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Manuscript NO.: 37113

Title: Behind the curtain of non-coding RNAs; long non-coding RNAs (LncRNAs) regulating hepatocarcinogenesis

Authors: Aya El Khodiry, Menna Afifi and Hend M. El Tayebi

Dear Editor,

Please find enclosed the resubmitted revised manuscript for the review titled;

Behind the curtain of non-coding RNAs; long non-coding RNAs (LncRNAs) regulating hepatocarcinogenesis; Manuscript NO.: 37113

We have read thoroughly all the reviewer comments with the constructive criticism which I do respect for the perfection of the manuscript.

We have taken all comments into consideration and we answered the questions and revised the text accordingly (all changes are highlighted in **Bold**).

I am herewith attaching the revised manuscript and the point to point replies to the reviewers.

I always do appreciate very much your support.

With my best regards,

Sincerely,

Hend M. El Tayebi

Reply to reviewers:

- 1. Reviewer #1: I congratulate the authors for their work. The paper is a full description of the role of long non-coding RNAs regulation on hepatocarcinogenesis describing all possible mechanisms involved in HCC formation and possible future targeted therapies. The manuscript can be published in the Journal.**

It's our utmost pleasure to have this feedback. Thank you.

- 2. Reviewer #3: I have only minor comments. 1) On page8 line 9, 'USC7 act as tumor suppressor' must be 'USC7s act as tumor suppressor'. 2) On page 28 line 14, 'These pathways are a good candidate' should be 'These pathways are good candidates' 3) SPRY4-IT1 is also strongly related to cell proliferation and EMT progression. They should refer the recent paper by Yu G et al (2017) in the literature review.**

Thank you for your comments. All these comments were modified and highlighted in bold within the revised review article submitted. The recent paper by Yu G et al has been added in page 22 as follows **interacting with Estrogen Related Receptor α (ERR- α)[193]**.

- 3. Reviewer #4: I think the authors should clarify why some lncRNAs are described in such detail; are they more relevant for HCC than others? Are they more studied than others? Are they more strictly related to HCC prognosis? It is not clear whether the lncRNAs described are uniquely dysregulated in HCC or also in the cirrhotic tissue; this information is relevant in term of the possibility to propose the use of some of the lncRNAs as novel specific HCC markers.**

Thank you for your comments. All these comments were modified and highlighted in bold in page 13 within the revised review article submitted. **The upcoming section discusses individual lncRNA that were found to be extensively studied.**

- 4. Reviewer #4: Major points It is not well explained the relation between epigenetic regulation and lncRNAs, i.e. how epigenetic regulates lncRNAs and if this is a relevant mechanism in HCC.**

Thank you for your comments. A paragraph titled "**Epigenetic regulation and lncRNAs in HCC**" has been added in page 6 discussing the relation between epigenetic regulation and lncRNAs.

- 5. Reviewer #4: It is not clear whether the lncRNAs described are uniquely dysregulated in HCC or also in the cirrhotic tissue; this information is relevant in term of the possibility to propose the use of some of the lncRNAs as novel specific HCC markers.**

Thank you for your comments. The significance of the lncRNAs in the cirrhotic liver was not emphasized in any of the papers reviewed. It was not the concern of the papers and wasn't mentioned or compared with HCC.

- 6. Reviewer #4: It would be helpful divide the data according to the fact that the studies have been conducted in vitro, in animal models or in humans and prepare a corresponding table.**

Thank you for your comment. A table has been added titled: **Table 1. Different models used in studies** in page 45.

- 7. Reviewer #4: it is not clear whether DNMT1 belongs to both maintenance methyltransferase and de novo methyltransferase or just to the maintenance methyltransferase.**

Thank you for your comment. In page 4 "**along with contributing to the de novo methylation process [8; 9]**" has been added to clarify the point of concern.

- 8. Reviewer #4: On page 4 section “Non-coding RNAs”, add some reference related to non coding RNAs different from lncRNAs. In addition, explain that the review will be focused on lncRNAs.**

Thank you for your comment. In page 5, a highlighted paragraph has been added to clarify the concern.