

Format for ANSWERING REVIEWERS



April 12, 2017

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 33214-review.doc).

Title: Implication of the Hedgehog pathway in hepatocellular carcinoma

Author: Carminia Maria Della Corte, Giuseppe Viscardi, Federica Papaccio, Giovanna Esposito, Giulia Martini, Davide Ciardiello, Erika Martinelli, Fortunato Ciardiello, and Floriana Morgillo

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 33214

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

RESPONSE OF AUTHORS TO REVIEWERS COMMENTS:

COMMENTS TO AUTHORS

In this manuscript, the author reviewed the current data on the role of HH pathway reactivation in the development and progression of HCC. The manuscript is of great interest and comprehensive. I suggest that it should be accepted for publication in the journal of WJG. However, there are some problems to be addressed. 1. In the part of evidence of HH activation in human tumor tissues, many researches were conducted on the expression and prognostic value of HH proteins in HCC specimen. I suggested that the author make a table to provide the details of each study.

We appreciate your suggestion, we added TABLE 1 containing data of studies on human tissues.

2. I suggested that the author provided a cartoon figures concerning the mechanisms of HH pathway in the carcinogenesis and evolution of HCC.

Thanks for the comment, we created Figure 2.

COMMENTS TO AUTHORS

1. The authors aimed at summarizing the role of Hedgehog(HH) pathway reactivation in development and progression of hepatocellular carcinoma(HCC). The emphasis should be how HH pathway play the crucial role in the process of carcinogenesis and progression, however the prognosis value of HH pathway was emphasized with an independent subtitle (Figure 1). Maybe it is more appropriate in the discussion part.

Thanks for your revision, we corrected Figure 1 according to your suggestion and we described the prognosis value of Hedgehog marker in tumoral tissue.

2. HH pathway activation can induce angiogenesis, which should be inferred in this article.

Thanks, we added data on angiogenesis and Hedgehog.

3. The subtitles in Figure 1 should be corresponding to the subtitles in the content. So, some point of the Figure 1 should be revised according to the advice above.

Thanks, we revised the figure.

4. The first sentence in last paragraph said that HH pathway deserves a future exploration as an independent prognostic marker for HCC progression and as a therapeutic target. The sentence is not accurate. Please change it.

Thanks, we changed it.

5. There are spelling mistakes like proliferation, limited and so on.

Thanks, we corrected and manuscript underwent language revision as requested.

COMMENTS TO AUTHORS

In this manuscript, the authors reviewed the literature and the role of the hedgehog pathway in patients with HCC. I read the manuscript with great interest that it is very comprehensive. I suggest that it should be accepted for publication in the journal of WJG. My suggestions are;

- The authors stated that sorafenib is still the only available therapeutic option of HCC advanced patients but we know that regorafenib have also significant activity in patients with HCC that relapse after sorafenib in a randomized trial ([http://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(16\)32453-9/abstract](http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(16)32453-9/abstract)).

Thanks for your suggestion, we added these new clinical data.

- The role and previous results of immunotherapy also promising and should be mentioned in the manuscript.

Thanks for your suggestion, we added recent clinical data on immunotherapy.