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MINIREVIEWS

Functional interaction of endoplasmic reticulum stress and hepatitis B virus in the pathogenesis of liver diseases

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Abstract

Hepatitis B virus (HBV) is a non-cytopathic virus that causes acute and chronic inflammatory liver diseases, often leading to the pathogenesis of hepatocellular carcinoma (HCC). Although many studies for the roles of HBV on pathogenesis of the liver diseases, such as non-alcoholic fatty liver disease (NAFLD), hepatic inflammation, cirrhosis, and HCC, have been reported, the mechanisms are not fully understood. Endoplasmic reticulum (ER) and mitochondria have the protective mechanisms to restore their damaged function by intrinsic or extrinsic stresses, but their chronic dysfunctions are associated with the pathogenesis of the various diseases. Furthermore, HBV can affect intra- or extracellular homeostasis through induction of ER and mitochondrial dysfunctions, leading to liver injury. Therefore, the mechanism by which HBV induces ER or mitochondrial stresses may be a therapeutic target for treatment of liver diseases.

Key words: Liver disease; Hepatitis B virus; Hepatitis B virus X protein; Endoplasmic reticulum stress; Unfolded protein response

Core tip: Endoplasmic reticulum (ER) is the major site of protein folding and calcium storage. Beside the role of ER in protein homeostasis, it controls the cholesterol production and lipid-membrane biosynthesis as well as surviving and cell death signaling mechanisms in the cell. It is well-documented that abnormal metabolic regulation induces adverse effects in liver disorders, such as non-alcoholic steatosis hepatitis,

fibrosis, cirrhosis, and hepatocellular carcinoma which are associated with hepatitis B virus (HBV) infection. Recent animal model and human studies have showed ER stress as an emerging factors involved in the development of metabolic and liver diseases. In this review, we will summarize the crucial effects of ER stress response in the pathogenesis of HBV-induced liver diseases.

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INTRODUCTION

Hepatitis B virus (HBV), a prototype member of the *Hepadnavirus* family, is a small enveloped DNA virus with a virion diameter of 42 nm. The HBV genome is a relaxed circular, partially double-stranded DNA molecule encoding four overlapping open reading frames (ORFs), named C, S, P, and X coding for core protein, surface proteins (pre-S1, pre-S2, and S), DNA polymerase, and X protein, respectively[1]. Of the HBV-encoded proteins, the function of hepatitis B virus X protein (HBx) is not clearly understood, but it may function as a multifunctional transactivator in HBV replication and host gene transcription through interaction with host proteins[2]. HBV primarily infects hepatocytes and causes acute and chronic liver diseases. In particular, chronic HBV infection can lead to cirrhosis of the liver, liver failure, liver cancer, and even death. According to the report of World Health Organization (WHO), there are more than 350 million people worldwide who have chronic HBV infections and more than 780 thousand people die every year due to the acute or chronic HBV infection[3]. To date, many studies have been reported on the molecular mechanisms for relation between HBV infection and pathogenesis of hepatic diseases, but the mechanisms are still not fully understood.

Cellular organelle is a specialized compartment enclosed by lipid bilayers within a cell and has specific functions. It is classified into major organelle such as endoplasmic reticulum (ER), Golgi apparatus, mitochondria, vacuole, and nucleus and minor organelle such as autophagosome, lysosome, peroxisome, and vesicle. Damage or dysfunction of cellular organelles by intra- or extra-cellular stress is associated with the pathogenesis of various diseases. For examples, mitochondrial dysfunction induces the diseases such as myopathy, diabetes, and multiple endocrinopathy[4] and ER dysfunction induces the diseases such as obesity, diabetes, atherosclerosis, and cancer[5]. Here, we review relation between the HBV-encoded proteins and damage of cellular organelles and the influence on pathogenesis of hepatic diseases.

HBV AND INTRACELLULAR ORGANELLE

HBV-mitochondria

Mitochondria are the double membrane-bound structure and consist of five compartments with specialized functions including the outer mitochondrial membrane, the inter membrane space, the inner mitochondrial membrane, the cristae space, and matrix. Mitochondria have their own independent genome which is a single circular DNA molecule encoding 37 genes[6]. Division and genome of mitochondria are similar to those of bacterial cell. Mitochondria play critical roles in production of cellular energy, calcium and redox homeostasis, cellular signaling, regulation of cellular metabolism and cell death, and heat production[7-9]. Of the functions of mitochondria, the most prominent function is to synthesize cellular energy, adenosine triphosphate (ATP), which is used as a source of chemical energy for metabolism and a substrate in signaling pathways[10].

Mitochondria are very dynamic and continually fuse and divide in response to physiological conditions. Moreover, mitochondria are fragmented as the consequence of enhanced fission during apoptosis[11] and elongated to maintain ATP production during starvation[12]. Many mitochondrial protein complexes are composed of nuclear or mitochondrial DNA-encoded proteins. Any imbalance in the complex assembly can lead to accumulation or aggregation of unassembled or unfolded proteins[13]. In order to cope with the accumulation of unassembled or unfolded proteins within mitochondria, mitochondria activates the mitochondrial unfolded protein response (UPR) that up-regulates the expression of mitochondrial chaperones and proteases like ER stress response[14]. Although the environmental conditions inducing mitochondrial stress are still not clearly understood, the accumulated evidences suggest that high levels of reactive oxygen species (ROS) or inhibition of mitochondrial genome replication and transcription can induce mitochondrial UPR[15-17]. Unfolded proteins accumulated in matrix activate mitogen-activated protein kinase kinase (MEK)/c-Jun N-terminal protein kinase 2 (JNK2)/c-Jun pathway and protein kinase R (PKR). Activated c-Jun increases the transcription of transcription factors C/EBP homologous protein (CHOP) and CCAAT/enhancer-binding protein β (C/EBPβ), and then the heterodimer of CHOP and C/EBPβ activate the transcription of mitochondrial proteases and chaperons[18]. Activated PKR phosphorylates eukaryotic translational initiation factor 2α (eIF2α), leading to attenuating translation similar with the protein kinase RNA-like ER kinase (PERK) pathway of ER stress response[19]. In addition, unfolded proteins accumulated

in the intermembrane space (IMS) activate estrogen receptor and NAD-dependent deacetylase sirtuin-3 (SIRT3). Activated estrogen receptor up-regulates the transcription of nuclear respiratory factor 1 (NRF1) and mitochondrial serine protease, high-temperature requirement A2 (HTRA2), and SIRT3 pathway induces anti-oxidant machinery and mitophagy to alleviate mitochondrial stress[20,21].

Accumulated evidences have suggested that HBx protein is associated with mitochondrial aggregation or damage. HBx protein induces an abnormal aggregation of mitochondrial structures at the periphery of nucleus, which may be eventually connected with cell death[22]. In HBx-expressing cells, the abnormal aggregation of mitochondria is induced by the increase of microtubule-dependent dynein activity through HBx-induced p38 mitogen-activated protein kinase (MAPK) activation[23]. Siddiqui group showed that HBx protein is associated with mitochondrial damage through interaction with voltage-dependent anion channel (HVDAC3) [24], which is known as mitochondrial porins and form pores in the outer membranes of mitochondria[25]. The interaction induces the alteration of mitochondrial transmembrane potential leading to generation of ROS, resulting in activation of transcription factors signal transducer and activator of transcription 3 (STAT3) and nuclear factor kappa B (NFκB)[24,26]. The ability of HBx protein to transactivate AP-1 and NFB is abolished by positioning HBx protein in the nucleus artificially[27]. These evidences represent the ability of HBx protein as a transactivator, which is to induce gene expression through cytoplasmic factors but not nucleus.

HBx protein can affect mitochondrial functions or cell fate by regulating gene expression or translocating a series of proteins to mitochondria, respectively. HBx down-regulates the expression of mitochondrial encoded subunit proteins of electron transport in oxidative phosphorylation, resulting in a high level of cellular ROS by impairment of electron transport[28]. Besides, HBx down-regulates the expression of nuclear encoded genes involved in mitochondrial β-oxidation of fatty acids, resulting in a low level of cellular ATP by deficiency of energy sources[29]. HBx translocates Raf-1 kinases involved in the Ras-induced MAPK pathway or apoptosis regulator bcl-2-associated X protein (BAX) to mitochondria, leading to hepatic cell proliferation or apoptosis, respectively[30,31]. These evidences suggest that mitochondria dysfunction by HBx contributes to the HBV-induced pathogenesis of hepatocellular carcinoma such as proliferation, metastasis, chemoresistance and other aspects of tumorigenesis.

To date a lot of researches have reported for relation between HBx protein and mitochondrial damage. However, the research for HBx protein and mitochondrial UPR has not yet been reported. Therefore, the research to clarify correlation between HBx protein or HBx-induced mitochondrial damage and mitochondrial UPR needs to be performed in future. In addition, it will be a worthy to research for association between HBx protein and the proteins activated by mitochondrial UPR such as SIRT3, estrogen receptor, CHOP, or C/EBPβ.

HBV-ER

The endoplasmic reticulum (ER) is dynamic tubular structure and forms an interconnected network with almost every membrane-bound organelles, including mitochondria, the Golgi apparatus, endosome, peroxisome, and plasma membrane through contact sites[32,33]. The ER acts as a sensor for intra- or extracellular stimuli and is essential for cell homeostasis. The ER is classified into rough ER and smooth ER, which are externally distinguished by ribosome, a molecular machine synthesizing biological protein. The rough ER has the ribosome binding sites, named translocon on the ER outer membrane and is involved in synthesis, folding, and glycosylation of secretary or integral membrane proteins[34]. Therefore rough ER is well-developed in specialized secretary cells such as hepatocytes, pancreatic islet cells and immune cells. The smooth ER lacks ribosome and involved in several metabolic processes including synthesis of lipids (phospholipids and steroids), metabolism of carbohydrates, regulation of calcium concentration, detoxification of drugs[35]. The smooth ER plays also a fundamental role in the assembly of very low density lipoprotein (VLDL) particles in liver. In addition to the above-mentioned functions, ER also participate in the following processes through contact sites with other organelles: *e.g.*, ER-mitochondria: mitochondria biogenesis, lipid exchange during biosynthesis, and Ca^{2+} transfer from ER to mitochondria[32,35]; ER-Golgi: transport of secretory proteins and non-vesicular lipid transport[36]; ER-endosome: regulation of the intracellular distribution of endosomes[37]; ER-peroxisome: non-vesicular lipid transport[38]; ER-plasma membrane: regulation of phosphatidyl inositol metabolism and non-vesicular sterol transfer[39,40].

Of the ER functions, the proper folding and modification of proteins are the most important and best characterized function of the ER, and are processed under strict quality-control process (QCR)[41]. QCR means that only correctly matured proteins are exported to the Golgi complex and misfolded proteins are left in the ER to complete the process or to degrade the proteins[42]. Many ER-resident proteins such as chaperones, foldases, and lectins are involved in the QCR. Most ER chaperones are Ca^{2+} dependent and have ATPase activities. N-linked glycosylation and disulfide bond formation by foldases also play significant roles in protein maturation[43]. Viral infection induces the synthesis of a vast amount of viral proteins, leading to protein overload in ER. Therefore, the QCR is inhibited by the various stimuli such as Ca^{2+} output, nutrient deficiency or overload, hypoxia, and viral infection. The unfolded or misfolded proteins induced by the stimuli are accumulated and aggregated in ER, leading

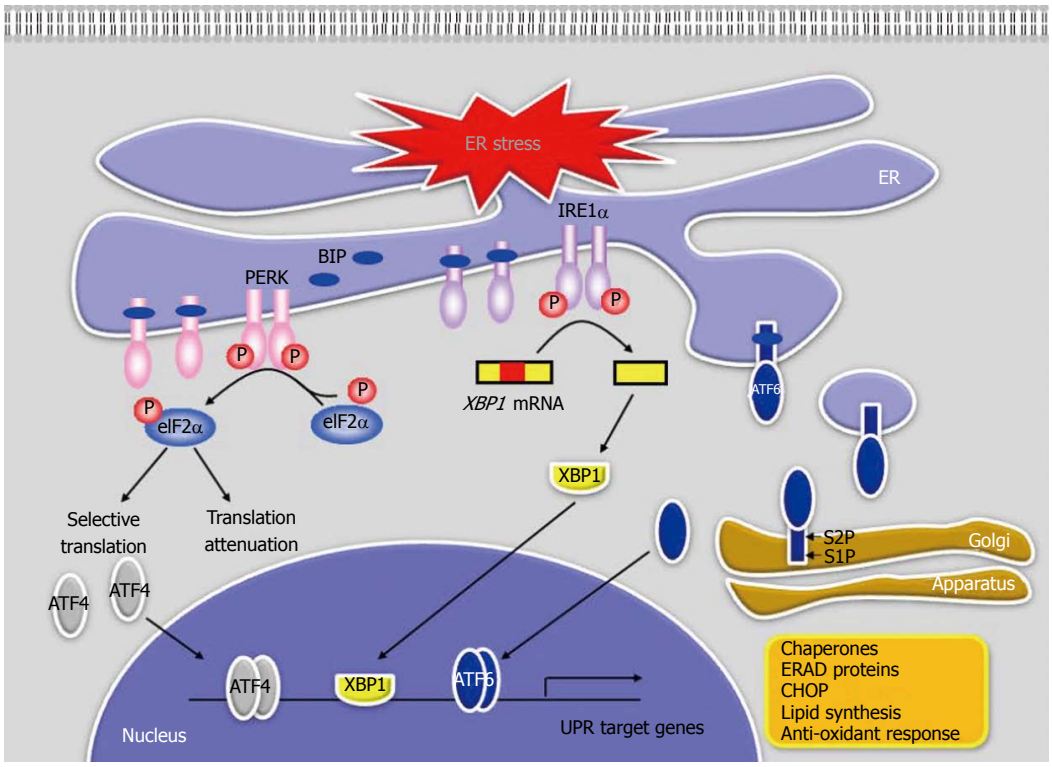

Figure 1 Endoplasmic reticulum stress and unfolded protein response signaling pathways. ER: Endoplasmic reticulum; BIP: Binding immunoglobulin protein; PERK: Protein kinase RNA-like ER kinase; eIF2α: Eukaryotic translational initiation factor 2α; ATF4: Activating transcription factor 4; IRE1: Inositol-requiring protein 1; XBP1: X-box binding protein 1; ATF6: Activating transcription factor 6; S1P: Site 1 protease; S2P: Site 2 protease; UPR: Unfolded protein response; ERAD: ER associated degradation; CHOP: C/EBP homologous protein; P: Phosphate.

to ER stress. Fortunately, the ER has four adaptive mechanisms, named UPR, to alleviate ER stress and restore ER to its normal physiological conditions[5,41]: (1) translational attenuation for reduction of protein load, (2) induction of the expression of ER chaperones and foldases for enhancement of folding capacity, (3) induction of the expression of ER associated degradation (ERAD) proteins for clearance of unfolded proteins, (4) induction of apoptosis for removal of cells impaired by ER stress. In mammalian cells, these four responses are regulated by the regulatory pathways as described below (Figure 1).

PERK pathway: PERK is a type Ⅰ transmembrane protein located in the ER. Under a normal condition, PERK exists as a monomer, an inactive state, by binding with ER chaperone, 78kD glucose-regulated protein (GRP78)/binding immunoglobulin protein (BiP)[44]. In response to ER stress, BiP is dissociated from PERK, which is activated through oligomerization and trans-autophosphorylation[45]. Activated PERK phosphorylates eIF2α, leading to translational attenuation[45]. Interestingly, phosphorylated eIF2α allows the translation of activating transcription factor 4 (ATF4) mRNA[46] and ATF4 induces the expression of UPR target genes involved in amino acid metabolism, antioxidant response, and ER-stress-induced apoptosis[47].

IRE1 pathway: Inositol-requiring protein 1 (IRE1) is a type I transmembrane protein that has a RNase domain. Under a normal condition, IRE1 exists as a monomer by binding with BiP like PERK[44]. In response to ER stress, BiP is dissociated from IRE1, which is activated through oligomerization and trans-autophosphorylation. Activated IRE1 triggers its RNase activity, which catalyses unconventional splicing of x-box binding protein 1 (XBP1) pre-mRNA to synthesize the active transcription factor spliced XBP1 (XBP1s)[48]. XBP1s induces the expression of UPR target genes involved in ERAD and lipid synthesis as well as the expression of ER chaperones[49,50].

ATF6 pathway: Unlike PERK and IRE1, activating transcription factor 6 (ATF6) is a type Ⅱ transmembrane protein and a basic leucine zipper transcription factor[51]. Under a normal condition, translocation of ATF6 to the Golgi apparatus is inhibited because Golgi-localization signal of ATF6 is covered by BiP[52]. In response to ER stress, ATF6 is released from BiP and translocates to the Golgi apparatus[53]. In the Golgi apparatus, ATF6 is cleaved by site 1 protease (S1P) and S2P, and then a functional fragment of ATF6 is released into the cytosol[54]. This fragment translocates to the nucleus and induces the expression of ER chaperone, ERAD components, and XBP1[55].

Hepatocytes have well-developed ER because liver is a highly active organ for protein and lipid synthesis. The UPR could alleviate and restore ER damaged

by extraordinary task as a protein synthesis factory. In addition to protein synthesis, ER has a variety of functions, which also are affected by physiological or pathological stress. The UPR activated by rhythmic or transient physiological conditions (*e.g.*, feeding-fasting cycles) is sufficient to restore ER stress[56]. However, the UPR activated by irreversible or chronic stress (*e.g.*, viral infection and obesity) is not sufficient to restore ER stress[56] and causes hepatic dysfunction, leading to the pathogenesis of the liver diseases including non-alcoholic fatty liver disease (NAFLD), cholestatic liver disease, insulin resistance, diabetes, viral hepatitis, and liver cancer[57-59].

In HBV-infected cells, a vast amount of HBV surface proteins is synthesized and folded in ER during its productive life-cycle, often leading to perturbation of the ER homeostasis, resulting in ER stress. This becomes known by identifying mutant surface proteins (preS1 and preS2 mutants) accumulated in the ER of the cells, termed ground glass hepatocyte (GGH) showing a hypertrophy of ER[60,61]. ER stress activated by HBV can lead to the expression of ER degradation enhancer, mannosidase alpha-like 1 (EDEM1) involved in ERAD pathway through the activation of IRE1/XBP1 pathway[62]. The activated ERAD pathway can limits the amount of surface proteins to alleviate ER stress and to protect the cells. Therefore, ER stress is essential for proper viral protein folding and HBV replication, enabling the chronic HBV infection. In general, autophagy is highly regulated catabolic process that removes the damaged organelles or intracellular microbial pathogens through the formation of double-membrane-bound structure called the autophagosome[63]. However, HBV can induce autophagy *via* ER stress or HBx protein for viral replication and envelopment[64-66]. Moreover, HBV can strategically protect itself from autophagic degradation through accumulation of immature lysosomes induced by HBx protein[67].

In vivo it seems insufficient to induction of ER stress by only surface proteins except productive life-cycle. ER stress can be induced by the change of intracellular conditions through other viral proteins. For example, HBx protein can generate ROS and decrease mitochondrial membrane potential and cellular ATP/ADP ratio through mitochondrial damage[29]. Although the molecular mechanisms by which HBx induces ER stress are not clearly understood, these changes by HBx protein may synergistically contribute to induction of ER stress in conjunction with surface proteins. In fact, some researchers reported that UPR or ERAD pathway are activated by HBx protein alone[62,68]. We also reported that ER stress is induced by low intracellular glucose or ATP levels as well as HBx protein[29].

As mentioned previously, rhythmic or transient ER stress is a protective mechanism for cell survival. However, chronic ER stress under the pathological conditions such as chronic HBV infection can cause various liver diseases. We showed that HBx up-regulates the expression of cyclo-oxygenase 2 (COX2) and stromal cell-derived factor-1 (SDF1) through PERK-eIF2α-ATF4 pathway and IRE1-XBP1 pathway activated by ER stress, respectively[29,69]. COX2 converts arachidonic acid to prostaglandin (*e.g.*, prostaglandin E2), which is an important mediator of inflammation. SDF1, a small cytokine, is strongly chemotactic for lymphocytes and induces the recruitment of immune cells into liver of HBx transgenic mice[69]. These evidences suggest that chronic ER stress induced by HBx protein may contribute to pathogenesis of hepatic inflammation and fibrosis (Figure 2).

Cyclic AMP responsive element-binding protein H (CREBH) is an ER-resident transmembrane bZIP transcription factor and a member of old astrocyte specifically induced substance (OASIS) family which show cell- or tissue-specific expression pattern[70]. CREBH is abandant expressed in liver and its activation mechanism is similar to that of ATF6[70]. Activated CREBH plays critical roles in iron metabolism, triacylglycerol metabolism, hepatic gluconeogenesis and lipogenesis, and inflammation by regulating the expression of various genes as a master gene[71-75]. Considering the published papers, activated CREBH plays essential roles in various hepatic metabolisms under physiological conditions and in hepatic inflammation and cell proliferation under pathological conditions. We showed that CREBH is activated by HBV and HBx protein as well as ER stress inducer, leading to hepatic cell proliferation by inducing the expression of oncogenic genes in cooperation with HBx protein[75]. These evidences suggest that ER stress may be closely associated with pathogenesis of HCC in patients with chronic hepatitis B.

THERAPEUTIC IMPLICATIONS

To date, the various drugs against HBV are developed and used to treat HBV patients, *e.g.* lamivudine, adefovir, entecavir, and tenofovir[76]. All of the drugs are nucleoside/nucleotide analogues that target reverses-transcriptase (RT) domain of HBV polymerase which play the essential role on viral replication[76,77]. Although the drugs can repress the viral replication efficiently, existing virus and covalently closed circular DNA (cccDNA) are not eliminated by the drugs from the infected cells. Since HBV polymerase lacks a proofreading exonuclease activity, misincorporated bases can't be removed from newly synthesized viral genome, leading to the mutations in the progeny DNA. Therefore, the resistance for the drugs often occurs in HBV patients during long-term therapy. Besides, there are the adverse effects of the drugs, including myopathy induced by depletion of mitochondrial DNA and myonecrosis, and nephrotoxicity induced by inhibition of kidney function[78].

In addition to nucleoside/nucleotide analogues, the non-nucleoside agents that target viral entry, protein, or replication are developing. The development of agents that target viral entry was available due to

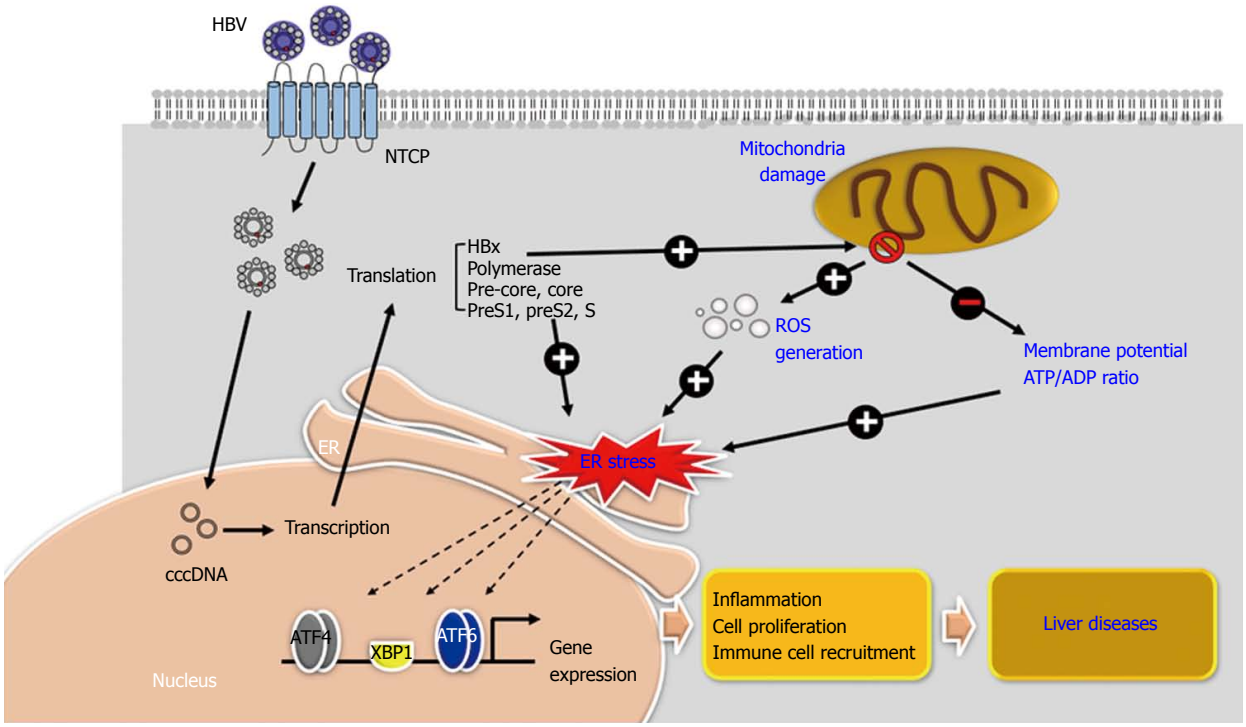

Figure 2 Mechanisms for the pathogenesis of hepatitis B virus-induced liver diseases *via* mitochondrial damage and endoplasmic reticulum stress. Plus and minus symbols are up- and down-regulated responses, respectively. HBV: Hepatitis B virus; cccDNA: Covalently closed circular DNA; ER: Endoplasmic reticulum; HBx: Hepatitis B virus X protein; ROS: Reactive oxygen species; ATF4: Activating transcription factor 4; XBP1: X-box binding protein 1; ATF6: Activating transcription factor 6.

identification of sodium taurocholate cotransporting polypeptide (NTCP) known as a HBV entry receptor[79]. Cyclosporin A and Myrcludex-B strongly inhibit HBV infection into hepatocytes by binding to NTCP on plasma membrane[80,81]. Anti-HBV agents that inhibit the secretion of viral proteins or the interaction between core and surface proteins have been reported[82,83]. Anti-HBV agents that inhibit the viral replication by blocking RNA packing or gene expression also have been reported[84,85]. Sorafenib, anti-liver cancer drug, suppresses the HBV gene expression, but it induces cell death at high-dose treatment[86,87]. On the other hand, since surface protein and HBx proteins can induce ER or mitochondria stress which lead to pathogenesis of liver diseases, the development of the agents which inhibit ER or mitochondria stress is necessary in future. The development of host-targeting anti-HBV agents makes patients expect some advantages, including the low frequency of drug resistance, the synergic effect with currently available anti-HBV agents, and supply an alternative therapy.

CONCLUSION

Under normal physiological conditions, our body has adaptive system to maintain homeostasis from various stresses. Even though faced with pathological conditions, our body can be protected from the conditions by removing and restoring the damaged cells and tissues through innate and adaptive immune system. However, HBV has the abilities to escape from the host's immune response and even to utilize autophagy for viral replication and envelopment. The abilities facilitate chronic infection of HBV, leading to chronic ER and mitochondrial stress, resulting in the pathogenesis of various liver diseases including NAFLD, cholestatic liver disease, viral hepatitis, and liver cancer. Here we indicated the mechanisms by which HBV proteins induce the dysfunction of cellular organelles and the hepatic diseases developed by the expression of UPR target genes or by disturbance of cellular signaling pathway. From a therapeutic perspective, it will be important to understand how HBV induce ER or mitochondrial dysfunctions and understanding the mechanisms will provide new treatment options to chronic HBV patients.

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