Format for ANSWERING REVIEWERS

April 30, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 6596-review-.doc).

Title: Pathogenetic mechanisms in gastric cancer

Author: Jing Shi, Yiping Qu, Peng Hou

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 6596 (Version 2)

The manuscript has been improved according to the suggestions of reviewers:
1. Format has been updated

2. Revision has been made according to the suggestions of the reviewer

We appreciate very much these expert reviewers' careful and critical review and very helpful comments. We carefully studied the comments and hope that these revisions are satisfactory. The critiques of these reviewers are addressed as follows:

(1) **Reviewer code:** 00000774

Question: This is a comprehensive review of biology of gastric cancer. Although the review covers the entire range of gastric carcinogenesis, it is, unfortunately, too long and redundant. In particular, similar arguments were described between the section 'ALTERED SIGNALING PATHWAYS IN GASTRIC CANCER' and the section 'GENETIC ALTERATIONS IN GASTRIC CANCER' or 'EPIGENETIC ALTERATIONS IN GASTRIC CANCER'. Authors should shorten the paper by reducing the three sections into one section of 'ALTERED SIGNALING PATHWAYS IN GASTRIC CANCER' with explanations of terminology such as MSI, CIN, LOH, mutation, epigenetic changes etc.

Answer: Done (see revised manuscript)

(2) **Reviewer code:** 00057951: Congratulations on your fine and extensive work.

(3) **Reviewer code:** 00058438

Question: Major concerns: 1.The section of "Risk Factors" (page 4): "Environmental Risk Factors" may be a better subtitle than "Risk Factors", and the authors should briefly focus on the interactions between environmental risk factors and pathogenetic mechanisms of gastric cancer. For being relevant to the subject of this review article, this section should be greatly revised. 2.Targets that can be detected in blood are mentioned in Table 2, and those that cannot be detected in blood or those without available data should be additionally mentioned. Minor concerns: 1.The section of "Risk Factors" (page 4): "The connection between H. pylori and GC is based on epidemiologic data and animal models." Not only from epidemiologic data and animal models, data from clinical trials have

suggested that H. pylori eradication therapy can effectively reduce the development of precancerous lesions and gastric cancer. H. pylori infection is not the only risk factor but is one of the key risk factors. 2.The capitals of "Wnt" or "wnt" should be consistent. 3.There are some errors in grammar or spelling. For example, HDAC inhibitors (HDACis) now also "be" considered as potential therapeutics. "trichostatin" A (TSA) and suberoylanilide hydroxamic acid (SAHA) are the classic HDACis. "orinostsat" (SAHA), also known as suberoylanilide hydroxamic acid, is the ?rst clinically approved HDACi, which has been recently approved for clinical use in CTCL (page 20). Carefully rechecking these errors is recommended.

Answer: Done (see revised manuscript)

(4) **Reviewer code:** 01438559

Question: I enjoyed reading the review article by Dr Shi et al regarding the pathogenic mechanisms in gastric cancer. It covers a broad area of carcinogenesis of gastric cancer. I have a few comments on this article. 1. In the abstract, "the fourth most common cancer and the second leading cause of cancer" is maybe "second leading cause of cancer-related death?" 2. In the Risk Factors; it is known that specific strain of *H. Pylori* has been associated with high prevelance of gastric cancer. It would be better to comment on this. 3. Several abbreviations such as DNMTs or EGCG should be spelled out at first appearance.

Answer: Done (see revised manuscript)

(5) **Reviewer code:** 02495270

Question: In this manuscript, the authors provide an extensive review of the recent advances in our understanding of the molecular pathology of gastric cancer (GC). The manuscript is timely and well written, easy to understand and deserves rapid publication. The authors should consider to describe in a separate paragraph the two main carcinogenetic cascades within gastric mucosa (intestinal vs diffuse) and their relative molecular alterations.

Answer: Gastric cancer can be divided into the diffuse and intestinal types according to the Lauren classification. The molecular mechanisms of two types of GC were not exactly same, for example, ERBB2 overexpression is common in intestinal-type GC, whereas ERBB3 overexpression has a significantly higher rate in the diffuse type cancer than the intestinal type. In this manuscript we elaborated the pathogenetic mechanisms and molecular alterations according to oncogenic signaling pathways in GC. According to the reviewer's suggestion, we supplemented some molecular alterations of diffuse and intestinal type carcinoma in Table 1 and some of important molecules were described in the revised manuscript.

(6) **Reviewer code:** 00033010

Question: The paper of Jing Shi et al "Pathogenetic mechanisms in gastric cancer" is an overview of molecular pathways and risk factors involved in gastric cancer. The paper is exhaustive and all the molecular mechanisms are detailed. However, due to the complexity of the topic, the argumentation appears to be cumbersome, so that the attention of the reader could not be easily caught. Do diffuse and intestinal type carcinoma show activation of different pathways? Emphasizing different pathways in different types of tumors may increase the attractiveness of the paper. What about early gastric cancer? A section dedicated to this topic must be enclosed in the revised manuscript. It is known that Wnt-beta catenin pathway is involved in cell adhesion and migration and therefore may play a role in metastasis development. This aspect needs to be elucidated. The exact term is "cardias" instead of "cardia" (Latin derivation of the word). May any of the cited molecules be considered as markers of good or bad prognosis? Have they been studied as bio-humoral indicators for an early diagnosis of cancer? Which of them are activated in pre-neoplastic conditions such as intestinal metaplasia and atrophy?

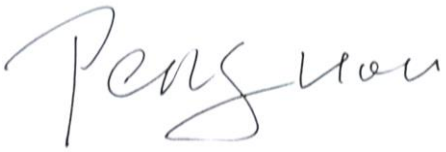
Answer: We want to thank the reviewer for positive comments and suggestions! We revised the manuscript according to the useful suggestions and hope that the reviewer is satisfied with our answer. Diffuse and intestinal type GC show activation of different pathways, wnt-beta catenin

pathway plays an important role in the invasion and metastasis in GC. The descriptions were supplemented in text. Furthermore, genetic and epigenetic molecular alterations are closely associated with poor clinical outcomes of GC patients, and a large number of biomarkers have been developed for the early detection and prognostic evaluation of GC, which were summarized in Tables 1 and 2.

3. References and typesetting have been corrected in the revised manuscript.

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,



Peng Hou, Ph.D.
Department of Endocrinology
The First Affiliated Hospital of Xi'an Jiaotong University School of Medicine,
Xi'an 710061, the People's Republic of China
Tel/Fax: 86-298-532-4039
E-mail: phou@mail.xjtu.edu.cn