July 5, 2021

Dear Prof. Lian-Sheng Ma,

World Journal of Gastrointestinal Oncology

RE: # NO: 66611, The Diverse Roles of FOXO Family Members in Gastric Cancers

Dear Prof. Lian-Sheng Ma.,

We would like to thank you for providing us an opportunity to revise the manuscript with revised title "**The Diverse Roles of FOXO Family Members in Gastric Cancers**". We do also thank the reviewers for giving us constructive comments and suggestions. We have revised the manuscript according to the reviewer's suggestions. All the changes are highlighted in yellow in the revised manuscript. And the point-to-point responses to the reviewer's comments were followed in the next part of this letter.

I believe the revised manuscript has been largely improved, and will be benefit to the readers of your journal. I hope the new version would be suitable to publish in "***World Journal of Gastrointestinal Oncology***". I look forward to hearing from you.

Best regards,

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The main corrections are in the manuscript and the responds to the reviewers' comments are as follows point-to-point (the replies are marked in blue).

To Reviewer #1:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (General priority)

Responses: Thank you again for your positive comments and valuable suggestions to improve the quality of our manuscript. We have revised the manuscript accordingly with tracked changes. And the manuscript has been polished by an English-native speaker with biological background.

Specific Comments to Authors:

1- why there is no universal guidelines for screening of gastric cancer

Responses: Thanks for your critical comments. Due to the lack of early symptoms as well as effective and widely adopted screening measures, most cases (over 60%) are diagnosed in the advanced stage of gastric cancer in the United States[1, 2]. However, in Japan, early diagnosis of GC reaches 50% and five-year survival rate attains 90%, because of the implementation of a national screening program for detection of early-stage gastric cancer[2, 3]. Screening for gastric cancer generally involves contrast radiography and endoscopy. In the updated Japanese guidelines for gastric cancer screening in 2015, upper gastrointestinal (UGI) series or endoscope are allowed to be used for screening[4]. Similarly, in Korea, endoscopy or UGI series is recommended every two years for individuals aged 40 years and older [2], yet the optimal interval for screening has not been established in randomized trials[5]. Endoscopy and UGI series are effective but invasive and applied in large-scale screening for GC only in

Japan and Korea where incidence of GC is high. In Western countries, where the incidence is relatively low, screening is cost-prohibitive and gastric cancers are routinely diagnosed in relatively advanced stage[6]. Another screening method is the detection of circulating biomarkers. However, the low sensitivity and specificity of the existing circulating biomarkers (CEA, CA19-9, CA72-4, CA125, CA24-2, CA50, pepsinogen and AFP) limit their application in the diagnosis of gastric cancer. Some of recently discovered circulating molecules (miRNAs, lncRNAs, circRNA), with a sensitivity more than 77.5%, may help for developing new strategies for early diagnosis of GC but still need to be confirmed by clinical trials. [3] Therefore, there is a lack of universal guidelines for screening of gastric cancer. We have added relevant content in Page 3.

2- your work is interesting, but is there any hope in the future for management of gastric cancer

Responses: Thanks for your comments. Although gastric cancer is the fifth most common cancer and the third most lethal cancer type in the world, there have been notable improvements in the 5-year relative survival rates for gastric cancer, especially in Japan and Korea, where 5-year survival rates above 70% for stage I and II gastric have been reported. Great achievement of these two countries suggest that aggressive screening programs have allowed for frequent early diagnosis and improved outcomes. Besides screening of GC, new gastric cancer classification systems based on next-generation genomic analysis was proposed in 2015 and analysis of TCGA genomic subtypes has identified potential therapeutic targets, which may help to facilitate the appropriate use of targeted therapies in a precise and efficient manner. In recent years, great progress has also been made in the treatment of gastric cancer. Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) have shown utility in patients diagnosed with early

disease. Cytoreductive surgery with heated intraperitoneal chemotherapy is an option that is being explored for peritoneal spread of GC. The employment of improved chemoradiotherapy regimens not only show survival gains, but also may facilitate the judicious use of aggressive surgical techniques for cure of relatively late-stage disease which previously would have been treated with palliative measures. Targeted therapies have become available and have recently become important aspects of multimodal therapy for gastric cancer. Treatment targets of GC include HER2, EGFR and VEGFR, have all been proved to increase progression-free and overall survival. The application of monoclonal antibodies against CTLA4 and PD-1/PD-L1 in gastric cancer is also being explored by ongoing research[6]. Therefore, moving forward, the management of gastric cancer is full of hope.

3- there are many tumor markers for gastric cancer but non is specific and there is lag between clinical implications and academic research.

Responses: Thanks for your critical comments. If a blood biomarker is to be used in a population-based screening program, it should be reliable in repeated applications and easily measurable in blood serum or plasma by common laboratory equipment. Moreover, it should be present in the bloodstream before the onset of manifestations and clinical symptoms, be able to distinguish between cancer and inflammation and have high positive predictive value for malignant tumors. CEA, CA19-9 and CA72-4 are regarded as clinically popular gastrointestinal tumor biomarkers, but their positivity rates are less than 40% in GC patients, and the sensitivity and specificity of these blood biomarkers are not sufficient. Other circulating biomarkers, such as CA125, CA24-2, CA50, pepsinogen and AFP, also have similar problems. Many resent researches focus on circulating tumor cells (CTCs), circulating cell free tumor DNA (ctDNA) and autoantibodies. The CellSearch system is the

first standardized semi-automatic technique approved by the FDA to enrich and detect CTCs in patients with breast, prostate or colorectal cancer. Recently, a few studies have shown that detection of CTCs in GC patients using the CellSearch system could be used for staging, predicting patients' overall survival and evaluating the treatment effectiveness. Evaluating ctDNAs that apoptotic and necrotic cancer cells discharge into the blood circulation is also accepted, together with CTCs, as a concept of "liquid biopsy". Moreover, several autoantibodies against specific tumor associated antigens (TAAs) that are expressed by cancer cells and can be detected in the blood plasma more than five years prior to diagnosis have already been identified. The field of CTCs, ctDNAs and autoantibodies is stimulating discovery regarding the tumor recurrence and metastasis, but it is still in the early stages. The transformation of these blood biomarkers into conventional clinical indicators is hampered by the absence of consistency among different technical methods[4]. The molecules mentioned in this review also have similar problems. Currently, the research on the role of FOXOs in gastric cancer is mostly limited to cell level, and there is no relevant clinical trial. Therefore, FOXOs has not been applied to clinical screening, prognosis assessment or therapeutic targets. We have added relevant content in Page 21.

4- can you mention the strong and weak points of your research.

Responses: Thanks for your comments. The strong points of our research: (1) This review introduces the FOXOs family in detail, including molecular structure, expression pattern, regulatory mechanism, and its role in cancer. (2) Previously, it is accepted that FOXOs are tumor suppressors in many types of malignant tumors. In recent years, some scholars believe that FOXOs may function to supported resilience in healthy and cancer cell, instead of typical real tumor suppressors. Our study

confirms this view in gastric cancer. We review literature on FOXOs family and gastric cancer and identified the inhibitory effects of FOXO4, the role of FOXO6 in promoting carcinogenesis, and the dual roles of FOXO1 and FOXO3 in gastric cancer. (3) We review recent literature on potential clinical significance of FOXOs and related signaling pathways, elaborate the clinical value of FOXOs in the aspect of prognosis and potential therapeutic targets in GC. The weak points of our research: (1) Our review focused more on the mechanism of FOXOs in GC, and the practical application of FOXOs in clinic is seldom mentioned due to lack of relevant research. Therefore, the clinical value of our study is limited. (2) The literature reviewed in this paper about FOXOs and gastric cancer is not abundant enough, and some of the articles have been published for many years, which fail to well reflect the research results in this field in recent years.

References

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2. Kim GH, Liang PS, Bang SJ, Hwang JH. Screening and surveillance for gastric cancer in the United States: Is it needed? Gastrointestinal endoscopy. 2016;84(1):18-28.
3. Necula L, Matei L, Dragu D, Neagu AI, Mambet C, Nedeianu S, et al. Recent advances in gastric cancer early diagnosis. World journal of gastroenterology. 2019;25(17):2029-44.
4. Li TT, Liu H, Yu J, Shi GY, Zhao LY, Li GX. Prognostic and predictive blood biomarkers in gastric cancer and the potential application of circulating tumor cells. World journal of gastroenterology. 2018;24(21):2236-46.
5. Rawla P, Barsouk A. Epidemiology of gastric cancer: global trends, risk factors and prevention. Przeglad gastroenterologiczny. 2019;14(1):26-38.
6. Johnston FM, Beckman M. Updates on Management of Gastric Cancer. Current oncology reports. 2019;21(8):67.

To Editorial Office's Comments:

(1) To Science editor:

The evaluation report of the first decision for 66611 1 Scientific quality: The manuscript describes on The Diverse Roles of FOXO Family Members in Gastric Cancers. The topic is within the scope of the WJGO. (1) Classification: Grade B (Very good) (2) Summary of the Peer-Review Report: this topic is interesting, but i have some comments: 1- why there is no universal guidelines for screening of gastric cancer 2- your work is interesting, but is there any hope in the future for management of gastric cancer 3- there are many tumor markers for gastric cancer but non is specific and there is lag between clinical implications and academic research. 4- can you mention the strong and weak points of your research (3) Format: There is 1 table and 1 figure. (4) References: A total of 131 references are cited, including 48 references published in the last 3 years. (5) Self-cited references: There is no self-citation. 2 Language evaluations: Classification: Grade B (Minor language polishing). The manuscript has been certified that it was e edited and proofread by a highly qualified native English speaker and medical professor (Stanley Li Lin, Ph.D.) in Shantou University, China. 3 Academic norms and rules: The authors need to provide the signed Conflict-of-Interest Disclosure Form and Copyright License Agreement. No academic misconduct was found in the Bing search. 4 Supplementary comments: This is an invited manuscript. The study was supported by some grants, including the National Natural Science Foundation of China, No. 81501539, the Natural Science Foundation of Guangdong Province, No. 2021A1515012180 and 2016A030312008, Science and Technology Planning Project of Shantou, China, No. 200617105260368, "Dengfeng Project" for the construction of high-level hospital in Guangdong Province—the First Affiliated Hospital of Shantou University College Supporting Funding, No. 202003-10, and Li Ka Shing Foundation Grant for Joint Research Program between Shantou University and Technion-Israel Institute of Technology, No. 43209501. The topic has not previously been published in the

WJGO. The corresponding author has not published articles in the BPG. 5 Issues raised: 1. Style for journal references should be modified according to the guidance. 2.recommendation from the peer-reviewer should be answered positively. 6 Re-Review: Required. 7 Recommendation: Conditional accepted.

Responses: Thank you again for your professional comments and valuable suggestions. Specifically, to (2), we have revised the manuscript with yellow highlights and answered the reviewer's question accordingly; to (3), the editable figure in ppt version is also uploaded in the system; to 3, all the authors signed the Conflict-of-Interest Disclosure Form and Copyright License Agreement, which are also uploaded in the system; to 4, the documents for the mentioned Approved Grants are provided and uploaded in the system; to 5, the style for journal references were modified according to the guidance.

(2) To Company editor-in-chief:

I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Gastrointestinal Oncology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors.

Responses: Thank you again for your professional comments and valuable suggestions. We have revised the manuscript according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors.