MiniReview

Research Progress of mRNA Modification in Chronic Liver Disease

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Abstract
Chemical markers that modified DNA and its protein scaffold had emerged as a crucial area of epigenetic research. As the research advanced, regulatory mechanisms similar to those discovered in DNA were identified in messenger RNA (mRNA) and other RNA types. The liver, the largest organ in the body, primarily responsible for metabolic functions, uniquely depended on mRNA modifications for its physiological functions and pathological states. In recent years, critical breakthroughs were made in the realm of methylation modifications, particularly in 6-methyladenosine (m6A), 5-methylcytosine, and 1-methyladenosine. This paper primarily focused on the role of m6A modifications in chronic liver diseases such as viral hepatitis, non-alcoholic fatty liver disease, and hepatocellular carcinoma, while also discussing the clinical implications of mRNA modifications.

Keywords: mRNA modification, chronic liver disease, apparent genetics

1 INTRODUCTION
Chronic liver disease is a condition that stems from diverse causes, marked most prominently by prolonged liver function impairment and fibrosis which lasting over six months. Fatty liver, viral hepatitis, alcoholic liver disease, drug-induced liver damage, autoimmune liver disease, liver cirrhosis, and liver cancer are all common chronic liver diseases encountered in clinical practice. Although progress has been made in the development of drugs to treat chronic liver diseases, most are still restricted to experimental stages, with no truly effective drugs emerging in clinical settings as of yet.

Messenger RNA (mRNA) modifications show potential therapeutic value in a variety of diseases such as infectious diseases and cancer. In 2010, Professor Chuan He proposed the concept of epigenetics of RNA and discovered reversible RNA modifications, of which 6-methyladenosine (m6A), 5'-methylcytosine (m5C) and 1'-methyladenosine (mA) are the three most common post-transcriptional modifications of RNA in eukaryotes. The m6A, m5C and pseudouridine together with mA form the epigenetic transcriptome that controls protein synthesis. The mA modifications regulate the stability of mRNA and also have functions such as
splicing, translocation, localization and translation; The m’C affects RNA structural stability and translation efficiency, while the m’A is related to the translation of mRNA-encoded transcripts\(^{[1,2]}\). Indeed, the recent discovery that low expression of SRSF9 mRNA inhibits the proliferation ability of hepatocellular carcinoma (HCC) cells and induces apoptosis suggests that mRNA modification is a promising research direction for treating liver disease. In addition, studies have shown that the expression levels of ALKBH1 and ALKBH5, two mRNA modification-related genes, are significantly decreased in liver cirrhosis\(^{[3]}\). This finding provides important guidance for the development of therapeutic targets targeting these genes.

More and more evidence suggests that mRNA modification has huge potential in the treatment of chronic liver disease and worth further exploration in our future research. Understanding the biological functions and mechanisms of these mRNA modifications can help us develop more effective treatments and then make substantial contributions to the health of patients. The study describes the role of modifications in chronic liver disease.

2 mRNA PROCESSING AND MODIFICATION PROCESS MODE

mRNA is a single-stranded ribonucleic acid transcribed from the DNA strand that carries information encoding protein synthesis and is further transcribed and processed into functional proteins. From infectious diseases to cancer and to many rare diseases, mRNA is showing potential therapeutic value in a variety of diseases. It is worth noting that mRNA therapy has become a safe and effective strategy for protecting patients from infectious and cancerous diseases, due to its high efficacy, relatively low severity of side effects, and ease to manufacture\(^{[4]}\). Based on the central law, we know that DNA forms RNA through transcription. But for eukaryotes, all DNA sequences are amenable to transcription into precursor RNA. It has been found that precursor mRNA undergoes 2’-O-methylation, pseudouracilization, m’A, m’G, m’A, 5’-cytosine methylation and other chemical modifications\(^{[5]}\).

Natural mRNA has a single-stranded structure consisting of a 5’-methyl guanosine residue bound at the 5’-terminus and a polyadenosine tail at the 3’-terminus, carrying the genetic code that directs the synthesis of the polypeptide chain. The open reading frame (ORF) encoding the protein is identified by a start codon and a stop codon, and the untranslated region (UTR) is located between the cap / tail and the ORF. The transcription process is mediated by T7, T3 or SP6 phage RNA polymerase to synthesize complementary RNA strands. During this process or after transcription, the 7-methylguanosine cap is enzymatically capped at the 5’ end of the mRNA. The cap structure at the 5’ end of the mRNA is required to initiate mRNA translation. It recognizes signals from the ribosome and mRNA, helps the ribosome and mRNA to bind, and enables translation to start from AUG. The cap structure improves mRNA stability and protects mRNA from attack by 5’-3’ nucleic acid ectoenzymes. Studies have demonstrated that the 5’ cap assumes a pivotal role in the process of mRNA maturation, splicing, translation and nonsense-mediated degradation. The polyadenylate tail at the 3’ end is also of paramount importance for mRNA stability and translation. Additionally, the 3’UTR has α and β globin sequences that augment mRNA stability and translation efficiency. There is an AAUAAA sequence at the 3’ end of most eukaryotic genes, which indicates the 3’ end of mRNA plus the poly(A) tail. 3’- and 5’UTR regions are both able to inhibit mRNA degradation and decapitation. Furthermore, the broken gene transcripts have to undergo the editing and processing processes of spacer deletion and expression splicing to form functional mature mRNA molecules. The process of mRNA processing and modification is illustrated in Figure 1.

2.1 Discovery of m’A Modifications and RNA Methylation

In the 1970s, scientists discovered m’A modification in RNA is the most commonly occurring internal modification for mRNA and long-stranded non-coding RNA in most eukaryotes. In 2012, further studies by scientists revealed that m’A modification is linked to mRNA stability, splicing processing, and translation processes\(^{[6]}\). In 2018, Huang et al\(^{[7]}\) increases mRNA stability and translational capacity through the IGF2BP protein. Moreover, m’A is also linked to stem cell fate and biological rhythms, which can trigger stem cells to transition from a self-renewal state to cell differentiation. Researchers have also observed that methylation can shorten the half-life of mRNA and decrease its abundance. It can thus be inferred that m’A modifications have an impact on virtually every step of RNA metabolism.

The m’A modifications comprise 0.2-0.6% of the total adenosine in mammalian RNA and play a pivotal role in cellular processes. This kind of modification is a reversible mRNA modification that involves its own set of writers, erasers, and readers. These terms, which are derived from the field of epigenetics, pertain to the trans-factors that are involved in the formation, removal, and functioning of various modifications. m’A methylation modifications involve a trio of enzymes, namely writers, erasers, and readers. These writers are typically represented by various methyltransferases, including METTL3, METTL14, WTP, KIAA1492, among others. While METTL3 and METTL14 form heterotrimers that catalyze m’A methylation of RNA both
**Figure 1.** Illustrates the process of mRNA processing and modification, including the common process of methylation modification.

*in vivo and in vitro*, they do not modify rRNA or snRNA. In addition, WTAP, KIAA1492, and other factors are also crucial components of these heterotrimers. Erasers, on the other hand, are the corresponding demethylases that can mediate demethylation modifications. Among these demethylases are FTO, ALKBH5, as well as other homologues. Moreover, erasers also include some auxiliary proteins, such as YTHDF1, YTHDF2, YTHDF3, and so on. These proteins are capable of recognizing the information conveyed by RNA methylation modifications and taking part in the translation and degradation of downstream RNAs. As an illustration, the YTHDF family members, including DF1, DF2, and DF3, employ their YTH domains to recognize m$\text{6}A$, while utilizing another domain for performing distinct functions. Specifically, DF1 facilitates translation and DF2 promotes mRNA degradation. Meanwhile, YTHDC1 is capable of regulating the splicing of specific transcripts and is also involved in the XIST-mediated inactivation of the female X chromosome, which is a non-coding RNA. Additionally, another reader, eukaryotic initiation factor 3 (eIF3), can assemble m$\text{6}A$ in the 5'UTR to generate a translation initiation process that is not reliant on eIF4; whereas normal translation initiation is contingent upon eIF3. Akin to eIF4E, eIF3 activity has been shown to be impaired under various stress and disease conditions, thereby enabling m$\text{6}A$ to facilitate selective and disease-specific translation. In terms of mechanistic action, the principle mode of operation for m$\text{6}A$ is the recruitment of m$\text{6}A$-binding proteins, commonly referred to as its readers, which include various proteins that harbor the YTH structural domain and the eIF3.  

### 2.2 m$\text{5}C$ RNA Methylation Modifications

One of the earliest discovered modifications presents in a range of RNAs (such as mRNAs, tRNAs, and rRNAs) is m$\text{5}C$, which serves various functions, including RNA stability and regulation of protein synthesis translation. As a reversible epigenetic modification, m$\text{5}C$ modification in mRNA has an impact on the destiny of modified RNA molecules, promoting mRNA stability, splicing, and nucleoplasmic transport, viral protein expression, DNA damage repair, cellular tolerance, proliferation, migration, stem cell development, differentiation, and reprogramming.

The RNA m$\text{5}C$ methyl group is added to the cytosine loop’s fifth position and triggered by RNA methyltransferase. According to research, the m$\text{5}C$ site is implicated in numerous biological processes, such as RNA structural stability and metabolism, tRNA recognition, and stress responses. Furthermore, m$\text{5}C$ distribution differs among different cell types, and m$\text{5}C$ modifications at specific sites in mRNA demonstrate distinct regulatory
activities[9]. The three primary protein classes that mediate m^C modifications are methyltransferases (writers), demethylases (erasers), and binding proteins (readers). The introduction of m^C into RNA is mainly carried out by two groups of methyltransferases: the DNMT family and the NSUN protein family, which includes TRDMT1 and nucleolin 1. The NSUN protein family has seven human members (NSUN1 to NSUN7). Among them, NSUN2 is an enzyme with a wide range of targets. One of the major biological functions of NSUN2-mediated RNA m^C modifications is the influence on protein translation, and modifications at varying mRNA sites can boost or deter translation. ALYREF acts as a reader in the nucleoplasmic export of mRNAs, and specifically binds to m^C-modified mRNAs via K171 (lysine at position 171) mRNA, regulating mRNA output through K171 (lysine at position 171) binding. Additionally, the TET2 protein may mediate mRNA m^C oxidation, and an unknown protein may convert hm^C back to m^C. This suggests that the m^C modification may be subject to reversible erasure.

2.3 RNA m^A

m^A is an important post-transcriptional modification of RNA, formed by adding methyl to the N1 position of adenosine. m^A modification, a novel class of RNA methylation, is urgently needed to explore both their function and mechanisms. In 2016, scientists at the University of Chicago and elsewhere revealed that m^A modifications can significantly enhance the process of gene to protein expression[9]. In recent years, high-throughput sequencing technology revealed the presence of m^A modifications in mRNAs, which was found to regulate the level of glycolysis in tumor cells by influencing the expression of ATP5D, a component of the delta subunit of mitochondrial adenosine triphosphate synthase. m^A exhibits a strong distribution specificity in the 5' non-transcribed region, with most methylation modifications enriched in the 5'UTR of mRNA. Additionally, only a small number of m^A sites conforming to the "GUUCRA" motif are modified by the known methylation enzyme complex TRMT6/61A. Furthermore, mitochondrial-encoded transcripts also undergo significant m^A methylation modifications. It was shown that m^A is located in the 5'UTR region, especially in the first and second positions of the transcript, promotes mRNA translation, while m^A located in the coding region represses the translational effect[9]. In addition to this, m^A modifies the demethylase ALKBH3 and has nearly one thousand ALKBH3 sites of action in the transcriptome[10].

3 mRNA MODIFICATIONS AND CHRONIC LIVER DISEASE

3.1 Role of m^A Modifications in Common Chronic Liver Diseases

m^A modification is the most abundant form of internal modifications in eukaryotic RNA, shown to be closely linked with the regulation of RNA metabolism. Additionally, m^A is intrinsically involved in a variety of physiological processes, such as neurodevelopment, T-cell homeostasis, glycolipid metabolism, and gametogenesis. Disruption of these modifications is associated with a wide range of diseases including autoimmune disorders, metabolic imbalances, infertility, and disturbed intracellular homeostasis. It has been demonstrated that m^A modifications have significant effects on liver growth and play a critical role in the development of liver-related diseases such as viral hepatitis, non-alcoholic fatty liver disease (NAFLD), and HCC[11]. Moreover, the relative expression of mRNA offers critical insight into the extent of liver fibrosis for patients with CHB liver fibrosis[12].

3.1.1 m^A and Viral Hepatitis

The hepatitis B virus (HBV) is an exclusive virus classified as a hepatophilic DNA virus. Seroepidemiological studies indicate that persistent HBV infection for a prolonged period of time contributes substantially to primary human HCC development. The common belief is that HBV causes HCC either directly by inducing increased genomic instability, insertional mutagenesis, pro-carcinogenic effects, and triggering cellular transformation, or indirectly by disrupting immune responses and leading to necrotrophic inflammation of the liver. A novel factor in the therapeutic progress of HCC research is the m^A modification of cellular RNA. HCV is an RNA virus belonging to the flavivirus family and is a major risk factor for cirrhosis and chronic hepatitis. Studies have shown that knockdown of METTL3 and METTL14 can increase HCV infection by promoting viral particle production without affecting viral RNA replication. Knockdown of FTO has the opposite effect, with YTHDF protein repositioning to lipid droplets and reducing HCV viral production. Gokhale et al.[13] found that alterations in m^A modification regulate HCV infection, while both m^A-bound YTHDF proteins relocalize to sites of HCV particle production and inhibit this phase of viral infection. In 2019, he conducted a study investigating the specific interactions of m^A modifications of cellular RNA is a major risk factor for cirrhosis and chronic hepatitis.

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alongside encoded proteins like RIOK3 and CIRBP can also impact viral infection\textsuperscript{[14]}. In conclusion, this work reveals that signaling pathways activated during viral infection lead to changes in m^6A modifications in host mRNAs that regulate infection, suggesting that post-transcriptional regulation of mRNAs with m^6A modifications can potentially affect viral replication. It was found that alterations in transcript m^6A due to Flaviviridae infection can affect innate immune activation and endoplasmic reticulum stress responses induced by viral infection, which in turn regulate signaling at m^6A levels in specific cellular mRNAs\textsuperscript{[15]}. The post-transcriptional regulation of specific transcripts by m^6A and other RNA modifications may be an important determinant of the degree of infection. In summary, m^6A modifications in the viral genome and transcripts are closely related to viral pathogenesis.

3.1.2 m^6A and NAFLD

As the incidence of obesity and weight-related metabolic diseases continues to rise, non-alcoholic fatty liver disease (NAFLD) has become a prevalent cause of chronic liver disease and is regarded as a manifestation of metabolic syndrome in the liver. NAFLD encompasses a spectrum of clinical presentations, ranging from simple hepatic steatosis and nonalcoholic steatohepatitis to liver fibrosis, cirrhosis, and HCC (refer to Figure 2). RNA modifications form an essential component of epigenetics, and among the various types of RNA modifications in eukaryotes, mRNA N^6-methyladenine (m^6A) methylation modifications represent the most abundant. Recent research has demonstrated that m^6A methylation modifications of mRNA are closely associated with lipid metabolism, and diet-induced changes in m^6A modification patterns in fatty liver can affect insulin sensitivity in the liver\textsuperscript{[16]}. Peng et al.\textsuperscript{[17]} has revealed that m^6A mRNA methylation modifications impact the lipid metabolism of hepatocytes by modulating autophagy, which represents an important mechanism in NAFLD’s pathophysiological process.

Research has indicated that an individual’s hepatic YTHDC2 expression, which recognizes m^6A-modified genes related to triglyceride synthesis and binds to their 3’UTR, reducing mRNA stability and regulating gene expression, is influenced by glucose and palmitate overnutrition, resulting in a reduced expression of the m^6A methylation recognition protein YTHDC2 in obese livers. This reduction in YTHDC2 expression leads to the accumulation of hepatic triglycerides and contributes to the development of NAFLD. Additionally, m^6A RNA methylation plays a crucial role in hepatic steatosis. Knockdown of METTL3 in hepatocytes resulted in reduced m^6A methylation and total mRNA levels of the FASN gene, thus inhibiting fatty acid metabolism. Furthermore, studies have indicated that there is a significant alteration in the m^6A methylation modification in the liver tissues of NAFLD patients when compared to normal liver tissue\textsuperscript{[18]}. In conclusion, m^6A methylation serves a significant role in treating NAFLD. Through m^6A modification, the regulation of obesity-related diseases is made possible. YTHDC2, by binding to and reducing mRNA stability of m^6A-modified genes related to triglyceride synthesis, offers a novel perspective for investigating NAFLD diseases associated with obesity.

The m^6A RNA methylation plays a significant role in various endocrine tissues and organs, such as adipose tissue, pancreatic islets, and the liver. Specifically, studies have shown that the m^6A demethylase FTO has a positive effect on autophagy, while promoting lipid deposition in preadipocytes in mice and pigs. Conversely, the knockdown of FTO has a negative impact on autophagy and inhibits lipid deposition. Wu et al.\textsuperscript{[19]} demonstrated that inhibiting FTO expression prolongs cell cycle progression during early adipocyte differentiation, resulting in the inhibition of adipogenesis. Forced expression or knockdown of FTO has been found to increase and decrease the activation of autophagy in 3T3-L1 and adipocytes, respectively\textsuperscript{[20]}. Moreover, differentially methylated genes of m^6A have been shown to be enriched in insulin-regulated and diabetes-related metabolic pathways, with several genes in the insulin IGF1-AKT-PDX1 signaling pathway displaying reduced methylation levels\textsuperscript{[21]}. Based on these findings, it can be concluded that FTO plays a critical role in hepatocyte fat metabolism and could serve as a potential therapeutic target for NAFLD.

3.1.3 m^6A and Liver Cancer

The modification of RNA by m^6A performs a substantial role in both tumorigenesis and metastasis, as it possesses the ability to modify gene expression, even across numerous levels of RNA splicing, stability, translocation, and translation. As the principal form of primary liver cancer that carries bleak prognosis and high mortality, HCC remains a significant public health challenge globally. In various cancers, such as HCC, the maladaptive actions of m^6A regulation-associated proteins enable the manifestation of certain cancer characteristics, including invasiveness, metastasis, and drug resistance.

Epigenetic regulation, including the RNA m^6A methylation modification, is identified as a crucial marker of HCC carcinogenesis. The m^6A modification regulation is extensively involved in the progression of HCC, and its methyltransferases, namely METTL14, METTL3, WTAP, and demethylases FTO and ALKBH5, are closely linked to HCC pathogenesis. It has been demonstrated that METTL14 significantly elevates the levels of miR-126 in tissues, thereby promoting its interaction with DGCR8, leading to the positive regulation of the miR-126 process. The latter has been demonstrated to
hinder metastasis\textsuperscript{[22]}. Nevertheless, METTL3, another m\textsuperscript{6}A writer, exhibits significantly elevated levels, and clinical evidence reveals that increased expression of METTL3 among patients with HCC is associated with poor prognosis. Functionally, its knockdown greatly reduces the proliferation, migration, and colony formation of HCC cells in vitro. Meanwhile, the inhibition of METTL3 significantly thwarts HCC tumorigenicity and lung metastasis in vivo\textsuperscript{[23]}. In addition, WTAP and the activated m\textsuperscript{6}A mechanism it stimulates play oncogenic roles in human HCC. The upregulation of WTAP contributes to the m\textsuperscript{6}A modification of ETS1, leading to its epigenetic silencing through a HuR-mediated approach\textsuperscript{[24]}. Notably, the epigenetic m\textsuperscript{6}A demethylase FTO promotes HCC tumorigenesis by mediating PKM2 demethylation\textsuperscript{[25]}. The progression of HCC is affected by ALKBH5-mediated m\textsuperscript{6}A modification, which regulates the expression of LYPD1. In contrast to normal tissues, HCC cancer tissues exhibit downregulation of ALKBH5 expression, leading to higher levels of m\textsuperscript{6}A modification within LYPD1. Consequently, IGF2BP1 recognizes m\textsuperscript{6}A-modified LYPD1, thereby augmenting its RNA stability and allowing it to accumulate. This promotes the proliferation and migration ability of cancer cells, thus contributing to the development of HCC.

3.2 The m\textsuperscript{5}C and Chronic Liver Disease

The m\textsuperscript{5}C is one of the earliest discovered modifications exists in various RNAs (mRNAs, tRNAs, and rRNAs) and plays important functions in RNA stability and translation regulation for protein synthesis. Moreover, m\textsuperscript{5}C RNA methylation is closely related to human diseases and has been demonstrated to be significantly associated with tumors, metabolic disorders, neurological disorders, viral infections, and individual development. In particular, abnormalities in m\textsuperscript{5}C methylation and transferases of specific genes are closely associated with the development of various diseases, such as abnormal differentiation of neural or cardiac myocytes, reproductive system defects, and the progression of tumors. Notably, mutations or deletions of the m\textsuperscript{5}C methylation enzymes NSUN2 and NSUN3 have been observed to lead to neurological defects, and mutations in the NSUN2 gene have been linked to autosomal recessive intellectual disability\textsuperscript{[26]}. Normal higher eukaryotic cells usually exhibit low expression levels of NSUN2, and its upregulation has been found to be closely associated with tumor development, highlighting its potential as a target for cancer therapy. In HCC cells, upregulated transcript levels of NSUN2 have been observed to enhance proliferation, migration, invasion, angiogenesis, and inhibit apoptosis\textsuperscript{[27]}. There are two potential mechanisms that may contribute to the upregulation of NSUN2 expression, the first being hypomethylation of the NSUN2 promoter region and the second being an increase in the copy number of the NSUN2 gene. Furthermore, Frye et al.\textsuperscript{[24]} identified that NSUN2 protein expression is upregulated in various types of cancer through immunohistochemical analysis.

Anomalous inactivation of oncogenes by DNA methyltransferases (including DNMT1, DNMT2, and DNMT3) is among the mechanisms implicated in HCC development. Studies have exhibited that knockdown of DNMT2 yields abnormalities in the differentiation of retinal, hepatic, and brain tissues in zebrafish, whereas DNMT2 knockdown in mice leads to defects in endochondral ossification, cardiac hypertrophy, and hematopoietic system differentiation, indicating a close correlation between DNMT2-mediated m\textsuperscript{5}C methylation and the cell differentiation and tissue developmental processes\textsuperscript{[29]}. Normal higher eukaryotic cells usually exhibit low expression levels of NSUN2, and its upregulation has been found to be closely associated with tumor development, highlighting its potential as a target for cancer therapy. In HCC cells, upregulated transcript levels of NSUN2 have been observed to enhance proliferation, migration, invasion, angiogenesis, and inhibit apoptosis\textsuperscript{[27]}. There are two potential mechanisms that may contribute to the upregulation of NSUN2 expression, the first being hypomethylation of the NSUN2 promoter region and the second being an increase in the copy number of the NSUN2 gene. Furthermore, Frye et al.\textsuperscript{[24]} identified that NSUN2 protein expression is upregulated in various types of cancer through immunohistochemical analysis.

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functional involvement of m^1A regulation in the modulation of immune cell infiltration in HCC tissues [30]. Inhibition of tumor cell proliferation has been suggested to be a key functional role of m^1A modification in promoting the cell cycle, as exemplified by silencing of ALKBH3.

4 DISCUSSION

Compared to DNA-based techniques for protein expression, mRNAs are able to function without entering the nucleus and do not have the potential to infect the genome, making them an attractive option for harnessing different mRNAs to control a range of diseases [31]. However, while mRNA shows great potential for disease prevention and treatment, the obstacles that prevent its development are still numerous, and the application of mRNA-based therapies for chronic liver diseases remains a distant prospect. Despite this, mRNA therapies remain a promising approach for targeting a broad range of protein-based diseases and are poised to play a pivotal role in the fight against various illnesses. The direct application of mRNA drugs involves expressing functional proteins in the target cells, which is particularly useful in treating rare genetic metabolic conditions by providing proteins that are either not expressed or are not acting in a tissue-specific or regulatory manner. Beyond encoding neurotrophic factors, mRNAs encoding tumor suppressor proteins have also demonstrated significant potential in cancer treatment. Moreover, mRNA technology has recently been applied in the treatment of a range of conditions, such as cancer, cardiovascular disease, and infectious diseases, as well as for genome editing and protein replacement, expanding its use in various biomedical domains.

Vaccines that activate active immune responses have successfully protected millions of individuals from disease. mRNA vaccines, in particular, have even greater potential to prevent both infectious and non-infectious diseases, as they can efficiently express multiprotein antigens and membrane-bound proteins, closely mimicking antigen expression during natural infection. In fact, over 1,000 clinical trials of mRNA-based therapies have been performed to date, and protein-based vectors have proven to be highly biocompatible for delivering mRNA [32]. However, given that proteins are by nature complex molecules, they can be unstable and sensitive to temperature, pH, ion concentration and other formulation properties. Although all types of delivery systems have their corresponding advantages and disadvantages, they all have the potential to be developed for generating effective next-generation mRNA drugs. The author also expects that with the continued efforts of scientists in different fields around the world, these current disadvantages will eventually be overcome and the potential of mRNA medicine will be maximized in the future.

5 CONCLUSION

Chemical modifications of mRNAs such as m^6A, m^1A and m^6C are important components of epigenetics. This review reveals that common modifications of mRNAs play very important role in the development of chronic liver diseases. Further revealing the diversity of post-transcriptional chemical modifications of mRNAs may provide new targets for disease prevention and new drug discovery.

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Conflicts of Interest

The authors declared no conflict of interest.

Author Contribution

Zheng Y and Huang Y contributed equally to this work. Wang J, Wang L, Zhao T and Liang T reviewed the work. All authors approved the final version.

Abbreviation List

eIF3, Eukaryotic initiation factor 3
HBV, Hepatitis B virus
HCC, Hepatocellular carcinoma
m^1A, N^6-methyladenosine
m^6A, N^6-methyladenosine
m^6C, N^6-methylcytosine
mRNA, Messenger RNA
NAFLD, Non-alcoholic fatty liver disease
ORF, Open reading frame
UTR, Untranslated region

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