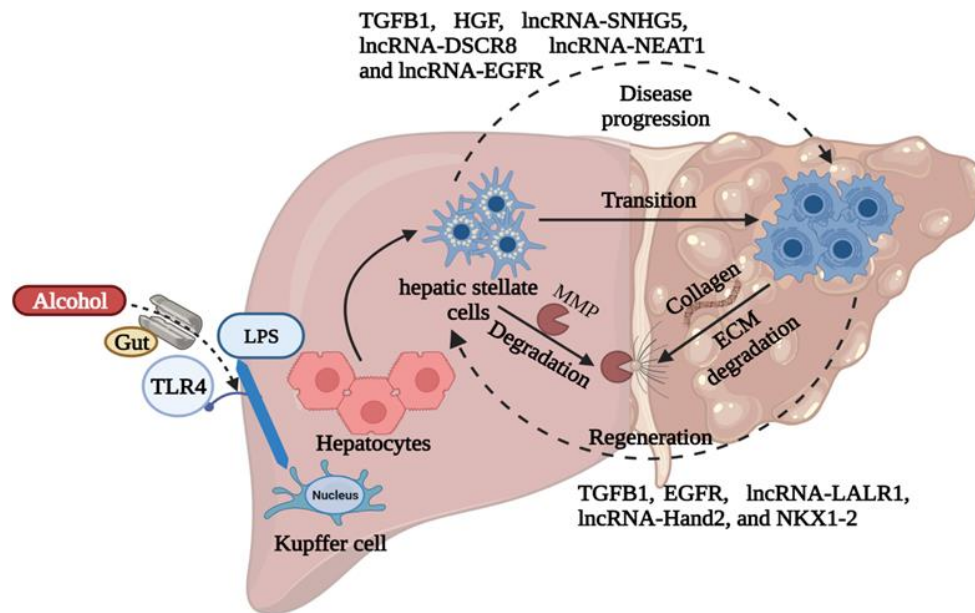
Figure 2: Schematic representation of involvement of long noncoding RNAs during liver regeneration

SIRT1, member of the sirtuins family, essential in sustaining the balance of glucose and fat metabolism. The disruption of SIRT1 in the livers of old mice is mediated by the CCAAT/Enhancer Binding Protein/Histone Deacetylase 1 (C/EBPβ-HDAC1) complex. This complex binds to and inhibits the SIRT1 promoter. SIRT1 is activated after partial hepatectomy (PHx) and maintains increased levels of lipids and glucose throughout liver regeneration (43). Wang et al. have shown the epigenetic regulation of liver regeneration, demonstrating the depletion of H3K27me3 from cell cycle genes. This shift in gene regulation is associated to early activation during the process of liver regeneration (44, 45).

Meng et al. found an increase of miR-34a in ethanol-exposed mice in vivo and its overexpression in ethanol-treated hepatobiliary cells. Their results reveal that miR-34a has a role in contributing to alcohol-related liver damage and tissue healing by affecting proliferation of cells, migration, and remodeling (46). Certain consequences are mediated by CASP2 and SIRT1, which are identified as regulatory genes in apoptosis. They also play a function in tissue remodeling by regulating miR-34a and modulating the production of MMP1 and 2. These mediators are implicated in hepatic rearrangement during alcohol-related fibrosis in the liver (46, 47). Xuxu et al. reported the chromatin remodeling, long noncoding RNAs, and the variable expression of SWI/SNF complexes. These were discovered to be related with histone modification indicators, possibly controlling various sets of gene expression throughout the phases of liver regeneration including damage and cell proliferation (48). Upregulated hepatocyte growth factor induced MALAT1 damages the durability of p-catenin breakdown group thereby initiates liver regeneration.

Perspectives of lncRNAs in liver disease

lncRNAs play a part in the degenerative advancement of liver disease connected to alcohol and hepatic fibrosis/cirrhosis. The cellular signaling networks of lncRNAs are essential mechanisms which are leading to liver disease progression and hepatic complications. Most of the lncRNAs studies were wide-spread attention in recent years, new lncRNAs with more applications have been implicated and need for the therapeutic approach is likely to be discovered in an advanced stage of ALD. This field needs to magnify, there is an emergency need to summarise the safety and efficacy by observational models, in both in-vivo and invitro field which requires to determine the functional mechanism of these lncRNAs translate the disease pathophysiology in alcohol-related liver injury. Detection of most circulating lncRNAs provide the potential therapeutic targets and biomarkers for the risk prediction as diagnostic markers, the need for the evolution of prognosis and diagnosis alcohol associated liver disease as

well as the anti-fibrotic and pro-fibrotic processes. It may be of interest to detect specific lncRNAs eventually replace the invasive method of diagnosis by liver biopsy.

Most of the studies reported the province of lncRNA-m6A modification can promote the HCC progression. lncRNAs bound with proteins involved in cellular mechanisms via activating the lncRNA-m6A that is specifically regulates the oncogenic lncRNAs functioning in development of HCC. The present challenge is to understand the lncRNA and its RNA sequences along with structural mechanisms of regulation in cellular progression, in the given small sequence conservation and is non-coding in nature. An attempt to determine the functional mechanisms of lncRNAs in HCC mainly depends on identification of RNA sequences and the aberrant regulation of lncRNAs between the non-tumor and tumor angiogenesis. However the aberrant regulation patterns of RNAs is not important to reflect the functional lncRNAs. Recently, many genetic and –omic approaches have come to elucidate the functional mechanisms of lncRNAs which particularly appear to be discouraging in identifying the functional lncRNAs at a specific points in time.

Over the last half-decade, CRISPR (Clustered Regulatory Interspaced Short Palindromic Repeat) technology used to cross-examine the functional coding proteins with genes and lncRNAs associated with the screening of phenotype of cellular proliferation and discovery of drug resistance. Screening of CRISPR can also use in discovery of functional lncRNAs and promote the development of lncRNAs based on therapeutic targets across a wide range of human diseases. The CRISPR/Cas system is an extraordinarily effective tool, although it contains severe limits. Delivering CRISPR material to mature cells in considerable numbers is tough, creating a recurring challenge for several therapeutic applications. The biochemical pathway employed for integrating DNA fragments is assisted by the DNA repair machinery triggered by the double-strand break generated by Cas. Since the main objective of the DNA repair mechanism is not the integration of DNA fragments into the genome, targeted alleles frequently display additional changes. These may comprise deletions, partial or numerous integrations of the targeted vector, and, in rare situations, duplications. Aberrant regulation of lncRNAs is nearly associated with fibrosis/cirrhosis progression. This field is still remains unanswered and needs to be explored. Studies on differentially expressed lncRNAs should go beyond its identification. Furthermore, lncRNAs are promoting maintenance of cellular functional and molecular modifications in HCC progression. These kinds of studies would make a great difference in the development of lncRNA-based more sensitive and specific biomarkers which has therapeutic importance in clinical practices.

Most of the lncRNAs have specific expressions in tissue, these are being determined as biomarkers in clinical management. In HCC, meta-analysis studies are ascertained/establish as a biomarker. This conclude the analysis of generated data from the cancer genomic atlas (TCGA) consortium, in this contracted messenger RNA (mRNA)-lncRNA as co-regulation networks. Hepatic cancer biomarkers such as lncRNAs-HULC transcripts may have a significant role and elevated in HCC patients. LncRNA-HULC plasma levels are suggested as a potential non-invasive biomarker.

lncRNAs are unusually performed in vivo models on the characterization of hepatic diseases, suggesting the therapeutic importance of lncRNAs based therapy. Irrespective of several challenges on the lncRNAs, they have safe and prospective/possible off-target effect. An advanced apperception and knowledge results in generating new ideas and information subsequently decoding the novel clinical approaches. Limitations, lncRNAs are highly sensitive and quantification accuracy are low in the transcript in cell. Most of lncRNAs are lower level molecules it cannot be quantified accurately. Natively specific for RNA strandedness for the both sense and antisense strands of lncRNAs

Conclusion

lncRNAs have played an essential part in the early diagnosis and detection of development of hepatic fibrosis/cirrhosis. These lncRNAs regulates each of the stages of liver cirrhosis and these are mainly involved in transcription factors like small fractional lncRNAs controlling the processes from the alcohol-related liver disease development. We emphasized the involvement of hepatic signaling in hepatocytes proliferation and the generation of functional lncRNAs in ALD. We postulated the plausible mechanism of liver regeneration and

establishment of these lncRNAs as therapeutic targets to treat liver disease and progression of these diagnostic biomarkers as non-invasive method in alcohol related liver disease.

Abbreviation
Nil

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Conflicts of Interest
The authors declare there is no competing interests.

Ethics Approval
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