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ORIGINAL RESEARCH

Antiviral Therapy-Induced Changes in Long Non-Coding RNA Expression Profiles in Umbilical Cord Blood and Placental Tissues of Hepatitis B Virus-Infected Pregnant Women

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Background: Hepatitis B virus (HBV) is a major global health concern, with maternal-fetal transmission being the primary route of transmission, which can lead to chronic HBV infection in newborns. Long non-coding RNAs (lncRNAs) play crucial roles in gene regulation and immune responses, but their involvement in HBV transmission during pregnancy remains unclear. This study aimed to assess the impact of tenofovir disoproxil fumarate (TDF)-based antiviral therapy on lncRNA expression profiles and immune signaling pathways in umbilical cord blood and placental tissues and to identify potential therapeutic targets for preventing intrauterine HBV infection.

Materials and Methods: Umbilical cord serum and placental tissues were collected from six HBV carriers. Three carriers received TDF-based antiviral therapy, and the remaining carriers who did not receive antiviral therapy served as controls. LncRNA microarray analysis and bioinformatics were used to evaluate the effects of antiviral therapy on lncRNA expression profiles and signaling pathways.

Results: Antiviral therapy exerted minimal effects on lncRNA expression profiles in umbilical cord blood. In placental tissues, significant alterations in lncRNA expression profiles were observed, including 249 upregulated and 381 downregulated lncRNAs. Antiviral therapy activated innate immune pathways, such as intracellular DNA sensing, chemokine signaling, type I interferon, Jak-Stat, and interferon-γ-mediated adaptive immunity. Through intersection analysis, CPED1 was found differentially expressed in both cord blood and placental tissues. KEGG pathway analysis suggested that low CPED1 expression may inhibit virus transmission via the JAK-STAT pathway.

Conclusion: This study demonstrated that TDF-based antiviral therapy altered lncRNA expression and activated immune signaling pathways in placental tissues, offering insights into the molecular mechanisms of maternal-fetal HBV transmission.

Keywords: hepatitis B virus, LncRNA, immune signaling, maternal-fetal tissues

Background

Hepatitis B virus (HBV) is a hepatotropic DNA virus belonging to the Hepadnaviridae family.[1] The most common HBV transmission routes include mother-to-child transmission during birth and early childhood, as well as exposure to infected blood or other bodily fluids through sexual contact with an infected partner, unsafe injections, or sharp instrument injuries.[2–4] HBV primarily infects hepatocytes, leading to either acute or chronic infection; chronic HBV infection significantly increases the risk of liver fibrosis, cirrhosis, and hepatocellular carcinoma (HCC).[5,6] According to the World Health Organization (WHO), an estimated 254 million people were living with chronic HBV infection in 2022, with

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1.2 million new infections that year. Additionally, HBV caused approximately 1.1 million deaths in 2022, mainly due to cirrhosis and HCC (primary liver cancer).[7,8]

In highly endemic regions, one of the most common transmission routes is mother-to-child transmission (perinatal transmission) during childbirth.[2–4] Pregnant women with a high viral load are particularly vulnerable, as a high viral load increases the risk of HBV transmission. Particularly, maternal-fetal vertical transmission stands as the primary route of HBV transmission, underscoring the potential transmission risk from mother to fetus. To reduce the risk of vertical transmission, many pregnant women choose antiviral therapy during pregnancy to lower maternal viral loads.[9–12] In this context, there is an urgent need to comprehend the mechanisms underlying antiviral therapy for intrauterine infection prevention.

Long non-coding RNAs (LncRNAs) refer to RNAs with a length of more than 200 nt, which are engaged in numerous biological processes across every branch of life.[13–16] In antiviral research, lncRNAs assume pivotal roles in viral infections and antiviral immune responses by regulating immune-related genes, interferon, and inflammatory factors. Moreover, certain lncRNAs have been demonstrated to interact with viral genomes to inhibit viral replication and transmission,[17–22] representing potential targets for innovative antiviral therapeutic strategies.

The present study aimed to assess the efficacy of antiviral therapy in late-pregnancy women with a high hepatitis B viral load, especially in reducing intrauterine infection. This study emphasized the differential expression profiles of lncRNAs in umbilical cord blood and placenta tissues after antiviral therapy, which may help us understand the role of antiviral therapy in maternal and fetal health and offer novel insights and strategies for preventing intrauterine HBV infection. Additionally, exploring changes in lncRNA expression profiles may contribute to identifying new biomarkers, as well as improving the identification and management of intrauterine infection risks in pregnant women. This study holds significant implications for safeguarding maternal and child health and curtailing the transmission of hepatitis B.

Methods and Materials

Collection of Clinical Serum Samples

Umbilical cord serum samples and placental tissues were collected from 6 pregnant women with chronic HBV infection. Clinical assessments confirmed that these women had high viral loads (HBV DNA >200,000 IU/mL) and normal liver function. Normal liver function was defined as alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels within the reference range (ALT <40 U/L, AST <40 U/L), with no clinical or imaging evidence of liver fibrosis or cirrhosis. Among these pregnant women, 3 received tenofovir disoproxil fumarate (TDF) antiviral therapy starting from the 24^{th} to 28^{th} week of gestation, and the remaining 3 women did not undergo antiviral intervention and served as controls.

The blood samples were centrifuged at 300 g for 5 minutes, with the supernatant collected and aliquoted into 2 mL tubes (0.5 mL for each tube). The samples were labeled with relevant information (including sample number, date, and time) and stored at −80°C to maintain lncRNA integrity. The placental tissues were preserved in liquid nitrogen after dissection.

All experiments involving humans were conducted following the ethical standards of the national research committee and the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Approval for this study was granted by the Ethics Committee of the People's Hospital of Guangxi Zhuang Autonomous Region (Approval number: KY-GZR-2019-061). All specimens were collected with the written consent of patients and ethical approval.

Arraystar LncRNA 5.0 Microarray

RNA was extracted from the samples using TRIzol reagent (Invitrogen, 15596018), and RNA quality was assessed using Agilent ND-1000 (Thermo Fisher Scientific, Rockford, IL, USA) to ensure non-degradation and determine concentration. The Arraystar Flash RNA labeling kit (AS-LE-007, Arraystar, Rockville, MD, USA) was employed for RNA labeling, followed by hybridization experiments using Agilent SureHyb. After cleaning, the Arraystar Human LncRNA Microarray (V5) was scanned with the Agilent microarray scanner (Agilent Technologies Inc). Agilent feature extraction software (v11.0.0.1) was used to collect microarray probe signal values. The Agilent GeneSpring GX v12.1 software was

employed for the standardization of the microarray and the selection of differentially expressed lncRNAs. The Arraystar Human LncRNA Microarray (V5) was specifically designed to study human lncRNAs and protein-coding transcripts. This microarray enables the detection of 39,317 lncRNAs (including 8393 gold-standard lncRNAs and 30,924 highly reliable lncRNAs) and 21,174 protein-coding transcripts. Next, differentially expressed lncRNAs were subjected to pathway annotation in the Kyoto Encyclopedia of Genes and Genomes (KEGG) database, followed by KEGG pathway enrichment analysis and gene set enrichment analysis (GSEA).

Results

Anti-HBV Therapy Slightly Changes lncRNA Expression Profiles in Umbilical Cord Serum

Previous research has highlighted the regulatory functions of lncRNAs in diverse physiological and pathological processes.[23,24] Notably, certain lncRNAs in serum have been recognized as potential biomarkers for disease diagnosis, prognosis, and therapeutic monitoring as they can reflect specific physiological or disease states.[25–27] Additionally, lncRNAs in umbilical cord blood influence the immune system and fetal development.[28–30] However, the impact of anti-HBV therapy on lncRNA expression profiles in umbilical cord serum has not been explored before.

This study analyzed for the first time the effects of TDF-based antiviral therapy on the lncRNA expression profile in the umbilical cord blood of pregnant women with high HBV viral loads (HBV DNA >200,000 IU/mL) utilizing lncRNA microarray technology. Differential gene analysis revealed that only 29 lncRNAs were upregulated, while 30 lncRNAs were downregulated (Figure 1a, Table S1). The top 10 significantly upregulated and downregulated lncRNAs are visually

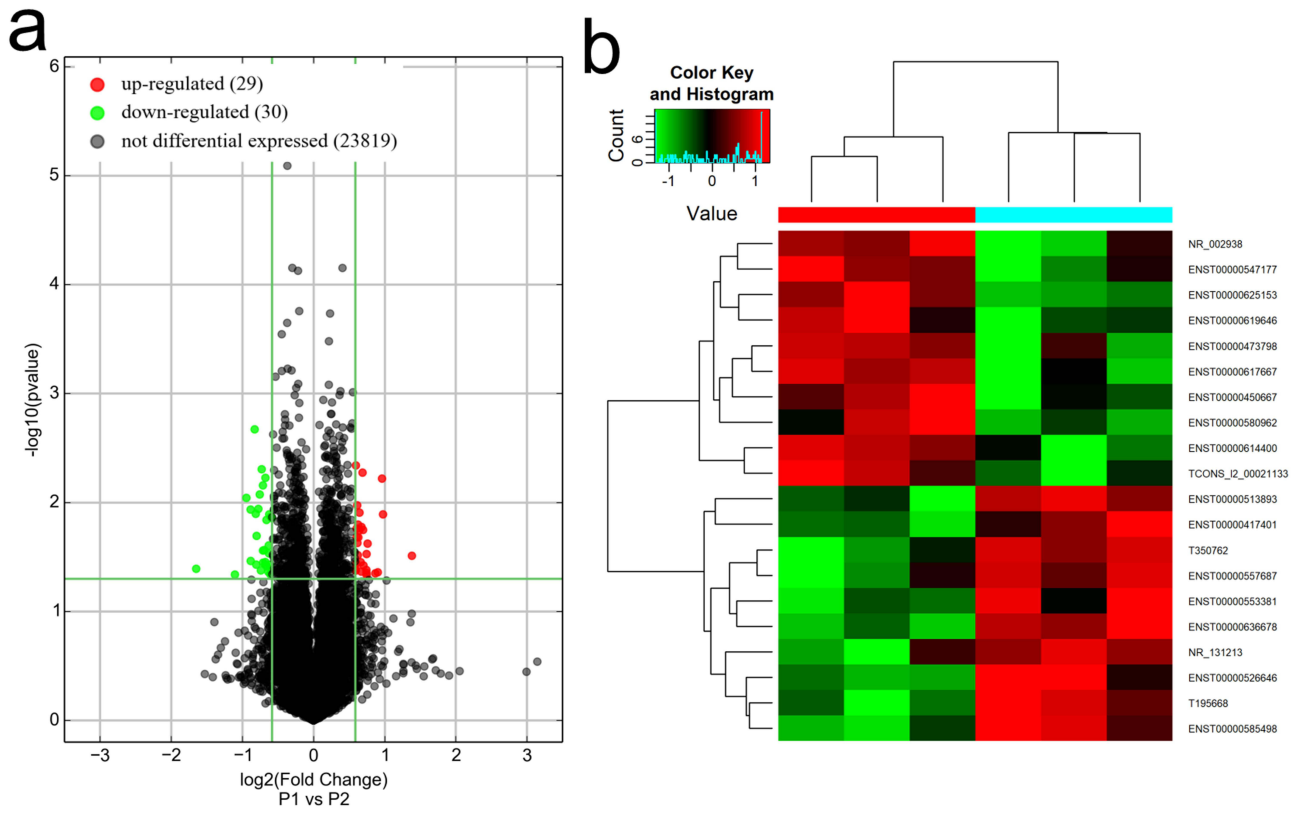

Figure 1 LncRNA microarray analysis of the effect of antiviral therapy on lncRNA expression profiles in umbilical cord blood after delivery. (**a**) In this study, umbilical cord blood was collected from 6 pregnant women with high HBV viral load but no intrauterine infection, 3 of whom did not receive antiviral therapy (p1) and 3 of whom received antiviral therapy (p2). LncRNA expression in serum P1 and P2 was detected by the microarray. Volcano map showed the effect of antiviral therapy on lncRNA expression profiles in umbilical cord blood. (**b**) Heat map showed the top 10 significantly upregulated and downregulated lncRNAs in umbilical cord blood after antiviral therapy.

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represented in a heat map (Figure 1b). These findings suggested that the impact of anti-HBV drugs on lncRNA expression in umbilical cord blood was relatively slight. In summary, our preliminary analysis indicated the mild effect of anti-HBV therapy on lncRNA expression profiles in umbilical cord blood, laying the groundwork for further exploration of these regulatory dynamics.

Anti-HBV Therapy Activates Innate Antiviral Immune Signaling Pathway in Umbilical Cord Serum

Anti-HBV drugs (such as lamivudine and Entecavir) impede the DNA synthesis of viruses by inhibiting HBV reverse transcriptase.[31] Furthermore, anti-HBV therapy may also be achieved by regulating cell cycle-related signaling pathways. The anti-HBV therapy typically involves activating the immune system to eliminate HBV from infected liver cells effectively. Notably, HBV infection is associated with the Wnt/β-catenin signaling pathway, and certain anti-HBV drugs influence viral replication and tumor development by modulating this pathway.[32,33] Additionally, some anti-HBV drugs can activate the retinoic acid-inducible gene I (RIG-I) signaling pathway to enhance the recognition and clearance of HBV by the immune system.[34,35]

In this study, GSEA of the identified differential genes revealed the activation of multiple innate immune signaling pathways by anti-HBV therapy, including the intracellular DNA sensing pathway, chemokine signaling pathway, type I interferon signaling pathway, and JAK-STAT signaling pathway (Figure 2a–d). These findings strongly suggested that anti-HBV therapy may activate innate antiviral immune signaling pathways to exert antiviral effects. However, further validation is warranted to gain a more comprehensive understanding of the impact of anti-HBV therapy on signaling pathways in umbilical cord blood. In summary, our results revealed a robust activation of innate antiviral immune signaling pathways triggered by anti-HBV therapy, shedding lights on the potential mechanisms underlying the therapeutic effects of these anti-HBV interventions. Further investigations are needed for confirmation of these observations in the context of umbilical cord blood.

Anti-HBV Therapy Affects lncRNA Expression in Placental Tissues

The placenta serves as a physiological barrier in maternal-fetal virus transmission. Immune cells in the placenta can resist virus transmission to the fetus, but certain hepatitis viruses can still breach the placenta, increasing the risk of transmission.[36] In the context of HBV infection, the placenta can reduce the risk of fetal infection through immune regulation and regulate the activity of immune cells to avoid damage to the fetus. LncRNAs play pluripotent roles in the placenta, encompassing placental development, immune regulation, inflammation, and the pathogenesis of placenta-related diseases.[37] Understanding the mechanisms of lncRNAs in these processes is crucial for comprehending maternal-fetal virus transmission. However, the impact of antiviral therapy on lncRNA expression profiles and signaling pathways in cord blood remains unexplored.

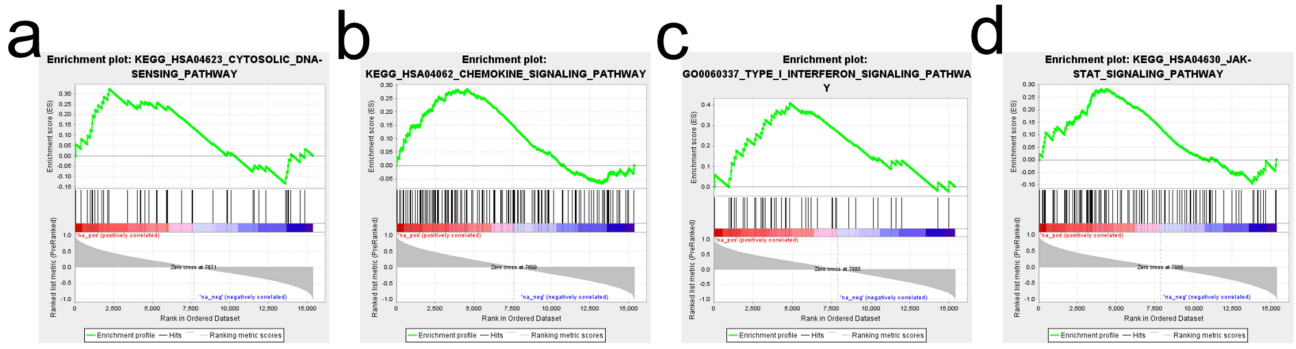

Figure 2 GSEA pathway enrichment analysis. (**a–d**) GSEA pathway enrichment analysis revealed 4 antiviral signaling pathways activated by lncRNA in umbilical cord blood.

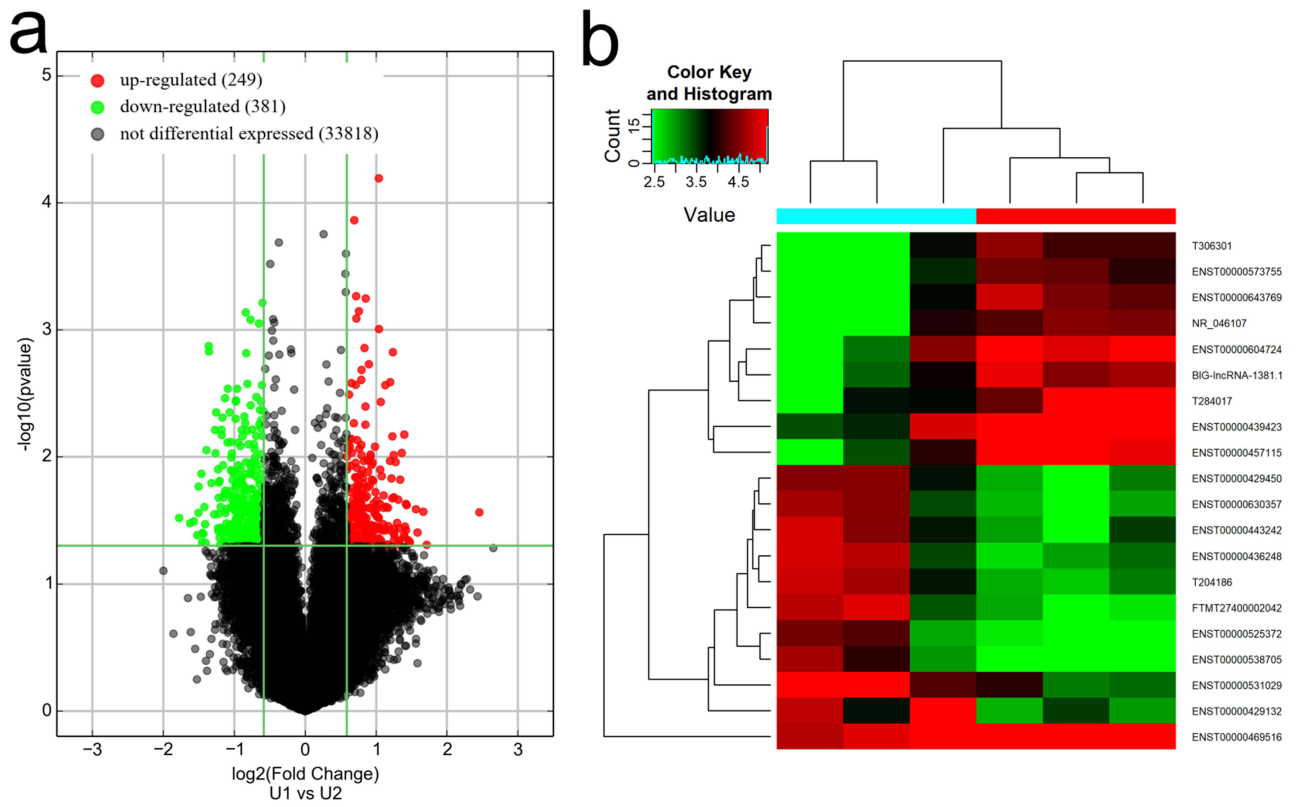

Figure 3 LncRNA microarray analysis of the effect of antiviral therapy on lncRNA expression profiles in placenta tissues. (**a**) Placenta tissues were collected from 6 postnatal women with high hepatitis B viral load but no intrauterine infection, 3 of whom did not receive antiviral therapy (U1) and 3 of whom received antiviral therapy (U2). LncRNA microarray was used to detect lncRNA expression in U1 and U2 placental tissues. Volcano map showed the effect of antiviral therapy on lncRNA expression profiles in placenta tissues. (**b**) Heat map showed the top 10 significantly upregulated and downregulated lncRNAs in placental tissues after antiviral therapy.

Our study revealed a significant influence of antiviral therapy on lncRNA expression profiles in placental tissues, with 249 lncRNAs upregulated and 381 downregulated (Figure 3a and Table S2). The top 10 significantly upregulated and downregulated lncRNAs are visually represented in a heat map (Figure 3b). These findings suggested that antiviral therapy may alter the biological functions of placental tissues by influencing lncRNA expression. In summary, our study provided insights into the impact of antiviral therapy on the lncRNA expression profile in placental tissues, laying a foundation for further exploration of how these alterations may contribute to the placental functions and reduce the risk of maternal-fetal transmission.

Anti-HBV Therapy Affects Signaling Pathways in Placental Tissues

Viral infections in placental tissues have been demonstrated to activate immune signaling pathways [such as toll-like receptors (TLR) and RIG-I receptors] to enhance the capacity of the immune system to combat the virus.[38] These activated pathways subsequently stimulate immune cells and induce the production of immune factors to resist viral infection, and simultaneously initiate inflammatory responses via various pathways (such as NF-κB, JAK-STAT, and MAPK).[39–43] However, the specific effects of anti-HBV therapy on signaling pathways in placental tissues require further analysis.

Our study revealed that antiviral therapy-induced significant changes in lncRNA expression, and pathway enrichment analysis of these differentially expressed lncRNAs demonstrated their potential impact on the activation or inhibition of various signaling pathways. Notably, a substantial activation of RIG-I-mediated innate immune signaling, B-cell signaling, and interferon-γ-mediated adaptive immune signaling was observed (Figure 4a–c). These findings suggested that lncRNAs in placental tissues mediate both innate and adaptive immunity to prevent HBV transmission. In summary,

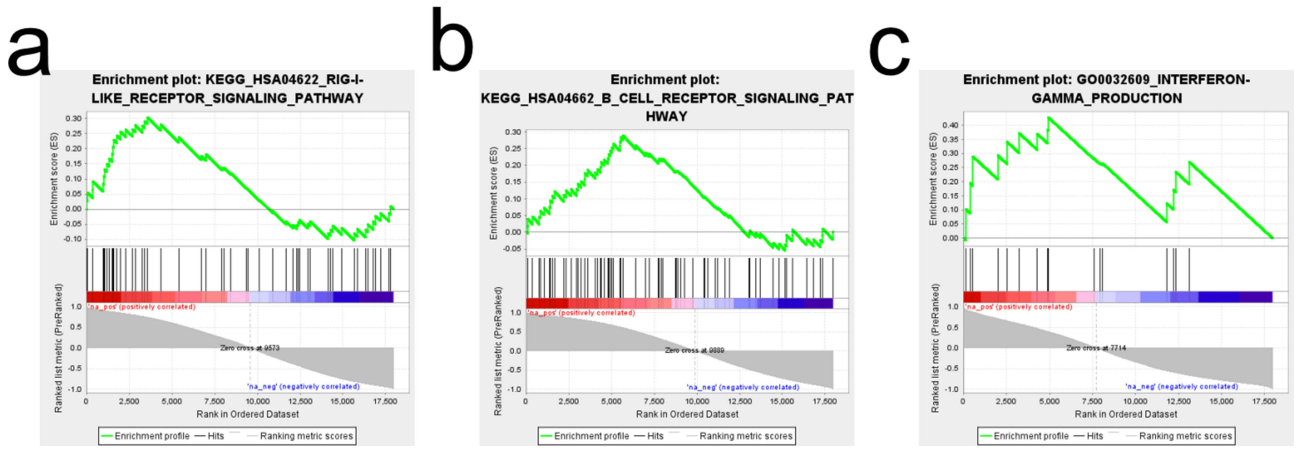

Figure 4 GSEA pathway enrichment analysis. (**a–c**) GSEA pathway enrichment analysis revealed 3 signaling pathways activated by lncRNA in placenta tissues.

our study provided insights into the impact of anti-HBV therapy on signaling pathways in placental tissues, indicating the potential involvement of lncRNAs in regulating innate and adaptive immune responses to prevent HBV transmission. Further investigations are warranted to validate these observations, thereby enhancing our understanding of the intricate interactions in placental immunity during anti-HBV interventions.

CPED1 Exerts Antiviral Function via the JAK-STAT Pathway

Both the umbilical cord and placenta are crucial to the survival and development of the fetus. The umbilical cord is a critical anatomical structure that connects the placenta with the fetus, fulfilling multiple functions during pregnancy such as supplying nutrients and oxygen and discharging metabolic waste. However, viruses may also invade the fetus through this channel, increasing the risk of maternal-fetal transmission of diseases. Through lncRNA differential expression analysis, CPED1 was identified to have a differential expression pattern in both cord blood and placental tissues (Figure 5a).

LncRNA CPED1 (ENST00000495036) is a lncRNA located on chr7:120629229–120,692,067:+, with its biological functions unreported yet. Co-expression network analysis revealed the binding potential of CPED1 to multiple miRNAs, suggesting that CPED1 may influence the expression of coding RNAs (Figure 5b and Table S3). Moreover, CPED1 is involved in various signaling pathways, among which the JAK-STAT signaling pathway is particularly emphasized for its ability to activate antiviral genes upon stimulation (Figure 5c). Consequently, we speculated that CPED1 may contribute to inhibiting virus transmission by modulating the JAK-STAT signaling pathway. These findings offer significant insights into the roles of the umbilical cord and placenta in the maternal-fetal transmission of diseases. In summary, our study identified CPED1 as a potential regulator in the JAK-STAT signaling pathway, suggesting its involvement in inhibiting virus transmission. These insights deepened our understanding of the intricate dynamics of maternal-fetal disease transmission through the umbilical cord and placenta. Further investigations into the functional role of CPED1 in antiviral mechanisms are warranted for a comprehensive understanding of its potential therapeutic implications.

Discussion

This study investigated the effects of anti-HBV therapy on lncRNA expression profiles and immune signaling pathways in umbilical cord blood and placental tissues of pregnant women and explored the potential role of lncRNA CPED1. This study has important clinical and scientific implications.

First, the study revealed for the first time that anti-HBV therapy resulted in differential expression of lncRNAs in cord blood and placental tissues, providing new clues to understand the impact of antiviral therapy on the risk of maternal-fetal virus transmission. Our results indicated that antiviral therapy had slight effects on lncRNA expression profiles in

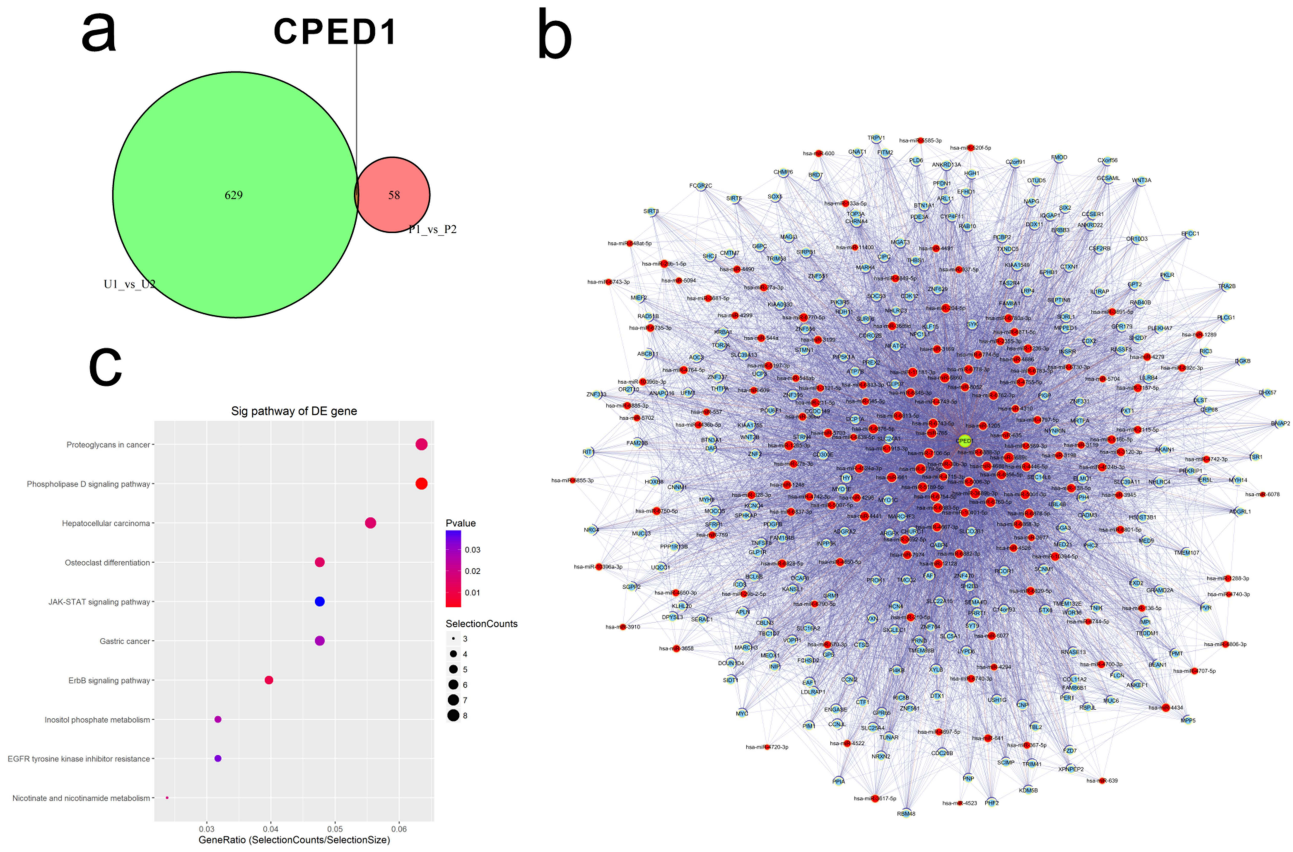

Figure 5 CeRNA co-expression network analysis. (**a**) Venn diagram showed the intersection of differential genes in placental tissues and umbilical cord blood after antiviral therapy. (**b**) CPED1 target genes regulated by miRNAs were screened by ceRNA co-expression network analysis. (**c**) KEGG analyzed the signaling pathway network involved in the regulation of CPED1.

cord blood, but significantly affected lncRNA expression profiles in placental tissues. This suggests that antiviral therapy may regulate placental immune responses, potentially influencing fetal antiviral immunity.

Second, the study also found that anti-HBV therapy activated innate immune signaling pathways, including intracellular DNA sensing pathway,[44,45] chemokine signaling pathway,[46] type I interferon signaling pathway,[47] etc. This suggests that antiviral therapy may enhance host immune responses against HBV infection, contributing to its therapeutic efficacy.

Despite these important findings, there are several limitations in this study. The precise role of CPED1 in HBV infection remains unclear, and further functional studies are necessary to determine its mechanistic involvement in maternal-fetal immunity. Additionally, although this study offers valuable insights into the effects of antiviral therapy on maternal-fetal HBV transmission, further research with larger cohorts and mechanistic validation is required to confirm these findings. Strengthening this understanding will provide a more robust theoretical foundation for optimizing antiviral strategies and improving prevention measures for intrauterine HBV transmission.

Conclusion

In conclusion, this study provides novel insights into the effects of TDF-based antiviral therapy on maternal-fetal HBV transmission, revealing distinct changes in lncRNA expression profiles and immune signaling pathways in umbilical cord blood and placental tissues. Furthermore, CPED1 was identified as a differentially expressed lncRNA in both umbilical cord blood and placental tissues, highlighting its possible involvement in HBV regulation through the JAK-STAT pathway. However, further functional studies are required to validate its precise role. These findings enhance our understanding of how antiviral

therapy influences maternal-fetal HBV transmission and lay the groundwork for future research on lncRNA-based therapeutic strategies aimed at reducing intrauterine HBV transmission.

Data Sharing Statement

All the data are deposited in GEO databases GSE248406 (https://www.ncbi.nlm.nih.gov/geo/). The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the National Research Committee and with the 1964 helsinki Declaration and its later amendments or comparable ethical standards. This study was approved by the Ethics Committee of the People's Hospital of Guangxi Zhuang Autonomous Region (No. KY-GZR-2019-061).

Informed Consent

Informed consent was obtained from all individual participants included in the study.

Author Contributions

All authors made a significant contribution to the work reported, whether in terms of conception, study design, execution, acquisition of data, analysis, and interpretation, or in all of these areas. They took part in drafting, revising, or critically reviewing the article and gave final approval of the version to be published. All authors have agreed on the journal to which the article has been submitted, and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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