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OPEN PEER REVIEW

Identification of Potential miRNA-mRNA Regulatory Axis of Intrahepatic cccDNA in Patients with Chronic Hepatitis B Virus Infection in the Grey Zone

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About this report

This open peer review (OPR) report shows the public comments made on this article during peer review, by the reviewers, the associate editor and the editor-in-chief, for every revision round, together with the authors' replies. Comments appear only with the consent of the people who wrote them. Reviewers who chose to sign their report are named; the others are shown as "Referee". Comments are edited for language only, and confidential remarks to the editors are not included.

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1 Original submission

2 comments · 13 Feb 2023 – 13 Feb 2023

Associate Editor

MAJOR REVISION 13 Feb 2023

Major Revision

Editor-in-Chief

MAJOR REVISION 13 Feb 2023

Dear Authors,

Please follow the peer-review comments and submit a revision.

Regards
EIC

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Revision 1

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

February 24, 2023

Subject: Revision and resubmission of manuscript 133782

Dear editor,

We would like to thank the reviewers for careful and thorough reading of this manuscript “Identification of potential miRNA-mRNA regulatory axis of intrahepatic cccDNA in patients with chronic hepatitis B virus infection in the grey zone” and for the thoughtful comments and constructive suggestions, which help to improve the quality of this manuscript. Below, we also provide a point-by-point response explaining how we have addressed each of the reviewers’ comments. We look forward to the outcome of your assessment.

Reviewer #1:

Congratulations for selecting UpToDate topic, your manuscript is well written and cohesive. But some major revisions need to be considered.

• Methods:

1) Please describe the reason for selecting a small amount of samples.

Response: Thank you for your suggestion. Although we performed a comprehensive analysis and successfully identified several potential miRNA-mRNA axes involved in the regulation of cccDNA in the liver of CHB-GZ patients, we acknowledge the small sample size as a limitation of this study. Although there are a large number of hepatitis B virus-infected people all over the world, but the patients who are in the grey zone and need liver biopsy only account for a small part. In the future, larger clinical samples and corresponding experiments are needed to verify our results.

2) The ethics code and approval ID for the study didn’t mention in the method section. Please add it in patients and liver tissue samples section.

Response: Thank you very much for your suggestion. This study was approved by the ethics committee of the Virgen Macarena-Virgen del Rocío University Hospitals (Approval ID: CEI-HUVM-VR-30/04/2019) and each patient signed informed consent. Based on your suggestion we have included the ethics approval ID for this study in the patients and liver tissue samples section. At the same time, the ethics committee certificate is attached.

3) In Quantification of intrahepatic cccDNA section, the cccDNA primers have not provided in the manuscript's text; I suggest you to mention them in form of a table or, etc.

Response: Thank you very much for your suggestion, we have included the primers and the probe of intrahepatic cccDNA quantification in the manuscript.

Table 1. The primers and the probe of intrahepatic cccDNA quantification

cccDNA	*Forward*	CCGTGTGCACTTCGCTTCA	1577–1595
	Reverse	GCACAGCTTGGAGGCTTGA	1884–1866
	Probe	CATGGAGACCACCGTGAACGCCC	1609–1631

4) Cite any datasets and databases in methods section.

(i.e. cite KEGG: Kanehisa, M. and Goto, S.; KEGG: Kyoto Encyclopedia of Genes and Genomes. Nucleic Acids Res. 28, 27-30 (2000). And provide the URL like: https://www.genome.jp/kegg/)

Response: Thank you very much for your suggestion, in the revised manuscript we have added references to the referenced datasets and databases and provided web URL links.

5) Cite and specified the package you used to illustrate the interactions by

cytoscape software.

Response: Thank you very much for your suggestion, in the revised manuscript we have added references to the cytoscape software, provided web URL links and specified the package we used.

• In the discussion section, in case of possibility more evidence and comparison need to prove and affirm your data and study.

Response: Thank you for your suggestion. This is the first study to reveal the relationship between miR-4295 - ZNF224 and the HBV infection process, so there are very few literatures and evidences that can be cited, but we try our best to search a large number of literatures to support our data. Based on your suggestions, we have reworked and enriched the discussion section.

• I recommend you to add a section entitled ‘limitations’ in your manuscript.

Response: Based on your suggestion we have included a limitations section in the manuscript.

Limitations

Although we performed a comprehensive analysis and successfully identify several potential miRNA-mRNA axes involved in the regulation of intrahepatic cccDNA in CHB-GZ patients, we acknowledge that this study has some limitations. The sample size is relatively small, it contains only 13 liver tissue samples. Moreover, the target miRNA-mRNA regulatory axis is not validated by in vivo and in vitro experiments. Therefore, larger clinical samples and corresponding experiments are needed to verify our results in the future, as well as long-term follow-up to observe the progress of the disease.

Yours sincerely

Authors

2 Revision 1

4 comments · 1 Apr 2023 – 9 Apr 2023

Referee 1 Reviewer — ACCEPT 1 Apr 2023

Thanks for the improvements and corrections to the manuscript. All the comments were answered correctly and appropriately.

Referee 2 Reviewer — ACCEPT 8 Apr 2023

Accept

Associate Editor — ACCEPT 8 Apr 2023

Accept

Editor-in-Chief — ACCEPT 9 Apr 2023

Dear Authors,

I am delighted to inform you that your manuscript is accepted for publication.

Regards,
EIC