

Role of long non-coding RNAs and related epigenetic mechanisms in liver fibrosis (Review)

NILADRI GANGULY and SUBRATA CHAKRABARTI

Department of Pathology and Laboratory Medicine, University of Western Ontario,
London, ON N6A 5C1, Canada

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Abstract. Liver fibrosis is one of the major liver pathologies affecting patients worldwide. It results from an improper tissue repair process following liver injury or inflammation. If left untreated, it ultimately leads to liver cirrhosis and liver failure. Long non-coding RNAs (lncRNAs) have been implicated in a wide variety of diseases. They can regulate gene expression and modulate signaling. Some of the lncRNAs promote, while others inhibit liver fibrosis. Similarly, other epigenetic processes, such as methylation and acetylation regulate gene transcription and can modulate gene expression. Notably, there are several regulatory associations of lncRNAs with other epigenetic processes. A major mechanism of action of long non-coding RNAs is to competitively bind to their target microRNAs (miRNAs or miRs), which in turn affects miRNA availability and bioactivity. In the present review, the role of lncRNAs and related epigenetic processes contributing to liver fibrosis is discussed. Finally, various potential therapeutic approaches targeting lncRNAs and related epigenetic processes, which are being considered as possible future treatment targets for liver fibrosis are identified.

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Correspondence to: Professor Subrata Chakrabarti, Department of Pathology and Laboratory Medicine, University of Western Ontario, Dental Sciences Building, 1151 Richmond Street, London, ON N6A 5C1, Canada
E-mail: subrata.chakrabarti@lhsc.on.ca

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1. Introduction

Hepatic fibrosis results from an aberrant wound healing process in the liver. In general, fibrosis results from an accumulation of extracellular matrix (ECM) proteins. Pathogenetically, apart from the abnormal deposition of ECM proteins, the improper degradation of ECM proteins also occurs (1,2). Liver fibrosis results from persistent wound repair and regenerative processes due to continued hepatic injury caused by chronic liver diseases, such as non-alcoholic steatohepatitis (NASH), the excessive consumption of alcohol, hepatitis B and C infection, obstruction in the bile ducts, etc. (3,4), ultimately leading to cirrhosis and predisposing affected patients towards the development of malignancies, such as hepatocellular carcinoma (HCC) (4-7). Although extensive research has been made into liver fibrosis (as discussed below), the mechanisms governing the process are not yet fully understood.

Hepatic stellate cells (HSCs), which are primarily involved in growth, regeneration and differentiation comprise 5-8% of total liver cells (8). The activation of HSCs is a key step in liver fibrosis, as it leads to the accumulation of the ECM proteins, α -smooth muscle actin (α -SMA) and type I collagen (9,10). Non-activated or quiescent HSCs lose their vitamin A stores and transdifferentiate into fibrogenic myofibroblast-like cells following liver injury (11-14). Therefore, the suppression of HSC activation is crucial for the therapy of liver fibrosis.

Transcriptome analysis, gene expression profiling by microarray and RNA sequencing have increasingly pointed to the role of non-coding RNAs (ncRNAs) as crucial regulators of gene expression and signal transduction (15). In liver carcinogenesis and fibrosis, ncRNAs have emerged as key regulators of gene expression (16-18). Therefore, ncRNAs may also be viewed as putative biomarkers for diagnosis and therapeutic targets for the treatment of liver fibrosis. Among the ncRNAs, major players include microRNAs (miRNAs or miRs) and long non-coding RNAs (lncRNAs). lncRNAs with sizes of ≥ 200 nucleotides, are categorized into 4 subgroups as follows: Exonic, intronic, intergenic and bidirectional, depending on their placement and orientation with respect to protein coding genes. In liver fibrosis, lncRNAs may act as

competitive endogenous RNAs (ceRNA), sponging miRNAs. This action releases the inhibition imposed by miRNAs on mRNA translation, thereby indirectly regulating gene expression. Other members of the ncRNA group include circular RNAs, PIWI-interacting RNAs, etc. (19).

Epigenetics encompass the changes in gene expression, that do not involve mutations in the DNA sequence. Epigenetic alterations are long-lasting and are heritable. Epigenetic alterations bring about changes in DNA properties along with transcriptional regulation. The epigenetic regulation of genes is significant in terms of gene expression and physiological function. Furthermore, epigenetic alterations are key pathogenic mechanisms involved in various, if not all chronic diseases (20) involving all organs, such as skeletal muscle (21), the brain (22), heart (23), ovaries (24) and bones (25).

Epigenetic regulators can turn 'on or off' the expression of genes, depending on the prevailing microenvironment. Along with ncRNAs, other epigenetic processes include DNA and histone methylations and other biochemical mechanisms, causing alterations of DNA and histones. Such processes control several biological processes, such as genome imprinting, transposon mediated gene silencing, X chromosome inactivation, etc. (26). DNA methylation is catalyzed by DNA methyltransferases (DNMT). There are 3 DNMTs, namely DNMT1, DNMT3a and DNMT3b. Histone methylation is carried out as a balancing act between histone methyltransferase and histone dimethyl transferase (26). Additional epigenetic histone modification involves the addition/removal of acetyl groups on histone proteins. Histone acetylation is carried out by a group of enzymes known as histone acetyl transferases (HATs) and deacetylation is carried by histone deacetylases (HDACs). These 2 enzymes play important regulatory roles in HSC activation and the development of liver fibrosis (27). Other less well-studied mechanisms include ubiquitination, NEDDylation and SUMOylation. The targeting of ubiquitin enzymes has been shown to improve the physiology in liver fibrosis (28). Transforming growth factor- β (TGF- β) is a cytokine secreted by the immune system. It has been demonstrated that the TGF- β signaling pathway plays a crucial role in the development and progression of liver fibrosis (29). The dynamic interactions of lncRNAs with various pathways, such as miRNAs, DNA, histone methylation and histone acetylation are illustrated in Fig. 1.

The present review focuses on the role of lncRNAs in the promotion and inhibition of liver fibrosis. Furthermore, the interaction of lncRNAs with signaling pathways and the regulation of liver fibrosis through DNA methylation and acetylation is explored. The present review also discusses possible therapeutic implications of such processes in the treatment of liver fibrosis.

2. Regulation of liver fibrosis by lncRNAs

The transcriptome profiling of quiescent and activated HSCs lead to a better understanding of the mechanistic roles of lncRNAs in the promotion or inhibition of liver fibrosis (30,31). A large volume of data have been obtained from the genome-wide screening of HSCs and tissues from human and animal models with respect to the expression patterns of lncRNAs. Understanding these expression patterns and their

resulting regulation of cellular pathways are important for the development of targeted therapies for liver fibrosis. As will be evident from the discussions below, lncRNAs play diverse roles in mediating liver fibrosis. Some function as activators of liver fibrosis, whereas others may exert inhibitory effects. In addition, some of them may also play a dual role.

lncRNAs as activators of liver fibrosis. lncRNAs which activate liver fibrosis are usually upregulated or overexpressed in liver tissues affected by fibrosis. These lncRNAs activate HSCs and promote ECM protein overexpression. Several of these lncRNAs also activate the TGF- β signaling pathway. As they are all upregulated, a potential therapeutic approach under consideration is lncRNA blockade using a small molecule or siRNA. The discussions below focus on specific lncRNAs and their roles in such processes.

The lncRNA, nuclear paraspeckle assembly transcript-1 (NEAT-1), may act as a miRNA sequestering agent. In a recent study, it was found that NEAT-1 regulated the localization of miR-29b to the cytoplasm (32). Insulin like growth factor binding protein related protein 1 (IGFBP1) interacts with the TGF- β signaling pathway to promote liver fibrosis (33). IGFBP1 induces the activation and autophagy of HSCs, which is regulated by Atg9a and NEAT-1, while miR-29b inhibits such a process (31), indicating that the NEAT-1/Atg9a/miR-29b pathway regulates liver fibrosis. NEAT-1 overexpression and its downstream effects on liver fibrosis are further prevented by Kruppel like factor 6 (KLF6) knockdown and miR122 overexpression (34). Therefore, NEAT-1/miR-122/KLF6 may function as another regulatory mechanism for liver fibrosis, modulating multiple signaling pathways.

Hox transcript antisense RNA (HOTAIR) has been found to be overexpressed in carbon tetrachloride (CCL4)-induced liver fibrosis in human and mouse models (30). HOTAIR binds to miR-148b and regulates the DNMT1/MEG3/p53 pathway in HSCs (35). It has also been reported that the HOTAIR-mediated downregulation of miR-29b attenuates its epigenetic control, inducing the hypermethylation of the phosphatase and tensin homolog (PTEN) gene, resulting in the progression of liver fibrosis (36). It is of further interest to note that one miRNA; i.e, miR29b, may regulate multiple, seemingly unrelated lncRNAs, such as NEAT-1 and HOTAIR, leading to the development of hepatic fibrosis.

Hox A distal transcript (HOTTIP) is a lncRNA which promotes HSC activation and fibrosis by functioning as a competitive endogenous RNA (ceRNA) for miR-148a and miR-150, and inducing the expression of serum response factor (SRF) (37). High HOTTIP levels reduce the expression of miR-148a, removing its inhibitory effects and thus increasing levels of TGF- β receptor type 1 (TGFBR1) and receptor 2 (TGFBR2), thereby promoting liver fibrosis (38).

Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) expression has been found to be upregulated in liver fibrosis; MALAT1 regulates the expression of sirtuin 1 (SIRT1), which deacetylates Smad3, a mediator of the TGF- β signaling pathway and inhibits its binding to its target genes like collagen type 1 promoter (39). Through such an activation of SIRT1, the downregulation of the TGF- β signaling pathway and the inhibition of liver fibrosis may occur. MALAT1 also induces mouse HSC activation via the regulation of RAS-Rac1

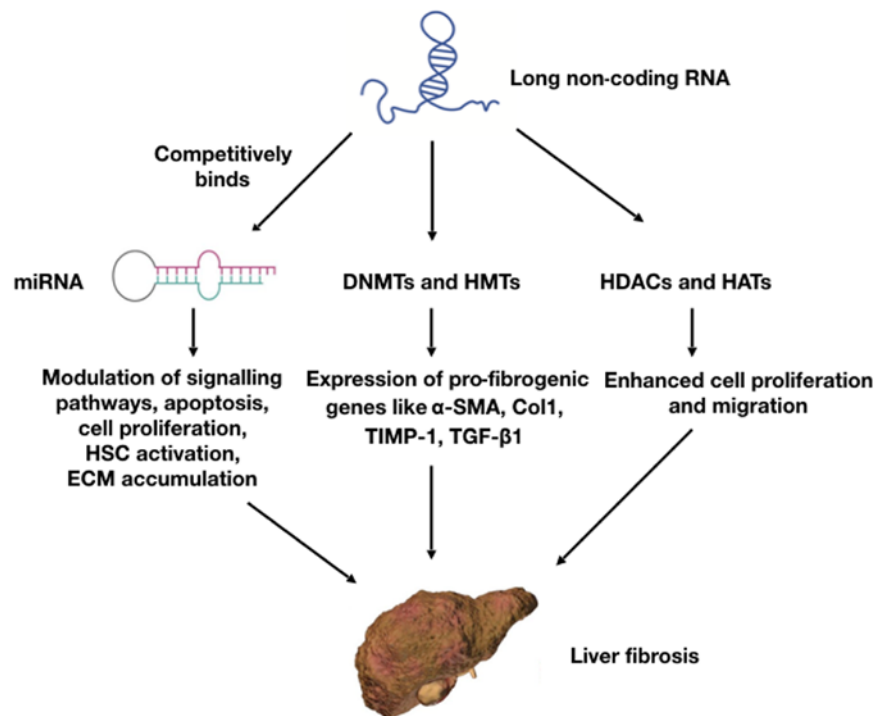


Figure 1. Mode of action of lncRNAs through different pathways for the development and progression of liver fibrosis. lncRNAs competitively bind to miRNAs and sequester them out of normal function. lncRNAs also affect epigenetic mechanisms, such as DNA and histone methylation by regulating the epigenetic enzymes, such as DNMTs. lncRNAs, long non-coding RNAs; miRNAs, microRNAs; DNMTs, DNA methyltransferases; HMTs, histone methyl transferases; α -SMA, α -smooth muscle actin.

by functioning as a ceRNA for miR-101b (40). In patients with NASH, MALAT1 has been found to be highly upregulated compared to normal tissues (41). MALAT1 can aggravate liver fibrosis through the generation of inflammatory chemokines, such as CXCL5 (41). Therefore, MALAT1, through its effects on the inflammatory processes, may modulate liver fibrosis.

Highly upregulated in liver cancer (HULC) plays an important role in liver fibrosis. HULC promotes liver fibrosis and is upregulated in tissues affected by non-alcoholic fatty liver disease (NAFLD) in rat models (42). The inhibition of HULC by siRNA results in the improvement of liver fibrosis and reduces the apoptosis of hepatocytes through the inhibition of the MAP kinase (MAPK) signaling pathway (42).

Small cajal body specific RNA 10 (SCARNA10) is a lncRNA which is elevated in serum and tissues of patients with liver fibrosis. It has also been shown to be upregulated in liver tissues in a mouse model of liver fibrosis (43). SCARNA10 is a positive regulator of the TGF- β signaling pathway and inhibits polycomb repressive complex 2 (PRC2), which blocks TGF- β signaling (43). TGF- β , TGF- β R1, Smad2, Smad3 and KLF6 levels decline upon SCARNA10 silencing (43).

Liver enriched fibrosis associated lncRNA 1 (LFAR1) is known to promote liver fibrosis. It has been demonstrated that TGF- β -induced hepatocyte apoptosis, CCL4-induced fibrosis and HSC activation are reduced upon lnc-LFAR1 silencing (44). LFAR1 directly binds to the Smad2/3 complex in the cytoplasm, and activates the TGF- β and NOTCH pathways (44). Another lncRNA, SCRG1, is also highly upregulated in fibrotic human liver tissues (45). SCRG1 binds to RNA binding protein tristetrarolin (TTP) and accelerates liver fibrosis (45). The overexpression of TTP leads to the

reduction of lncRNA SCRG1 and increases the degradation of matrix metalloproteinase 2 (MMP2) and TNF- α mRNAs, and vice versa (45).

In humans, small nuclear RNA host gene 7 (SNHG7) is significantly upregulated in fibrotic liver tissues (45). The knockdown of SNHG7 prevents HSC activation and collagen overproduction (46). SNHG7 binds to miR-378a-3p. Blocking miR-378a-3p production releases its inhibitory effects on liver fibrosis induced by SNHG silencing. SNHG7 further activates the Wnt/ β -catenin pathway to promote liver fibrosis. miR-378a-3p targets disheveled segment polarity 2 (DVL2) protein, which is a component of the SNHG7-mediated Wnt/ β -catenin pathway of liver fibrosis (46).

Plasmocytoma variant translocation 1 (PVT1) is a lncRNA which is upregulated in fibrotic liver tissues and activates HSCs (47). PVT1 knockdown reduces type I collagen and α -SMA levels and inhibits HSC activation (47). PVT1 competitively binds to miR-152 and inhibits patched 1 (PTCH1) expression, which in turn activates the Hedgehog pathway, and promotes cell migration and liver fibrosis (47). Activated by transforming growth factor beta (ATB) is a lncRNA which is upregulated in hepatitis C virus (HCV)-mediated liver fibrosis. ATB silencing induces the aberrant expression of miR-200a and reduces β -catenin expression, thereby suppressing HSC activation (48).

lncRNA-p21 is overexpressed during liver fibrosis (49) and promotes liver fibrosis by acting as a downstream effector of the TGF- β signaling pathway by binding to miR-30 (49). In hepatocytes, the knockdown of lncRNA-p21 suppresses CCL4-induced liver fibrosis and inflammation; however, the ectopic expression of miR-30 promotes

liver fibrosis (49). lncRNA-p21 also binds to miR-17-5p and inhibits the Wnt/ β -catenin pathway (50). It can modulate the miR-181b/PTEN cascade (51) and inhibit HSC proliferation through p21 (52). lncRNA-p21 has also been shown to be a potential biomarker of fibrosis in patients with hepatitis B infection (53).

lncRNAs as inhibitors of liver fibrosis. There are several lncRNAs which act as suppressors of liver fibrosis; these are usually downregulated in liver fibrosis, and inhibit HSC activation and migration. Conceptually, they can be used as biomarkers. Furthermore, therapeutic strategies involving the overexpression of these RNAs may potentially be a therapeutic approach for liver fibrosis.

Maternally expressed gene 3 (MEG3) is a lncRNA which is significantly downregulated in human liver fibrosis and CCL4-induced fibrosis in experimental models (54). MEG3 prevents fibrosis following TGF- β 1-induced LX-2 cell activation. The overexpression of MEG3 in TGF- β 1-stimulated LX-2 cells induces p53 activation, cytochrome *c* release and apoptosis (54). The overexpression of MEG3 also reduces α -SMA and type I collagen levels. Furthermore, as circulating serum MEG3 levels are negatively associated with liver fibrosis in patients with hepatitis, it may further be a useful diagnostic marker (55). Smoothed (SMO) is involved in Hedgehog pathway for EMT; MEG3 binds to SMO and reduces EMT and thereby inhibits HSC activation (56). miR-212 targets MEG3 and acts as a negative regulator of MEG3. Hence, MEG3 possibly regulates EMT and HSC activation through SMO and miR-212. Growth arrested specific transcript 5 (GAS5) is a lncRNA, the expression of which is reduced in fibrotic liver tissues of mice, rats and humans (57). The overexpression of GAS5 inhibits collagen production and HSC activation. GAS5 acts as a ceRNA for miR-222 in the cytoplasm and increases the levels of p27 tumor suppressor protein, leading to suppressed HSC activation and proliferation (57). GAS5 also acts as a ceRNA for miR-23 in CCL4-induced liver fibrosis and increases miR-23 expression, leading to PTEN inhibition, resulting in the activation of the phosphatidyl-3 kinase/protein kinase B/mammalian target of rapamycin/Snail (PI3K/Akt/mTOR/Snail) pathway (8). Overall, it appears that GAS5/miR-222/p27 and GAS5/miR-23/PI3K/Akt/mTOR/Snail pathways play regulatory roles in this process.

Gm5091 is an intergenic lncRNA which is downregulated in mouse hepatic stellate cells during alcohol-induced hepatic fibrosis (58). Gm5091 binds to miR-27b/23b/24 and negatively regulates cell migration, ROS production, IL-1 β secretion, type I collagen expression and HSC activation markers, such as α -SMA and Desmin (58). lncRNA hypoxia inducible factor 1A-antisense RNA 1 (HIF1A-AS1) levels also significantly increase when ten-eleven translocation (TET) family protein TET3 is silenced in HSCs (59). The silencing of HIF1A-AS1 further promotes the proliferation of HSCs and suppresses apoptosis (59). Antisense noncoding RNA in the INK4 Locus (ANRIL) is an inhibitor of liver fibrosis and is negatively regulated by DNMT3A (60). In activated HSCs and liver fibrotic tissues, ANRIL is downregulated. The silencing of ANRIL by DNMT3A results in HSC activation and liver fibrosis (60). Conversely, the overexpression of ANRIL suppresses HSC activation and reduces the expression levels of

DNMT3a, Coll1a1 and α -SMA, and inhibits adenosine monophosphate-activated protein kinase (AMPK) signaling (60).

lncRNAs with regulatory dual roles in liver fibrosis. lncRNA H19 is involved in the regulation of cell proliferation and differentiation. It is genetically imprinted, maternally expressed and conserved in mice and humans (61). H19 is upregulated in human liver diseases and animal models of critical limb ischemia (62,63). H19 plays a dual role liver fibrosis (both an inhibitory and promoting role) through distinct cellular targets. The inhibitory roles of H19 in liver fibrosis involve its effects on DNA methylation. In activated HSCs and rat liver fibrotic tissue, the reduced expression of H19, coupled with the elevated expression of DNMT1 and the increased methylation of H19 promoter are present (64). The silencing of H19 in HSCs increases the expression of phospho-extracellular signal regulated kinases 1/2 (p-ERK1/2) (65). Methyl CpG binding protein 2 (MeCp2) is upregulated liver fibrosis and in activated HSCs. In a rat model of liver fibrosis, the overexpression of MeCp2 has shown to reduce H19 levels and the knockdown of MeCp2 leads to increased levels of H19 (65). The silencing of MeCp2 blocks HSC proliferation. Furthermore, the overexpression of H19 downregulates insulin like growth factor 1 receptor (IGF1R) and vice versa (65). Therefore, MeCp2 possibly targets IGF1R to promote liver fibrosis by negatively regulating H19 and the MeCp2/H19/IGF1R pathway (64,65). H19 is further involved in the regulation of liver fibrosis in the context of cholestasis by modulating cell migration. Epithelial cell adhesion molecule (EpCAM) is negatively regulated by E box binding homeobox 1 (ZEB1) protein. In a mouse model of cholestatic liver fibrosis, H19 was shown to bind to ZEB1 to inhibit EpCAM expression and promote cell migration (66). In patients with biliary atresia (BA)-related liver fibrosis, H19 promotes cholangiocyte proliferation and cholestatic liver fibrosis via the regulation of sphingosine 1 phosphate receptor 2 (S1PR2)/sphingosine kinase 2 (SphK2) and the let-7/high mobility group AT-hook 2 (HMGA2) pathway (67). Cholangiocyte-derived H19-enriched exosomes induce the activation and differentiation of cultured HSCs and HSC-derived fibroblasts (68). Hence, the mechanisms of liver fibrosis involving H19 warrant further thorough investigations in order to develop therapeutic interventions for liver fibrosis modulating such processes. Various lncRNAs, their cellular targets and their roles in liver fibrosis are presented in Table I.

3. Modulation of signaling pathways by lncRNAs

As discussed above, lncRNAs are known to interact with and regulate multiple signaling pathways, such as TGF- β , p53, Hedgehog, PI3 kinase/Akt/mTOR, Wnt/ β -catenin and MAP kinase, which dictate the initiation and progression of liver fibrosis (12,69). The above-mentioned discussions outline some such pathways. The most well-studied pathway for liver fibrosis is the TGF- β signaling pathway, which has been shown to interact with a number of lncRNAs. TGF- β and its downstream effectors, such as Smad proteins control the progression of liver fibrosis, beginning from initial liver injury and inflammation (70-72). The regulation of liver

Table I. lncRNAs in liver fibrosis.

lncRNAs	Cellular target	Role in liver fibrosis	(Refs.)
Activation of liver fibrosis			
NEAT-1	miR-122, miR-29b	NEAT-1 promotes liver fibrosis through miR-122/KLF6 and miR-29b/Atg9a pathways	(31-34)
HOTAIR	miR-148b, miR-29b	Acts as ceRNA for miR-148b, miR-29b. HOTAIR regulates miR-148b/DNMT1/MEG3/p53 and miR-29b/PTEN pathways in liver fibrosis	(35,36)
HOTTIP	miR-148a, miR-150	Acts as ceRNA for miR-148a and miR-150. Activates TGF- β pathway and induces HSC activation	(37,38)
MALAT1	miR-101b, miR-26b	Promotes liver fibrosis through miR-26b/SIRT1/Smad3 and miR-101b/Ras-Rac1 and CXCL5 pathways	(39-41)
HULC	None identified yet	Silencing of HULC improves liver pathology in NAFLD rats through inhibition of MAP kinase pathway	(42)
SCARNA10	PRC2	Positively regulates TGF- β pathway by inhibiting PRC2	(43)
Lnc-LFAR1	Smad2/3	Binds to Smad2/3 in cytoplasm to activate TGF- β and NOTCH pathway.	(44)
Linc-SCRG1	TTP	Binds and inhibits TTP and prevents TTP induced degradation of TNF- α and MMP-2.	(45)
SNHG7	miR-378a-3p	Activates Wnt/ β -catenin pathway by negatively regulating miR-378a-3p	(46)
PVT1	miR-152	Binds as ceRNA to miR-152 which leads to PTCH1 inhibition, resulting in activation of Hedgehog pathway to promote cell migration and liver fibrosis	(47)
Lnc RNA-ATB	miR-200a	ATB knockdown reduced β -catenin expression by upregulating miR-200a expression and suppressed LX-2 cells activation	(48)
LincRNA-p21	p21, miR-30, miR-181b, miR-17-5p	Promotes liver fibrosis through multiple pathways involving p21, miR-181b/PTEN miR-17-5p/ β -catenin and miR-30	(49-53)
Inhibition of liver fibrosis			
MEG3	miR-212, SMO	Overexpression of MEG3 inhibited HSC activation, induced hepatocyte apoptosis and reduced α -SMA and type I collagen	(54-56)
GAS5	miR-23a, miR-222	Binds as a ceRNA to miR-23a and miR-222 to inhibit PTEN and increase p27 levels respectively	(8,57)
Gm5091	miR-27b, miR-23b, miR-24	Alleviates alcoholic liver fibrosis by sequestration of miR-23b, miR-27b, miR-24 and down regulation of HSC activation, cell migration, type I collagen expression	(58)
HIF1-AS1	TET3	HIF1-AS1 inhibits LX-2 cell proliferation and is negatively regulated by TET3	(59)
ANRIL	DNMT3A, AMPK	Overexpression of ANRIL inhibits DNMT3A and AMPK	(60)
Dual role in liver fibrosis			
H19	MeCP2, IGF1R	Overexpression of H19 inhibits liver fibrosis by downregulating pERK1/2 and MeCP2/IGF1R pathways	(64,65)
	let7, ZEB1	Promotes cholestatic liver fibrosis by binding to ZEB1 and inhibiting cell migration and activates SIPR2/SphK2/let7/HMGA2 pathway	(66-68)

The table lists several lncRNAs and their corresponding cellular targets. Most of these targets are miRNAs and in some cases, signaling proteins. Depending on their role in liver fibrosis, they have been categorized in to activators or inhibitors of liver fibrosis. lncRNAs, long non-coding RNAs; miRNAs, microRNAs.

fibrosis-related pathways by lncRNAs is illustrated in Fig. 2. Some of these pathways promote liver fibrosis, while others suppress it.

The mechanisms of action by lncRNAs are usually directed through its complex secondary structures, and the ability to bind to other RNA and protein molecules. This endows them

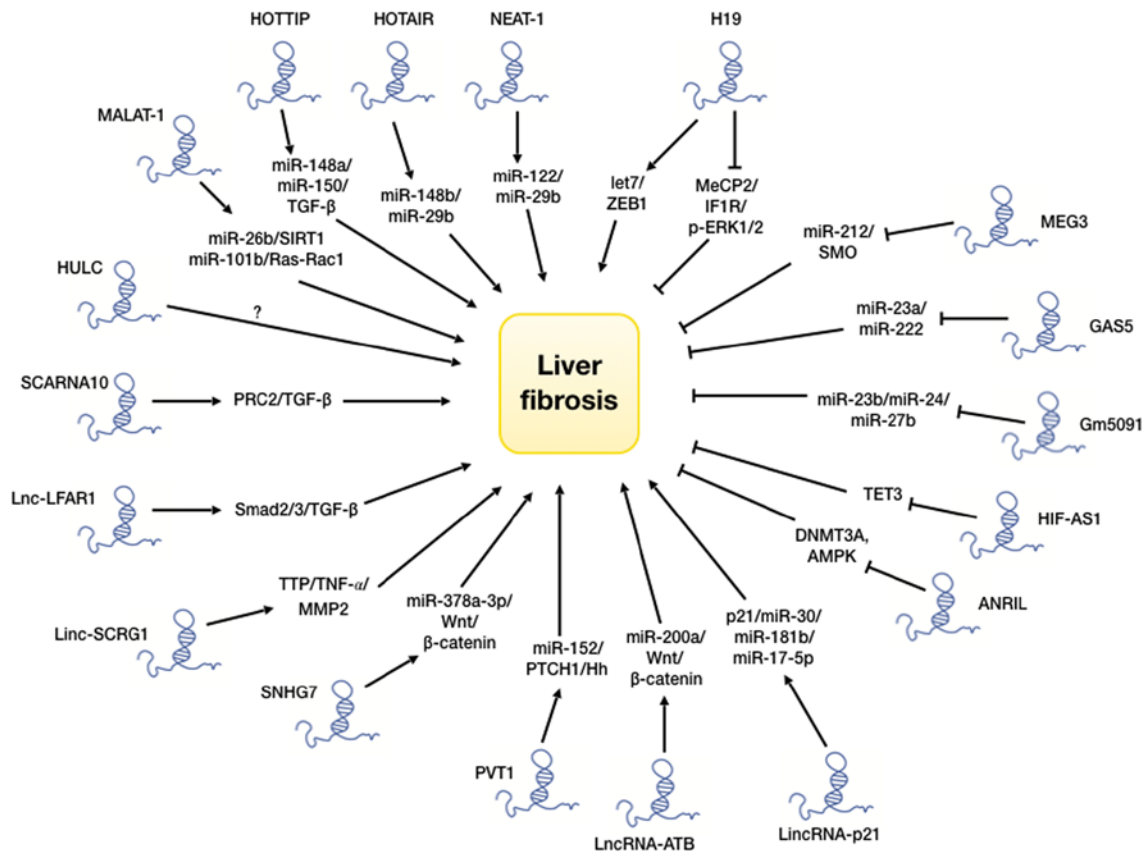


Figure 2. Diagram illustrating the mechanisms through which various lncRNAs mediate their effects through intermediate miRNAs and signaling molecules. lncRNAs modulate the functions of various miRNAs and cellular pathways, such as TGF-Smad, Wnt/ β -catenin, Hedgehog, SIRT1, ERK1/2, AMPK and TNF- α . The second row of arrows indicate lncRNAs which are activators of liver fibrosis, while the blocked line represents inhibitors of liver fibrosis. lncRNAs, long non-coding RNAs; miRNAs, microRNAs.

with both unique and diverse traits with which to regulate other molecules (73-76). There are broadly 2 types of mechanisms through which lncRNAs regulate the activity of the target molecule; firstly, acting as a ceRNA to bind to a miRNA through complementary base pairing and inhibiting the normal function of the miRNA; secondly, by directly binding to a signaling protein through its complex secondary structure and blocking/activating the protein function. An additional mechanism of lncRNA functions includes the binding to DNA to form a triple helical structure. This helical structure can function as a docking site for binding of proteins which can regulate gene expression (77). Recent advances in ncRNA studies have enabled their use as a diagnostic tool (78,79). Circulating ncRNAs from patients with liver fibrosis may be quantified and monitored over the course of time as surrogate markers for disease progression (80). Studies on lncRNA-based therapy have also been successfully implemented in preclinical models (81). However, clinical trials to verify the efficacy and toxicity of these therapies remain to be performed, at least to the best of our knowledge. Nonetheless, lncRNAs may represent a novel molecular therapeutic approach for liver fibrosis.

4. Regulation of liver fibrosis by other epigenetic mechanisms

The epigenetic control of gene expression is a well-studied area. The present review focuses on DNA methylation, as well as histone methylation and acetylation. DNA methylation

is one of the better understood epigenetic mechanisms. The methylation of DNA occurs at the cytosine residue located 5' to guanosine residue in a stretch of CpG dinucleotides termed CpG islands. The methylation of CpG stretches in the promoter region of a gene and is known to inhibit or repress gene expression. The methylation of cytosine residues prevents the binding of DNA binding proteins required for transcription (82). DNA methylation is carried out by a group of enzymes known as DNA methyltransferases (DNMTs), which are divided into 2 subcategories: Those involved in the *de novo* methylation of DNA (DNMT3a and DNMT3b) and those involved in maintenance of methylation patterns post-DNA replication (DNMT1) (83-87).

During the development of liver fibrosis, changes in patterns of DNA methylation, altered activity and the expression of associated enzymes have been observed. These changes are crucial for the establishment and progression of liver fibrosis (88-90). As previously demonstrated, activated cultured rat HSCs, when treated with the DNA methylation inhibitor, 5-aza, 2-deoxycytidine, have failed to differentiate into myofibroblasts (91). During HSC activation or trans-differentiation, a global DNA hypomethylation is observed (92,93). Although there is an overall demethylation during HSC activation, genome-wide methylation studies have revealed that hypo- or hypermethylation occurring in the promoter region is specific to each gene (92). During HSC activation, the Wnt signaling pathway has been found to be epigenetically

Table II. Epigenetic regulation of genes involved in liver fibrosis.

Gene	Gene expression	Epigenetic mechanism involved	(Refs.)
<i>Apc2</i>	Upregulated	Hypomethylation of gene promoter	(92-95)
<i>Wnt5a</i>		Hypomethylation of gene promoter	(93-95)
<i>Actg2</i>		Hypomethylation of gene promoter	(87)
<i>Loxl1</i>		Hypomethylation of gene promoter	(87)
<i>Loxl2</i>		Hypomethylation of gene promoter	(87)
<i>Col4a1/2</i>		Hypomethylation of gene promoter	(87)
<i>Col1a1/2</i>		H3K4 methylation by COMPASS and ASH1	(100,101)
<i>Elastin</i>		H3K4 methylation by MLL1	(98)
α -SMA		Transcriptional activation by p300	(100,101)
TGF- β 1		H3K4 methylation by ASH1 HMT	(100,101)
TIMP-1		H3K4 methylation by ASH1 HMT	(100,101)
<i>Adamts9</i>	Downregulated	Hypermethylation of promoter DNA	(95)
<i>MMP-15</i>		Hypermethylation of promoter DNA	(95)
<i>Smad7</i>		Hypermethylation of promoter DNA	(96)
<i>Pten</i>		Hypermethylation of promoter DNA	(97)
PPAR- γ		Hypermethylation of promoter DNA by EZH2 at H3K27 and G9a at H3K9	(105-107,131)

The table shows the epigenetic regulation of genes involved in liver fibrosis. Hypermethylation or hypomethylation of gene promoters can upregulate or downregulate the gene expression, respectively. Epigenetic enzymes and their targets are shown.

regulated; *Apc2* and *Wnt5a* are upregulated upon promoter hypomethylation (93-95). Similarly, pro-fibrogenic genes, such as *Actg2*, *Loxl1*, *Loxl2* and *Col4a1* are activated upon the hypomethylation of their respective promoters (87). Conversely, DNA hypermethylation causes the transcriptional repression in genes, such as *Adamts9* and *Mmp15* (95), which produce matrix metalloproteinases involved in ECM breakdown and cell migration. Similarly, *Smad7*, TGF- β R1 antagonist (96) and pro-apoptotic *PTEN* (97) are also negatively regulated by DNA hypermethylation.

DNMTs are not the only methylating agents in cells. The methylation of histones is another form of epigenetic regulatory mechanism. There are 2 types of histone regulatory enzymes; histone methyl transferases (HMTs) and histone demethyltransferases (HDMTs). Recent studies have indicated the roles of these enzymes in liver fibrosis. The exposure of HSCs to ethanol increases the expression of histone-3 lysine-4 (H3K4) methyl transferase, MLL1, which is recruited the promoter of the pro-fibrogenic elastin gene (98). The TGF- β stimulation of mouse embryonic fibroblasts (MEFs) increases dimethylated (H3K4me2) and trimethylated (H3K4me3) histone levels in the promoters of the pro-fibrogenic genes, *Colla1* and *Colla2*. H3K4me2 and H3K4me3 histone signatures are imprinted by a complex protein associated with Set1 (COMPASS). This protein complex COMPASS contains HMTs, such as ASH2 and SET1, which binds to the promoters of pro-fibrogenic genes upon the TGF- β stimulation of HSCs and MEFs (98). ASH1 is also a HMT, which targets H3K4 methylation and is upregulated during HSC transdifferentiation (99). ASH1 binds to the promoters of α -SMA, *Colla1*, TIMP-1 and TGF- β 1, and causes the transcriptional activation of these genes (100,101).

Enhancer of zeste homologue 2 (EZH2) further acts as a HMT, which is part of polycomb repressor complex 2 (PRC2)

that cause H3K27 methylation and promotes the progression of liver fibrosis (102). In CCL4-mediated liver injury, EZH2 expression is increased in activated HSCs (103). The TGF- β stimulation of HSCs can also induce EZH2 (104). The increased expression of EZH2 in activated HSCs causes H3K27 methylation in exons A1 and A2 of peroxisome proliferator activator receptor- γ (PPAR- γ) causing transcriptional repression of PPAR- γ (105,106). The methylation of exons leads to the recruitment of polycomb repressor complex 1 (PRC1) and causes chromatin condensation, thus preventing the transcriptional elongation of downstream exons (107). The downregulation of PPAR- γ is necessary to enable HSC transdifferentiation into myofibroblasts. The epigenetic regulation of genes involved in liver fibrosis through methylation is presented in Table II. Histone acetylation/deacetylation is an important epigenetic mechanism which regulates gene expression and action. Studies have suggested a greater role of HDACs compared to HATs in HSC activation and fibrogenesis. Based on their structure and mechanisms of action, HDACs are grouped into 4 classes: Class I-HDAC1, 2, 3, 8; Class II-HDAC4, 5, 6, 7, 9, 10; Class III-Sirt 1-7; Class IV-HDAC11. During HSC activation, HDAC1 and 2 protein levels have been found to be downregulated (108). In a previous study, in the culture of primary HSCs, HDAC5 and 6 levels peaked at day 4 before decreasing back to baseline levels (109). It was further observed that the pharmacological or siRNA-mediated inhibition of class II HDACs resulted in the upregulation of anti-fibrotic miR-29 (110). The inhibition of HDACs reduced the levels of HSC activation markers e.g., α -SMA, collagen and lysyl oxidase, and also inhibited cell proliferation (109). The inhibition of HDAC1, 2 and 4 by nilotinib has been shown to result in the increased apoptosis and autophagy of activated rat HSCs and human LX-2 cells (110).

Cell death occurs in activated HSCs only, not quiescent ones. MMPs are metalloproteinases, which play an important role in liver injury and ECM accumulation (111). MMPs are produced by quiescent HSCs, which release growth factors required for wound healing and ECM production (112). However, their levels decrease during HSC transdifferentiation and in liver fibrosis. An interesting link has been found between MMPs and HDACs, which indicates that the ectopic expression of HDAC4 in quiescent HSCs suppresses *Mmp9* and *Mmp13* gene expression (112). As lncRNAs are regulated in a similar manner as protein-coding genes, a regulatory association of lncRNAs through acetylation is present (113-116). These studies have demonstrated that HDACs play a regulatory role in liver fibrosis and HSC activation, and may be considered as drug targets.

Pharmacological inhibitors of DNMTs, such as 5-azacytidine, decitabine, guadecitabine, etc. are being tested for the treatment of hematological cancers and for solid tumors, such as hepatocellular carcinoma (HCC) (117-119). These drugs have been shown to be reasonably effective in safety trials and may have potential for use in the treatment of liver fibrosis. Inhibitors of HDACs are also being used to treat malignancies. These inhibitors block cell proliferation and induce apoptosis, and also suppress HSC activation (120,121). Largazole, an HDAC inhibitor, has been shown to suppress liver fibrogenesis and angiogenesis by inhibiting TGF- β and VEGF signaling (18,122). It has also been shown that sodium valproate, a class I and II HDAC inhibitor, when added to cultured HSCs, blocked TGF- β signaling and downregulated TGF- β induced *Coll1a1* expression (123). Trichostatin A (TSA), another HDAC inhibitor, has been shown to suppress HSC differentiation into myfibroblasts, and to downregulate α -SMA, and type I and III collagen (124). In CCL4-induced liver fibrosis, TSA has been found to suppress HSC activation through the acetylation of CAAT/enhancer binding protein α (C/EBP- α) (125). These epigenetic inhibitors provide promising therapeutic targets for liver fibrosis.

5. Interplay between histone and DNA methylation in liver fibrosis

The histone code is defined as the epigenetic signature (methylation and/or acetylation) imprinted on histones. The expression of genes is regulated by chromatin remodeling, which in turn is regulated by epigenetic modifications. The interaction between DNA methylation and histone code represents a functional regulatory mechanism which influences chromatin structure (126,127). The epigenetic modifications on DNA provides docking sites for many transcriptional regulatory proteins which determine gene expression.

Methyl CpG binding protein-2 (MeCP2) binds to methylated cytosine residues on stretches of CpG dinucleotides. MeCP2 regulates the expression of the α -SMA gene. MeCP2 knockout mice exhibit a reduced α -SMA expression and collagen deposition in alveolar cells (128,129). Similar effects have been observed in liver fibrosis (103), establishing the role of MeCP2 in myfibroblast differentiation and liver fibrosis. One of the key steps in HSC transdifferentiation is the epigenetic repression of the *PPAR- γ* gene, which inhibits HSC apoptosis and promotes fibrogenesis. MeCP2 binds to

the *PPAR- γ* promoter and methylates histone H3K9, thereby causing the transcriptional silencing of *PPAR- γ* (103). MeCP2 also induces the expression of EZH2 histone methyl transferase, which methylates histone H3K27 as a part of PRC2 causing the silencing of *PPAR- γ* (102). MeCP2 also induces the expression of histone methyl transferase ASH1, which activates the transcription of profibrogenic genes, such as α -SMA, *Coll1a1*, *TIMP-1* and *TGF- β 1* during myfibroblast differentiation (103). Hence, a coordinated crosstalk between DNA methylation and the histone code, and the epigenetic enzymes can cause transcriptional activation or repression, depending on the specific molecular interactions near the promoters of target genes. MeCP2 causes the transcriptional repression of genes when it binds to 5-methyl cytosine whereas it activates gene expression when it binds to 5-hydroxymethyl cytosine (130,131). It has been demonstrated that both DNMT1 and H3K9 methyl transferase inhibits *PPAR- γ* by binding to its promoter during HSC activation (131), whereas the inhibition of DNMT1 and G9a results in *PPAR- γ* upregulation and the suppression of HSC activation (131).

6. Interactions of lncRNAs with other epigenetic mechanisms

It is of interest to note that the production and/or action of lncRNAs are also regulated by DNA and histone methylation. For example, DNMT1 regulates the lncRNA H19/ERK signaling pathway, which promotes HSC activation and liver fibrogenesis (64). ANRIL is regulated by DNMT3a during HSC activation. DNMT3a suppresses ANRIL expression in activated HSCs with a concomitant increase in the expression of α -SMA, *Coll1a1* and AMPK and p-AMPK in rat and human model of liver fibrosis (60). MeCP2 as discussed above is an epigenetic regulator of pro and anti-fibrogenic genes. However, MeCP2 has also been reported to silence the expression of lncRNA H19 through the IGF1R pathway and to promote HSC proliferation (65). The pro-fibrogenic activity of MeCP2 is regulated by phosphorylation at Serine 80 and its deletion in HSCs results in the altered expression of 284 mRNAs and 244 lncRNAs (132). The understanding of the crosstalk between epigenetic regulators and lncRNAs may help to broaden our understanding of the pathogenesis and subsequent potential therapeutic approaches for liver fibrosis (12,132). EZH2, which is a HMT, methylates H3K27 histone within the exons of *PPAR γ* (102). The methylation of histones leads to the recruitment of the PRC1 complex, which causes the reorganization of the chromatin structure. The binding of PRC1 causes chromatin condensation, which prevents the binding of RNA polymerase II to the DNA template, causing premature termination of transcription (106), indicating that epigenetic mechanisms indirectly regulate gene expression by changing chromatin dynamics.

7. Other considerations

One of the main external stimuli that may affect epigenetic changes is the food that is consumed by an individual. The type of food, as well as the method through which food is prepared, may influence DNA and or histone damage, and subsequent epigenetic alterations, leading to alterations in gene expression. In addition, exposure to environmental

toxins, such as smoking and other pollutants may also affect cells through epigenetic mechanisms (133). However, the detailed analyses of such an etiology and how the aforesaid changes are influenced, are beyond the scope of the present review. Similarly, as the present review focused on lncRNAs, miRNAs and their effects on liver fibrosis either directly or distally through an exosome-mediated mechanism were not addressed. A previously published review article has addressed this topic (134,135).

8. Conclusions

The present review aimed to highlight the importance of lncRNAs in the initiation and progression of liver fibrosis. The present review also outlined how such processes are regulated by histone and DNA methylation and histone acetylation. The recent impetus into the study of lncRNAs has provided a clearer picture into their roles in HSC activation and liver fibrosis. However, the complex regulatory network of lncRNAs and their associations with a plethora of molecules, renders the elucidation of the underlying mechanisms challenging. A diagrammatic outline is illustrated in Fig. 2. As there may also be disease-specific variation, a therapeutic strategy may involve a combination of disease-specific targets. Furthermore, the majority of the studies have focused on HSCs and the potential contribution by other cells may also have to be investigated in order to obtain a better understanding of the mechanisms involved.

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Competing interests

The authors declare that they have no competing interests.

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