

Trieste, January 30, 2022

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Editors-in-Chief
World Journal of Hepatology
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Dear Respected Editors,

We submit the revised version of our Ms (ID: 05188931) with the title "The role of Hepatitis B virus in the development of hepatocellular carcinoma: Focus on cccDNA" to be considered in the World Journal of Hepatology.

We thank the overall similar comment by both reviewers which leads a straightforward revision of this Ms. In response to the letter of the editorial office, we had extensively revised the previous version and prepared answers that address the comments by the reviewers.

We hope to have comprehensively and successfully dealt with the critiques, which further helped to improve the quality of the Ms, and expect this may be now officially accepted for publication. On behalf of all the co-authors, I thank you for your attention and send you our best regards.

Sincerely yours,

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ANSWERS TO THE REVIEWERS

Reviewer 1

This review is a comprehensive summary of the role of cccDNA in the pathogenesis of CHB, especially in HBV replication. And the review also well summarizes the current choice of cccDNA detection and which as a current target for treatment. But unfortunately, the above aspects have been related reported. This article is not deep enough for the mechanism of cccDNA and HCC. However, this should be a key point and mostly interest. On the other hand, it is still possible in the pathogenesis of HCC although HBV has been inhibited even HBsAg has been cleared.

We sincerely thank the Reviewer for their evaluation together with careful and constructive comment, in particular, in pointing out that the manuscript comprehensive and well summarized.

In the revised Ms, we had extensively revised our Ms by deleting the known-information on HBV pathogenesis and DNA integration in host genome, and adding a comprehensive review on the mechanisms of cccDNA in the development of HCC in a new section. We cited for more than 20 new appropriate references to strengthen the message of the Ms (Ref. 55-61, 67-83, and 120 of the revised Ms). The new designed Figure 2 (below) summarized the complete mechanisms of the role of cccDNA in hepatocarcinogenesis.

Reviewer 2

While the title is "role of Hepatitis B virus in the development of hepatocellular carcinoma: Focus on cccDNA", this review actually summarizes the general information of HBV, with a focus on the function of cccDNA on viral replication and our current efforts to the detection and targeted inhibition of cccDNA. The authors have discussed three major mechanisms underlying HBV-related carcinogenesis (1 chronic inflammation; 2. HBV DNA integration; 3. expression of oncogenic viral proteins), but cccDNA was not even mentioned in that part. Thus, how cccDNA promotes the initiation and progression of HCC is still unclear after reading the whole text. And there was also no evidence showing that using the approach targeting cccDNA can prevent the development of HCC.

We sincerely thank the Reviewer for their evaluation together with careful and constructive comment. In the previous Ms, cccDNA is one focus of the Ms and not the whole intent. Nevertheless, we agree that HBV pathogenesis in known and here we would focus only on the cccDNA. Our answer to the Reviewer query is similar as to the other Reviewer.

In the revised Ms, we had extensively revised our Ms by deleting the known-information on HBV pathogenesis and DNA integration in host genome, and adding a comprehensive review on the mechanisms of cccDNA in the development of HCC in a new section. We cited for more than 20 new appropriate references to strengthen the message of the Ms (Ref. 55-61, 67-83, and 120 of the revised Ms). The new designed Figure 2 (below) summarized the complete mechanisms of the role of cccDNA in hepatocarcinogenesis.

Figure 2. Proposed mechanisms for the role of cccDNA in hepatocarcinogenesis. **A.** Modulation of miR-154/PCNA/HBV cccDNA signalling. **B.** Modulation of HBx/STAT3/miR-539/APOBEC3B. **C.** Positive feedback loop of HULC and HBx/MSL2/HBV cccDNA. **D.** HBx/DLEU2 interaction to activate cccDNA. **E.** HBx/DLL4/Notch 1 signaling pathway. **F.** Reduction of cccDNA levels to avoid immune recognition.

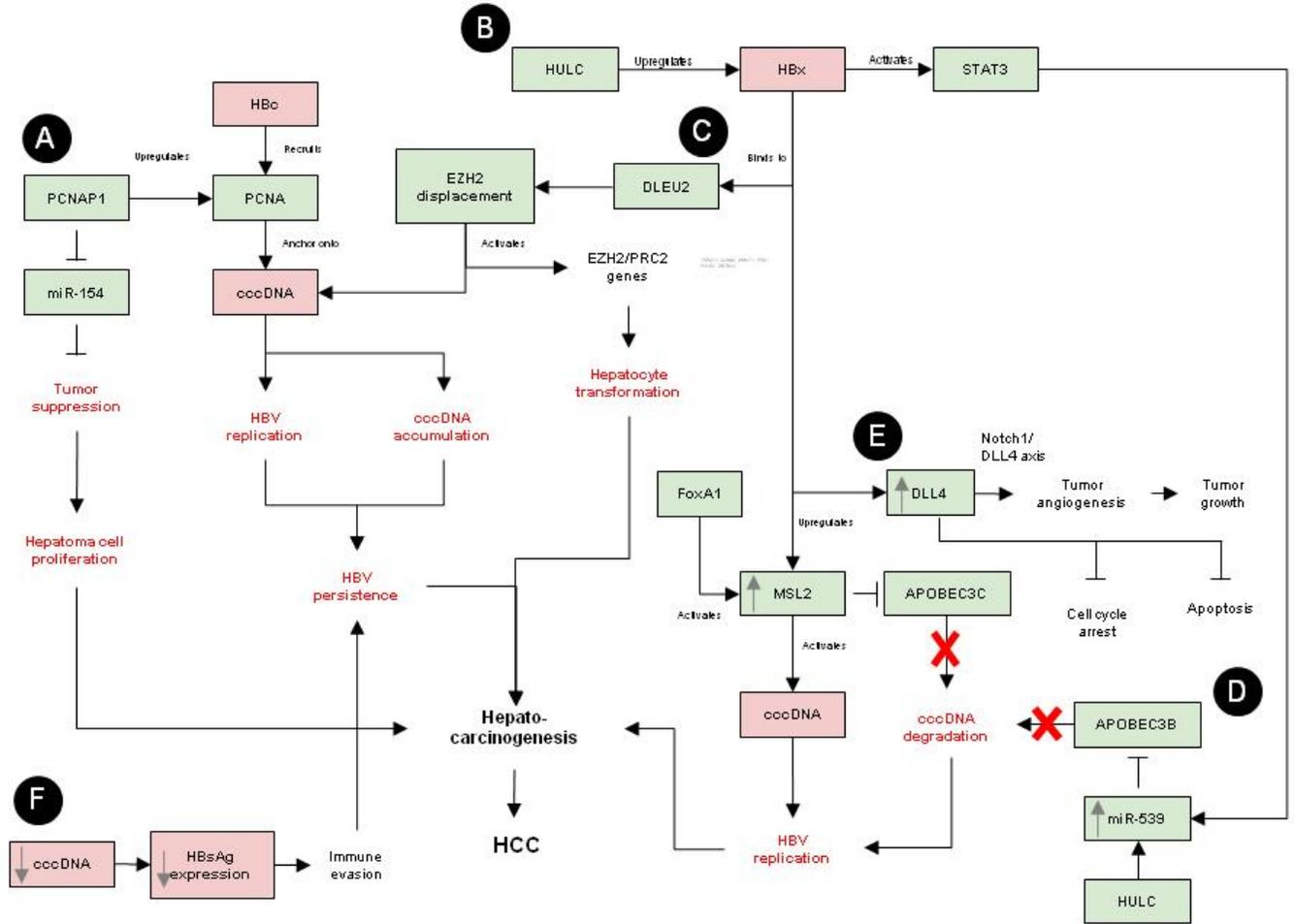


Figure 1. HBV life cycle and cccDNA **A.** HBV entry and replication in host cell (adapted from [44]). **B.** rcDNA conversion into cccDNA

