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September 2, 2018

Dear Editor:

I am grateful to you and the reviewers for providing me the opportunity to revise my manuscript entitled "Uba2 promotes cell migration and invasion through Wnt/β-catenin signaling in gastric cancer" (Manuscript NO: 41240).

In accordance with the comments from the Editorial Board and the reviewers, we have carefully considered all the associate editor's and reviewers' comments. Our responses are attached and we have revised the manuscript point-by-point. We have highlighted in red where in the manuscript the additions and revisions were made.

I respectfully hope it could be accepted and published in your Journal.

With best regards,

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Response (Res.) to the comments from the reviewers
Manuscript NO: 41240

Reviewer #1: It is a well-design manuscript, however I have some questions as follows:
1. I agree with the author's opinion that most patients are in the advanced stage when they were diagnosed, however, 5-year survival rate is around 40% or more. It is unbelievable that the 5-yrs overall survival is less than 10%.
Res: Thank you for your question and we are very sorry for the mistake. We retrieved recent literature and found that the 5-year survival rate for patients with advanced gastric cancer ranged from 20% to 40%. We corrected the mistake in the manuscript.
2. Is Uba2 a prognostic factor of gastric cancer?
Res: According to our results, high expression of Uba2 was correlated with diffused and mixed type of Lauren's classification, poor differentiation, and worse TNM stage, which all indicated worse prognosis. Thus, we speculate that Uba2 is a prognostic factor of gastric cancer. We would like to follow up more patients and prolong the follow-up time to further confirm its role as a prognostic factor in gastric cancer. It should be discussed in our future work.

Reviewer #2: In the experimental study UBA2 is shown as an enhancer of tumour cell migration in gastric cancer via activation of Wnt/beta-signaling.
Comments 1. Introduction: GC cell lines: details are necessary to the reader
Res: These details were added in the part of cell culture in *MATERIALS AND METHODS*.
2. In the tumour cell lines of gastric cancer the effects of UBA 2 are different; this should be intensively discussed. There are lines from signet cell carcinoma or the intestinal type?
Res: Most of the gastric cancers are gastric adenocarcinoma. So the three gastric cancer cell lines we choose are all gastric adenocarcinoma cell lines. Moreover, there is a certain degree of difference in differentiation and Lauren's type among the three cell lines. According to Table1, Uba2 expression was associated with differentiation. BGC-823 and MGC80-3 were poorly differentiated, SGC-7901 was well differentiated. The former two was observed with worse differentiation than SGC-7901, which might be the reason why Uba2 expression was lower in SGC-7901 than BGC-823 and MGC80-3. There was no signet cell carcinoma cell line used in the study. We added the explanation in the discussion.
3. Figures 1D: The main tumour cells are shown in a structure like a lymph vessel; why?
Res: Signet-ring cell carcinoma is a special type of gastric cancer that

contains a lot of mucus. Because the cells are full of mucus, the nucleus is pushed to one side of the cell, making it look like a ring. The structure like a lymph vessel was the mucus.

4. In signet cell carcinoma / diffuse type Lauren 'formation of colonies' is not typical. In the cell culture colony formation is described.

Res: Colony formation was performed in two intestinal-type gastric adenocarcinoma cell lines BGC-823 and SGC-7901. No signet cell carcinoma or diffuse type cell line was used.

5. In the study changes in E-cadherin expression/ synthesis in GC cell lines after overexpression or knockdown of UBA2 were found, but is there any regulation of the interacting protein p120?

Res: P120 is a cytoplasmic molecule associated with E-cadherin. It regulates E-cadherin turnover at the cell surface to determine the level of E-cadherin available for cell-cell adhesion. Former studies revealed that p120 and β-catenin had distinct but complementary roles in strengthening cadherin-mediated adhesion. Sumoylation which Uba2 took part in has been proved to affect the expression of β-catenin, so we chose to investigate whether Uba2 could regulate Wnt/β-catenin in gastric cancer. There were few studies about the effect of Uba2 on p120, so we didn't regard it as the focus of mechanism research. We would like to investigate which molecular mechanism regulating the expression of E-cadherin via Uba2 including p120 in the future to further elucidate the effects of Uba2 on E-cadherin.