

Dear Editor:

Thank you for your letter and for the reviewers' comments concerning our manuscript entitled "Cyclooxygenase-2 expression is associated with initiation of hepatocellular carcinoma, while prostaglandin receptor-1 expression predicts survival" (ID: 27739). Those comments are all valuable and very helpful for revising and improving our paper.

We have studied comments carefully and have made correction which we hope meet with approval. Revised portion are marked in red in the paper. the responds to the reviewer's comments are as flowing:

Responds to the reviewer's comments:

Reviewer 1

Comment 1: The manuscript is interesting and original because there are few studies about COX2 and HCC. However. the english is not good and there are grammatical errors . Also, the discussion needs to improve. It is so concise. The references must be written in agreement with the recommendations of the journal.

Response:

1. According to the reviewer's comments, we revise the language of our manuscript and provide a language editing certificate in the attachments .

2. The discussion has been improved and highlighted in the updated version of the manuscript
3. References have been revised in agreement with the recommendations of the journal.
4. All of the revisions have been highlighted in the updated version of the manuscript

Comment 2: Despite its limitations, the article is interesting and useful. It can contribute to better understanding of the pathogenetic mechanism of HCC. There are several grammatical errors that must be corrected (COX-2 catalyses, cytokines may involve in different aspects, in future studies, and so on). References must be written in agreement with the recommendations of the journal.

Response:

1. According to the reviewer's comments, we revise the language of our manuscript and provide a language editing certificate in the attachments .
2. The references have been revised in agreement with the recommendations of the journal and all of the revisions have been highlighted in the updated version of the manuscript

Comment 3:

1. As AFP >400 ng/mL, tumor size ≥ 5 cm, and EP1 receptor expression are inversely related to overall survival, the Hazard Ratio in Table 2 should be less than 1 (and not more than 1) in all 3 parameters. 2. In the introduction section, "COX-2 catalyses the conversion of arachidonic acid into prostaglandin E2, which binds to the G-protein-coupled EP1 receptor, promoting progression of various types of tumors" needs rephrasing. 3. In the limitations section of the discussion "First, in this draft, the authors used only HE method, more accurate and quantitative method should be applied in future studies" needs rephrasing. 4. Studies instead of studies. 5. Cox hazards model instead of Cox hazards modeling.

Response:

1. I'm sorry to let you misunderstand my meaning, I just want to express that AFP ≥ 400 ng/mL, tumor size ≥ 5 cm, and EP1 receptor expression are related with poor overall survival, so the Hazard Ratio in Table 2 should be more than 1 (and not less than 1) in all 3 parameters.
2. "COX-2 catalyses the conversion of arachidonic acid into prostaglandin E2, which binds to the G-protein-coupled EP1 receptor, promoting progression of various types of tumors" was rephrased as "COX-2 catalyzes the conversion of

arachidonic acid to prostaglandin E2, which promotes progression of various types of tumors by binding to G-protein-coupled EP1 receptor”

3. “First, in this draft, the authors used only HE method, more accurate and quantitative method should be applied in future studies” was rephrased as “First, in this draft, the authors used only HE method, more accurate and quantitative method , such as Western blot ,polymerase chain reaction et al,should be applied in future studies”

4. Stuties and cox hazards modeling are revised in updated version of the manuscript.

We would like to express our great appreciation to you and reviewers for comments on our paper. Looking forward to hearing from you.

Thank you and best regards.

Yours sincerely,

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