Dear *Reviewer 03478635*,

Thank you very much for your letter and the comments from the referees about our paper (38348) submitted to World Journal of Gastroenterology.

We have checked the manuscript and revised it according to the comments. We submit here the revised manuscript as well as a list of changes.

For the first comment: We are very sorry for our incorrect writing the title should be "Expression of P4HB…", but not "Overexpression of P4HB…", and the data constitute Fig 1 were download from http://gepia.cancer-pku.cn/ which is analyzed based on TCGA. We have re-check the authenticity of the pictures.

For the second comment: we have made corresponding modification in the Result "Univariate and Multivariate analysis in the cohort of GC patients", revised portion are marked in red in the paper. And we also recheck the title of Table 3, We are very sorry for our negligence.

For the third comment: it is the reference 33 explain that GC cell with ERp19 knockdown dramatically suppressed cell growth and inhibited cellular migration. The word *39* is a clerical error. We are very sorry for our negligence.

If you have any question about this paper, please don't hesitate to let me know.

Sincerely yours, Yan Zhao.

Dear *Reviewer 00505440,*

Thank you for your letter and for the comments concerning our manuscript 38348. Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to us. We have studied comments carefully and have made correction which we hope meet with approval. We have made corresponding modifications in the Fig 3 and delete all edit markers according to the opinion.

Sincerely yours, Yan Zhao.

Dear *Reviewer 02544209*,

We very much appreciate the careful reading of our manuscript and valuable suggestions of the reviewer. We have carefully considered the comments and have revised the manuscript accordingly.

1. The information of P4HB and cancer（*(P4HB[Title/Abstract]) AND CANCER[Title/Abstract]*）was re-searched in Pubmed, but no literature has been studied on the development of P4HB in gastric cancer so far. Our study may be the first to report on the prognosis of gastric cancer by P4HB. The role of P4HB in tumorigensis in hepatocellular carcinoma and malignant glioma has been mentioned in this paper (ref. 12-14). However, in the modification, we supplemented the role of P4HB in the treatment of NSCLC (ref. 15, red in introduction). Besides, P4HB functions primarily as the beta subunit of prolyl 4-hydroxylase, forming a tetrameric enzyme with P4HA1 or P4HA2 subunits, we added some information about P4HA1/2 associated hypoxic and tumor (red in discussion).

2. As we described, we have demonstrated P4HB was a potential target of HIF-1a (*P4HB, a novel hypoxia target gene related to gastric cancer invasion and metastasis*), this paper is also under minor revision. We will add it to the reference once the article is accepted.

3. After of the successful of Toga test, the Department of pathology of our hospital carried out the detection of Her-2 gene in all gastric cancer specimens. However, the positive rate of the Her2 immunohistochemistry of gastric cancer was very different between different organs in China and the rate in our hospital is about 5%. At some stage, FISH detection was performed on all medical records, but the positive rate was still relatively low. So we didn't include this part of the data. We use the standard test methods and equipment, but why is there such a difference? Is it a race difference or a testing system? Cause is unknown, but the industry insiders do have the same concerns. Based on the heterogeneity of gastric cancer, Her-2 detection is still lacks an operable and convincing standard.

It is a very interesting topic to discussion the relationship between Her gene family and hypoxia associated signaling pathway. We will explore this mechanism in

subsequent studies *in vitro* and *in vivo* and seek evidence in clinical studies in a follow-up study. At the same time, we hope to find new therapeutic targets and serve clinical practice by elucidating the mechanism of interaction between them. Thank you for your valuable advice.

4. We have made corresponding modifications to the abstract based on the opinions of the professors and the format requirements of the magazine (marked in red in revised paper “abstract”).

Thank you again for your positive comments on our manuscript and hope these will make it more acceptable for publication.

Sincerely yours, Yan Zhao.

Dear *Reviewer 00071054,*

Thank you for your kind comments on our manuscript “38348”. We have carefully revised the manuscript according to the reviewer’s comments. Based on the suggestions, we have made an extensive modification on the revised manuscript. Detailed revision was shown as follows. The changes to our manuscript within the document was also highlighted by using red colored text.

1. As we described, we have demonstrated P4HB was a potential target of HIF-1a (*P4HB, a novel hypoxia target gene related to gastric cancer invasion and metastasis)*, this paper is also under minor revision. We will add it to the reference once the article is accepted.

2. The genes mentioned in Fig.1, except P4HB, are well-known hypoxia-related genes. Their expression is all associated with HIF-1α, and are all positively correlated with the expression of HIF-1α. The correlation of expression is a necessary condition for regulatory relations. We prove that P4HB expression is related to a variety of hypoxic genes through Fig.1, suggesting that P4HB may also be a "hypoxic gene".

3. We add the corresponding data and red in the text. The score of cutoff in **Evaluation of IHC stain** (Materials and Methods, marked in red). The other data showed in **HIF-1α and P4HB expression in GC specimens** (Results).

4. Through our previous studies, we found that P4HB may be a potential target gene of HIF-1α. But the specific regulation mechanism is unclear. We can only get the correlation between the two genes and the clinical data by survival analysis, but the research effect on the mechanism is very little. But some subtle patterns can still be found by retrospect the data. HIF-1α is more meaningful than P4HB in clinical data: HIF-1α is associated with DFS and OS, but P4HB is only meaningful in DFS. HIF-1α is associated with hepatic metastases. This may indirectly prove that HIF-1α, as the upstream gene, is involved in more signaling pathways than P4HB. But P4HB is concern in Tumor differentiation and Bormann type, which may indict P4HB is close with GC specificity. In all, HIF-1α have get more attention as a crucial member of tumor hypoxia microenvironment, and also plays an important role in biological survival. But the more specific mechanism of HIF-1α still needs to be explored.

5. We have submitted a new high-resolution Fig 2 to replace the previous one.

We appreciate for Reviewers' warm work earnestly, and hope that the correction will meet with approval.

Once again, thank you very much for your comments and suggestions.

Sincerely yours, Yan Zhao.