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Unraveling the Mechanisms of MicroRNA in Suppressing Hepatitis B Virus Progression: A Comprehensive Review for Designing Treatment Strategies

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Abstract

Liver cancer and cirrhosis caused by the Hepatitis B virus (HBV) remain significant global health challenges due to the virus's high prevalence and contagious nature. Hepatitis B virus can be transmitted through various means, leading to mild or severe liver disease. Although an effective prophylactic vaccine is available, it offers limited benefits for those already chronically infected. Current treatments often fail to consistently eliminate the virus and can cause severe adverse effects. In response to these challenges, researchers have begun exploring microRNAs (miRNAs) as novel therapeutic targets. Studying miRNA-virus interactions presents a promising opportunity to identify potential therapeutic targets. By manipulating host miRNAs, researchers aim to enhance antiviral defenses, restore cellular balance, and prevent viral replication. The text concludes by highlighting the potential for personalized medicine in Hepatitis B treatment, guided by individual miRNA profiles. Numerous studies have been conducted to understand how different miRNAs inhibit HBV replication, paving the way for the development of innovative and effective therapeutic strategies.

Keywords: MiR-122, MicroRNA, HBV Proteins, HBV DNA, HBV Life Cycle, Anti-Viral Treatment

1. Context

Hepatitis B virus (HBV) remains a significant global health concern, causing approximately 880,000 deaths annually, a figure comparable to HIV-1 mortality rates (1). The HBV life cycle begins when the virus binds to the hepatocyte surface receptor sodium taurocholate co-transporting polypeptide (NTCP). Prophylactic vaccination works by generating neutralizing antibodies against HBsAg, which prevents receptor engagement. The virus then utilizes cellular pathways, such as endocytosis, to release the nucleocapsid into the cytoplasm and transport it to the nuclear pores. HBV replication involves the formation of nucleocapsids, reverse transcription, and the synthesis of relaxed circular DNA (rcDNA). Managing chronic Hepatitis B (CHB) remains challenging due to the limited efficacy of existing vaccines and treatments, with some therapies causing intolerable side effects (2).

In response, researchers have been exploring the potential of microRNAs (miRNAs or miRs) as a novel therapeutic approach. miRNAs are small non-coding RNA molecules essential for regulating gene expression, and their dysregulation has been linked to various aspects of HBV infection (3). Scientists are investigating two primary miRNA-based strategies: (1) directly targeting viral miRNAs to impede replication and (2) modifying host miRNAs to enhance antiviral responses. The abnormal expression of specific miRNAs in the liver tissues of CHB patients indicates their involvement in disease progression. This evolving field aims to identify therapeutic targets and innovative treatment

approaches by unraveling the complex interactions between miRNAs and HBV (4).

This study aimed to explore the intricate roles of miRNAs in modulating HBV infection and to identify potential therapeutic targets. By understanding how miRNAs regulate viral replication, immune responses, and liver pathology, researchers can develop more precise and effective treatment strategies for managing HBV infection (5). The role of miRNAs in the pathophysiology and treatment of Hepatitis B is rapidly evolving, with ongoing studies revealing that miRNAs are closely linked to disease development and may serve as potential treatment targets. miRNA-based therapies have the potential to cause sustained viral suppression, reduce viral load, and prevent disease progression. Certain miRNAs influence immune responses by regulating cytokine production, antigen presentation, and T cell activation, thereby improving HBV clearance and reducing liver inflammation. Targeting specific miRNAs may also prevent or reverse fibrosis and preserve liver function by controlling aberrant gene expression. Personalized miRNA-based therapies could optimize treatment outcomes by tailoring interventions to patient-specific miRNA expression patterns, thereby enhancing efficacy. Combining miRNA-based approaches with existing antiviral drugs or immunomodulators could have synergistic effects, boosting antiviral activity and reducing drug resistance (6, 7).

2. Objective

This article reviews studies systematically to elucidate the mechanisms by which different miRNAs are used to prevent HBV spread and replication, thereby opening up possibilities for developing new and effective treatment approaches. However, challenges such as delivery systems, off-target effects, and safety concerns remain associated with this treatment, and ongoing research aims to address these hurdles and further explore the potential of miRNA-based HBV therapies.

3. Methods

3.1. Search Strategy

Researchers collected a total of 956 articles on HBV and miRNA from various databases, including ScienceDirect, PubMed, Scopus, Web of Science, and Google Scholar. To identify additional relevant studies, they manually reviewed the reference lists of pertinent articles using search terms such as HBV, HBV proteins, HBV DNA, HBV infection, HBsAg expression, HBV replication, HBV gene expression, HBV genome, HBV transcription, inhibiting HBV, promoting HBV, HBV life cycle, antiviral treatment, microRNA, and miRNA mechanisms. After a thorough review of the collected articles, they focused on 113 studies that discussed liver alterations and the therapeutic effects of miRNAs. Out of these, 49 studies, conducted between January 2015 and April 2024, were selected for an in-depth exploration of miRNA-virus interactions.

3.2. Inclusion and Exclusion Criteria

We included original studies and review articles published in English in our study. Additionally, we excluded editorials, letters, conference abstracts, abstracts without full text, duplicated publications, and studies that were irrelevant or did not address our research question.

3.3. microRNAs' Mechanisms Suppressing Hepatitis B Virus Infection

Both human and viral miRNAs play crucial roles in reducing HBV replication through diverse mechanisms. Human miRNAs directly bind to HBV DNA, modify signaling pathways, and inhibit HBsAg secretion, thereby contributing to the suppression of HBV infection. Additionally, research has shown that miRNAs are involved in various aspects of HBV biology, including DNA replication, gene expression, receptor interactions, cell cycle regulation, and immune responses (8, 9).

3.4. miR-302c-3p and MiR-3188

Among the miRNAs that suppress HBV replication, miR-3188 has recently been shown to exhibit remarkable antiviral activity. Overexpression of miR-3188 suppresses HBV transcription by targeting Bcl-2, a process linked to the regulation of cccDNA transcription, suggesting new potential targets for HBV treatment. Similarly, further investigations have demonstrated a significant reduction in cccDNA levels in cells transfected with miR-302c-3p. Notably, miR-302c-3p interacts with the ε-loop sequence, offering an alternative pathway for addressing HBV infection (10).

Additionally, miR-302c-3p has been found to regulate HBV transcription by interacting with critical host factors, including the bone morphogenetic protein (BMP) signaling pathway mediated by bone morphogenetic protein receptor type 2 (BMPR2) and hepatocyte nuclear factor 4 alpha (HNF4A). The downregulation of BMPR2 or HNF4A resulted in reduced HBV replication and HBsAg production. The study

highlighted the crucial role of HNF4A in HBV transcription, indicating that miR-302c-3p's inhibitory effect on viral mRNAs involves the suppression of HNF4A expression (11).

3.5. miR-122

One key miRNA, miR-122, plays a complex role in HBV infection by regulating p53 activity through cyclin G1, which impacts HBV transcription. Notably, serum miR-122 levels increase in patients with chronic Hepatitis B (CHB), showing a positive correlation with albumin levels at different stages of HBV infection. This correlation highlights the multifaceted functions of miR-122 in Hepatitis, particularly in maintaining liver health and providing antioxidative properties.

In addition, miR-122's inhibitory effect on HBV replication extends to patients with liver cancer, where lower miR-122 expression is associated with compromised liver function, as indicated by elevated alkaline phosphatase (AKP) levels. Further research has demonstrated a negative association between miR-122 levels and key indicators of hepatocyte damage, including HBsAg, alanine aminotransferase (ALT), and HBV DNA levels in CHB patients. Lower miR-122 expression is linked to a poorer prognosis and a higher degree of hepatocyte damage, underscoring its potential as both a therapeutic target and a biomarker for liver disease progression (12, 13).

3.6. miR-125-5p

The hsa-miR-125a-5p exhibits anti-HBV activity and is associated with HBV exposure. In HepG2.2.15 cells, which produce HBV, hsa-miR-125a-5p levels are higher than those in the parent HepG2 cell line and are influenced by the HBV X protein. Elevated hsa-miR-125a-5p levels correlate with higher HBV DNA levels, suggesting that this miRNA is induced by HBV exposure and may play a role in limiting HBV replication. In PLC/PRF/5 cell cultures, increased hsa-miR-125a-5p expression significantly reduces HBsAg levels.

Additionally, miR-122 is known to inhibit HBV replication through various mechanisms. miR-125b-5p and miR-3613-3p also contribute to the inhibition of HBV protein expression by interfering with the regulation of signal transducer and activator of transcription 3 (STAT3), which impacts liver injury and fibrosis. However, serum analysis in patients with acute viral Hepatitis suggests that these miRNAs have limitations as biomarkers. Ongoing investigations into plasma miR-125b-5p aim to assess its potential in suppressing viremia in patients with chronic Hepatitis B (14).

3.7. miR-141

miR-141-3p, identified as a suppressor in various cancer types, is dysregulated in colorectal, bladder, ovarian, and liver cancers. Additionally, some miRNAs can negatively impact HBV replication. For instance, miR-141 targets peroxisome proliferator-activated receptor-α (PPARα) in HepG2 cells, significantly suppressing both HBV replication and gene expression. Various miRNAs that target positive regulators of HBV have demonstrated antiviral properties, particularly those that act on HBV transcripts (15).

One such target of miR-141 is PPARα, which is known for its role in binding and transactivating HBV promoters. In HepG2 cells transfected with HBV, the introduction of synthetic miR-141 resulted in reduced HBV transcription by inhibiting PPARα expression. A luciferase assay showed that miR-141 significantly diminished the luciferase activity of a reporter plasmid containing binding sites 2, 3, and 4, but had no effect on the plasmid containing only binding site 1. These findings suggest that miR-141 targets either binding site 2, 3, or 4 of the PPARA 3′-UTR. To further investigate this, different deletants of the PPARA 3′-UTR, each containing only one of the binding sites 2, 3, or 4, were subsequently cloned into the pGL3M vector (16).

3.8. miR-199a-3p and miR-210

miR-199a-3p and miR-210 have been identified as effective contributors to the suppression of HBsAg expression and HBV replication, a finding supported by previous research. These miRNAs exhibit inhibitory effects on HBV by directly targeting the HBsAg-encoded and pre-S1 regions of the HBV genome, as revealed by bioinformatics analyses. One particular study clarified the inhibitory impact of miR-199a-3p and miR-210 on HBsAg expression in HepG2 cells. The results demonstrated that miR-199a-3p and miR-210 effectively suppressed HBsAg expression and HBV replication by targeting the HBsAg-encoded and pre-S1 regions of the HBV genome. This underscores the critical role of miRNAs in the regulation of gene expression (17).

3.9. miR-15a and miR-16-1c

The study investigates the antiviral efficacy of miR-15a and miR-16-1 in the treatment of HBV infection. In vitro experiments using HepG2 cells and a green fluorescent protein (GFP) reporter DNA assay revealed a significant inverse correlation between miR-15a and miR-16-1 levels and HBV replication. Additionally, the miR-17-92 cluster and miR-1236 also target HBV mRNAs,

further inhibiting replication. The miR-15a/miR-16-1 cluster specifically enhances the coding region of the HBV polymerase, which overlaps with HBx, ultimately leading to the inhibition of DNA replication.

On the other hand, certain epi-miRNAs, such as miR-15b and miR-18, boost HBV Enhancer I activity, thereby increasing replication through the modulation of hepatocyte nuclear factor-1 alpha (HNF1A) and estrogen receptor 1 (ESR1) (18).

3.10. miR-21

A noteworthy discovery involves a feedback loop comprising miR-21, activation protein-1 (AP-1), and programmed cell death protein (PDCD) in activated hepatic stellate cells (HSCs). This mechanism sustains elevated miR-21 expression, which concurrently enhances the transforming growth factor beta (TGF-β) signaling pathway (19). Manipulating miR-21 levels, particularly by reducing them with a specialized virus, has been shown to not only slow the progression of liver fibrosis but also mitigate hepatocyte damage, offering protection against the fatal consequences of *Schistosoma japonicum* infection in mice.

This study highlights the collaborative role of TGF-β and interleukin 13 (IL-13) in the induction of miR-21 in activated HSCs. miR-21 plays a pivotal role in targeting the death receptor and Fas ligand, thereby linking ethanol-induced liver damage and HSC activation via the IL-6/Stat3 pathway (20, 21).

3.11. miR-221 and miR-222

miRNA-222 and miR-221, recognized as onco-miRs, play a crucial role in angiogenesis and have a significant impact on liver cancer (22). In a notable study, elevated expression of miR-221/222 was observed in patients with non-alcoholic steatoHepatitis (NASH) and HCV infection, correlating with the progression of liver fibrosis. This increase was associated with elevated mRNA expression of α-smooth muscle actin (α-SMA) and collagen 1A1, indicating their involvement in fibrotic processes (23).

Phosphatase and tensin homolog (PTEN), a target of miR-21, functions as a phosphatase that dephosphorylates phosphatidylinositol (3,4,5)-trisphosphate (PIP3), converting it into phosphatidylinositol (4,5)-bisphosphate (PIP2). This dephosphorylation process results in the inhibition of the AKT signaling pathway, which can lead to cell death, thereby providing a potential target for reducing HBV replication and progression (24).

3.12. microRNAs' Mechanisms Promoting Hepatitis B Virus Infection

miRNAs play crucial roles as orchestrators in various stages of the HBV life cycle, including viral entry, replication, and evasion of the host immune response. These specialized miRNAs exert their influence by directly targeting viral transcripts or by modulating key host factors essential for HBV propagation. The recognition of miRNAs' role in promoting HBV infection has spurred the development of innovative therapeutic approaches. One promising strategy involves designing treatments to inhibit these miRNAs, offering a potential method for disrupting the complex viral life cycle (Table 1).

3.13. miR-1

Overexpression of miR-1 boosts HBV replication by enhancing core promoter activity, an effect attributed to the presence of farnesoid X receptor alpha (FXRα) in the nucleus. Elevated levels of miR-1 are correlated with increased HBV transcription, antigen expression, and progeny secretion. In contrast, miR-210 has an opposing effect on HBV replication. The impact of miR-1 on HBV transcription is dependent on FXRα, which is regulated by the core promoter.

miR-1 targets and inhibits histone deacetylase 4 (HDAC4), which is paradoxically known as an inhibitor of HBV replication. When miR-1 was introduced into HepG2.2.15 cells, HDAC4 expression decreased, correlating with increased HBV transcription. Co-transfection of HDAC4 with miR-1 led to reduced HBV mRNA levels, indicating that HDAC4 plays a critical role in mediating the effects of miR-1. By adjusting HDAC4 expression, miR-1 enhances the transcriptional activity of the HBV core promoter, leading to elevated FXRα expression and a noticeable increase in HBV DNA and protein levels (25, 26).

3.14. miR-99

The miR-99 family, including miR-99a, miR-99b, and miR-100, actively enhances HBV replication through the AKT-mammalian target of rapamycin (Akt-mTOR) pathway by targeting autophagy (27). Akt is a serine/threonine kinase that is activated in response to various extracellular signals, such as growth factors, hormones, and cytokines. Upon activation, Akt phosphorylates and activates downstream targets that promote cell growth and survival.

Activation of the Akt-mTOR pathway occurs when Akt phosphorylates mTOR, leading to the activation of the

Table 1 . MicroRNAs' Mechanisms Inhibiting and Promoting Hepatitis B Virus Transcription

Variables	Values
miR-302c-3p and miR-3188	Decreased viral cccDNA copy numbers, diminished pgRNA, interact with the sequence within the ε-loop, inhibited the binding of the HBV polymerase to pregenomic RNA
miR-122	Inhibited the binding of the HBV polymerase to pregenomic RNA, enhanced p53's anti-HBV activity by cyclin G1
miR-125-5p	Inhibited HBV protein expression and interfered with signal transducer and activator of transcription 3 (STAT3) regulation
miR-141	Bind PPARα
miR-199a-3p/ miR-210	Bind pre-S1 region of the HBV genome
miR-15a/miR-16-1c	Targeted HNF1A and estrogen alpha (ESR1)
miR-21	Targeted the death receptor and Fas ligand, linking ethanol-induced liver damage and HSC activation via IL-6/Stat3
miR-221/miR222	Targeted protein phosphatase 2 A subunit B
miR-1	Inhibited the cellular histone deacetylase member HDAC4
miR-18a	Repressed estrogen receptor alpha (ER-α) translation
miR-99a/99b/100	Enhanced HBV replication through the AKT- mammalian target of rapamycin (Akt-mTOR) pathway
miR-501	Targeted HBXIP
miR-29	Inhibited SMARCE1 expression
miRs-372/miR-373	3'-UTR of nuclear factor I/B (NFIB)
miR-15b	Directed down regulatory of HNF1α-mRNA

Abbreviations: HBV, Hepatitis B virus; PPARα, peroxisome proliferator-activated receptor-α; HSC, hepatic stellate cell; HBXIP, Hepatitis B x-interacting protein.

mTORC1 complex. Once activated, mTORC1 phosphorylates a variety of downstream targets, including ribosomal protein S6 kinase (S6K) and eukaryotic initiation factor 4E-binding protein 1 (4E-BP1), which in turn promote protein synthesis and cell growth. Additionally, mTORC1 regulates autophagy by inhibiting the ULK1 complex and promoting the synthesis of autophagy-related proteins. Dysregulation of the Akt-mTOR pathway has been implicated in HBV infection, as activation of this pathway can promote viral replication by enhancing protein synthesis and virion production (28).

3.15. miR-29

In the HepG2.2.15 HCC cell line infected with HBV, an increased expression of miR-29 was observed. This irregularly expressed miR-29a partially impacted HBV replication and expression by specifically inhibiting SMARCE1 expression. The role of SMARCE1 in HBV replication and expression had been largely unexplored. However, several studies have revealed that overexpression of SMARCE1 reduces HBV replication and expression, whereas suppressing SMARCE1 enhances HBV replication and expression. SMARCE1 was found to suppress HBV replication by binding to the mutant core promoter of HBV in HepG2 cells, suggesting that SMARCE1 could inhibit HBV replication.

However, the functional mechanism of SMARCE1 in HBV replication might differ from observations in subsequent studies. Molecular assessments confirmed that SMARCE1 is a target of miR-29a and is regulated by miR-29a at the protein level. Reintroducing SMARCE1 expression via pcDNA-SMARCE1 countered the enhancing effect of miR-29a on HBV replication and expression. These findings imply that miR-29a enhances HBV replication and expression by specifically inhibiting SMARCE1 expression, providing a theoretical basis for the potential clinical application of miRNAs in HBV infection treatment (29, 30).

3.16. miR-501

Certain miRNAs, such as miR-501, promote HBV replication by targeting negative cellular regulators. Notably, Hepatitis B x-interacting protein (HBXIP) is a cellular protein known to interact with the HBV X protein (HBx), a key viral protein involved in HBV replication. By targeting the HBXIP gene, miR-501 can downregulate HBXIP expression, leading to increased HBV replication. In HepG2.2.15 cells, a negative correlation was observed between miR-501 and HBXIP expression. Suppressing miR-501 hinders HBV DNA replication, and downregulating HBXIP mitigates this inhibitory effect, highlighting miR-501's role in enhancing HBV replication by targeting HBXIP (31, 32).

3.17. miR-372 and miR-373

miR-372 and miR-373 are closely related microRNAs that play roles in cell proliferation, differentiation, and

tumorigenesis. One of their identified targets is nuclear factor I/B (NFIB), a transcription factor involved in regulating gene expression. The interaction between miR-372/373 and NFIB occurs through the binding of these microRNAs to the 3' untranslated region (UTR) of NFIB mRNA. This binding leads to the inhibition of NFIB expression at the post-transcriptional level, as microRNAs can degrade mRNA or inhibit its translation into protein.

A negative correlation exists between miR-372/373 and NFIB, where downregulation of NFIB, a key transcription factor, is linked to increased HBV gene expression. This is due to the downregulation of HBV enhancer I and core promoter activity, leading to enhanced HBV replication and expression (33).

3.18. miR-15b

miR-15b can bind to the 3' untranslated region (UTR) of hepatocyte nuclear factor 1α (HNF1α) mRNA, leading to the downregulation of HNF1α expression. HNF1α is known to regulate the transcription of HBV genes, including the viral surface antigen (HBsAg) and core protein (HBcAg). Additionally, miR-15b downregulates HNF1α, which in turn triggers the transactivation of HBV Enhancer I. HNF1α plays a crucial role in maintaining liver function and homeostasis, and its dysregulation by miR-15b may lead to hepatic dysfunction, thereby creating an environment that supports HBV replication.

This intricate interplay highlights the mechanisms by which miRNAs, such as miR-15b, regulate HBV replication. By targeting HNF1α, miR-15b may indirectly influence the expression of host factors involved in viral entry, replication, or protein synthesis, ultimately promoting HBV replication (3).

3.19. miR-18a

The estrogen pathway, a key regulator of HBV replication, is influenced by miRNAs, adding a layer of complexity to the control of viral transcription. miR-18a plays a significant role in this process by repressing the translation of estrogen receptor alpha (ER-α), which sets off a cascade that ultimately promotes HBV transcription. Normally, the estrogen pathway acts as an adversary to HBV by elevating ER-α expression, which then interacts with hepatocyte nuclear factor 4 alpha (HNF-4α) in a molecular interplay. This interaction hinders HNF-4α from binding to HBV enhancer I, thereby applying brakes to HBV transcription.

These complex molecular interactions underscore the multifaceted nature of miRNA-mediated regulation of HBV replication. Changes in estrogen levels or activity can significantly alter the cellular environment, potentially affecting the permissiveness of liver cells to HBV infection (34).

3.20. Challenges in Nucleic Acid-based Therapeutics

3.20.1. Off-target Effects

RNA interference (RNAi) is an advanced technique used to silence specific genes by introducing small RNA molecules, such as short interfering RNAs (siRNAs) or small hairpin RNAs (shRNAs), that target and degrade complementary mRNA sequences. However, RNAi molecules can also interact with unintended mRNA targets, leading to off-target effects. To address this issue, researchers have focused on designing RNAi molecules with minimal off-target effects. Short double-stranded RNAs (dsRNAs) of 15-30 base pairs are commonly used because longer dsRNAs have an increased likelihood of off-target interactions and nonspecific cytotoxicity (35).

Naked DNA/RNA molecules are rapidly degraded by nucleases and have low efficiency of cellular uptake when administered intravenously. To overcome these challenges, nanoparticles are employed as carriers to protect and deliver nucleic acids to target cells and tissues. Researchers have selected safe and stable transport carriers that minimize off-target effects and enhance delivery efficiency (36).

Phosphorothioate-modified oligonucleotides (PS-ONs) are used in antisense therapy, where complementary oligonucleotides are designed to hybridize to specific target mRNA. This hybridization inhibits mRNA maturation, triggers RNase H-mediated degradation of the mRNA, and blocks translation. During the sulfurization process, stereogenic α-phosphorus atoms are introduced, resulting in diastereomers. Phosphorothioate bonds can negatively affect antisense efficiency, but careful incorporation minimizes the impact of these diastereomers. To optimize this process, researchers have carefully designed and synthesized S-oligos, and computational modeling is used to predict the most stable diastereomers. Purification techniques, such as high-performance liquid chromatography (HPLC), are employed to separate and isolate the desired diastereomer (37).

3.20.2. Delivery and Stability

Efficient delivery of miRNAs into target cells is crucial for achieving therapeutic efficacy. To enhance cellular uptake, researchers have explored various delivery

vectors, including both viral and non-viral methods. Among non-viral approaches, liposome-based and nanoparticle (polymer)-based strategies have been particularly considered. These approaches offer the advantage of protecting miRNAs from rapid clearance and degradation in the bloodstream. By formulating miRNAs with protective carriers, such as nanoparticles, researchers have significantly improved the stability and pharmacokinetics of miRNA-based therapies (38).

3.20.3. Clinically Viable Therapies

To advance miRNA-based therapies from preclinical studies to clinical trials, it is essential to conduct rigorous safety and efficacy evaluations, address regulatory requirements, and optimize delivery strategies (39).

3.21. Developed Available Treatments

3.21.1. Helper-Dependent Adenoviruses

Helper-dependent adenoviruses (HD AdVs) have been employed to efficiently deliver cassettes encoding primary miRNAs into liver tissue. For instance, researchers have investigated the short-term blockade of HBV replication in vivo by expressing anti-HBV pri-miRNA mimics, such as pri-miRNA-122/5, pri-miRNA-31/5, or pri-miRNA-31/5–8-9, using HD AdVs (40).

3.21.2. Gene Editing and Homology-Directed DNA Recombination

To achieve a durable antiviral effect, scientists have proposed a strategy that combines gene editing with homology-directed repair (HDR). This approach involves introducing HBV-silencing artificial primary miRNAs into specific HBV DNA targets. The goal of this method is to sustain the suppression of HBV (41).

3.22. Future Research Directions

3.22.1. MiRNA-based Therapeutics

MiRNAs can target viral replication, protein expression, or immune evasion mechanisms, making them promising tools for antiviral therapy. However, to advance miRNA-based therapies, it is essential to thoroughly explore their safety and efficacy in preclinical models and clinical studies. This includes optimizing delivery systems to ensure efficient and targeted delivery of miRNAs to liver cells, which is necessary (42).

3.22.2. Combination Therapies

Evaluating the synergistic effects of combining miRNA-based therapies with existing antiviral drugs, such as nucleos(t)ide analogs, is crucial for enhancing treatment outcomes and preventing drug resistance. By combining these approaches, researchers can investigate whether miRNAs can sensitize HBV-infected cells to immune-mediated clearance, potentially improving the overall immune response against the virus (43).

3.22.3. Functional Cure Strategies

The ultimate goal is to achieve a functional cure for HBV, where sustained virological suppression leads to long-term remission without the need for lifelong therapy. This approach aims to achieve sustained suppression of viral replication, antigen production, and the persistence of covalently closed circular DNA (cccDNA) (44, 45).

3.22.4. Hepatitis B Virus Host Interactions

Studying HBV-host interactions that influence viral replication, immune evasion, and liver disease progression offers a valuable opportunity to identify miRNAs that regulate host factors, such as hepatocyte receptors and cytokines, which are critical for HBV infection and pathogenesis (33).

3.22.5. Epigenetic Regulation

Investigating epigenetic modifications mediated by miRNAs can affect HBV gene expression, chromatin structure, and cccDNA stability and contribute to epigenetic control of HBV persistence (46, 47).

3.22.6. Personalized Approaches

Developing miRNA-based therapies customized to individual patient profiles, including factors such as viral genotype, host genetics, and immune status, may influence treatment responses, and miRNAs can be considered potential biomarkers for disease progression and treatment outcomes (48, 49).

4. Conclusions

Considering the complex interaction between miRNAs and HBV infection, the development of targeted therapeutic strategies can be advanced by selectively modulating the expression of specific miRNAs. For instance, increasing the expression of miRNAs such as

miR-302c-3p, miR-3188, miR-122, miR-125-5p, miR-141, miR-199a-3p, miR-210, miR-15a, miR-16-1, miR-21, miR-221, and miR-222, which have demonstrated inhibitory effects on HBV, could enhance antiviral responses. Concurrently, reducing the expression of miRNAs like miR-1, miR-501, miR-99a, miR-99b, miR-100, miR-29, miR-372, miR-373, miR-15b, and miR-18a, which are known to promote HBV infection, may further suppress viral replication and disease progression.

Future studies focused on unraveling the complexities of miRNA-HBV interactions will be crucial in identifying more effective treatments against HBV. These efforts could lead to the development of personalized and more precise therapeutic strategies, ultimately addressing this significant public health challenge.

Footnotes

Authors' Contribution: H. S., Q. Z., Y. Z., and A. H. designed the study and interpreted the data. G. F., X. L., D. W., and H. L. performed statistical analyses, collected and interpreted the data, and drafted the manuscript. K. Z., X. Z., F. X., H. S., and Q. Z. critically revised the manuscript and provided continuous guidance throughout the study. All authors have read and approved the final manuscript.

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