

Re: World journal of gastroenterology-45788, The predictive and prognostic implications of the autophagy-related proteins 4E-BP1, Beclin-1 and LC3 for cetuximab treatment combined with chemotherapy in advanced colorectal cancer with wild-type KRAS: analysis from real-world data

February 28, 2018

Dear Editor:

Thank you very much for your letter and advice. We have revised the manuscript, and would like to re-submit it for your consideration. We have addressed the comments raised by the academic editors and the reviewers, and the amendments are highlighted in the revised manuscript. Point by point responses to the reviewers' comments are listed below this letter.

We hope that the revised version of the manuscript is now acceptable for publication in your journal.

I look forward to hearing from you soon.

With best wishes,

Yours sincerely,

Guifang, Guo

We would like to express our sincere thanks to the academic editor and the reviewers for the constructive and positive comments.

Replies to Reviewer 1

Comment 1: Please define the abbreviation while firstly use, including the official symbol or official full name of genes.

Response: Thank you for your advice. We have revised and all the abbreviations were defined while firstly used.

Comment 2: In figure 1C, the quality of western blot is poor. Over exposure and poor transfer quality is noted.

Response: Thank you for your good suggestion. We have revised this in figure 1C.

Comment 3: In figure 2, the authors provide the IHC staining of LC3. Would it possible to provide staining results of BP1 and Beclin-1?

Response: Thank you for your useful suggestion. We have revised this in figure 2. We provide the IHC staining of 4E-BP1 and Beclin-1

Comment 4: The prognostic results is confusing. Please define the reference in the table 3. For example, the HR of Beclin-1 is 0.209 which suggest favorable outcome in the gene. However, the true result is opposite.

Response: Thank you for your worthwhile suggestion and sorry for our mistakes. We make sure the results showed in table 3 are right. We have revised this in figure 4.

Replies to Reviewer 2

Comment 1: Please provide a numbered reference list!

Response: Thank you for your advice. We have revised it and provided a numbered reference list.

Replies to Reviewer 3

Comment 1: in the discussion section, you did not discuss your work with other studies, it means that your work is pioneer in this issue is that true, or other investigators also work on this issue, so you need to mention that.

Response: Thank you for your helpful suggestion. We have revised this and mentioned in Page 13, line 380.

Comment 2: some grammar comments are present in the uploaded file.

Response: Thank you for your good suggestion and sorry for our mistakes. We have revised this.

Replies to Reviewer 4

Comment 1: I have difficulties with understanding the wording –patients with advanced colorectal cancer – what does this mean? Are these patients with metastatic colorectal cancer?

Response: Thank you for your advice. Patients with advanced colorectal cancer also means patients with metastatic colorectal cancer.

Comment 2: Page 7, line226: Please explain more exactly what are the tissue samples – biopsy specimens taken from colon or from other organs as well? What was the pathological diagnosis of samples – In World Health Organization (WHO) classification, a number of histologic variants of colorectal carcinomas are listed, such as mucinous, signet ring cell, medullary, micropapillary, serrated, cribriform comedo-type, adenosquamous, spindle cell, undifferentiated. It is known that some histological types of carcinomas have typical molecular pathology, therefore it is important to state the histological type of the samples.

Response: Thank you so much for the suggestion. We have revised biopsy specimens taken from colorectal primary tumor and all pathological diagnosis were adenocarcinoma in Page 9, line 247.

Comment 3: Page 9, line 279: COCA-2 cells correct into CACO-2 (已修改)

Response: Thank you for your advice and sorry for our mistakes. We have revised this.

Comment 4: Page 11, line346: the authors write about the degree of pathological differentiation but in the results section they do not mention anything about the degree of differentiation or histological type of tumors.

Response: Thank you for your advice. We have revised this and mention this in Page 11, line322.

Comment 5: Table 1: what was meant by the word “pathological level”?
Please correct.

Response: Thank you for your advice. We have revised this in table 1. We deleted the word “pathological level”, and wrote pathological grade instead.

Comment 6: Table 3: the term pathological differentiation is not correct – what does it means? Please use correct terminology or explain what does it mean.

Response: Thank you for your advice. We have corrected this in table 3, and we also have changed pathological differentiation into pathological grade as mentioned in other part.