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Therapeutic Potential of Targeting lncRNA-Mediated Epigenetic Modification's in Liver Fibrosis

M Kishore Babu[1], N. Danamurthy[2]T. Sujatha[3], M.Jalaiah[4]

1.Professor , Department of pharmaceutics , QIS College of pharmacy , Ongole , A.P

2.Assistant Professor , Department of Pharmacology , QIS College of pharmacy , Ongole , A.P

3Assistant Professor , Department of Pharmacology , QIS College of pharmacy , Ongole , A.P

4.Associate Professor , Department of Pharmacology , QIS College of pharmacy , Ongole , A.P

Abstract

Excessive growth of connective tissue in an organ that is prone to cirrhosis is the hallmark of the dangerous condition known as liver fibrosis. New approaches to the diagnosis and therapy of liver fibrosis can only be developed by first understanding the processes that cause this illness to progress. There is mounting evidence that a subset of RNAs known as long non-coding RNAs (lncRNAs) contribute significantly to the development of liver fibrosis and might represent promising new treatment targets. This article provides a comprehensive overview of long non-coding RNAs (lncRNAs) in liver fibrosis, including their function, pathogenetic pathways, relevant investigations, and potential diagnostic markers and therapeutic targets. Potentially ground-breaking methods for detecting and treating liver fibrosis may emerge from the discovery and investigation of these lncRNAs. To identify lncRNAs as possible biomarkers and treatment targets and to comprehend the molecular pathways linked to liver fibrosis, more study is required.

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

- Corresponding Author
Kishore babu
kishorebabu@gmail.com

INTRODUCTION

The unchecked growth of connective tissue characterizes fibrosis, a condition that develops as a result of persistent liver injury and compromises the liver's structure and function [1, 2]. There aren't many options for treating liver fibrosis right now, and cirrhosis sufferers still have a bad outlook. In order to create novel diagnostic and therapeutic tools, we require a better knowledge of the pathogenetic pathways that cause liver fibrosis [3, 4]. Currently, researchers are concentrating on lncRNAs, or long non-coding RNAs.

A class of RNAs known as long non-coding RNAs (lncRNAs) are those that are longer than 200 nucleotides but do not code for proteins [5, 6]. Recent research has shown that long non-coding RNAs (lncRNAs) regulate gene expression and cellular processes[7,8], despite the fact that they do not encode proteins. Long non-coding RNAs (lncRNAs) have intricate biological roles and processes. One way to categorize lncRNAs is by their genomic arrangement in relation to protein-coding genes. There are six main types of lncRNAs, as described in previous studies [9, 10]. Cancer, cell differentiation, cell death, and proliferation are only a few of the physiological and pathological processes that lncRNAs play a role in [11, 12]. lncRNAs have the ability to impact cellular processes and cellular processes by use of several pathways. They have the ability to drive methylation complexes, start chromatin remodeling, impact transcription factors, and prevent the transcription of neighboring genes, among

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other things [13, 14]. Various long non-coding RNAs (lncRNAs) bind ceRNAs to microRNAs and directly bind proteins, all of which have an impact on the development and progression of liver fibrosis. Table 1 shows the abundance of long-chain RNAs (lncRNAs) that are not protein-encoding:

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

A significant function for lncRNAs in the development of liver fibrosis has been shown in recent research (Figure 1). They have the ability to influence the migration and activation processes of fibroblasts and Kupffer cells, the primary producers of connective tissue in the liver, in addition to hepatocyte proliferation and activation. The enhanced fibrous process is connected with greater quantities of certain lncRNAs, such as MALAT1, H19, and TAG 1, which have been discovered in the fibrotic liver. Low levels of other lncRNAs were also detected; these include GAS5 and MAG3, which are linked to the inhibition of liver fibrosis [15–17].

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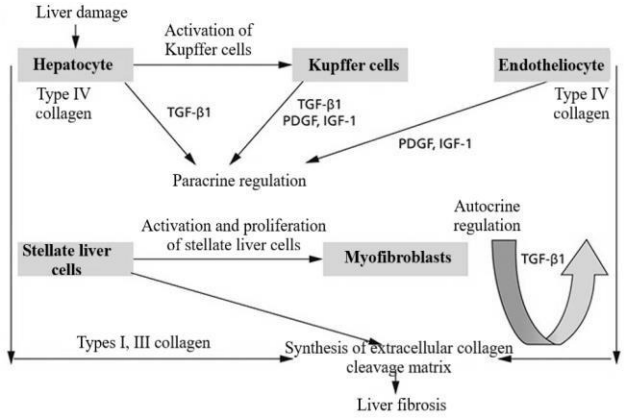

Figure 1. General scheme of the pathogenesis of liver fibrosis

Long non-coding RNAs have the ability to effect metabolic pathways, control gene expression, and communicate with molecular targets linked to liver fibrosis. Molecular "sponsors" or "leaders" like these may influence the production and activities of other RNA molecules, such as miRNAs and mRNAs, [18, 19]. The expression of growth transformation factors beta (TGF-β) and alpha-smooth muscle actin (α-SMA), which are involved in fibroblast activation and connective tissue development, may be influenced by lncRNA MALAT1, for instance [20]. Additionally, it has the ability to interact with messenger RNAs (mRNAs) and microRNAs (miRNAs) that regulate cell growth and cell death [21].

The function and pathogenetic pathways of lncRNAs in hepatic fibrosis were investigated using a variety of research methodologies. Examining the differences in lncRNA expression between a healthy liver and one with fibrosis is one of the most typical methods. This opens the door to the possibility of identifying lncRNAs whose expression is associated with fibrosis progression and maybe contributes to its etiology [22]. Alternatively, cellular models of liver fibrosis might be used for the functional investigation of lncRNAs. One example is the study of lncRNAs and their effects on fibrosis-related cellular processes made feasible by c-RNA interference or cluster-regularly interspersed short repeats (CRISPR)/Cas9, which allow for the suppression or modification of lncRNA expression [23]. Studying how lncRNAs interact with other molecules, including miRNA and mRNA, is another area of active investigation. In the setting of liver fibrosis, RNA sequencing methods like RNA-seq and miRNA sequencing allow for the discovery of connections between lncRNAs, miRNAs, and mRNAs. In addition, chromatin immunoprecipitation (ChIP), interaction analysis by rescue and immunoprecipitation (CLIP and iClip), and other approaches for assessing protein-RNA interactions may be used to investigate the interactions between lncRNAs and proteins, such as ribosomes and transcription factors [24].

There is hope for the future of lncRNAs as a diagnostic and therapeutic tool for liver fibrosis if their function and pathogenetic pathways can be better understood. Since the expression of lncRNAs may be changed in a fibrotic liver, they might be used as biomarkers to diagnose liver fibrosis. Researchers have shown that some long non-coding RNAs (lncRNAs) are very sensitive and specific in identifying cases of liver fibrosis [2]. On top of that, long non-coding RNAs (lncRNAs) might be a promising avenue for future research into liver fibrosis therapies. Reducing the production of connective tissue in the liver may be achieved by modulating the expression or activity of certain lncRNAs, which impact cellular processes related to fibrosis. There is some evidence that inhibiting lncRNA MALAT1 expression may have an antifibrotic impact by reducing hepatocyte

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and fibroblast activation [3, 6, 10]. Nevertheless, more investigation is necessary to fully realize the promise of lncRNAs in the identification and management of liver fibrosis. For lncRNA expression regulation, it is critical to determine the precise mechanisms of action, locate the related molecular targets, and create efficient delivery systems.

Materials and Methods

The researchers relied on a mouse model of induced liver fibrosis [11]. Collagen or transforming growth factor beta-1 (TGF-β1) was used to convert the mice. Using the phenol-chloroform extraction procedure, the RNA was isolated from mouse liver tissue. Next, cDNA synthesis based on lncRNAs was carried out by means of reverse transcription (RT). lncRNAs of the next generation (NGS) were processed and evaluated to ascertain the expression pattern of long non-coding RNAs in liver tissue. Bioinformatic approaches were used to assess the expression of lncRNAs after processing the collected sequencing data.
The pathogenetic processes and functional significance of lncRNAs in liver fibrosis were investigated using in vitro and in vivo investigations. Experiments on gene transfection and siRNA knockdown were conducted, in addition to cultures of hepatocytes and other cells.

Results and Discussion

We discovered novel long non-coding RNAs (lncRNAs) whose expression was linked to the progression of liver fibrosis by next-generation sequencing research. Several lncRNAs showed either an upregulation or a downregulation of expression. Some of the discovered lncRNAs regulate hepatocyte activation and extracellular matrix secretion, two processes linked to liver fibrosis, according to in vitro and in vivo studies. Our findings provide further evidence that lncRNAs play a significant role in the development of liver fibrosis. We discovered novel long non-coding RNAs (lncRNAs) that have a functional role in the progression of liver fibrosis. These findings have the potential to inform the design of novel lncRNA expression regulation–based therapeutic strategies for the management of liver fibrosis.

Conclusion

lncRNAs are promising targets for the creation of novel diagnostic and treatment methods due to their important roles in the pathophysiology of liver fibrosis. Liver fibrosis patients' prognoses and treatments may be improved by learning more about the function and pathogenetic pathways of lncRNAs. Additional study in this field will help in the creation of new approaches to fight liver fibrosis and enhance the well-being of patients.

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