



## PEER-REVIEW REPORT

**Name of journal:** World Journal of Hepatology

**Manuscript NO:** 57925

**Title:** Pivotal role of LncRNA-XIST in regulating immune checkpoint PD- Y through a shared pathway between miR-194-5p and miR-155-5p in hepatocellular carcinoma

**Reviewer's code:** 03251421

**Position:** Editor-in-Chief

**Academic degree:** MD

**Professional title:** Professor

**Reviewer's Country/Territory:** China

**Author's Country/Territory:** Egypt

**Manuscript submission date:** 2020-06-30

**Reviewer chosen by:** Jia-Ping Yan

**Reviewer accepted review:** 2020-08-24 03:18

**Reviewer performed review:** 2020-08-24 13:21

**Review time:** 10 Hours

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 Grade E: Do not publish            |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



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## **SPECIFIC COMMENTS TO AUTHORS**

The manuscript focuses on the potential epigenetic regulators of immune checkpoint PD-1/PD-L1 in HCC. The data has implied a regulatory pathway between paradoxically acting miRNAs, tumor suppressor miR-194-5p and oncomiR miR-155-5p on immune checkpoint PD-1/PD-L1 in HCC context through XIST expression modulation. Major comments 1. In table 1, Alanine aminotransferase and Aspartate aminotransferase are showed with  $85.6\pm 95.6$  and  $100.5\pm 65.8$ , respectively, reflecting the severity of hepatocellular damage and inflammation. Whether can the expression of PD-L1 be influenced by inflammation or not. For example, is there significant difference of the expression of PD-L1 between patients with 2 times ALT and patients with 3 times ALT. As oleuropein has been demonstrated to have an anti-inflammatory and immunomodulatory effect via down-regulation of MAPKs and NF- $\kappa$ B signaling pathways as well as controlling the production of inflammatory mediators as IL-6 and TNF- $\alpha$  cytokines, MMP-1 and MMP-3 levels quoted from the manuscript, it has been showed to be effective to reduce the level of PD-L1, upregulate miR-194-5p expression, and downregulate miR-155-5p, which indirectly reflects the inflammation role. However, Huh-7 cells are not in the similar inflammatory microenvironment. And how to consider the effect of inflammation. 2. In figure 1, why is the bar of HCC tissues lower than that of cirrhotic tissues, but with more significant difference, compared with healthy control? 3. The number of biopsy specimen is small and not clearly showed.



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**Title:** Pivotal role of LncRNA-XIST in regulating immune checkpoint PD- Y through a shared pathway between miR-194-5p and miR-155-5p in hepatocellular carcinoma

**Reviewer's code:** 03261241

**Position:** Peer Reviewer

**Academic degree:** MD, PhD

**Professional title:** Associate Professor

**Reviewer's Country/Territory:** Japan

**Author's Country/Territory:** Egypt

**Manuscript submission date:** 2020-06-30

**Reviewer chosen by:** Jia-Ping Yan

**Reviewer accepted review:** 2020-08-23 10:06

**Reviewer performed review:** 2020-08-27 12:41

**Review time:** 4 Days and 2 Hours

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



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## **SPECIFIC COMMENTS TO AUTHORS**

The paper entitled “Pivotal role of LncRNA-XIST in regulating immune checkpoint PD-L1 through a shared pathway miR-194-5p and miR-155-5p in hepatocellular carcinoma” is a manuscript that reports a novel signaling pathways for immune checkpoint. The authors propose that the possibility of a novel shared upstream regulatory signaling pathway for PD-1/PD-L1 immune checkpoint between paradoxically acting miR-194-5p and miR-155-p through XIST expression modulation may exist in hepatocellular carcinoma, and they also suggest that such ceRNA circuits’ key regulators could be employed as therapeutic targets for hepatocellular carcinoma. To make this paper better, however, the manuscript should be revised. Comments: 1. In Introduction, the authors should refer to several papers by Dr. Tasuku Honjo’s group and Dr. James P. Allison’s group, in the part of cancer therapy using immune checkpoint. Especially regarding PD-1, the authors should need several more references, because Dr. Tasuku Honjo discovered it, another protein expressed on the surface of T-cells in 1992. Ishida, Y., Agata, Y., Shibahara, K., & Honjo, T. (1992). Induced expression of PD-1, a novel member of the immunoglobulin gene superfamily, upon programmed cell death. *EMBO J.*, 11(11), 3887–3895. 2. It is not needed the descriptions about the oleuropein from olive leaves and its effect for PD-L1 pathway, although it seems to have an effect on PD-L1 pathway. The authors need to fully explain the necessity of the description about the oleuropein. 3. In discussion, the authors should add the figure of the flowchart of pathway that the authors proposed in this study. 4. It is not sufficient to explain the limitations of this study. The authors should describe the limitation.



## RE-REVIEW REPORT OF REVISED MANUSCRIPT

**Name of journal:** World Journal of Hepatology

**Manuscript NO:** 57925

**Title:** Pivotal role of long non-coding ribonucleic acid-X-inactive specific transcript in regulating immune checkpoint programmed death ligand 1 through a shared pathway between miR-194-5p and miR-155-5p in hepatocellular carcinoma

**Reviewer's code:** 03261241

**Position:** Peer Reviewer

**Academic degree:** MD, PhD

**Professional title:** Associate Professor

**Reviewer's Country/Territory:** Japan

**Author's Country/Territory:** Egypt

**Manuscript submission date:** 2020-06-30

**Reviewer chosen by:** Le Zhang

**Reviewer accepted review:** 2020-10-04 22:36

**Reviewer performed review:** 2020-10-05 07:43

**Review time:** 9 Hours

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



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#### **SPECIFIC COMMENTS TO AUTHORS**

The authors propose that the possibility of a novel shared upstream regulatory signaling pathway for PD-1/PD-L1 immune checkpoint between paradoxically acting miR-194-5p and miR-155-p through XIST expression modulation may exist in hepatocellular carcinoma, and they also suggest that such ceRNA circuits' key regulators could be employed as therapeutic targets for hepatocellular carcinoma. This is the well-written paper that presents interesting data and information. It will be of interest to readers of this journal, and is sufficient for publication.



## RE-REVIEW REPORT OF REVISED MANUSCRIPT

**Name of journal:** World Journal of Hepatology

**Manuscript NO:** 57925

**Title:** Pivotal role of long non-coding ribonucleic acid-X-inactive specific transcript in regulating immune checkpoint programmed death ligand 1 through a shared pathway between miR-194-5p and miR-155-5p in hepatocellular carcinoma

**Reviewer's code:** 03251421

**Position:** Editor-in-Chief

**Academic degree:** MD

**Professional title:** Professor

**Reviewer's Country/Territory:** China

**Author's Country/Territory:** Egypt

**Manuscript submission date:** 2020-06-30

**Reviewer chosen by:** Le Zhang

**Reviewer accepted review:** 2020-10-04 13:58

**Reviewer performed review:** 2020-10-06 13:00

**Review time:** 1 Day and 23 Hours

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



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#### **SPECIFIC COMMENTS TO AUTHORS**

This is a very interesting paper. It based on the analysis in silico further verified the epigenetic regulation in the anti-programmed death therapy in a solid cancer in vitro and in vivo. However, there are some questions should be answered. For example, how many candidates' miRNAs totally were predicted to target PD-L1? How to rule out the others? Were they verified some other candidates in vitro or in vivo? The two candidates which called miR-155-5p and miR-194-5p, were examined only in huh-7 cell line, what about the situation in vivo?