

The Role of HBx Protein in Diseases Beyond the Liver

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Abstract: HBX gene is essential for HBV replication, evading the surveillance of the immune system by integrating its sequence into the human genome. It also exists stably in human cells by inhibiting the expression and activity of mismatch repair-related pathway genes. Previous reviews have comprehensively summarized the role of HBx in liver-related diseases. Our article complements the summary of research on HBx in diseases other than liver disease. Through a comprehensive literature search and reading, we found that HBx is expressed in the kidney, placenta, lung and other organs of HBV-infected patients, and is closely related to the occurrence and development of diseases such as nephritis, diffuse large B-cell lymphoma, and gastric cancer. However, in the clinical treatment of these diseases, HBV infection and the role of HBx have not attracted sufficient attention, and there is no corresponding treatment strategy. Therefore, more research on HBx in diseases other than the liver is particularly necessary, and we hope that our article can provide some insight into the treatment of related diseases.

Keywords: HBx protein, disease, treatment, molecular mechanism, explore

Hepatitis B virus (HBV) is a hepatotropic virus and an important human pathogen. Worldwide, an estimated 296 million people are chronically infected with the virus, many of whom develop severe liver diseases, including hepatitis, cirrhosis, and hepatocellular carcinoma (HCC).¹ In addition, it plays a crucial role in diseases related to organs other than the liver.

HBV is a hepatotropic DNA virus, a 3.2kb circular partial double stranded DNA molecule with four overlapping open reading frames. They encode viral envelope protein (HBsAg), core protein (HBcAg), viral polymerase (DNA-P) and HBV x protein (HBx) (Figure 1). The HBsAg, HBcAg, and DNA-P are all involved in the assembly of HBV virus. The HBV X gene is the smallest open reading frame in the HBV genome, with a length of 462 bp, encoding a protein of 154 amino acids.² The HBX gene can be integrated into the human genome and has been shown to be closely related to a variety of human diseases.³ We found through literature search that Hepatitis B x protein (HBx) plays an important role in diseases related to organs such as the kidney, blood system, reproductive system and breast (Figure 1).

HBV-GN

The main pathological features of glomerulonephritis are diffuse glomerular lesions, including apoptosis of epithelial cells, proliferation of endothelial cells and mesangial cells, accompanied by a large amount of immune cell infiltration in the acute phase, and hyperplasia and compression of capillaries by infiltrating cells in severe lesions. Vascular rings to narrow or block the lumen. Among these, HBV-related glomerulonephritis (HBV-GN) accounts for a large proportion of GN, and its treatment must be differentiated from GN caused by other etiologies.⁴ The role of HBx in kidney disease has been closely monitored by several researchers. The results showed that HBx mainly acts on the main cells (epithelial cells, podocytes and mesangial cells, etc.) that cause pathophysiological changes in HBV-GN disease through apoptosis, proliferation and Epithelial-mesenchymal transition (EMT) (Figure 2).

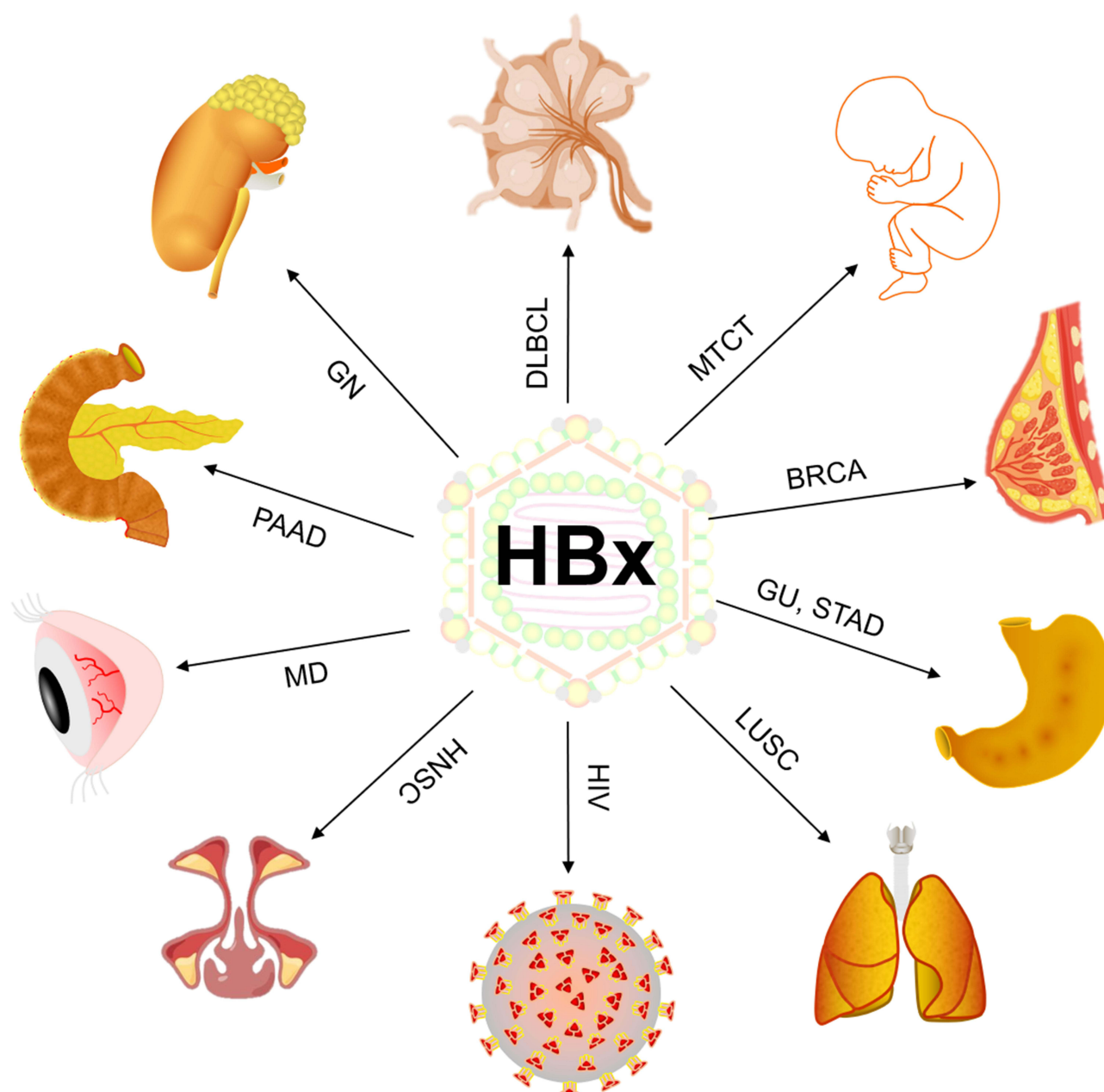


Figure 1 HBx promotes the occurrence and progression of various diseases.

Abbreviations: HBx, HBV x protein; GN, glomerulonephritis; DLBCL, Diffuse large B-cell lymphoma; MTCT, Mother-to-child transmission; BRCA, Breast Cancer; GU, gastric ulcers; STAD, Stomach adenocarcinoma; LUSC, Lung Squamous Cell Carcinoma; HIV, human immunodeficiency virus; HNSC, Head and Neck Cancer; MD, macular degeneration; PAAD, Pancreatic Cancer.

HBx is highly expressed in the epithelial cells of HBV-GN patients. High expression of HBx increases epithelial cell apoptosis by activating multiple molecular pathways, such as: MLK3-MKK7-JNKs, PI3K/AKT, NOTCH, PKC/ERK and NF- κ B pathways.^{5–11} Apart from this, HBx can also promote EMT of epithelial cells through PI3K/AKT/mTOR, NOTCH, NF- κ B and other pathways, thereby accelerating the development of GN.^{12–14} The remodeling of the immune microenvironment plays a crucial role in disease development. HBx can regulate the secretion of cytokines such as IL1, IL6, TNF, IL4 and IFN by up-regulating the expression of CD40, TLR4 and MHCII and other molecules in epithelial cells, thereby promoting the formation of an inflammatory microenvironment.^{15,16} Additionally, the proliferation and cycle changes of epithelial cells also play an important role in the development of the disease.¹⁷

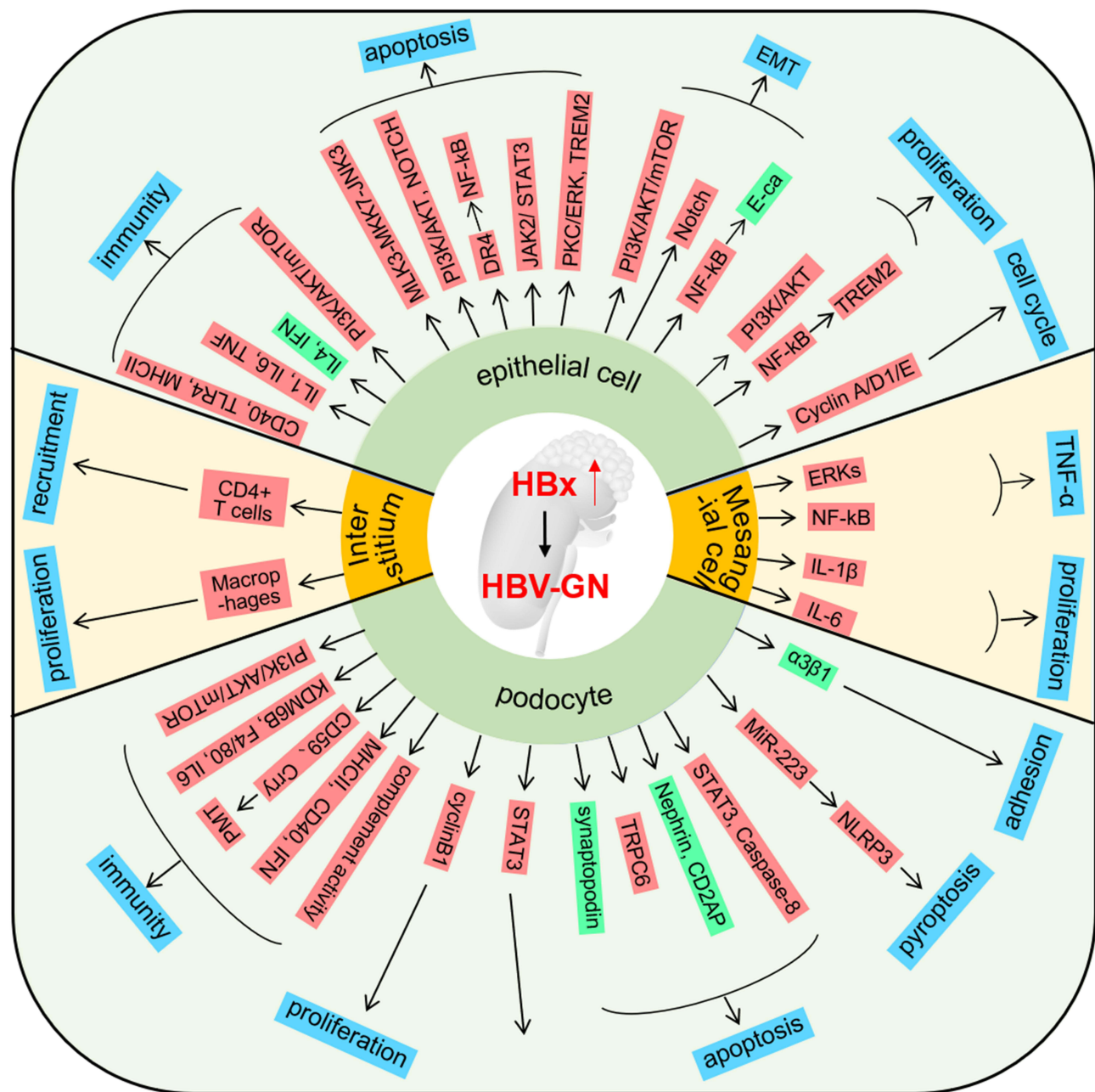


Figure 2 The role of HBx in HBV-GN HBx promotes the progress of HBV-GN by influencing the phenotypes of epithelial cells, interstitium, podocyte, and mesangial cells. The blue box represents the phenotype; The red box represents the upregulated gene; The green box represents the downregulated gene.

In addition to its role in epithelial cells, HBx can influence disease progression by modulating the biological processes of podocytes, the major constituent cells of the glomerulus. Similarly, HBx can promote GN formation through podocyte immunity, apoptosis, pyroptosis, proliferation and cell adhesion. Besides, it influences the glomerular immune micro-environment through cellular pathways including PI3K/AKT/mTOR. Yang et al reported that podocytes can upregulate the expression of macrophage biomarkers KDM6B, F4/80, MHCII, and CD40, and promote podocyte-to-macrophage transformation (PMT).¹⁸ Ying et al found that HBx can up-regulate CD59 and Crry expression in podocytes by activating the P38 pathway, resulting in decreased complement activation, which may facilitate latent HBV infection in podocytes and play a role in the development of HBV-GN.¹⁹ HBV-GN is characterized by a reduced number of podocytes due to apoptosis and shedding from the basement membrane.^{20–22} He et al found that HBx reduced podocyte adhesion and

expression of $\alpha 3\beta 1$ integrin, and increased apoptosis.²³ In addition, HBx-induced changes in podocyte pyroptosis, proliferation, and cell activity also play a role in GN.^{24,25} Changes in the mesangial cells and mesangial interstitium caused by HBx are also the main causes of HBV-GN. Researchers have found that HBx can promote the formation and secretion of TNF- α , IL1 β and IL6 by activating the ERKs and NF- κ B pathways in mesangial cells, thereby promoting their proliferation of mesangial cells.^{26,27} On top of that, HBx can accelerate HBV-GN formation by recruiting CD4+ T cells and macrophages to the mesangial interstitium.²⁸

In conclusion, HBx plays an important role in HBV-GN progression. When HBV-GN occurs, patients may exhibit kidney related symptoms such as proteinuria, hematuria, edema, and liver related symptoms. Therefore, antiviral drugs, including lamivudine and entecavir, are the first choice for the treatment. Additionally, immunomodulators (IFN- α) and hormonal drugs are also top priorities.⁴ Some researchers have also proposed that Chinese herbal medicines such as Echinacoside and Cordyceps sinensis have a certain therapeutic effect on HBV-GN-induced nephropathy.^{9,29}

Mother-to-Child Transmission

HBV infection is a global epidemic disease. More than 50% of chronic HBV infections are caused by Mother-to-child transmission (MTCT) as HBV vaccines become widespread in the population.³⁰ However, the mechanism underlying intrauterine HBV infection remains unclear. Existing studies have shown that HBxAg can be detected in placental trophoblast cells of HBV-infected patients. Here, we review the role and mechanism of HBx in trophoblasts.

HBx inhibits apoptosis and promotes the invasion, proliferation and inflammatory response of HBV-infected trophoblasts through Smad and PI3K/p-AKT signaling.³¹ Cui et al used HTR-8/SVneo cells to establish a trophoblast model with HBx overexpression and confirmed that HBx and its different fragments can activate the Smad signaling pathway, accompanied by the downregulation of E-cadherin, and upregulation of vimentin and N-cadherin. After the signaling pathway was activated, reduced apoptosis, increased invasive ability and enhanced inflammatory response were observed in HTR-8/SVneo cells.³² Wang et al and other research teams confirmed that high expression of HBx in trophoblast JEG-3 can reduce apoptosis by activating the PI3K/p-AKT pathway.^{33,34}

It is worth noting the roles of EGFR in HBx-mediated activation of the PI3K/AKT pathway; however, the conclusions of different research groups are not completely consistent. Lin et al demonstrated that HBx promotes HBV replication in trophoblasts via downregulation of Smc5/6, activates the EGFR promoter and inhibits trophoblast apoptosis via the PI3K/p-AKT downstream signalling pathway, thereby increasing the risk of HBV intrauterine infection.³⁵ However, Wang W et al found that HBxAg suppresses apoptosis and promotes the secretion of placental hormones in human placental trophoblasts via activation of the EGFR/Akt pathway.³⁴ In other words, The specific location of EGFR activation in HBx inhibiting trophoblast apoptosis through the PI3K/AKT pathway need to be further determined.

MTCT of HBV has become the main route of transmission of chronic hepatitis B in China; therefore, prevention of MTCT of HBV is the key to controlling chronic hepatitis B. All pregnant women need to be tested for HBsAg and other hepatitis B serological indicators before birth. Newborns of HBsAg-positive pregnant women need to be injected with hepatitis B immunoglobulin and hepatitis B vaccine within 12h after birth.³⁶

Diffuse large B-cell lymphoma Data from researchers showed that the positive rate of serum HBV was significantly increased in Diffuse large B-cell lymphoma (DLBCL) patients (23.6%) compared to that in the general Chinese population (7.2%, $P < 0.001$), especially in advanced stage lymphoma patients ($P = 0.003$).³⁷ HBx was also strongly expressed in tissues from patients with HBsAg-positive HBV surface antigen (HBsAg) positive.^{37,38} And it is closely related to the poor prognosis of DLBCL. Therefore, it is necessary to conduct in-depth research on the mechanism of action of HBx in DLBCL development.

Multiple research teams have confirmed that high HBx expression in DLBCL tissues leads to resistance to various chemotherapeutic drugs. Li et al found that the core component of HBV (HBX) directly upregulated the expression of lncNBAT1, which was closely associated with the chemotherapy outcomes of HBV-infected individuals with DLBCL through in vitro and in vivo experiments. lncNBAT1 interact with signal transducer and activator of transcription 1 (STAT1) to prevent its enrichment at the promoter region of the functional target gene apolipoprotein B mRNA editing enzyme catalytic subunit 3A (APOBEC3A), inhibiting the expression of APOBEC3A and inducing resistance to MTX in DLBCL cells.³⁹ Zhao et al found that HBX specifically inhibited the phosphorylation of checkpoint kinase 2 (CHK2,

a key DNA damage response protein). CHK2 depletion similarly conferred resistance to S-phase arrest-inducing chemotherapeutic, consistent with HBx overexpression in DLBCL cells. In addition, some researchers have confirmed that HBx can promote the expression of c-Myc in DLBCL tissues, and c-Myc is a marker of poor prognosis.⁴⁰

In terms of treatment, for HBV antigen-positive patients, rituximab (R) and chemotherapy (chemo), the first-line treatments for DLBCL, may cause HBV reactivation, which affects the continuation of chemotherapy. Therefore, patients with hepatitis B antigen-positive DLBCL should continue to use entecavir to prevent HBV activation after R-CHOP chemotherapy.⁴¹

Gastric Ulcers and Stomach Adenocarcinoma

Guo et al indicated that HBx could induce apoptosis and G1 arrest in GES-1 (a gastric mucosal cell line) cells. They further confirmed the aggravation of Gastric ulcers (GU) by HBx using clinicopathological parameters.⁴²

Cui et al found that HBV infection is associated with an increased risk of Stomach adenocarcinoma (STAD) based on a meta-analysis. Histological examination showed that gastric epithelium positive for HBx demonstrated a higher nuclear-cytoplasmic ratio than HBx-negative cells.⁴³ In a more in-depth mechanistic study, Du et al found that HBx can promote the expression of URG11, which in turn activates the β -catenin signaling pathway to promote the growth and metastasis of GC.⁴⁴

Breast invasive carcinoma Klein et al suggest that although BRCA formation is rare (<1%) in WAP-HBX animals, HBX can immortalize ME cells derived from mammary tissue segments in a p53-independent manner, a process that is cell cycle-dependent. The protein D1 gene was overexpressed. Finally, both cyclin D1 induction and HBX mitotic activity are dependent on p38 and c-Jun N-terminal kinase, but not on MEK-1 kinase activity.⁴⁵ Through epidemiological studies on BRCA, Adhikari et al found that HBV may also directly affect breast cells through its cis and trans effects of HBx which may act as oncoproteins.⁴⁶

Other Diseases

In nasopharyngeal carcinoma (NPC), using a xenograft mouse model, it was confirmed that HBx promoted the EMT process of epithelial cells by up-regulating the expression of YAP1, and further promoted cell invasion. Anti-YAP1 can also decrease metastasis in vivo.⁴⁷ In pancreatic ductal adenocarcinoma (PDAC), HBx expression significantly enhances cell proliferation and migration and induces an EMT phenotype. The expression of ErbB4 and TGF- α increased in parallel with HBx expression, and several downstream pathways including PI3K/AKT, MAPK, and ERK were upregulated. Inhibition of PI3K/AKT pathway reversed the effects of HBx in PDAC cell lines. HBx promotes pancreatic carcinogenesis by regulating the PI3K/AKT signaling pathway.⁴⁸ Similarly, HBx upregulates the expression of Hepatoma upregulated protein (HURP), promotes the progression of lung squamous cell carcinoma (LUSC), and induces cisplatin resistance in H1299 lung cancer cells.⁴⁹

In addition to tumors, HBx has also been shown to play a role in other diseases. HBx has also been shown to play a role in other diseases. The risk of macular degeneration (MD) was significantly higher in the HBV-infected cohort than that in the non-HBV-infected cohort (adjusted HR = 1.31; 95% CI = 1.17–1.46). In vitro, researchers demonstrated that overexpression of HBx in the human retinal pigment epithelial (RPE) cell line, ARPE19, significantly reduced cell viability and clonogenic survival upon UV and blue light irradiation. Using gene microarray analysis, we further showed that almost all genes in DNA repair pathways including base excision repair, nucleotide excision repair, mismatch repair, and homologous recombination were significantly down-regulated in UV-induced cell death of HBx-transfected ARPE19 cells.⁵⁰ That is to say, the HBx may sensitize RPE cells to UV and blue light irradiation and increase the risk of HBV-infection-associated MD through the down-regulation of multiple DNA repair pathways. Multiple research teams have demonstrated that HBx may help HBV-HIV co-infected individuals developed AIDS more rapidly than patients co-infected with HBV and HIV.^{51–53}

Conclusion

HBV is mainly transmitted through blood, mother-to-child and sexual contact. Although HBV is a hepadnavirus, infection has been reported in multiple organs in humans, including the kidneys, lymph nodes, and placenta, as described

in this review. At present, it is known that persistent HBV antigenemia can form HBV antigen antibody circulating immune complex and deposit in the glomerulus. In addition, it is speculated that the mechanism of HBV intrauterine infection may be that HBV enters the fetus through the placenta or causes intrauterine infection due to placental rupture or maternal blood mixing with fetal blood, but these hypotheses lack direct evidence. Therefore, the specific mechanism by which HBV enters organs outside the liver is also a topic that deserves more attention from researchers. From our literature study of all HBx in non-liver diseases, we know that HBx in organs such as the kidney, lymph node and placenta is less studied. Except for kidney diseases, research on HBx in other diseases has only focused on its expression promoting the occurrence and development of various types of diseases. However, the specific mechanism still needs further exploration. Therefore, we call for more researchers to explore the mechanism of HBV in diseases other than the liver.

Additionally, apart for the corresponding treatment guidance for HBV-GN, MTCT and DLBCL, there is no corresponding treatment for HBV-related GU, STAD and BRCA (Breast Cancer) diseases. Therefore, more in-depth mechanistic research and exploration of individualized treatment methods are necessary to pay attention. We hope that our article can provide some support for research on HBx in other diseases.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; 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

This manuscript has not been published previously and is not currently under consideration by any other journals. All authors declare no competing interests in this work.

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Infection and Drug Resistance

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