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Editorial: Perilipin2 inhibits the replication of hepatitis B virus deoxyribonucleic acid by regulating autophagy under high-fat conditions

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Abstract

Hepatitis B virus (HBV) infection poses a global health concern without a definitive cure; however, antiviral medications can effectively suppress viral replication. This study delves into the intricate interplay between lipid metabolism and HBV replication, implicating molecular mechanisms such as the stearoyl coenzyme A desaturase 1 (SCD1)-autophagy pathway, SAC1-like phosphatidylinositol phosphatase (SACM1L/SAC1), and galectin-9 mediated selective autophagy of viral core proteins in regulating HBV replication. Within lipid droplets, perilipin-2 (PLIN2) emerges as a pivotal guardian, with its overexpression protecting against autophagy and downregulation stimulating triglyceride catabolism through the autophagy pathway. This editorial discusses the correlation between hepatic steatosis and HBV replication, emphasizing the potential role of perilipin-2 (PLIN2) in this process. The study underscores the multifaceted roles of lipid metabolism, autophagy, and perilipins in HBV replication, shedding light on potential therapeutic avenues.

INTRODUCTION

Hepatitis B virus (HBV) infection represents a significant global health concern[1]. The main objective of treatment is to achieve prolonged suppression of hepatitis B replication. Nevertheless, it is important to note that no method can completely

eradicate (sterilizing cure) the hepatitis B virus[2]. Therefore, it is imperative to explore novel mechanisms of HBV DNA replication, investigate biological processes linked to its replication, and discern effective methods for clearing the virus. This exploration aims to establish a foundation and generate renewed ideas for the treatment of hepatitis B virus.

Autophagy is a cellular process responsible for delivering and degrading cytoplasmic components within lysosomes to support intracellular stability. These components include misfolded proteins, damaged organelles, and various intruding pathogens[3].

Many infectious microorganisms either inhibit autophagy, thereby dampening the immune response, or manipulate autophagy to favor pro-microbial activities[4]. Viruses that specifically target the liver, such as HBV, hepatitis C virus (HCV), dengue virus (DENV), and SARS-CoV-2, exploit autophagy for their pro-viral objectives. This mechanism assumes a crucial role in the life cycle of HBV, actively participating in viral assembly, envelope formation, and degradation processes[5]. Autophagy has also been shown to be associated with lipid metabolic diseases[6]. The accumulation of excess triglycerides (TG) in the liver is a fundamental factor in the development of fatty liver disease, a highly prevalent condition. The correlation between HBV infection and metabolic dysfunction-associated fatty liver disease (MAFLD), formerly known as non-alcoholic fatty liver disease (NAFLD)[7], has been a persistent focus in research.

The study by Choi *et al* suggests that the combination of MAFLD and chronic hepatitis B can collectively exacerbate liver damage. The coexistence of chronic hepatitis B and MAFLD amplifies the likelihood of liver fibrosis, increases the risk of cancer, and contributes to an overall elevated mortality rate[8]. However, another study has shown that individuals with MAFLD concurrent with chronic HBV infection ~~were examined alongside those suffering solely by MAFLD. The results unveiled that the HBV-infected group~~ exhibited lower levels of serum lipid metabolism-related index compared to the uninfected group. This indicates that chronic HBV infection may have a beneficial impact on lipid metabolism and liver impairments related to steatosis, potentially due to improvements in lipidomic profiles[9]. The relationship between HBV infection,

MAFLD, and the effects of chronic HBV infection on lipid metabolism is still controversial and deserves further studies to elucidate the precise mechanism.

HBV can induce autophagy and use to increase replication[5]. The removal of fat by autophagy, also known as lipophagy, is currently considered an alternative pathway for lipid metabolism in liver cells[10]. This degradation of autophagy prevents hepatotoxicity and steatosis[11]. However, it is not known whether there is a correlation between HBV-related autophagy and the progression of MAFLD. Consequently, it is imperative to investigate this relationship from various approaches and explore multiple directions to gain clarity on the pathogenesis of HBV complicating MAFLD. Hence, we postulate that delving into autophagy represents a crucial avenue for research to understand the mechanism underlying the association of HBV with MAFLD.

The molecular mechanisms involved in the relationship between autophagy, lipids and HBV replication has been started to be elucidated in the last two years. Among these, the stearoyl coenzyme A desaturase 1 (SCD1)-autophagy pathway has been implicated in inhibiting HBV replication by fatty acids stimulation[12], SAC1-like phosphatidylinositol phosphatase (SACM1L/SAC1), a membrane protein integrated into the endoplasmic reticulum, promotes the autophagic degradation of HBV virions[13], and galectin-9 mediated selective autophagy of viral core proteins to restrict HBV replication[14].

In the present issue of WJV, Wang C *et al* study aims to explore mechanisms underlying the association between lipid metabolism and HBV-DNA replication. The study included 1603 HBsAg-seropositive patients, of which 661 were HBeAg-seropositive, and 942 were HBeAg-negative, with no prior antiviral treatment. The aim was to evaluate the effect of the lipid profile on HBV viral replication. The findings revealed a negative correlation between hepatic steatosis, serum triglyceride load, and blood HBV-DNA load in both HBeAg-positive and HBeAg-negative groups. These results suggest that heightened lipid metabolism in the body may exert an inhibitory effect on HBV replication. A crucial factor to consider is that the patients enrolled in the study were

untreated, emphasizing that the observed outcomes stem directly from the virus's unmitigated impact. This significance arises from prior research, which suggests that IFNα-2a treatment could potentially disrupt various intracellular signaling pathways, initiate autophagy, and impede autophagic degradation, potentially leading to a modest increase in HBV replication[15].

TG are stored in lipid droplets, which serve as the primary organelle for lipid storage in the liver. Within these lipid droplets, a group of proteins known as perilipins (PLINs) resides, with PLIN2 being the most abundant. Encoded by five different genes (Plin1 to Plin5), PLIN2 stands out as the only constitutive and widely expressed lipid droplet protein. Consequently, PLIN2 is commonly utilized as a protein marker for lipid droplets. In liver PLIN2 functions as a guardian of its own domain, the lipid droplet[16]. When PLIN2 is overexpressed, it acts as a protective shield against autophagy. Conversely, when PLIN2 is downregulated, it triggers TG catabolism through the autophagy pathway[17].

In the present issue of WJV, Wang C *et al* revealed, using *in vitro* assays, that the treatment of HepG2.2.15 cells with fatty acids (oleic and palmitic acid) increased lipid droplet deposition but decreased the level of HBsAg, HBeAg, and HBV-DNA load in cell supernatant. This mechanism was found to involve PLIN2 by inhibiting autophagy, as revealed by knocking down and overexpressing the protein. These results are in contrast with previous findings demonstrating that HBV replication is inhibited when autophagic degradation of HBV virions is promoted[12-14]. The article by Popescu *et al* revealed that the depletion of SAC1 Leads to the accumulation of phosphatidylinositol 4-phosphate (PI4P), hindering the trafficking of the HBV envelope protein to multivesicular bodies in SAC1-knockout Huh7 cells. Consequently, this disruption inhibits the envelopment and secretion of HBV nucleocapsids, suggesting that SAC1 could play a crucial role as a host cell factor in controlling viral morphogenesis[18]. SAC1 plays a vital role in inducing autophagy, and its deficiency hinders the fusion of autophagosomes with lysosomes[19]. A series of experiments conducted by Zheng *et al* further supports the conclusion that SAC1 actively facilitates the autophagic

degradation of HBV virions[13]. Also, Du *et al* demonstrated that under conditions of elevated lipid levels, SCD1 acts to inhibit HBV replication by regulating autophagy[12]. Alternatively, galectin-9 could inhibit HBV replication *via* selective autophagy of viral core proteins in a mechanism that involved type I IFN genes[14].

The study in the present issue of WJV by Wang C *et al*, together with previous findings, offers a theoretical foundation and innovative concepts for the treatment of individuals with chronic HBV infection and disrupted lipid metabolism.

CONCLUSION

In summary, Wang C *et al*'s study suggests that the stimulation of fatty acids inhibits the replication of the Hepatitis B Virus (HBV) by increasing the expression of Plin2 and suppressing autophagy in hepatocytes. This process is linked to lipid metabolism, the autophagy pathway, and HBV replication. Further research on the interplay between Plin2, and autophagy is crucial for gaining a better understanding of HBV host interactions and its pathogenesis. It also proposes a potential avenue for treating individuals with chronic HBV infection coupled with MAFLD. These findings contribute to comprehending the intricate dynamics of HBV infection, lipid metabolism, and autophagy-opening an important potential link in the study of new drug targets in the process. While the role of autophagy in HBV infection has become evident, it remains unclear whether selective autophagy plays a crucial role in restricting HBV.

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