LncRNA NEAT1: Shedding light on mechanisms and opportunities in liver diseases

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Abstract
With advances in genome and transcriptome research technology, the function and mechanism of IncRNAs in physiological and pathological states have been gradually revealed. Nuclear Enriched Abundant Transcript 1 (NEAT1, a long non-coding RNA), a vital component of paraspeckles, plays an indispensable role in the formation and integrity of paraspeckles. Throughout the research history, NEAT1 is mostly aberrantly upregulated in various cancers, and high expression of NEAT1 often contributes to poor prognosis of patients. Notably, the role and mechanism of NEAT1 in liver diseases have been increasingly reported. NEAT1 accelerates the progression of non-alcoholic fatty liver disease (NAFLD), liver fibrosis and hepatocellular carcinoma, while exerting a protective role in the pathogenesis of acute-on-chronic liver failure by inhibiting the inflammatory response. In this review, we will elaborate on relevant studies on the different casting of NEAT1 in liver diseases, especially focusing on its regulatory mechanisms and new opportunities for alcoholic liver disease.

KEYWORDS
HCC, liver fibrosis, lncRNA, NAFLD, NEAT1, paraspeckle

1 | INTRODUCTION

It is acknowledged that the protein-coding genes account for <2% of the genome, whereas a myriad of the genome is transcribed into RNA transcripts that lack protein-coding ability. Scientists have named these RNA transcripts as non-coding RNAs (ncRNAs), including transfer RNAs, microRNAs, siRNAs, circular RNAs and long non-coding RNAs (lncRNAs). LncRNAs are a group of ncRNAs whose length is >200 nucleotides, many of which are transcribed by RNA polymerase II (RNA pol II) and derived from different DNA elements, such as promoters, enhancers and intergenic regions in eukaryotic genomes. In contrast to mRNAs, they exhibit obviously lower abundance, less evolutionary conservation and lack of protein-coding potential. Nevertheless, lncRNAs possess versatile functions in modulating gene expression at the transcriptional and post-transcriptional levels, which mostly depends on their subcellular location. Separately, nuclear lncRNAs are involved in the regulation of chromatin architecture, chromatin remodelling, integrity...
and function of nuclear bodies, whereas cytoplasmic lncRNAs play essential roles in modulating mRNA stability and translation, competing with endogenous RNAs and interfering with protein modification.\textsuperscript{5-7} More importantly, lncRNAs have been reported to be impressive regulators in diverse aspects of biology, thus, playing critical biological functions in mammals, such as development and growth, immune responses and substance metabolism.\textsuperscript{8-10} However, various emerging diseases show aberrant depletion, amplification or disruption of some crucial lncRNAs.\textsuperscript{11}

Accumulating evidence suggests that many lncRNAs are abnormally changed in liver diseases and might play an indispensable role as potential non-invasive therapeutic biomarkers.\textsuperscript{12-15} Moreover, profound mechanistic studies have revealed that lncRNAs can regulate cellular metabolism,\textsuperscript{16} inflammatory responses,\textsuperscript{17} autophagy,\textsuperscript{18,19} cell proliferation and apoptosis\textsuperscript{20-23} in liver diseases by directly or indirectly modulating key protein-coding gene expression (Figure 1). For example, lncRNA HULC (highly upregulated in liver cancer), MALAT1, H19, CASC9 (Cancer Susceptibility 9) and lncRNA EGFR contribute to the deterioration of hepatocellular carcinoma (HCC) by regulating lipid and glucose metabolisms, cell aggressiveness, autophagy and immune evasion, whereas lncRNA TSLNC8 ameliorates HCC progression by impairing the aggressiveness of cancer cells.\textsuperscript{16,24-28} Therein, lncRNA H19 is involved in several liver diseases, playing an important role in the regulation of hepatic lipid metabolism in non-alcoholic fatty liver disease (NAFLD) via interaction with poly-30 pyrimidine tract-binding protein 1 (PTBP1),\textsuperscript{29} promoting the activation of hepatic stellate cells (HSCs) in cholestatic liver fibrosis via repressing ZEB1-mediated inhibition of EpCAM,\textsuperscript{30} and aggravating cholestatic liver injury by inhibiting small heterodimer partner (SHP) expression in hepatocytes.\textsuperscript{31} In addition, cholangiocyte-derived exosomal lncRNA H19 mediates vital cell-cell communication between cholangiocytes with hepatocytes and HSCs.\textsuperscript{31,32} Interestingly, lncRNA MEG3 plays promotive and suppressive roles in different liver diseases, which promote the apoptosis and steatosis of hepatocytes by targeting miR-let-7c-5p/NLRC5 in alcoholic liver disease (ALD),\textsuperscript{33} disrupt the homeostasis of bile acids by facilitating SHP mRNA decay in cholestatic liver injury\textsuperscript{34} while alleviate lipid over-deposition via regulation of the miR-21/LRP6 axis in NAFLD.\textsuperscript{35} Importantly, serum lnc AK054921 and lnc AK128652 in patients can be viewed as potential biomarkers for predicting ALD progression.\textsuperscript{36} However, some functions of lncRNA, such as H19 in HCC and GAS5

**FIGURE 1** The known role and mechanism of lncRNA in diverse liver diseases, and representative lncRNAs are outlined. In different liver disease, lncRNAs regulate cell metabolism, inflammatory response, autophagy, cell proliferation and apoptosis by directly or indirectly modulating key protein-coding gene expression. ECM: extracellular matrix, EpCAM: epithelial cell adhesion molecule, NASH: non-alcoholic steatohepatitis. The upward arrow represents upregulation in liver disease, the downward arrow represents downregulation, the dotted arrow represents indeterminacy and the asterisk (*) represents the expression and function of GAS5 in liver fibrosis and H19 in HCC are controversial.
growth arrest-specific transcript 5) in liver fibrosis, are controversial. In hepatocarcinogenesis, H19 was reported to be decreased in valuable models and exert tumour suppressor function, whereas large patient cohorts reported both up- and downregulation of H19 in HCC, which is probably resulted from a panel of studies using rather small sample sizes. These studies suggest that variations in some lncRNAs may be correlated with specific liver diseases, and large patient sample studies are more conducive to elucidating the role of lncRNA in certain diseases. However, the regulatory role of lncRNA nuclear-enriched abundant transcript 1 (NEAT1) in diverse liver diseases is poorly understood.

In this study, we summarized the function and mechanism of NEAT1 in distinct liver diseases and proposed new potential regulatory opportunities for ALD.

2 | BIOGENESIS AND FEATURES OF NEAT1

NEAT1, a familial tumour syndrome multiple endocrine neoplasia type 1 locus (Chr 11q13.1) transcript, is a structural lncRNA that plays an essential role in the constitution and assembly of nuclear paraspeckles, a group of extremely dynamic nuclear subdomains. A recent gene-wide analysis of lncRNA stability revealed that NEAT1 is highly unstable, but the instability does not limit the function of NEAT1. Instead, the high turnover of NEAT1 may be beneficial to the extremely dynamic characteristics of paraspeckles. NEAT1 has two variant isoforms, NEAT1_1 (3735bp) and NEAT1_2 (22741bp). The two isoforms share an identical promoter and 5′-end, and the different 3′-end make them two separate subtypes. As we know, paraspeckles are shaped in the form of a core-shell spheroidal structure, and the middle part of NEAT1_2 is organized to the core, which is encircled by NEAT1_1 and the 5′- and 3′-ends of NEAT1_2 (Figure 2). Of note, NEAT1_2, and not NEAT1_1, is requisite for paraspeckle formation and potent for restoring the effect of NEAT1 knockdown. Yamazaki et al proposed that NEAT1_2 has one modular domain structure, which plays an important role in the stabilization of NEAT1_2, switching of NEAT1 isoform and induction of paraspeckle assembly through phase separation. Moreover, a recent genome editing study revealed that NEAT1_1 is not a major component of paraspeckles, and that the vast non-paraspeckle foci of NEAT1_1 is probably responsible for its paraspeckle-independent functions. In brief, NEAT1 can act as a scaffold for paraspeckles, allowing paraspeckle proteins, including PSCP1, P54NRB/NONO and SFPQ/PSF, to form ordered, compact structures. It has been reported that MALAT1 localizes to nuclear speckles and NEAT1 overlaps with MALAT1 in many genomic sites. A study by West et al revealed that NEAT1 and MALAT1 interact with proteins located in nuclear bodies and specifically target active chromatin sites, and they showed distinct binding patterns at these sites, indicating their independent but complementary functions. The main features of NEAT1 are shown in Figure 2.

More importantly, progressive evidence suggests that NEAT1 not only contributes to vital physiological processes, such as immune responses, organogenesis and myogenesis, but also serves as a pivotal regulator in various pathological processes, such as lung cancer, gastric cancer, breast cancer and HCC.
infection and stress responses, NEAT1 may play an indispensable role in certain cellular processes owing to its inalienable component of paraspeckles.\textsuperscript{31} In recent years, scientists have confirmed that NEAT1 plays an important role in the formation, integrity and assembly of paraspeckles. Clemson et al. reported that NEAT1 could sequester parasite protein, and that silencing NEAT1 by RNAi could eradicate paraspeckles. For example, PSP-1 and PS4 in the nucleoplasm were increased in NEAT1-silenced conditions, suggesting that these proteins would stay in the nucleoplasm without NEAT1 to nucleate paraspeckles.\textsuperscript{42} Notably, this protein sequestration effect of SFPQ, a parasite protein, inhibited RNA-specific adenosine deaminase B2 (ADARB2) gene expression.\textsuperscript{52} In addition, NEAT1 was also reported to be affected by mitochondrial proteins, as knockdown of ATF2 and BCL2 resulted in the downregulation of NEAT1 and increased generation of elongated paraspeckles. Intriguingly, the percentage of NEAT1 was increased in cells depleted of mitochondrial genes, such as ATP2 and BCL2, although there was a 50% reduction in the overall levels of NEAT1 expression. Enhanced NEAT1 could promote the formation of elongated paraspeckles and nuclear retention of mito-mRNAs, which subsequently inhibits their translation of mito-mRNAs. Further studies indicated that NEAT1 and paraspeckles can regulate mitochondrial homeostasis, at least partially, through the nuclear sequestration of multiple mitochondria-related mRNAs.\textsuperscript{53} Therefore, NEAT1 may indirectly control the expression of some genes via protein sequestration.

Hirose et al also reported that NEAT1\textsuperscript{62} fibroblasts were more sensitive to protoasome inhibition that triggered cell death, which revealed that paraspeckles or NEAT1 attenuated the cell death pathway.\textsuperscript{52} In 2014, a study by Nakagawa et al identified NEAT1 as indispensable for the formation of corpus luteum and subsequent establishment of pregnancy under suboptimal condition in mice.\textsuperscript{54} They found that NEAT1 \textsubscript{2} was expressed during the development of the corpus luteum, which further induced the formation of paraspeckles in luteal cells, as indicated by the enrichment of SFPQ. However, these phenomena disappeared in NEAT1-knockout mice.\textsuperscript{54} Another study indicated that genetic ablation of NEAT1 could lead to abnormal mammary gland morphogenesis and lactation defects.\textsuperscript{55} Through RNA FISH using a NEAT1\textsubscript{2} probe, they found that NEAT1-containing paraspeckles assembled in luminal epithelial cells of the mammary gland.\textsuperscript{55} These studies suggest that NEAT1 is essential for mammalian breeding and feeding. It has been frequently reported that NEAT1 (two isoforms) is associated with inflammatory processes such as chemokine modulation, cytokine production and inflammasome activation.\textsuperscript{56,57} Of note, Zhang et al reported that NEAT1 enhances the activation of NLRP3, NLRC4 and AIM2 inflammasomes as well as facilitates caspase-1 activation, cytokine production and pyroptotic cell death. Further mechanistic studies revealed that NEAT1 is transferred from paraspeckles upon various inflammasome-activating signals, and then promotes the assembly of inflammasomes in the cytoplasm.\textsuperscript{58} Interestingly, a recent study by Wang et al found another important role of NEAT1 in mouse muscle development and regeneration. They found that NEAT1 expression gradually increased during myogenic differentiation and muscle regeneration. A functional study showed that NEAT1 promotes myoblast proliferation in vitro and in vivo, while impeding the differentiation of myoblasts. In this mechanism, NEAT1 recruited EZH2 to the promoter of P21, subsequently inhibiting P21 expression and augmenting \textsubscript{C2C12} cell proliferation.\textsuperscript{59} In parallel, NEAT1 inhibits the expression of Myog, Myh4 and Tnni2, three muscle-specific genes, by recruiting EZH2 to promoters of the target genes, thus, inhibiting myogenic differentiation.\textsuperscript{59}

Above all, these studies emphasized that NEAT1 plays an important role not only in cellular processes but also in vital physiological processes.

4 | ROLE OF NEAT1 IN LIVER DISEASES

The liver, a multifunctional organ, is essential for metabolism, immunity, digestion and detoxification. Importantly, the liver has a great capacity to repair itself after minor damages.\textsuperscript{60} However, morbidity and mortality caused by liver diseases have sharply increased in recent decades. Fortunately, increasing studies have indicated that many lncRNAs are abnormally changed in liver diseases (Figure 1), and they may be regarded as promising biomarkers for treating liver diseases. NEAT1 was reported to be involved in various liver diseases (Figure 3), and the concrete mechanisms are listed in Table 1.

4.1 | HCC

Recent epidemiology data showed liver cancer as the sixth-most commonly diagnosed cancer and the fourth leading cause of cancer-related deaths, which results in a great burden for people worldwide.\textsuperscript{61} HCC is the most common type of primary liver cancers.\textsuperscript{62} Increasing evidence has indicated that the diversity of non-coding RNAs is significantly altered in HCC.\textsuperscript{63} Encouragingly, lncRNAs are reported to be aberrantly dysregulated in HCC and viewed as a budding star in predicting and diagnosing HCC based on its non-invasive advantage.\textsuperscript{63,64} In 2014, Guo et al first showed that NEAT1 was detected highly in 95 cases of Chinese HCC tissues compared with that in non-cancerous liver tissues.\textsuperscript{65} This study also highlighted that the redundant expression of NEAT1 exacerbated the clinical features of HCC, such as increasing the number of tumour nodes, aggressive metastasis and TNM stage.\textsuperscript{65} Subsequently, a whole-genome mutational study showed that NEAT1 \textsubscript{2} was recurrently mutated in 66% of 300 Japanese liver cancer patients, including 268 HCC patients. Moreover, this preliminary study also revealed that silencing of NEAT1 in HepG2 repressed cell invasion.\textsuperscript{66} In 2017, a Chinese population-based study on HCC prognosis after hepatectomy reconfirmed the ectopic expression of NEAT1 in HCC tissues and cell lines, and revealed that NEAT1 overexpression was independently associated with poor prognosis.\textsuperscript{67} In general, these three studies showed that NEAT1 may be a promising regulatory biomarker in
HCC. Subsequently, Mang et al confirmed that NEAT1 was aberrantly increased, and NEAT1 promoted cell proliferation, migration and invasion in HCC cell lines. Growing studies have shown that the lncRNA-protein complex plays a crucial role in HCC. Further studies indicated that NEAT1 formed a complex with U2AF65, thus, promoting the expression of hnRNP A2, a driver in HCC. Zheng et al found that HIF-2α promoted the expression of NEAT1, and the active NEAT1 then advanced the progression of HCC by affecting the epithelial-mesenchymal transition. In addition, a body of reports have underlined that NEAT1 accelerates HCC progression by acting as sponges for miR-129-5p, miR-613, miR-139-5p, miR-124-3p, miR-296-5p, miR-22-3p and miR-let-7b, thus, restoring the expression of specific genes that are handcuffed by miRNAs. Fang et al found a negative correlation between NEAT1 and miR-129-5p in HCC tissues. Silencing of NEAT1 significantly augmented the level of miR-129-5p. Further studies proved that NEAT1 directly combined with miR-129-5p, and then regulated the expression of the target molecules, Valosin-containing protein and IκB, both of which are promoters of HCC. Coincidentally, a recent study by Shaker et al identified NEAT1 was obviously increased in the serum of HCC patients, and there was also a negative correlation between serum NEAT1 and miR-129-5p. Wang et al found that NEAT1 intensified the proliferation and invasion of HCC cells by repressing miR-613, a known tumour driver, by inhibiting DLCK1. In the case of miR-139-5p, researchers revealed that NEAT1 downregulation limited the development of HCC by regulating the miR-139-5p/TGF-β1 axis in vitro and in vivo. Recently, some studies reported that inadequacy of ATGL could alleviate the growth and motility of some tumour cells. Liu et al first reported that ATGL was aberrantly expressed in human HCC tissues, which predicted poor prognosis. Notably, NEAT1 was found to adjust the expression of ATGL by sponging miR-124-3p, thus, promoting HCC cell growth. Unlike the usual mechanism, NEAT1 was initially reported to regulate abnormal lipolysis in hepatocarcinogenesis, mainly by indirectly destroying the normal expression of PPAR-α. Persistently, Li et al revealed that NEAT1 indirectly regulated calponin 2 (CNN2) expression by competing with miR-296-5p in HCC cell lines and in a murine xenograft model, consequently promoting the progression of HCC. It has been reported that AKT2 is overexpressed in HCC and independently correlated with the prognosis of human HCC. In particular, a study by Zhou et al revealed that NEAT1 positively regulated AKT2 expression by inhibiting miR-22-3p, thus, promoting HCC development. Liu et al found that NEAT1 reduced apoptosis and promoted the proliferation of HepG2/Huh7 cells by sponging miR-let-7b, thereby emancipating the downstream signalling of insulin-like growth factor type 1 receptor (IGF-1R). In addition to regulating downstream gene expression, NEAT1 is also modulated by other biomolecules, such as RNA-binding proteins (RBPs). Yang et al reported that polyribonucleoside tract-binding protein 3 (PTBP3), a nuclear enriched RBP, exacerbated cell proliferation and metastasis of HCC by regulating the balance between NEAT1 (NEAT1_1 and NEAT1_2) and miR-612. PTBP3 was highly expressed in HCC tissues compared with that in paracarcinoma tissues, which is positively correlated with NEAT expression and negatively related to miR-612. Notably, patients who manifested PTBP3high and NEAT1high/miR-612low showed a shorter overall survival.

Currently, chemotherapy and radiotherapy are two common treatment methods for HCC and are frequently needed, although surgical resection is the priority for early-stage HCC patients. Nevertheless, the emergence and development of drug resistance and radio-resistance pose as clinical obstacles in the ideal therapy of HCC. Therefore, improving the drug sensitivity and radio-sensitivity of HCC is urgently needed. In 2016, an unprecedented study by Adriaens et al identified that NEAT1 targeting augmented the sensitivity of human cancer cells to genotoxic chemotherapeutics, such as doxorubicin or platinum compounds, and to P53 reactivation therapy.
| Disease type                      | Cell lines                  | NEAT expression | Downstream regulators | Upstream regulators | Mechanisms                                                                 | References          |
|----------------------------------|-----------------------------|-----------------|----------------------|--------------------|----------------------------------------------------------------------------|---------------------|
| HCC                              | HepG2/SMMC7721/HCCM3        | Upregulation    | NA                   | NA                 | NA                                                                         | NA                  |
|                                  | HepG2/Huh7                  | Upregulation    | NA                   | NA                 | NA                                                                         | NA                  |
|                                  | Huh7/BeL7404/Huh6           | Upregulation    | NA                   | NA                 | NA                                                                         | NA                  |
|                                  | HCC (drug resistance)       | Upregulation    | NA                   | NA                 | NA                                                                         | NA                  |
|                                  | HCC (radio-resistance)      | Upregulation    | NA                   | NA                 | NA                                                                         | NA                  |
|                                  | SMMC7721/Huh7               | Upregulation    | NA                   | NA                 | NA                                                                         | NA                  |
|                                  | Huh7/BeL7404                | Upregulation    | NA                   | NA                 | NA                                                                         | NA                  |
|                                  | HCC (drug resistance)       | Upregulation    | NA                   | NA                 | NA                                                                         | NA                  |
|                                  | HCC (radio-resistance)      | Upregulation    | NA                   | NA                 | NA                                                                         | NA                  |
|                                  | Huh7/BeL7404                | Upregulation    | NA                   | NA                 | NA                                                                         | NA                  |
|                                  | HCC (drug resistance)       | Upregulation    | NA                   | NA                 | NA                                                                         | NA                  |
|                                  | HCC (radio-resistance)      | Upregulation    | NA                   | NA                 | NA                                                                         | NA                  |
|                                  | Huh7/BeL7404                | Upregulation    | NA                   | NA                 | NA                                                                         | NA                  |
|                                  | HCC (drug resistance)       | Upregulation    | NA                   | NA                 | NA                                                                         | NA                  |
|                                  | HCC (radio-resistance)      | Upregulation    | NA                   | NA                 | NA                                                                         | NA                  |
|                                  | Huh7/BeL7404                | Upregulation    | NA                   | NA                 | NA                                                                         | NA                  |
|                                  | HCC (drug resistance)       | Upregulation    | NA                   | NA                 | NA                                                                         | NA                  |
|                                  | HCC (radio-resistance)      | Upregulation    | NA                   | NA                 | NA                                                                         | NA                  |
|                                  | Huh7/BeL7404                | Upregulation    | NA                   | NA                 | NA                                                                         | NA                  |
|                                  | HCC (drug resistance)       | Upregulation    | NA                   | NA                 | NA                                                                         | NA                  |
|                                  | HCC (radio-resistance)      | Upregulation    | NA                   | NA                 | NA                                                                         | NA                  |
|                                  | Huh7/BeL7404                | Upregulation    | NA                   | NA                 | NA                                                                         | NA                  |
|                                  | HCC (drug resistance)       | Upregulation    | NA                   | NA                 | NA                                                                         | NA                  |
|                                  | HCC (radio-resistance)      | Upregulation    | NA                   | NA                 | NA                                                                         | NA                  |
|                                  | Huh7/BeL7404                | Upregulation    | NA                   | NA                 | NA                                                                         | NA                  |
|                                  | HCC (drug resistance)       | Upregulation    | NA                   | NA                 | NA                                                                         | NA                  |
|                                  | HCC (radio-resistance)      | Upregulation    | NA                   | NA                 | NA                                                                         | NA                  |
|                                  | Huh7/BeL7404                | Upregulation    | NA                   | NA                 | NA                                                                         | NA                  |
|                                  | HCC (drug resistance)       | Upregulation    | NA                   | NA                 | NA                                                                         | NA                  |
|                                  | HCC (radio-resistance)      | Upregulation    | NA                   | NA                 | NA                                                                         | NA                  |
|                                  | Huh7/BeL7404                | Upregulation    | NA                   | NA                 | NA                                                                         | NA                  |
|                                  | HCC (drug resistance)       | Upregulation    | NA                   | NA                 | NA                                                                         | NA                  |
|                                  | HCC (radio-resistance)      | Upregulation    | NA                   | NA                 | NA                                                                         | NA                  |
|                                  | Huh7/BeL7404                | Upregulation    | NA                   | NA                 | NA                                                                         | NA                  |
|                                  | HCC (drug resistance)       | Upregulation    | NA                   | NA                 | NA                                                                         | NA                  |
|                                  | HCC (radio-resistance)      | Upregulation    | NA                   | NA                 | NA                                                                         | NA                  |
|                                  | Huh7/BeL7404                | Upregulation    | NA                   | NA                 | NA                                                                         | NA                  |
|                                  | HCC (drug resistance)       | Upregulation    | NA                   | NA                 | NA                                                                         | NA                  |
|                                  | HCC (radio-resistance)      | Upregulation    | NA                   | NA                 | NA                                                                         | NA                  |
|                                  | Huh7/BeL7404                | Upregulation    | NA                   | NA                 | NA                                                                         | NA                  |
|                                  | HCC (drug resistance)       | Upregulation    | NA                   | NA                 | NA                                                                         | NA                  |
|                                  | HCC (radio-resistance)      | Upregulation    | NA                   | NA                 | NA                                                                         | NA                  |
|                                  | Huh7/BeL7404                | Upregulation    | NA                   | NA                 | NA                                                                         | NA                  |
|                                  | HCC (drug resistance)       | Upregulation    | NA                   | NA                 | NA                                                                         | NA                  |
|                                  | HCC (radio-resistance)      | Upregulation    | NA                   | NA                 | NA                                                                         | NA                  |
|                                  | Huh7/BeL7404                | Upregulation    | NA                   | NA                 | NA                                                                         | NA                  |
| Disease type   | Cell lines                        | NEAT expression | Upstream regulators | Downstream regulators | Mechanisms                                                                 | References                  |
|---------------|-----------------------------------|-----------------|---------------------|-----------------------|-----------------------------------------------------------------------------|-----------------------------|
| NAFLD         | BRL3A                             | Upregulation    | NA                  | mTOR/S6K1             | NEAT1 promotes mTOR/S6K1 signalling pathway                                 | Xiang Wang., 2018          |
|               | HepG2                             | Upregulation    | miR-140             | AMPK/SREBP-1          | miR-140 promotes NEAT1 expression                                           | Sun et al, 2019            |
|               | BRL3A                             | Upregulation    | NA                  | miR-506/GLI3          | Functioning as sponge for miR-506                                           | Jin et al, 2019             |
|               | HepG2                             | Upregulation    | NA                  | miR-146a-5p/ROCK1     | Promoting hepatic steatosis by regulating miR-146-5p/ROCK1 axis             | Chen et al, 2019           |
| Liver fibrosis| Pri-HSC/pri-hepatocyte             | Upregulation    | NA                  | miR-122/KLF6          | Regulating miR-122-KLF6 axis                                               | Yu et al, 2017              |
|               | JS1                               | Upregulation    | IGFBP1              | miR-29b/Atg9a         | NEAT1/miR-29b/Atg9a axis regulates IGFBP1-induced autophagy                | Kong et al, 2019           |
| Liver injury  | Kupffer cells/Raw264.7             | Upregulation    | LPS                 | Let-7a/TLR4           | Regulating Let-7a/TLR4 axis                                                | Zhang et al, 2019          |
| Liver failure | Pri-hepatocyte/pri-macrophage/HepG2/Raw264.7 | Upregulation | LPS                 | TRAF6                 | Blocking TRAF6-mediated inflammatory response                               | Xu et al, 2019              |
|               | HL7702                            | Upregulation    | D-GalN/LPS          | LAST2/YAP             | Promoting apoptosis of hepatocyte through recruiting EZH2 to the promoter region of LAST2 | Wang et al, 2020           |
| Viral hepatitis| NA                                | Downregulation  | NA                  | NA                    | The NEAT1 expression closely correlated with TLR6 and RIG-I                | Zeng et al, 2019           |

Abbreviation: NA, not available.
including pharmacological therapy or oncogene-induced replication stress. Moreover, the level of NEAT1_2, not NEAT1_1, could predict platinum-based chemotherapy response in human ovarian cancer. This important finding suggested that various human cancers may benefit from NEAT1-targeted therapy, considering the close regulatory effect between NEAT1 and PS3. Expectantly, a study by Ru et al reported that NEAT1_2 and SFQ (a known paraspeckle protein) synergistically enhance cisplatin resistance in QGY-7703 and Huh-7 liver cancer cells in vitro. However, alteration of NEAT1_2 was absent to regulate the mRNA and protein expression of SFQ, indicating indirect regulation between them. To the best of our knowledge, NEAT1_1 and NEAT1_2 are vital for maintaining the integrity of paraspeckles, and NEAT1_2 is indispensable for paraspeckle assembly. Significantly, Kessler et al identified that both NEAT1_1 and NEAT1_2 were highly expressed in sorafenib- and doxorubicin-resistant HCC cell lines. Moreover, paraspeckles are more abundant in chemoresistant cells than in chemosensitive cells, and paraspeckle proteins, including PSPC1, NONO, and RBM14, were associated with poor survival in HCC. This study indicated the induction of NEAT1 in HCC chemoresistance, and highlighted that paraspeckle-associated protein transcripts are correlated with short survival in HCC. Chen et al showed that knockdown of NEAT1_2 increased the radiosensitivity of HCC cells. In this study, NEAT1_2 served as a miR-101-3p sponge, and then promoted the expression of the miR-101-3p target, Wee1. Besides, silencing of NEAT1 in HepG2 and Bel7404 cells promoted sorafenib sensitivity, as reflected in the increase in the percentage of drug-induced apoptosis cells, and resulted in smaller tumour size in nude mice compared with that in mice treated with sorafenib intervention alone. Mechanistic studies indicated that NEAT1 acts as a ceRNA for miR-335 and indirectly regulates the c-Met/AKT pathway. Furthermore, another study by Li et al found that high expression of NEAT1 promoted autophagy and inhibited sorafenib efficacy in HCC, and NEAT1 upregulated the expression of ATG3 by sponging for miR-204, instead of relying on miR signals. NEAT1 is also regulated by other important molecules. Mou et al found that Bcl-2-associated transcription factor 1 (BCLAF1), a multifunctional protein, aggravated the progression of HCC and promoted 5-Fluorouracil (5-Fu) resistance in HCC cells by improving NEAT1 expression. It has been acknowledged that cancer stem cells (CSCs) impede the improvement of HCC, as they have some malignant features, such as tumour-initiating ability, resistance to conventional chemotherapeutic and radiotherapy and high metastatic potential. Fortunately, a recent study impressively elucidated that NEAT1_1 is required for the expression of CD44, a liver CSC marker that is necessary for maintaining CSC properties and associated with poor prognosis in HCC. Interestingly, NEAT1_1 overexpression could restore CSC properties in CD44-deficient cells, indicating that the ability of NEAT1_1 to maintain CSC properties is in a CD44-independent manner. These studies suggest that NEAT1 promotes the progression of HCC conceivably by increasing the drug- and radio-resistance of HCC cells and maintaining the properties of liver CSCs.

Nowadays, immunotherapy has become a popular method for treating HCC. A research by Yan et al showed that NEAT1 and Tim-3 were increased in the PBMCs of patients with HCC. Silencing of NEAT1 by si-NEAT1 in CD8+T cells isolated from healthy donor PBMCs inhibited apoptosis and enhanced the cytolytic activity of CD8+T cells, accompanied by decreased cleaved caspase 3, indicating that NEAT1 promoted the apoptosis of CD8+T cells through a caspase-dependent pathway. A mechanism study suggested that NEAT1 is involved in the immune escape of HCC by regulating the miR-155/Tim3 axis. Overall, NEAT1 aggravates the progression of HCC, and disturbance of NEAT1 may contribute to chemotherapy, radiotherapy and immunotherapy of HCC as well as interfere with the maintenance of liver CSC properties. The mechanisms are described in Figure 4. Furthermore, the detection of serum NEAT1 in HCC makes NEAT1 a promising therapeutic biomarker.

### 4.2 | NAFLD

Non-alcoholic fatty liver disease, a chronic liver metabolic disorder, is prevalent worldwide and is associated with human health. Recently, IncRNAs have emerged as potential regulators in NAFLD, such as Inc18q22.2, Inc SRA and Inc Blnc1. Intriguingly, research has revealed that NEAT1 is a candidate regulator of NAFLD. A study by Wang Xiang found that NEAT1 was obviously increased, accompanied by abnormal ACC and FAS expression in a high-fat diet-induced rat NAFLD model and BRL3A cells, a rat hepatic cell line. Functionally, NEAT1 knockdown inhibited the mRNA and protein expression of ACC and FAS by regulating the mTOR/S6K1 signalling pathway, which plays an essential role in the biosynthesis of lipid and insulin signalling transduction. In 2019, Sun et al reported that NEAT1 and miR-140 were significantly highly expressed in liver tissues from mice with NAFLD and in HepG2 cells pretreated with free fatty acids. In contrast, silencing of miR-140 inhibited NEAT1 expression and alleviated deposition in HepG2 cells; thus, NEAT1 may be a target molecule of miR-140. Chen et al found that NEAT1 promoted hepatic lipid deposition by sponging miR-146a-5p, subsequently liberating the expression of Rho-kinase1 (ROCK1), which is repressed by miR-146-5p, and significantly inducing the AMPK/SREBP pathway. According to the double-hit theory, accumulation of excess triglycerides in hepatocytes is the first hit, which leads to the second hit, characterized by liver injury, inflammation and fibrosis resulting from inflammatory mediators. Most importantly, NEAT1 was reported to be involved in the modulation of fibrosis and inflammatory responses in NAFLD, except for the regulation of lipid metabolism. A study by Jin et al revealed that silencing of NEAT1 alleviated fibrosis and inflammatory responses by regulating the miR-506/GLI3 axis in a NAFLD cellular model. The known regulatory mechanisms are shown in Figure 5A.

However, there is a lack of detection of NEAT1 in the serum and liver tissues of human NAFLD, and whether NEAT1 is correlated with disease risk, severity and prognosis of NAFLD remains unknown. Moreover, which of the two variant isoforms plays a profound role remains to be clarified. Therefore, further studies are needed to
examine circulating NEAT1 levels and validate the potential function as well as the mechanism of NEAT1 in NAFLD.

4.3 | Liver fibrosis

It is widely acknowledged that the activation of HSCs is a pivotal event in liver fibrosis. Recently, Yu et al found that NEAT1 was aberrantly upregulated in primary HSCs isolated from CCl₄-induced fibrotic liver at different weeks. In parallel, gradual elevation of NEAT1 was observed with the differentiation of primary HSCs. Functionally, silencing of NEAT1 via Ad-shNEAT1 delivery suppressed CCl₄-induced collagen deposition in mouse liver, and hindered the activation and proliferation of primary HSCs in vitro. Comprehensive studies using luciferase reporter and pull-down assays indicated that NEAT1 negatively regulated the expression of miR-122, thus liberating the expression of KLF6. Importantly, NEAT1 was positively correlated with α-SMA and Col1A1 in human cirrhosis. Autophagy has been reported to be closely related to the activation of HSCs, and insulin-like growth factor binding protein-related protein 1 (IGFBPrP1) promotes autophagy in HSCs. In 2019, Kong et al found that NEAT1 and Atg9a were increased in Ad-IGFBPrP1-treated mouse liver tissues and JS1 (immortalized mouse cell line), and decreased expression of miR-29b was observed. Further studies suggested that NEAT1...
BU et al. promoted the expression of Atg9a by sponging miR-29b, thereby intensifying autophagy in Ad-IGFBPrP1-treated mice. The known roles of NEAT1 in liver fibrosis are shown in Figure 5B. Intriguingly, a recent review proposed that NEAT1 might regulate liver fibrosis by influencing P53 owing to the intimate regulatory relationship between NEAT1 and P53 in tumorigenesis. This suggests another underlying mechanism of NEAT1 in liver fibrosis. Therefore, NEAT1 may be a potential biomarker for predicting liver fibrosis, and further studies are needed to investigate the deep mechanism of NEAT1_1 or NEAT1_2 in the pathogenesis of liver fibrosis.

4.4 | Liver injury

Sepsis, a systemic inflammatory syndrome, tends to stimulate inflammatory cascades and promotes ROS production, ultimately leading to multiple organ dysfunction. Notably, the liver is vital for defensive responses, such as scavenging bacteria and producing inflammatory mediators. However, the liver is vulnerable to sepsis-induced injury in the progression of sepsis as a result of systemic or microcirculatory disturbances, bacteria and endotoxin (lipopolysaccharide, LPS). In 2018, Huang et al found that NEAT1...
was highly prevalent in the plasma of sepsis patients in contrast to healthy controls. Further analysis revealed that circulating NEAT1 expression correlates with higher risk, increased severity and poor prognosis in sepsis patients, and concurrently positively relates to elevated levels of pro-inflammatory cytokines, including TNF-α, IL-1β, IL-6 and IL-8.109 Interestingly, a recent study by Zhang et al indicated that NEAT1 and toll-like receptor 4 (TLR4) were simultaneously augmented in liver tissues of sepsis-induced liver injury patients, together with the upregulation of TNF-α, IL-1β and IL-6. However, there was a decrease in the expression of miR-Let-7a, an anti-inflammatory regulator, in sepsis patients. Functionally, knockdown of NEAT1 by sh-NEAT1 suppressed the secretion of inflammatory factors, whereas intervention by miR-Let-7a reversed the effect of sh-NEAT1. Further studies identified NEAT1 as a sponge for miR-Let-7a and that it indirectly regulated the miR-Let-7a target, TLR4.110

Universally, immediate immune responses are common phenomena in acute-on-chronic liver failure (ACLF). In ACLF patients, NEAT1 was increased in PBMCs and positively correlated with IL-6 and IL-22, as reported by Xu et al On the contrary, administration of NEAT1 adenovirus in LPS- and Gal-N-induced rat ACLF significantly alleviated liver injury, as indicated by fewer liver lesions, lower plasma IL-6, IL-22 and HMGB1, and decreased percentage of CD45+/CD11b+ macrophages compared with those in the ACLF group. Overexpression of NEAT1 inhibited IL-6 and IL-22 production post-LPS stimulation 6 hours in HepG2. Further studies in LPS-treated HepG2 cells suggested that Stat1 might be an upstream regulator of NEAT1, which obviously affects the ubiquitination level of TRAF6.111

Fulminant hepatic failure (FHF), a fatal complication of acute hepatic injury, is characterized by an unfavourable occurrence of hepatic encephalopathy and damaged hepatic function.112 In this serious disease, hepatocyte liver failure plays a deteriorated role, as it can promote liver failure and act as an activator of violent inflammatory response, which further aggravates liver injury.112 Notably, NEAT1 was found to be an important regulator in FHF. A study by Wang et al reported that NEAT1 was aberrantly upregulated in FHF models induced by D-galactosamine (D-GalN)/lipopolysaccharide (LPS) in cells and animals. Functional investigations revealed that NEAT1 could promote apoptosis and repress the proliferation of hepatocytes in vitro and in vivo. Moreover, overexpression of NEAT1 could inhibit large tumour-suppressor kinase 2 (LATS2) expression by recruiting enhancer of EZH2 to its promoter, which can suppress LAST2 expression by methylation of H3K27. Further mechanistic studies demonstrated that NEAT1 indirectly blocked the activation and nucleus entry of Yes-associated protein1 (YAP1) via LAST2, which contributes to P73 binding to YAP1 and apoptosis mediated by P73.113

In conclusion, NEAT1 plays a crucial role in the above-mentioned liver injury types (Figure 5C) and may be a promising therapeutic biomarker. However, it is not known whether NEAT1_1 or NEAT1_2 exert a greater role in regulating liver damage and whether serum NEAT1 levels could predict the progression of liver injury remains to be clarified.

4.5 | Viral hepatitis

Recently, growing evidence has emphasized that NEAT1 is involved in virus infection and innate immune response, either acting as antiviral or promoting viral effect.114,115 It has been reported by Beeharry et al that P5F, p54rb and PSP1, three paraseckle proteins, were required for the replication of Hepatitis Delta Virus (HDV). Notably, NEAT1 cooperated with PSP1 and p54 to form paraseckles and controlled the genesis of paraseckles in cell division. Consistently, the expression of NEAT1 was increased and the loci of NEAT1 were enlarged during HDV replication in HEK293 cells. Meanwhile, the mRNA of IL-8 was upregulated approximately twofold upon HDV replication. The authors predicted that NEAT1, induced by HDV, might lead to the sequestration of paraseckle proteins and the activation of the innate immune response.116 Conversely, another research team found NEAT1 was significantly decreased in the peripheral blood of HBeAg-positive chronic HBV infection (CHB) patients in the active phase compared to healthy controls. In addition, NEAT1 was positively correlated with TLR6 and RIG-I, two central players in innate immunity response during acute viral infection. They speculated that the reduction in NEAT1 might delay host innate immune responses and promote HBV replication.117 In short, NEAT1 acts as different characters upon different hepatic virus infections, and advanced studies are needed to shed light on the function and mechanism of NEAT1 in HBV infection in order to study its therapeutic potential.

5 | CONCLUSION AND FUTURE PROSPECTS

As an architectural IncRNA, NEAT1 is critical for the formation, integrity and assembly of paraseckles. Nevertheless, scientists have unveiled the potential regulatory role of NEAT1 in various physiological and pathological processes in recent years. Of note, substantial research has been performed to explore the enigmatic role of NEAT1 in liver diseases, ranging from viral hepatitis to HCC (Figure 3). On the one hand, NEAT1 accelerates the progression of HCC, NAFLD, liver fibrosis, sepsis-induced liver injury and FHF. On the other hand, NEAT1 alleviates ACLF and probably inhibits HBV replication, but enhances HCV replication. These contradictory findings indicate the diverse role of NEAT1 in different conditions of liver diseases. Mechanistically, NEAT1 mostly acts as a sponge for specific miRNAs. Certain modulators, such as PTPB3, BCLAF1, P53 and miR-140, particularly contribute to the expression of NEAT1 in liver diseases. Although growing studies indicate the potential role of NEAT1 in liver diseases, there is still a lack of concrete molecular mechanism studies on NEAT1 based on its architectural features. Recently, an excellent work by Wang et al found that there exists an unexpected cross-regulation between paraseckles and mitochondria by a series of novel methods. Notably, knockdown of some mitochondrial proteins or treatment of mitochondrial stressors both result in the abnormal expression
of NEAT1 via ATF2 and altered morphology as well as the amount of paraspeckles.\textsuperscript{1,11,18,19} Given the important function of mitochondria in different liver diseases, whether NEAT1 exerts its role by regulating mitochondrial proteins is far from comprehension.

Recently, exosome-derived IncRNAs and mechanisms of intercellular IncRNA shuttling via exosomes have gradually been revealed in different liver diseases, which can assist in signal communication between cells.\textsuperscript{31,118,119} Notably, NEAT1 was also identified as an exosomal IncRNA, inhibition of which could influence inflammatory responses in inflammatory bowel disease (IBD) through exosome-mediated polarization of macrophages.\textsuperscript{120}

Moreover, NEAT1 was enriched in large extracellular vesicles secreted by hypoxic cardiomyocytes, which were taken up by fibroblasts, causing the expression of profibrotic genes.\textsuperscript{121} However, it has not been reported whether NEAT1 exists in exosomes secreted by liver cells and whether exosome NEAT1 has a certain effect on mediating cellular communications in liver diseases, regardless of origin from the liver or other distant organs. Given that circulating NEAT1 may become a potential biomarker in several liver diseases, it is necessary for future investigators to detect NEAT1 expression in plasma exosomes.

In addition, it is unclear whether NEAT1 is involved in the process of ALD. Further mechanistic studies are urgently needed to achieve a comprehensive understanding of NEAT1 in various liver diseases.

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CONFLICTS OF INTEREST

All authors listed in this review declare no conflicts of interest.

AUTHORS’ CONTRIBUTIONS

FT. B and J. L conceived and designed the review. FT. B and J. L drafted the manuscript, figures and tables. A. W, Y. Z and HM. Y contributed to the writing and checking of the manuscript. FT. B, A. W, HM. Y, YF. Z, XM. M and C. H contributed to the critical figure design and revision of the manuscript. FT. B, A. W, Y. Z, HM. Y, YF. Z, XM. M, C. H and J. L approved the final version of the manuscript.

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