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COMMENTARY

The butterfly effect in viral infection: From a host DNA single nucleotide change to HBV episome steadiness

Elena S. Kim, Haitao Guo*

Department of Microbiology and Immunology, Indiana University School of Medicine, Indianapolis, IN, USA

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Chronic hepatitis B virus (HBV) infection is one of the major health care burdens throughout the world. The chronicity of HBV infection is supported by the intracellular persistence of a multicopy viral episome called covalently closed circular DNA (cccDNA), which is the *bona fide* viral transcription template and resistant to currently available antivirals.[1] Therefore, noncytolytic elimination of cccDNA is considered as the "holy grail" for a cure of hepatitis B, and the metabolism and transcription regulation of cccDNA have become a hot topic in basic, translational, and clinical HBV research.[2]

In a recent publication, Zhou et al conducted a case control study and identified a single nucleotide variant (SNV), rs59391722, located at −1128 bp of the promoter region of ubiquitin-conjugating enzyme E2L3 gene (UBE2L3, also called UBCH7), which is associated with susceptibility to HBV infection in children.[3] The SNVs at this site were found to be GG as a major SNV, and CC as a minor one, with transitional CG in Chinese Han population. GG and CG SNVs are associated with a higher binding efficiency of transcription activator NF-E2, leading to UBE2L3 upregulation compared to that in CC. Furthermore, via overexpression and knockdown approaches, the authors demonstrated that UBE2L3 facilitates HBV replication and antigen production primarily through maintaining cccDNA stability. Mechanistic studies revealed that UBE2L3 catalytically promotes the ubiquitin-dependent proteasomal degradation of a cellular cytidine deaminase APOBEC3A (A3A), which has been shown to cause base-pair mismatch hypermutations in cccDNA for apurinic/apyrimidinic endonuclease (APE1)-dependent degradation.[4] In addition, considering that A3A is an interferon-stimulated gene (ISG), the authors showed that UBE2L3 silencing could potentiate the antiviral activity of alpha-interferon (IFN-α) in cell culture model. Taken together, this study has further validated the function of A3A in editing and removing cccDNA, and established a proviral role of rs59391722-UBE2L3-A3A nexus in cccDNA persistence (Fig. 1).

One of the strong sides of the work is that the authors analyzed HBV-associated SNVs from a small cohort of pediatric patients, as most chronic hepatitis B (CHB) patients acquire the infection through vertical transmission or during early childhood.[5] Besides the immunological dysfunction, the SNVs, such as rs59391722(C→G), may also contribute to the development of chronic HBV infection. Previous genome-wide association studies (GWASs) have largely focused on adult cohort and identified HBV-associated SNVs at 8 loci, including 7 HLA-related genes and UBE2L3, but

* Corresponding author. Department of Microbiology and Immunology, Indiana University School of Medicine, 635 Barnhill Drive, Indianapolis, IN 46202 USA.
E-mail address: haitguo@iupui.edu (H. Guo).
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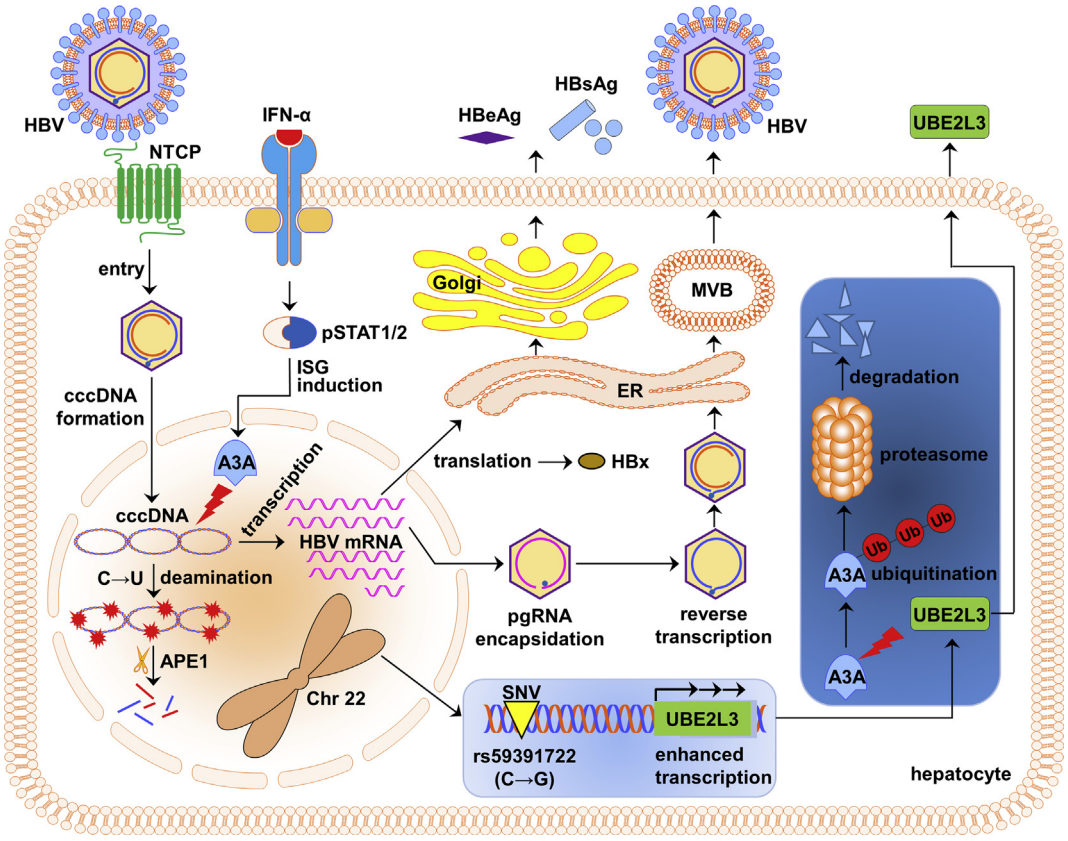

Figure 1 The rs59391722-UBE2L3-APOBEC3A nexus regulates HBV cccDNA stability. HBV establishes and maintains persistent infection in hepatocyte via the viral episomal cccDNA, which serves as transcription template to produce progeny virus and viral antigens (HBeAg, HBsAg, HBx). IFN-α treatment induces cccDNA degradation through ISG APOBEC3A (A3A)-mediated cccDNA cytidine deamination and subsequent APE1 cleavage. Zhou et al[3] identified a SNV rs59391722(C→G) that upregulates the expression of UBE2L3, which ubiquitinates A3A for proteasomal degradation, thereby maintaining the persistence of cccDNA and HBV infection.

lacked functional validations.[6–8] The study by Zhou et al, for the first time, established the positive correlation of UBE2L3 expression with the clinical outcome of HBV infection in both adult and children patients; and delineated the UBE2L3-A3A axis as a novel regulatory mechanism of cccDNA longevity in cell culture infection models.

This study has opened a new venue for future HBV research. It would be interesting to perform an extended study with wider sampling of CHB patients with different age and ethnic background to further justify the link between rs59391722 SNVs and HBV persistence. The co-evolution of HBV subtypes and SNVs patterns could also be assessed along with estimate of evolutionary advantage of the rs59391722 haplotypes. The UBE2L3-A3A axis can be further explored to identify additional viral/host factors that regulate cccDNA metabolism and function. One question would be whether HBV enhances the expression of UBE2L3 for its benefits. The answer might be yes because the authors showed that IFN-α downregulated UBE2L3 when HBV was inhibited by the cytokine. UBE2L3 is an E2 ubiquitin-conjugating enzyme, and even though it has been reported to have an E3-independent reactivity with lysine,[9] whether a specific E3 ubiquitin ligase, such as the UBE2L3-interacting UBE3A/E6AP,[10] is required for UBE2L3-mediated ubiquitination of A3A awaits further investigation.

From the translational medicine perspective, the rs59391722(C→G) SNV may represent a risk factor for neonatal and childhood HBV infection, and the serum UBE2L3 may serve as a novel biomarker for monitoring the progression of hepatitis B and for prediction of response to IFN-α therapy. However, these potential diagnostic and prognostic values of rs59391722 and UBE2L3 should be further evaluated in larger cohort of patients. Since both cccDNA persistence and eradication largely rely on host functions, this study suggests that UBE2L3, or ideally the more-specific E3 ubiquitin ligase, if any, may be exploited as an antiviral target to promote A3A-mediated cccDNA decay and more importantly, to synergize IFN-α therapy.

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