

March 24, 2015

Dear Editor,

Please see the attached edited manuscript in MS Word format (16395-edited.docx).

Title: HBV and miRNAs: Complex interactions affecting HBV replication and HBV-associated diseases

Authors: Jason Lamontagne, Laura F. Steel, and Michael J. Bouchard

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 16395

We thank the reviewers for their evaluation of our manuscript. As Reviewer 2 had no comments and suggested accepting the manuscript as is, we have addressed the suggestions of Reviewer 1. Therefore, this manuscript has been updated to address suggestions from Reviewer 1 and the Editor. Specifically:

1. A review by Thirion, et al. was published with a similar topic. The reviewer asked how our manuscript advances the field beyond the information presented in this previous review. The manuscript mentioned by the Reviewer, Thirion et al., was published in 2013, and as such our review has important and updated information on the field. In addition, our manuscript presents results in the context of the model system or techniques used in an attempt to help the reader make more informed interpretations of the results. By presenting the information this way, we hope to help to clarify some of the confusing and often-contradictory results found in the literature.

2. The reviewer suggested that a section on the role of circulating miRNAs in HBV pathogenesis be included in the review. While we appreciate the reviewer's suggestion, we feel that we have addressed the relationship of circulating miRNAs and HBV in our section titled "miRNAs and HBV-associated HCC". Specifically, we discuss the utility of profiles of serum biomarkers as early detection markers for chronic HBV infection and development of HBV-associated HCC. As the research involving HBV and secreted miRNAs has mainly focused on their utility as biomarkers, their role in HBV pathogenesis remains largely unexplored. Therefore, we feel it is most suitable to concentrate on the use of secreted miRNAs as biomarkers for HBV and HCC detection.

3. The reviewer pointed out that multiple studies have described varying expression levels of miRNAs, particularly miR-122. The reviewer suggested that we attempt to explain these study-to-study variations. In this manuscript we have made a strong attempt to put forth multiple potential explanations for the cases of study-to-study variability. While we chose not to

directly address these issues when discussing individual experiments or reports, we did give broad overviews of the model systems and techniques that are used in these HBV-miRNA studies, and explained the benefits, drawbacks, and limitations of each. With this information we feel we are not simply listing studies and their results, but instead are giving the reader the information to interpret results in the context of each experiment.

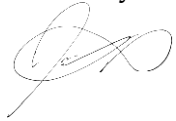
4. The reviewer suggested further emphasis should be placed on the clinical impact of miRNAs in HBV infection. As stated above, we have discussed the use of panels of miRNAs as biomarkers for HBV infection and HCC development. Additional research involving the clinical implications of HBV-miRNA research has been limited to correlative studies involving miRNA expression levels in patient samples. These types of studies have been included in our review. In addition, we also discuss the use of synthetic miRNAs designed to target HBV transcripts as a potential therapeutic application, in the "Future Directions" section of the manuscript.

5. The reviewer suggested shortening the introduction to make it more concise and improve organization. We have removed some of the more detailed points in the introduction that may not be necessary for the overall point of the review. We have entirely deleted the section describing "miRNAs and Viruses", as this was general background and not related to HBV.

The manuscript has also been edited to address comments from the Editor regarding figures and formatting. Each figure was placed on an individual page, and figures were uploaded as individual PowerPoint documents. Similarly, all tables were constructed in Excel and copied into Word.

Thank you for considering our manuscript for publication in *World Journal of Gastroenterology*. We hope that we have adequately addressed all suggestions of reviewers and the Editor and that this manuscript is now acceptable for publication.

Sincerely,



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