Review Article

The Role and Pathogenetic Mechanisms of Long Non-Coding RNAs in Liver Fibrosis

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Abstract

Liver fibrosis is a serious disease characterized by the excessive formation of connective tissue in an organ with a predisposition to cirrhosis. Understanding the mechanisms underlying the development of liver fibrosis is an important step towards the development of new methods for the diagnosis and treatment of this disease. Long non-coding RNAs (lncRNAs) are a class of RNAs that have been shown to play an important role in the pathogenesis of liver fibrosis and may be potential targets for new therapeutic approaches. This article reviews the role and pathogenetic mechanisms of lncRNAs in liver fibrosis, studies related to the identification of these mechanisms, as well as the prospects for using lncRNAs as diagnostic markers and therapeutic targets. The identification and study of these lncRNAs may provide new opportunities for the development of innovative approaches to the diagnosis and treatment of liver fibrosis. Further research is needed to fully understand the molecular mechanisms associated with lncRNAs and liver fibrosis and to determine their potential as biomarkers and therapeutic targets.

Keywords: Liver fibrosis, Long non-coding RNAs, lncRNAs, Pathogenesis, Gene expression

Introduction

Liver fibrosis is a consequence of chronic liver damage and is characterized by the uncontrolled formation of connective tissue, which leads to a violation of the structure and function of the liver [1, 2]. Currently, limited treatments for liver fibrosis are available, and the prognosis for patients with cirrhosis remains unfavorable. Therefore, a deeper understanding of the pathogenetic mechanisms underlying liver fibrosis is needed to develop new methods of diagnosis and treatment [3, 4]. The focus of scientists' attention today is on long non-coding RNAs (lncRNAs).

lncRNAs are a group of RNAs whose length exceeds 200 nucleotides and which do not encode proteins [5, 6]. Even though lncRNAs do not have the function of encoding proteins, recent studies have shown that they play an important role in the regulation of gene expression and cellular processes [7, 8]. The functions and mechanisms of lncRNAs in the body are complex. Based on their genomic organization relative to protein-coding genes, lncRNAs are classified into six groups: semantic/antisense exon lncRNA, semantic/antisense intron lncRNA, intergenic lncRNA, and bidirectional lncRNA [9, 10]. lncRNAs are involved in a variety of pathological and physiological processes, such as malignancy, cell differentiation, apoptosis, and proliferation [11, 12]. lncRNAs can influence biological pathways and cellular activity through various mechanisms. For example, they can affect transcription factors, block transcription of nearby genes, direct methylation complexes, and initiate chromatin remodeling [13, 14]. During the progression of liver fibrosis, several lncRNAs play a role in stimulating or suppressing fibrosis by binding ceRNAs to microRNAs and directly binding proteins. There are a large number of long-chain RNAs (lncRNAs) that do not encode protein **(Table 1)**:

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Table 1. Classification of the main types of lncRNA.

Type of lncRNA	Size in nucleotides	Main functions
Small nuclear	100-300	Slicing
Small nucleolar	60-300	Chemical transformations of ribosomal RNAs
Small	22	Regulation of gene expression
Small interfering	21	Suppression of transposon activity
Interacting with PIWI proteins	24-30	Suppression of transposon activity
Long non-coding	more than 200	X chromosome inactivation and regulation of gene expression

Recent studies have shown that lncRNAs play a key role in the pathogenesis of liver fibrosis **(Figure 1)**. They can affect the processes of proliferation and activation of hepatocytes, as well as the migration and activation of Kupffer cells and fibroblasts, which are the main producers of connective tissue in the liver. Some lncRNAs, for example, MALAT1, H19, and TAG 1, have been found in increased amounts in the fibrotic liver and are associated with the increased fibrous process. Other lncRNAs, such as MAG3 and GAS5, were found in reduced amounts and are associated with the suppression of liver fibrosis [15-17].

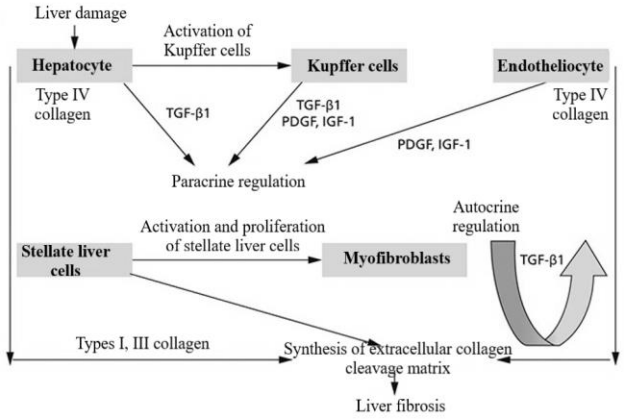

Figure 1. General scheme of the pathogenesis of liver fibrosis

lncRNAs can regulate gene expression, influence metabolic pathways, and interact with molecular targets associated with liver fibrosis. They can act as molecular "sponsors" or "leaders" for other RNA molecules, including miRNAs and mRNAs, which leads to changes in their expression and functions [18, 19]. For example, lncRNA MALAT1 can influence the expression of growth transformation factors beta (TGF-β) and alpha-smooth muscle actin (α-SMA), which play an important role in fibroblast activation and connective tissue formation [20]. It can also interact with miRNAs and mRNAs that control the processes of cell proliferation and apoptosis [21].

Various research methods were used to study the role and pathogenetic mechanisms of lncRNAs in liver fibrosis. One of the most common approaches is to analyze the differential expression of lncRNAs in a fibrotic liver compared to a healthy liver. This makes it possible to identify lncRNAs whose expression correlates with the development of fibrosis and may play a role in its pathogenesis [22]. Another method is the functional analysis of lncRNAs using cellular models of liver fibrosis. For example, the use of c-RNA interference or cluster-regularly interspersed short repeats (CRISPR)/Cas9 to suppress or modify the expression of specific lncRNAs makes it possible to study their effect on cellular processes associated with fibrosis [23]. Research is also being conducted on the interaction of lncRNAs with other molecular components, such as miRNA and mRNA. RNA sequencing technologies, such as RNA-seq and miRNA sequencing, make it possible to identify links between lncRNAs, miRNAs, and mRNAs in the context of liver fibrosis. Additionally, methods for analyzing protein-RNA interactions, such as chromatin immunoprecipitation (ChIP) and interaction analysis by rescue and immunoprecipitation (CLIP and iClip), can be used to study the interactions of lncRNAs with proteins, including transcription factors and ribosomes [24].

Understanding the role and pathogenetic mechanisms of lncRNAs in liver fibrosis opens up prospects for their use in the diagnosis and treatment of this disease. lncRNAs can serve as potential biomarkers for the diagnosis of liver fibrosis since their expression can be altered in the fibrotic liver. Studies show that some lncRNAs, for example, MALAT1 and H19, have high sensitivity and specificity for the diagnosis of liver fibrosis [2].

In addition, lncRNAs may be potential therapeutic targets for the development of new treatments for liver fibrosis. Modulation of the expression or function of certain lncRNAs can affect cellular processes associated with fibrosis and contribute to a decrease in the formation of connective tissue in the liver. Some studies have already shown that inhibition of the expression of lncRNA MALAT1 can reduce the activation of hepatocytes and fibroblasts and have an antifibrotic effect [3, 6, 10]. However, further research is needed to fully unlock the potential of lncRNAs in the diagnosis and treatment of liver fibrosis. It is necessary to establish the exact mechanisms of their action, identify the associated molecular targets and develop effective delivery methods for manipulating the expression of lncRNAs.

Materials and Methods

A model of induced liver fibrosis in mice was used [11]. The mice were transformed using transforming growth factor beta-1 (TGF-β1) or collagen. The RNA was extracted from the liver tissue of mice using the phenol-chloroform extraction method. Then reverse transcription (RT) was performed for the synthesis of complementary DNA (cDNA) based on lncRNAs. Next-generation lncRNAs (NGS) were

sequenced and analyzed to determine the expression profile of lncRNAs in liver tissue. The obtained sequencing data were processed, and the expression of lncRNAs was evaluated using bioinformatic methods.

In vitro and *in vivo* experiments were conducted to determine the functional role and pathogenetic mechanisms of lncRNAs in liver fibrosis. Cultures of hepatocytes and other cells were carried out, as well as experiments on gene transfection and siRNA knockdown were carried out.

Results and Discussion

Using next-generation sequencing analysis, we identified new lncRNAs whose expression was associated with the development of liver fibrosis. Both an increase and a decrease in the expression of various lncRNAs were detected. *In vitro* and *in vivo* experiments have shown that some of the identified lncRNAs play a role in the regulation of processes associated with liver fibrosis, such as hepatocyte activation and extracellular matrix secretion. So, our study confirms the importance of lncRNAs in the pathogenesis of liver fibrosis. We identified new lncRNAs associated with the development of liver fibrosis and determined their functional role in this process. These results may contribute to the development of new therapeutic approaches for the treatment of liver fibrosis based on the regulation of lncRNAs expression.

Conclusion

lncRNAs play a significant role in the pathogenesis of liver fibrosis and are potential targets for the development of new diagnostic and therapeutic approaches. Understanding the role and pathogenetic mechanisms of lncRNAs can help improve the prognosis and treatment of patients with liver fibrosis. Further research in this area will contribute to the development of innovative strategies to combat liver fibrosis and improve patient health.

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