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Pathogenic Mechanisms and Involvement of Long Non-Coding RNAs in Liver Fibrosis

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ABSTRACT

Liver fibrosis is a significant medical condition characterized by the abnormal accumulation of fibrous tissue in the liver and can lead to cirrhosis. A deeper understanding of the biological processes that drive liver fibrosis is crucial for the development of more effective diagnostic and therapeutic strategies. Long non-coding RNAs (lncRNAs) have emerged as key regulators in the development of liver fibrosis and may serve as promising targets for future therapies. This article examines the involvement of lncRNAs in liver fibrosis, explores the mechanisms of their pathogenic effects, and also investigates their potential for use as diagnostic tools and therapeutic targets. The discovery and investigation of these lncRNAs could pave the way for innovative approaches to the diagnosis and treatment of liver fibrosis. However, further research is needed to fully comprehend the molecular interactions between lncRNAs and liver fibrosis and to evaluate their viability as biomarkers and therapeutic candidates.

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

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Introduction

Liver fibrosis is a progressive condition that arises from ongoing liver injury and is characterized by excessive deposition of extracellular matrix components, leading to alterations in the liver's structure and function [1, 2]. Currently, the therapeutic options for liver fibrosis are limited, and cirrhosis remains a challenging and often fatal consequence. Hence, there is a need for a more comprehensive understanding of the molecular mechanisms involved in liver fibrosis to facilitate the development of improved diagnostic and therapeutic strategies [3, 4]. Long non-coding RNAs (lncRNAs) have recently emerged as significant regulators in the pathogenesis of liver fibrosis.

LncRNAs are a class of RNA molecules longer than 200 nucleotides that do not encode proteins [5, 6]. Although these RNAs do not translate into proteins, recent research highlights their critical involvement in gene regulation and cellular functions [7, 8]. The biological roles and mechanisms through which lncRNAs function are intricate and multifaceted. Based on their position relative to protein-coding genes, lncRNAs are classified into several categories: sense/antisense exon lncRNAs, sense/antisense intron lncRNAs, intergenic lncRNAs, and bidirectional lncRNAs [9, 10]. These molecules are involved in various physiological and pathological processes, including cancer progression, cell differentiation, apoptosis, and cell proliferation [11, 12]. LncRNAs exert their

influence by interacting with transcription factors, hindering gene expression, recruiting methylation complexes, and promoting chromatin modifications [13, 14]. In the context of liver fibrosis, a variety of lncRNAs regulate the disease's progression, either by promoting or inhibiting fibrosis through their interactions with microRNAs or direct binding to proteins. The list of such long non-coding RNAs is extensive, as presented in **Table 1**.

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 findings highlight the significant role of lncRNAs in the development of liver fibrosis **(Figure 1)**. These molecules influence several critical cellular activities, including the proliferation and activation of hepatocytes, and the movement and activation of Kupffer cells and fibroblasts, which contribute to the formation of connective tissue in the liver. Specific lncRNAs, such as MALAT1, H19, and TAG1, are upregulated in fibrotic liver tissue, correlating with the progression of fibrosis. In contrast, the expression of lncRNAs like MAG3 and GAS5 is decreased, and their reduction is linked to a suppression of the fibrotic process [15-17].

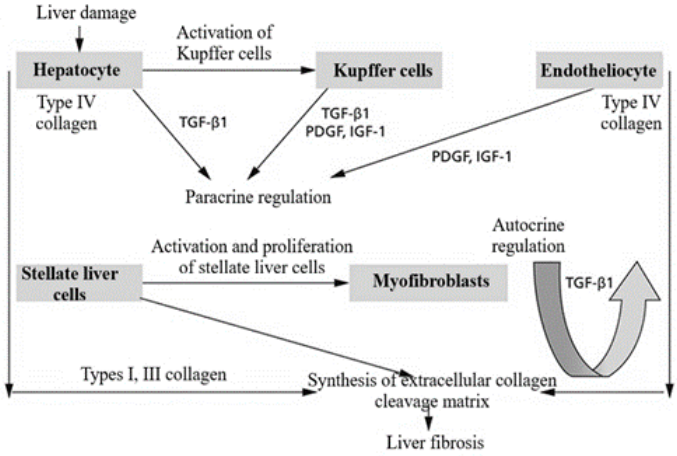

Figure 1. General scheme of the pathogenesis of liver fibrosis

Long non-coding RNAs (lncRNAs) are involved in regulating gene expression and influencing key metabolic pathways that contribute to liver fibrosis. They function as modulators for other RNA species like miRNAs and mRNAs, affecting their activity and expression levels [18, 19]. A notable example is MALAT1, an lncRNA that regulates the expression of proteins such as TGF-β and α-SMA, which are vital in promoting fibroblast activation and connective tissue production within the liver [20]. Additionally, MALAT1 interacts with various miRNAs and mRNAs that control cell proliferation and apoptosis [21].

To investigate the role of lncRNAs in liver fibrosis, several approaches are employed. A common technique involves comparing the expression of lncRNAs between fibrotic and healthy liver tissues, helping identify those linked to fibrosis progression [22]. Another method involves manipulating lncRNA expression in cellular liver fibrosis models, using technologies like RNA interference or CRISPR/Cas9 to explore their influence on fibrosis-related cellular functions [23]. Additionally, interactions between lncRNAs, miRNAs, and mRNAs are studied using RNA sequencing technologies such as RNA-seq and miRNA sequencing. Techniques like chromatin immunoprecipitation (ChIP) and cross-linking immunoprecipitation (CLIP) further allow the examination of protein-lncRNA interactions, including with transcription factors and ribosomal proteins [24].

Exploring the involvement and mechanisms of long non-coding RNAs (lncRNAs) in liver fibrosis paves the way for their application in both diagnosing and treating the condition. LncRNAs hold potential as biomarkers for liver

fibrosis, as their expression patterns are often altered in fibrotic tissues. For instance, research has demonstrated that specific lncRNAs, including MALAT1 and H19, exhibit high sensitivity and specificity, making them suitable for use in diagnostic tests for liver fibrosis [2].

Moreover, lncRNAs represent promising therapeutic targets in the development of novel treatments for liver fibrosis. By modulating the expression or activity of certain lncRNAs, it is possible to influence cellular processes involved in fibrosis and reduce the accumulation of connective tissue within the liver. Initial studies have shown that targeting lncRNA MALAT1 expression can effectively decrease hepatocyte and fibroblast activation, yielding potential antifibrotic effects [3, 6, 10]. However, additional research is essential to fully realize the clinical potential of lncRNAs for liver fibrosis diagnosis and therapy. This includes clarifying their precise mechanisms of action, identifying their molecular targets, and improving delivery methods to manipulate their expression effectively.

This article examines the involvement of lncRNAs in liver fibrosis, exploring the mechanisms behind their pathogenic effects, as well as research on their potential for use as diagnostic tools and therapeutic targets.

Materials And Methods

A mouse model of liver fibrosis was established using transforming growth factor beta-1 (TGF-β1) or collagen to induce the condition [11]. Liver tissue was collected from the mice, and RNA was extracted using a phenol-chloroform method. Reverse transcription (RT) was then performed to generate complementary DNA (cDNA) for analysis of lncRNAs. Next-generation sequencing (NGS) technology was used to sequence the lncRNAs, and the resulting data were processed to examine the expression profile of lncRNAs within the liver. Bioinformatic approaches were employed to evaluate the expression patterns.

The functional roles and underlying mechanisms of lncRNAs in liver fibrosis were investigated through both in vitro and in vivo approaches. These included culturing hepatocytes and other relevant cell types, as well as performing gene transfection and siRNA silencing experiments.

Results and Discussion

Through next-generation sequencing, we discovered novel lncRNAs whose expression correlates with the progression of liver fibrosis. Our analysis revealed both upregulation and downregulation of various lncRNAs. Further investigations, including both in vitro and in vivo studies, demonstrated that several of these lncRNAs are involved in regulating processes tied to liver fibrosis, such as hepatocyte activation and extracellular matrix production. These findings underscore the critical role of lncRNAs in liver fibrosis pathogenesis. We have identified new lncRNAs linked to liver fibrosis and elucidated their functional involvement in this disease. These insights could pave the way for innovative therapeutic strategies targeting the modulation of lncRNA expression in liver fibrosis treatment.

Conclusion

Long non-coding RNAs (lncRNAs) are critical contributors to the development of liver fibrosis and offer promising avenues for the advancement of diagnostic and therapeutic techniques. Gaining a deeper understanding of the molecular mechanisms through which lncRNAs influence fibrosis progression could significantly enhance the clinical management and outcomes for patients suffering from liver fibrosis. Continued exploration in this field holds the potential for innovative approaches to address liver fibrosis, ultimately leading to better patient care and health improvement.

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Ethics Statement: All animal research was conducted following the ethical standards set by the European Convention for the Protection of Vertebrate Animals used in experimental research.

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