Emerging role of mitochondria in response to HBV infection

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Abstract  
Hepatitis B is a major global health problem that potentially life-threatening liver infection caused by the hepatitis B virus (HBV), which can lead to death due to liver cirrhosis and hepatocellular carcinoma (HCC). A considerable of research has demonstrated that mitochondrial dysfunction exists in patients with HBV infection, indicating that there is clinical relation between HBV infection and mitochondrial alterations. To explore the complex interplay between the functions of mitochondria and HBV infection in greater depth, we systematically summarized these mitochondrial alterations due to HBV infection in recent years. The liver is the central organ of metabolism that is a mitochondria-rich tissue and represents strong defense and regeneration capabilities in the body. Infested cells and their microenvironment must upregulate energy production for proliferation, growth, and effector functions to restrain the damage imposed by HBV. The changes in metabolic pathways caused by HBV infection are nothing more than those in the cytoplasm and mitochondria. Thus, this article brings into focus the effects of novel reprogramming of inner and outer mitochondria on HBV infection and then derives novel insights and new approaches for HBV diagnosis and therapy.

KEYWORDS  
diagnosis, hepatitis B virus (HBV), infection, mitochondria, therapy

1 | INTRODUCTION

Chronic hepatitis B (CHB) remains a global public health concern, which is a viral infection that affects around 296 million people worldwide in 2019 with 1.5 million new infected each year and carries a significantly increased risk of serious liver failure and cancer.¹ Approximately, 820,000 deaths in 2019 mostly from liver cirrhosis and hepatocellular carcinoma (primary liver cancer).² However, the intrinsic mechanisms of hepatitis B-related diseases are unclear, and none of the methods can ensure a complete cure for CHB currently. Therefore, it is urgent to investigate the complex host responses to viral infection, which may, in turn, provide a more detailed understanding of pathogenesis and help discover potential novel antiviral drugs and targets.

Hepatitis B virus (HBV) is one of the smallest enveloped animal DNA viruses belonging to the Hepadnaviridae family, which of genome is a 3.2 kb partially double-stranded, relaxed circular DNA (rcDNA), mainly regulated by four promoters (core, preS1, preS/S2, and X promoters) and two liver-specific enhancers (Enh1 and Enh2). HBV enters into hepatocytes and releases the uncoated nucleocapsid by binding the sodium taurocholate cotransporting polypeptide (NTCP) with its preS1 region in the envelope protein, and then the rcDNA will be converted to a covalently closed circular DNA (cccDNA) in the nucleus. For viral RNA transcription, the cccDNA
serves as the template for the pregenomic RNA (pgRNA) and other viral mRNAs. Once pgRNA is encapsidated, reverse transcription into rcDNA occurs with either enveloping and secreting to form progeny viral particles or re-entering into the nucleus to replenish the cccDNA pool, in closing finish intracellular cycling \(^3\) (Figure 1).

The function of mitochondria is fundamental for cells to survive and function. Since the viruses do not have their complete metabolic system, it is vital for viruses to actively with cell signal transduction to control cellular energy and nutrition metabolism to accomplish a successful replicate cycle.\(^4\) In a healthy body, the liver contains more abundant mitochondria than other tissues, the number of which can reach 500–4000 mitochondrion per cell, occupying about 20% of the entire liver cell volume, and reveals mitochondria serve an important role in hepatic metabolism.\(^5\) Metabolic reprogram in mitochondria has emerged as a common mechanism that underlies the progression of all kinds of cancers, which like viruses, require amounts of energy production and macromolecule biosynthesis to grow and propagate. Increasing concerns have been paid to the association between HBV infection and host hepatic metabolism recently.\(^6\) There exist many transcription factors in the genome of HBV, most of which are nuclear receptors, some are ubiquitous such as nuclear respiratory factor 1 and specificity protein 1.\(^7\) And some are liver-specific nuclear receptors such as hepatocyte nuclear factor 4 alpha (HNF4\(\alpha\)), peroxisome proliferator-activated receptors alpha (PPAR\(\alpha\)),\(^8\) and farnesoid X receptor (FXR).\(^9\) Interestingly, accumulated studies have shown that these transcription factors closely interact with mitochondrial metabolism. For example, HNF4\(\alpha\) plays an important role in liver glucose metabolism. PPAR\(\alpha\) controls fatty acid \(\beta\)-oxidation and is a key regulator of genes involved in the fasting response of cells.\(^10\) In the meanwhile, Jarcuska et al.\(^11\) summarized strong associations between CHB and metabolic syndrome, dyslipidemia or non-alcoholic fatty liver disease, and even diabetes mellitus. The above reports indicate that HBV has applied a smart mode of regulation, which is similar to that of major mitochondrial metabolic genes. However, there is still controversy with respect to the clinical relationship between HBV infection and mitochondrial alterations. Therefore, in order to further understand the unique interaction between HBV infection and mitochondrial function, we systematically reviewed the ongoing research into the changes in mitochondria in HBV infection.

**Figure 1** Overview of the HBV life cycle and interactions between HBV and mitochondria. HBV infects hepatocytes by interacting with NTCP followed by uncoating and is transported to the nucleus where cccDNA is formed. Then, the cccDNA serves as a template for transcription of the subgenomic RNAs and the pregenomic RNAs (pgRNAs). One of pgRNAs is reverse-transcribed into new partially double-stranded DNA genomes, and the other of which is encapsidated, enveloped, and secreted into the extracellular space. The subgenomic RNAs can be translated into polymerase, Pre-core, core, HBx protein, and so on. These products of HBV replication target and localize in the inner and outer mitochondrial membranes and disrupt mitochondrial function by causing oxidative stress, ROS production, and Ca\(^2+\) changes. Eventually, the above alterations cause inflammation in the liver.
2 | MITOCHONDRIAL METABOLISM IN HBV INFECTION

Energy generation and the regulation of cell metabolism are the most important functions of mitochondria, which also can control cell apoptosis and transfer calcium signaling to other organelles in the cells. Previous studies have shown that the NAFLD can disrupt the functions of mitochondria, which results in the depletion of mtDNA, impaired activity of respiratory chain complexes, and abnormal morphological alteration. Recently, it is reported that the ATP in serum produced by mitochondria is associated with hepatitis B disease progression. Increasing studies have demonstrated that mitochondria can exert antiviral effects by regulating their intrinsic antiviral proteins. It is reported that mitochondria can change their shape and position, and perform fusion, fission, and mitochondrial autophagy in response to cellular stresses to maintain homeostasis (Figure 1).

2.1 | HBx in mitochondria

Mitochondria are organelles with composed of mitochondrial matrix, cristae intermembrane, inner membrane (IMM), and outer membrane (OMM) in eukaryotic cells. HBx is a multifunctional protein almost localized in either the matrix, IMM, or OMM, which is encoded by ORF X and controls the replication of HBV. Yoo et al. found more than 50% HBx in the cytoplasm tends to be distributed into the mitochondria by overexpressing the HBx-Flag at 48h after transfection. As a part of the hepatitis B virus, HBx affects various intracellular metabolic activities by regulating the signaling pathways in mitochondria.

Once HBV invades into hepatic cells, it can induce the production of ROS, including mitochondrial ROS (mROS). Clippinger and Bouchard showed that HBx in OMM of mitochondria can elevate the ROS level by activating the NF-κB signaling pathway in HepG2 cells transfected with HBx. Moreover, higher levels of ROS can elicit the activation of transcription factors such as Foxo-4 and STAT-3. ROS level by activating the NF-κB signaling pathway in HepG2 cells transfected with HBV DNA.

 Mitochondrial antiviral signaling protein (MAVS), which localizes at mitochondrial membranes, plays a vital role in the antiviral innate immune response. Recently, it is reported that MAVS ablation can lead to a significant downregulation of the tricarboxylic acid (TCA) cycle and oxidative phosphorylation (OXPHOS) metabolites, with a compensatory upregulation of glycolytic metabolites in Mavs-KO mice. And, the aggregation and localization of MAVS on mitochondria can be restricted during HBV infection by lactate, which is the product of glycolysis. On the contrary, much research has reported that HBx seems to interact with MAVS and attenuates the immune response. HBx can stimulate parkin to ubiquitinate MAVS and disrupt the activation of IRF3. HBx also attenuates the MAVS-mediated IFN-β induction by ubiquitinating MAVS. HBx-mediated MAVS degradation has a strong correlation with the results from clinical HCC samples in HBV patients and HBx transgenic mice. Therefore, taking together all of the above results, it is suggested that HBx acts an important role in the development of HBV-induced liver disease and the therapeutic potential of targeting HBx protein to inhibit HBV infection.

2.2 | mtDNA and mtRNA in mitochondria

mtDNA is about 16.5 kbp circular DNA that serves as the only non-nuclear genome in eukaryotic cells. It is an important part of mitochondria, which encodes a total of 37 genes, containing 13 protein components of the oxidative phosphorylation machinery, 2 ribosomal RNAs, and 22 transfer RNAs essential for translation in the mitochondria. mtDNA plays a key role in regulating energy production and cellular metabolism to ensure cell homeostasis and organismal health under normal circumstances. Many studies have shown that the mtDNA in peripheral blood (PB) of chronic hepatitis B patients is higher than in healthy men. It is reported that the mtDNA copy number in serum mainly correlated with the reactive oxygen species (ROS) activities in mitochondria, manifest in higher mtDNA levels with increased ROS activities.

mtDNA is elaborately packaged by its associated proteins, such as mitochondrial transcription factor A (TFAM), which can function as a protective shell coating of mtDNA and shield it from oxidative damage induced by increased mitochondrial reactive oxygen species (mtROS), presenting with a so-called “nucleoid-like” structure. The stress in mitochondria that triggered by a variety of factors, such as pathogen infection, ROS accumulation, and ion depletion, can cause multiple mitochondrial metabolisms downstream. For example, much research showed that damaged mtDNA elicited by TFAM deficiency or herpesviruses invasion could be detected by cGAS, which is a cytosolic nucleotide synthase that binds DNA. Then cGAMP synthesized by cGAS directly engages STING to recruit and enable TANK-binding kinase 1 (TBK1). And, IRF3 phosphorylated by TBK1 translocated into the nucleus, where it enhances IFN-stimulated gene expression, elevates type I interferon responses, and confers broad viral resistance.
Coincidentally, relative to mtDNA, Tigano et al. demonstrated that cytoplasmic accumulation of mitochondrial RNA (mtRNA) also can serve as an intrinsic immune surveillance mechanism for cells and potential intracellular antiviral signaling in the Nature journal recently. They show that mitochondrial DNA double-strand breaks (mtDSBs) activate a type I interferon response through the phosphorylation of STAT1 and activation of interferon-stimulated genes. Once the formation of breaks in the mtDNA, mitochondrial RNA is released into the cytoplasm where triggers a RIG-I-MAVS-dependent antiviral immune response. Collectively, we conclude that mtRNA synergizes with mtDNA to mount a robust cellular immune surveillance in viral infection.

3 | CALCIUM SIGNALING IN HBV INFECTION

Calcium (Ca2+) is a cellular second messenger, which can mediate amounts of proteins to regulate multiple diseases that involve a variety of physiological processes, including HBV infection. At present, many studies have shown that HBV can enhance cytosolic Ca2+ levels through the plasma membrane (PM), mitochondria, and endoplasmic reticulum (ER). In HBV-infected cells, elevated calcium ions promote viral replication via some related molecular mechanisms. Here, we summarized the correlation between the calcium (Ca2+) metabolism and HBV infection, in order to find a therapeutic target for inhibiting HBV replication.

3.1 | Calcium signaling in mitochondria

The calcium (Ca2+) in mitochondria is an important cellular messenger, which contributes to the tricarboxylic acid cycle and ATP synthesis. Ca2+ fluxing into mitochondria is mainly via voltage-dependent anion channel (VDAC) in OMM and (mitochondrial Ca2+-uniporter) MCU in IMM. Increasing data show that HBx can induce mitochondrial Ca2+ uptake by interacting with VDAC3 and increasing MCU expression. As Ca2+ is overloaded in the mitochondrial matrix, mitochondrial Na+/Ca2+ exchanger (mNCX) and mitochondrial permeability transition pore (mPTP) are activated to open, in turn, which leads Ca2+ to escape the mitochondria and is released into the cytoplasm. However, it has been demonstrated that the outflow of Ca2+ from mitochondria into cytoplasm can be augmented through controlling mPTP and mNCX by HBx. And, tons of studies have proved that elevated calcium ions in the cytoplasm can promote HBV replication.

3.2 | Calcium signaling in plasma membrane and endoplasmic reticulum

The regulation of calcium signaling in PM and ER depends on diverse ion channels. For instance, for the PM, Ca2+ enters cells principally rely on PM store-operated Ca2+ (SOC) channels and voltage-operated Ca2+ channels (VOCs). And conversely, it is excreted by Na+/Ca2+ exchanger (NCX) and PM Ca2+ ATPase (PMCA) channels. Recently, it is reported that HBx can enhance the capacity of Ca2+ influx via binding the ORAI1 protein, which is one of the key components of SOC channels. On the contrary, Chami et al. demonstrated that HBx is capable of inhibiting the outflux of Ca2+ by restricting the activity of the PMCA channel. In the ER, calcium ion sensors and sarco/endoplasmic reticulum ATPase (SERCA) pump Ca2+ into the lumen of ER, where Ca2+ is extruded by ryanodine receptor (RyR) and inositol 1,4,5-trisphosphate receptor channels (IP3R).

In recent years, more and more studies have shown that the activation of Ca2+ signaling pathway is closely related to virus replication, and HBx, which is not a viral structural protein, plays a key role in HBV replication. At present, it is reported that HBx can activate Pyk2/Src and FAK signals through increased calcium ions to promote HBV replication. In addition, under the higher level of Ca2+ circumstances in the cytoplasm, HBx can harness the cell cycle, and mitochondria will make robust responses and undergo fusion, fission, and mitochondrial permeability transition pore (mPTP) channels on mitochondria and activation of the IP3 signaling pathway on the endoplasmic reticulum.

4 | CONCLUSIONS

The evidence displayed in this review implied that HBV infection elicits various metabolic alterations intracellularly, and the host body has the ability to engage adaptive metabolic reprogramming to inhibit the invasion of HBV. Liver tissue is the pivotal metabolic organ, and mitochondria play a major role in metabolic reprogramming since their high content in liver tissue. Once HBV enters into the cell, the encoded HBx protein will be embedded in the mitochondria and interferes with mitochondrial metabolic activities, including destroying the mitochondrial structure, increasing the activity of ROS in the cytoplasm, and inhibiting the antiviral signaling pathway by interacting with the MAVS protein. Correspondingly, mitochondria will make robust responses and undergo fusion, fission, and mitochondrial permeability transition pore (mPTP) channels on mitochondria and activation of the IP3 signaling pathway on the endoplasmic reticulum.
pathway may be a potential target for anti-HBV infection therapy and diagnosis.

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CONFLICTS OF INTEREST
We declare that we have no conflicts of interest.

DATA AVAILABILITY STATEMENT
No primary datasets have been generated and deposited. Additional data related to this study may be requested from the corresponding author at ouqishui@fjmu.edu.cn.

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