Correspondence

Correspondence on Editorial regarding “Class II Transactivator Restricts Viral Replication and Extends Its Effect to HBV”

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Abbreviations:

HBV, hepatitis B virus; HBx, HBV X protein; IFN-γ, interferon gamma; MHC, major histocompatibility complex; CIITA, class II transactivator; SARS, severe acute respiratory syndrome; HNF, hepatocyte nuclear factor; ERK1/2, extracellular signal-regulated kinase; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; HTLV-2, human T-cell leukemia virus type 2; HCMV, human cytomegalovirus; EBV, Epstein-Barr virus; KSHV, Kaposi’s sarcoma-associated herpesvirus; HIV, Human immunodeficiency virus
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Dear Editor,

We are grateful to Cho-Rong Lee and Professor Sung-Gyoo Park for the insightful comments and the opportunity to respond to the editorial correspondence regarding our recent publication, “Novel role of MHC class II transactivator in hepatitis B virus replication and viral counteraction”⁴. We appreciate the detailed overview provided on the significant role of major histocompatibility complex (MHC) class II transactivator (CIITA) as a master regulator of MHC class II gene expression and its broader implications in antiviral defense mechanisms⁵. The comprehensive summary of how various viruses, including Human Cytomegalovirus (HCMV), Epstein-Barr virus (EBV), Kaposi’s sarcoma-associated herpesvirus (KSHV) and Human immunodeficiency virus (HIV), interact with and modulate CIITA function underscores the critical importance of this transcription factor in immune regulation and viral pathogenesis. Our study extended current knowledge on anti-viral function of CIITA by demonstrating that CIITA inhibits HBV replication through the downregulation of hepatocyte nuclear factors HNF1α and HNF4α via the ERK1/2 signaling pathway. We were particularly interested in exploring CIITA’s role beyond its canonical function in antigen presentation, prompted by previous reports of CIITA’s antiviral activity against other pathogens such as Ebola virus (EBOV) and SARS-CoV-2⁶. Importantly, in the editorial, they pointed out the non-DNA-binding co-activator characteristic of CIITA⁶ which reinforces our findings regarding the indirect down-regulation of HBV transcription by reducing the expression of HNF1α and HNF4α through the ERK1/2 pathway.

MHC class II molecules are known to be predominantly expressed on antigen-presenting immune cells and not normally expressed on hepatocytes. However, since aberrant MHC class II expression has been reported in patients with hepatitis or cirrhosis⁷⁻⁹, it is likely that the expression of CIITA is well induced in hepatocytes by IFN-γ in chronic hepatitis B patients, which in turn induces the expression of MHC class II molecules on the surface of hepatocytes. Moreover, our findings corroborated its induced expression in primary human hepatocytes (PHHS) under IFN-γ stimulation. Therefore, it is likely that the increased expression of CIITA by IFN-γ enhances the antiviral activity of CIITA not only through the non-canonical pathway that we found in this study, but also by increasing the expression of MHC class II molecules on the surface of hepatocytes, which promotes anti-HBV activity by immune cells. This induction suggests a broader functional spectrum for CIITA, particularly in liver cells during HBV infection.
CIITA exerts an antiviral response against many viruses, including HIV, SARS-CoV-2, EBOV and Human T-cell lymphotropic virus (HTLV) as highlighted in the editorial2, 3, 7. The predominant mechanism of CIITA's antiviral activity in these viruses is through the suppression of viral replication by blocking viral transactivators. In the case of HBV, CIITA inhibits viral replication by reducing the activity of its enhancers and promoters1.

Our research paper focused on unveiling the mechanism of IFN-γ-induced CIITA anti-HBV activity and the counteraction of HBx with its antiviral function. Meanwhile, the editorial emphasized the regulation of MHC class II expression by CIITA, which is essential for a specific immune response, along with the immune evasion mechanisms adopted by other viruses to interfere with CIITA’s role in promoting MHC class II expression. As clearly noted in the editorial, aside from HIV that interferes with the function of CIITA at the protein level8, it appears that other viruses mostly interrupt the regulatory function of CIITA at the level of transcription to escape the host immune system2,9-12. We showed that HBx interacts with CIITA through protein-protein binding, thereby blocking CIITA's anti-HBV function. Therefore, we concur with the commentary that HBx’s direct binding to CIITA represents a novel immune evasion mechanism. Our data suggest that while HBx increases CIITA protein stability, it simultaneously impairs its functional activity, likely through mechanisms involving nuclear translocation, masking domain required for ERK activation or post-transcriptional modifications. This dual role of HBx adds complexity to the HBV-host interaction landscape and identifies potential therapeutic targets.

Additional research will be needed to determine the precise interfering role of HBx in the antiviral activity of CIITA. HBx might as well compete with CIITA for binding to the promoter of MHC class II gene in HBV infected hepatocytes to attenuate the antigen presenting on the cell surface. Therefore, through further research on these hypotheses, we hope to accumulate knowledge about the mechanism and role of immune evasion of HBV in liver diseases and apply its potential as a target for antiviral strategies to treatment. The editorial rightly points out the multifaceted role of CIITA in various viral infections and its potential therapeutic utility. We agree that further elucidation of the precise molecular mechanisms by which CIITA modulates HBV replication and its interplay with HBx will be crucial. The global effort to identify new therapeutic targets for HBV cure is enormous, with a number of drugs currently in clinical trials13. Therefore, investigating CIITA’s role in the broader context of the host immune response, including its effects on other cytokine pathways and immune cell interactions, will provide deeper insights into its antiviral potential.
Author contributions

M Dezhbord drafted the manuscript. KH Kim edited and finalized the manuscript.

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Conflicts of Interest

The authors have no conflicts to disclose.
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