



PEER-REVIEW REPORT

Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 67569

Title: Hepatitis B core antigen modulates exosomal miR-135a to target VAM Y promoting proliferation and Doxorubicin chemoresistance in hepatocellular carcinoma

Reviewer's code: 03648086

Position: Editorial Board

Academic degree: MD, PhD

Professional title: Assistant Professor, Director, Senior Scientist

Reviewer's Country/Territory: United States

Author's Country/Territory: China

Manuscript submission date: 2021-04-27

Reviewer chosen by: AI Technique

Reviewer accepted review: 2021-05-11 17:51

Reviewer performed review: 2021-05-17 20:38

Review time: 6 Days and 2 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input checked="" type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input type="checkbox"/> Anonymous <input checked="" type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



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SPECIFIC COMMENTS TO AUTHORS

Review report General comments: This study was carried out with the goal at trying to elucidate the role of exosomal miR-135a in the chemoresistance of hepatocellular carcinoma. The assays covered the expression levels of miR-135a-5p and target gene VAMP2 in HCC tissue and cell culture samples, various functional tests with mimic and inhibitor of miR-135a-5p, and specific assays for detection of apoptosis, cell proliferation and drug dox effects. The manuscript provided ample experimental findings and computational prediction of miR-135a-5p target gene. All these works were quite straight forward towards the elucidation of potential role of miR-135a that could play in the chemoresistance of HBV-associated hepatocellular carcinoma. While the study is interesting, the writing needs a great of efforts to improve the manuscript to a professional grade, both wording/grammar and clear/accurate description of the findings. Major issues Somewhat Subjective Conclusions/Claims: Authors carried out a lot of wet-lab experiments and bioinformatic analysis, with a main goal at trying to elucidate the role of miR-135a in hepatocellular carcinoma (HCC). Among the wet-lab assays, the level of miR-135 and target gene VAMP2 were measured in both HCC cells and derived exosomes. However, authors chose to make conclusions/claims for findings only in exosomes and did not mention the role of miR-135 in whole cells. This includes the title of the manuscript and the first 2 subtitles in Results section. Exosomal miRs would be good to be utilized as diagnostic tools when they reflect the changes in cellular activities. They may also exert their biological role by affecting adjacent and distal cells. Since miR-135a was elevated in both HCC cells and exosomes, the claim "HBV up-regulates the expression levels of miR-135a-5p in exosomes" would be better worded as "HBV may up-regulate the expression levels of miR-135a-5p in HCC cells and exosomes". The in vitro experiments revealed that miR-135a played a role in cell



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survival and proliferation by targeting VAMP2 and even induced chemoresistance via exosome route. It is suspected that miR-135a would paly the same role in whole cell level. Thus, why had authors to make conclusion “Hepatitis B core antigen modulates exosomal miR-135a to target VAMP2...” in the title of the manuscript? Did authors exclude the possibility that those effects of miR-135a might play out at the whole cell level? In addition, VAMP2 was identified as the target gene of miR-135a. However, it is suspected that miR-135a would target other genes as well. Thus, the claim “VAMP2 is the target gene of miR-135a-5p in HCC cells” should modified as “VAMP2 is a potential target gene of miR-135a-5p in HCC cells.” Inappropriate figure legends: Figure legends should mainly be used to explain things shown in the figures, such as the purpose of figure (i.e., what is this figure for?), labels, group definition, etc. Authors did not write up the necessary information. Instead, they put in a lot of interpretations for the findings, which should be placed in the Results section. Poor English: Ambiguous, inaccurate, and incorrect English wording and grammar were found throughout the whole manuscript, from abstract to introduction, methods, results and to discussion. Although authors provided a Certificate Service Confirmation on manuscript editing and proofreading service, these language errors indicate that no serious English editing and proofreading was performed responsibly. Specific comments The title of the manuscript would be better worded as “Hepatitis B core antigen modulates cellular and exosomal miR-135a to target VAMP2 and induce doxorubicin chemoresistance in hepatocellular carcinoma.” The “clinical” word was used in multiple places in the manuscript. By reading through the whole contents of the study, the reviewer found that it was wrongfully worded. Anything “clinical” would be referred to as patient characteristics such as age, gender, symptoms, etc. or at most could cover some clinical lab testing results but not the tissue samples taken from patients for basic research. Thus, authors should modify it accordingly. The reviewer has taken a liberty to correct some of those as indicated in the



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tracking changes file. The “Eighteen paired HCC tissues” description was not entirely clear. Since “paired” was used, authors should make sure what was the pair, normally it refers to as normal and cancer. See the “tracking changes” file for details. The “Hepatitis B virus ... and human VAMP2 ... were amplified separately according to sequences of these genes” needs a clarification. The “amplified” means a template should have been used. Otherwise, the “synthesized” may be the correct word here. See details in the “tracking changes” file. The “Total RNA was extracted using TRIzol reagent” was not clear for readers to understand what samples of origin was used in this process. Please show what samples were used in this process. See details in the “tracking changes” file. The “R software for bioinformatics analysis.” was not clear for readers to know/replicate how analysis was performed in R environment. Please list which R packages were used. See details in the “tracking changes” file. Authors have put some results in supplementary figures. However, those results had been used by authors to make major claims. Thus, these supporting findings should be presented in main figures. Particularly the supplementary figures 1-3 should be merged into Figure 1-2. See details in the “tracking changes” file. Throughout the whole manuscript, there are words, especially verbs that were used inaccurately, such as illustrate (better to use elucidate), manifest (better to use show), certify (better to use verify), signified (better to use suggested), disclose (better to use demonstrate), etc. See details in the “tracking changes” file. A lot of more English polishes were made by the reviewer. It is too many to list here. See details in the “tracking changes” file.



PEER-REVIEW REPORT

Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 67569

Title: Hepatitis B core antigen modulates exosomal miR-135a to target VAM Y promoting proliferation and Doxorubicin chemoresistance in hepatocellular carcinoma

Reviewer's code: 05562744

Position: Editorial Board

Academic degree: FACS, MD, PhD

Professional title: Professor, Senior Scientist

Reviewer's Country/Territory: Turkey

Author's Country/Territory: China

Manuscript submission date: 2021-04-27

Reviewer chosen by: AI Technique

Reviewer accepted review: 2021-05-11 04:52

Reviewer performed review: 2021-05-20 09:33

Review time: 9 Days and 4 Hours

Scientific quality	<input checked="" type="checkbox"/> Grade A: Excellent [] Grade B: Very good [] Grade C: Good [] Grade D: Fair [] Grade E: Do not publish
Language quality	<input checked="" type="checkbox"/> Grade A: Priority publishing [] Grade B: Minor language polishing [] Grade C: A great deal of language polishing [] Grade D: Rejection
Conclusion	<input checked="" type="checkbox"/> Accept (High priority) [] Accept (General priority) [] Minor revision [] Major revision [] Rejection
Re-review	<input checked="" type="checkbox"/> Yes [] No
Peer-reviewer statements	Peer-Review: [] Anonymous <input checked="" type="checkbox"/> Onymous Conflicts-of-Interest: [] Yes <input checked="" type="checkbox"/> No



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SPECIFIC COMMENTS TO AUTHORS

I would like to commend the authors for the excellent work. This in vitro study has shown that miR-135a-5p decreases apoptosis and increases the proliferative capacity of HCC cell lines through the VAPM signalling. It has very good insights to the HBV driven hepatocarcinogenesis.



RE-REVIEW REPORT OF REVISED MANUSCRIPT

Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 67569

Title: Hepatitis B core antigen modulates exosomal miR-135a to target VAM promoting proliferation and Doxorubicin chemoresistance in hepatocellular carcinoma

Reviewer's code: 03648086

Position: Editorial Board

Academic degree: MD, PhD

Professional title: Assistant Professor, Director, Senior Scientist

Reviewer's Country/Territory: United States

Author's Country/Territory: China

Manuscript submission date: 2021-04-27

Reviewer chosen by: Yun-Xiaojian Wu

Reviewer accepted review: 2021-08-04 15:17

Reviewer performed review: 2021-08-05 12:13

Review time: 20 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS



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No further revision warned