

Dear Editor,

We do appreciate the time you have taken to deal with our manuscript entitled "*Blockage of ETS homologous factor inhibits the proliferation and invasion of gastric cancer cells through c-Met pathway*"(ID: 58405) and prompt response. The comments and suggestions from you and the reviewers are really helpful for improving our manuscript. We have prepared a revision strictly according to the comments and the alterations have been highlighted in the revised manuscript (red color). Please feel free to contact us if you have any further questions.

Best regards and we look forward to your final decision.

Sincerely yours,

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Responses to reviewers:

Reviewer #1:

Blockage of ETS homologous factor inhibits the proliferation and invasion of gastric cancer cells through c-Met pathway Title: In 17 words (it should be no more than 12 words) included key elements of the studied: being ETS homologous factor a member of ETS family of relevant activity in the pathogenesis of multiple cancers, but nowadays it is not clear if it participation in gastric cancer is via c Met signaling pathway Authorship: Is correct. Institutions: are correct ORCID number is correct Authors contribution is correct Abstract. Is a structured abstract according to the required format. In 305 words authors showed a summary of the content of the manuscript. Key words: 5 that reflect the content of the study Core Tip: In 76 words author reflect properly

aspects that should call attention to the readers

Background: It is a basic study with a high importance for the clinical practice. Gastric cancer is a common disease and important cause of cancer-related mortality. Clinical behavior and risk factors are known. Surgery represents the principal therapeutic option, but the five years overall survival is poor. Authors consider of crucial interest to investigate more about the oncogenic mechanism in gastric cancer. Activation of Met signaling promotes tumor cell growth, survival, migration and tumor angiogenesis. Its activation can be by several pathways, but this have not sufficiently explored. Then they proposed to investigated if epithelium homologous transcription factor expression in gastric cancer is involved in the biological behavior of gastric cancer via promoting c-Met expression. That is the rational of this work

Method: Authors made the detailed description of the investigations: the tissue sampling procedure, cell culture, Transfection of small interfering RNAs, Quantitative real-time PCR and so on.

Results: Authors demonstrated that the expression of c-Met was increased in gastric tumors tissue and cell lines with high EHG expression, they fulfill the aim of the study.

Discussion: Authors made a detailed an informative discussion of the results. They interpreted properly and precisely all the finding, highlighting that EHF plays a key role in cell proliferation, invasion, apoptosis, the cell cycle and EMT via the c-Met pathway that is significant for the medical practice in future

Illustrations: They show 6 figures with their corresponding legend. All figures are showing clearly making and adequate support of the results

Biostatistics: This work met the requirements of biostatistics

References: Authors cited properly actualized references of high interest for their propose in introduction and discussion

Organization of the study: It was properly organized

Research method reporting. As a basic study it has been reported according with the corresponding guidelines

Comments to the author: In this manuscript authors confirmed the hypotheses that EHF plays a key role in cell proliferation, invasion, apoptosis, the cell cycle and EMT via the c-Met pathway. The relevance of this study is according to the interest of the scientific community to achieve a target treatment for gastric cancer by the via of the inhibition of important issue in the cascade of events in the molecular develop of this deadly disease following investigators perspective that refers I the work: EHF may serve as a antineoplastic target for the diagnosis and treatment of GC It is necessary to make further investigations like this with a wide number of patients involved. This was recognized by authors as a point of

recommendation for the future.

Question 1: Title: In 17 words (it should be no more than 12 words) included key elements of the studied.

Reply: Thank you very much for your kind reminding. According to the Guidelines for manuscript preparation (<https://www.wjgnet.com/bpg/GerInfo/218>), the title of basic study should be no more than 18 words. The present title consists of 17 words and it could summarize the specific content and key concepts of the manuscript.

Question 2: It is necessary to make further investigations like this with a wide number of patients involved.

Reply: Thanks a lot for your positive comments and suggestions. Further investigations with larger sample size will be made to clarify the relationship between EHF expression and clinical outcomes in patients with gastric cancer.

Reviewer #2:

Author concluded that EHF plays a key role in cell proliferation, invasion, apoptosis, the cell cycle and EMT via the c-Met pathway, and results were from 3 gastric cancer cell lines. However, the evidence was not enough to support the conclusion.

Question 1: In clinical samples, IHC should be used to detect expression of EHF.

Reply: Thank you very much for the constructive advice. According to your suggestion, immunohistochemistry staining was performed to detect the protein levels of EHF in gastric cancer tissues and adjacent control tissues. The results of experiments we have gained in the study have been added in the Result 1 and Figure 1 (P9 line30-P10 line2, P34).

Question 2: More detailed molecular mechanisms should be investigated.

Reply: We do appreciate the valuable advice from the reviewer. In the present study, we demonstrated that EHF and c-Met were both upregulated in gastric cancer tissues and cell lines. It is well-acknowledged that c-Met pathway play crucial roles on tumorigenesis of gastric cancer. Blockage of EHF expression downregulated expression of c-Met and led to the antineoplastic effects on the gastric cancer cell lines. We investigated many previous literatures during the research and found that Ras/c-Raf/Erk1/2, PTEN and STAT3 participated in the downstream signaling of c-Met.

Therefore, we checked the activity of these pathways following EHF downregulation. However, the molecular mechanisms involved remain to be further elucidated. We will further investigate more detailed mechanisms underlying the antineoplastic effects induced by EHF downregulation in future. In future studies, we will carry out experiments to counteract the effects on these downstream cascades induced by EHF silencing and then detect the changes of cell biological functions and the expression of corresponding molecules.

Question 3: More proliferation, invasion, apoptosis related genes should be tested.

Reply: Many thanks for the good suggestion. We agree with the reviewer that more genes involving tumorigenesis and progression should be tested. In the current study, the results indicated that EHF may promote cell proliferation and cell cycle progression and inhibit the apoptosis of GC cells via regulating the c-Met pathway. In addition, EHF may contribute to the migration and invasion of GC cells by inducing EMT via the STAT3 pathway. However, it still has some limitations. The suggestion from reviewer will play a guiding role in the following studies. We will detect more genes involved in proliferation, invasion and apoptosis in future.

Question 4: English should be revised.

Reply: Thank you for your suggestion. Firstly, we have already used the language editing services provided by American Journal Experts according to the official recommendation (<https://www.wjgnet.com/bpg/gerinfo/240>). The language editing certificate issued by AJE was also provided. Secondly, we have consulted expertise to improve the language and we revised English strictly following the professional instructions before this revision was submit. The alterations have been highlighted in the revised manuscript (red color).