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Non-coding RNA-mediated epigenetic regulation of liver fibrosis

Jing-Jing Yang[a], Hui Tao[b], Zi-Yu Deng[d,**], Chao Lu[d], Jun Li[c,*]

[a] Department of Pharmacology, The Second Hospital of Anhui Medical University, Hefei, China, 230601
[b] Department of Cardiothoracic Surgery, The Second Hospital of Anhui Medical University, Hefei, China, 230601
[c] School of Pharmacy, Anhui Medical University, Hefei, China, 230032
[d] Department of Scientific and Educational, The Second Hospital of Anhui Medical University, Hefei, China, 230601

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ABSTRACT

Hepatic stellate cells (HSC) activation plays a key role in liver fibrosis. Numerous studies have indicated that non-coding RNAs (ncRNAs) control liver fibrosis and fibroblasts proliferation. Greater knowledge of the role of the ncRNAs-mediated epigenetic mechanism in liver fibrosis could improve understanding of the liver fibrosis pathogenesis. The aim of this review is to describe the present knowledge about the ncRNAs significantly participating in liver fibrosis and HSC activation, and look ahead on new perspectives of ncRNAs-mediated epigenetic mechanism research. Moreover, we will discuss examples of non-coding RNAs that interact with histone modification or DNA methylation to regulate gene expression in liver fibrosis. Diverse classes of ncRNAs, ranging from microRNAs (miRs) to long non-coding RNAs (LncRNAs), have emerged as key regulators of several important aspects of function, including cell proliferation, activation, etc. In addition, recent advances suggest the important role of ncRNAs transcripts in epigenetic gene regulation. Targeting the miRs and LncRNAs can be a promising direction in liver fibrosis treatment. We discuss new perspectives of miRs and LncRNAs in liver fibrosis and HSC activation, mainly including interaction with histone modification or DNA methylation to regulate gene expression. These epigenetic mechanisms form powerful ncRNAs surveillance systems that may represent new targets for liver fibrosis therapeutic intervention.

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1. Introduction

Liver fibrosis occurs in response to any etiology of chronic liver injury, including alcohol consumption, fatty liver disease, cholestasis, and autoimmune hepatitis [1,2]. Hepatic stellate cells (HSCs) are the primary source of activated myofibroblasts that produce extracellular matrix (ECM) in liver fibrosis [3,4]. Various inflammatory and fibrogenic

Abbreviations: miRs, microRNAs; LncRNA, long non-coding RNA; ncRNAs, non-coding RNAs; LincRNAs, large intergenic non-coding RNAs; RNAPII, RNA polymerase II; α-SMA, α-smooth muscle actin; RNAi, RNA interference; RISC, RNA-induced silencing complex; DNMTs, DNA methyltransferases; HAT, histone acetyl transferase; HDACs, histone deacetylases; HSCs, hepatic stellate cells; ECM, extracellular matrix; MTD, myofibroblastic transdifferentiation; TGF-β, transforming growth factor-β; MMPs, matrix metalloproteinases; TIMPs, tissue inhibitors of matrix metalloproteinases; UTR, untranslated region; Xist, X-inactive specific transcript; PTEN, phosphatase and tensin homologue deleted on chromosome 10; CCN2, connective tissue growth factor; SIRT1, sirtuin 1; MEG3, maternally expressed gene 3; 5-azadC, 5-aza-2-deoxycytidine.

* *Corresponding author at:* School of Pharmacy, Anhui Medical University, Mei Shan Road, Hefei, Anhui Province, China, 230032. Tel./fax: +86 551 65161001.
** *Corresponding author.*
E-mail addresses: yncs01@hotmail.com (J. Li), zydengsy@163.com (Z.-Y. Deng).

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pathways contribute to the activation of HSCs [5,6]. There is increasing evidence for regulatory roles of non-coding RNAs (ncRNAs) during liver fibrosis development and in response to stress and environmental stimuli [7,8]. The most widely accepted definition of epigenetic includes stably inherited modulations in the expression of genes that do not involve changes in their DNA sequence [9,10].

In recent years, there has been increasing focus on the role of ncRNAs as regulators of post-transcriptional gene expression [11]. ncRNAs represent a functionally and structurally diverse class of RNA species that participates in a wide range of basic cellular processes, including protein translation, mRNA splicing, chromatin organization, etc. [12,13]. Insights from such studies are providing mounting evidence that ncRNAs and ncRNAs regulatory processes are important players in the pathogenesis of liver fibrosis disease [14]. Furthermore, dysregulation of ncRNAs activities has been closely linked to the pathophysiology of liver fibrosis and HSC functional disorders [15]. Experimental fibrosis models have been used for global profiling of tissue or cell ncRNAs in animals, or to manipulate specific ncRNAs or their targets to examine their potential as protective strategies for liver fibrosis [16].

This review will present the current state of knowledge regarding evidence for specific families of ncRNAs in liver fibrosis and HSC: microRNAs (miRs) and long non-coding RNAs (LncRNAs). Increasing emphasis is being placed on the ability of ncRNAs transcripts to modulate gene expression and, on their role as epigenetic modifiers. Specifically, we discuss the links between epigenetic mechanisms and two major classes of functional ncRNAs in liver fibrosis (Fig. 1).

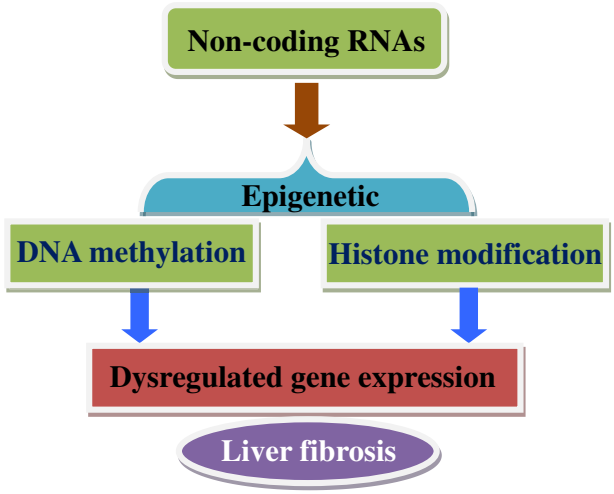

Fig. 1 – Environmentally stimulus, dynamic regulation of gene expression by long and short ncRNAs occurs through interaction with classical epigenetic mechanisms, forming a larger epigenetic network.

2. Overview of Liver Fibrosis

Liver fibrosis is a wound healing process that results from chronic liver damage, such as alcohol abuse, chronic hepatitis, nonalcoholic steatohepatitis and overload of metal ions [17,18]. Wound healing is a complex multi-step and multicellular process occurring in all metazoans that operates to restore tissue architecture and function following trauma or damage caused by environmental insults [19]. In general, liver fibrosis is an imbalance between the synthesis and degradation of ECM, in which type I and III collagens are the major component [20]. Myofibroblastic transdifferentiation (MTD) is the pivotal event during liver fibrosis, and research in the past few years has identified key mediators and molecular mechanisms responsible for MTD of hepatic stellate cells (HSCs) [21]. HSCs are undifferentiated cells, which play an important role in liver regeneration [22]. Upon activation, HSCs orchestrate the responsiveness of the liver to different types of injury, leading to deposition of excessive scar matrix into the interstitium as a wound healing response [23].

In response to liver injury or disease, HSCs differentiate into myofibroblast-like cells and undergo changes in gene expression, morphology, proliferation and ECM production [24,25]. Activated HSC myofibroblasts are characterized by the presence of specific cytoskeletal stress fibers, including α-smooth muscle actin, and by up-regulated expression and secretion of profibrogenic factors such as transforming growth factor-β (TGF-β), ECM proteins such as collagens I and III, the ECM-remodeling enzymes matrix metalloproteinases (MMPs) and tissue inhibitors of matrix metalloproteinases (TIMPs) [26–28]. The key enzymes in the degradation of ECM collagens are MMP-1 in humans and MMP-13 in rodents [29,30]. However, during liver fibrosis, the expression of MMP-1 or MMP-13 is very limited, whereas that of MMP-2 increases [31,32]. On the other hand, fibrotic livers have high expression of the TIMPs, including TIMP-1 and TIMP-2 [33,34]. Thus, there is a combination of low expression of interstitial collagenases and high TIMPs that prevents the degradation of the fibrillar collagens [35].

Furthermore, HSCs are an important source of growth factors in the liver, but also respond to these factors, emphasizing the importance of tightly regulated autocrine control of growth factor activity within the pericellular milieu [36,37]. Liver fibrosis progression and regression require specific signaling pathways [38]. There are several signals among the characterized pathways of HSC activation, including MAPK signaling pathway, Wnt/β-catenin signaling, PI3K/PKB signaling pathway, Hedgehog/Gli signaling pathway, etc. [39–42]. All these events ultimately lead to cellular proliferation [43].

Many genes and cytokines in HSCs have been demonstrated to be involved in the pathogenesis of liver fibrosis [44]. However, the exact regulating mechanisms of these genes are largely unknown. Recently studies have highlighted the regulatory effect of epigenetic modifications at gene expression level [45]. Increasing modification manners in fibrosis processes are brought to our attention, including LncRNAs, miRs, DNA methylation and histone modification [46–48]. Additionally, recent studies have shown that significant numbers of ncRNAs, such as miRs and LncRNAs have the remarkable ability to regulation of pathological fibrosis [14,15,49]. miRs are the short non-coding endogenous RNAs that post-transcriptionally regulate the expression of a large number of genes, and play important roles in liver fibrosis [50]. LncRNAs are functional ncRNAs that are

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