Format for ANSWERING REVIEWERS

August 25, 2012

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 4763-review.doc).

Title: Role of Cyclooxygenase-2 in Gastric Cancer Development and Progression

Author: Jian Cheng, Xiao-ming Fan

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 4763

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

(1) reviewer 02456089:

①In the paragraph of "Expression of COX-2 in Gastric Cancer", please illustrate the the expression of the COX-2 was gene expression or the protein expression.

Thank you for your constructive advice, as required, we added more detailed information for the expression of COX-2 in this paragraph.

② Some of the expressions in English were not appropriate, please pay attention to the language.

We appreciate your advice very much. And we have sent our manuscript to a language-editing company for English polishing.

(2) reviewer 01135743:

Gastric cancer is the leading cause of cancer-related death in China, and the mechanism of its carcinogenesis and prognosis remains unclear. The authors attended to investigate the role of COX-2 in gastric cancer. This is well-organised review article. The authors reviewed the COX, its expression in gastric cancer, mechanism of elevated COX-2expression in gastric cancer, and the mechanism of COX-2 in gastric carcinogenesis. However, if they paid much attention to the internal relationship, importance of their work become remarkable.

Thank you very much for your favorable evaluation. COX-2 is mainly involved in many pathological processes such as inflammation and tumorigenesis. And inflammation responses play crucial roles in the microenvironment of carcinogenesis. One of the most crucial networks is COX-2/PGE_2 pathway.

The aforesaid aspect is the core concept of this review. In this review, most of the reasons (such as ***Helicobacter pylori*** infection, the participation of **NF-κB**) for over-expression of COX-2 in gastric cancer are related to inflammation response. Moreover, most molecular mechanisms that COX-2 involved in gastric carcinogenesis are also have relationship with the inflammation network, and a growing number of scientific studies confirmed this point of view. In order to elucidate the internal relationship of sections illustrated in this manuscript, we added some sentences and references to bridge them well.

The added information are as follows:

Paragraph 'Cyclooxygenase', Line30-33 : it was reported that more than 15%of malignant tumors have correlation with infection [25]. Various of inflammation networks are confirmed to play crucial roles in microenvironment of carcinogenesis [26], and the most important network is the COX-2/PGE_2 pathway [27].

Paragraph 'NF-κB', Line 6-9: Some inflammatory cytokines, such as TNF-α, can activate NF-κB, and this activated transcription factor can induce overexpression of inflammatory factors including COX-2 and TNF-α itself, forming the inflammatory network in tumor microenvironment [67].

Paragraph 'Cell Proliferation and Apoptosis', Line 1-7: Accumulating evidence indicates that inflammation plays important roles in the development of cancers [72, 73]. TNF-α, which is a mediator of PGE_2, plays a crucial role in mediating the inflammatory process through activation of NF-κB. It has been found that stromal NF-κB could enhance proliferation of epithelial cells by inducing cytokines, chemokines, and growth factors, such as IL-6, IL-1β, macrophage inflammatory protein-2 and TNF-α, while epithelial NF-κB could suppress apoptosis by inducing anti-apoptotic proteins, such as GADD45β, A1/Bfl1, and cIAP1[74,75].

Paragraph 'Invasion and Metastasis', Line 11-13: A large number of CD44(+) gastric glands was found in human adenocarcinomas and adjacent metaplasias, but not in the normal gastric epithelium. And the CD44(+) tumor cell expansion is triggered by cooperative actions of PGE_2 and Wnt in gastric tumorigenesis[93].

Line 15-17: A study demonstrated that CD44v, a variant form of CD44, could protect tumor cells from oxidative stress in a mouse gastric cancer model, thus it plays an important role in tumor development[96].

Paragraph 'Conclusion', Line 1-2: COX-2/PGE_2 pathway which involved in the inflammatory response

plays a critical role in the microenvironment of gastric tumorigenesis.

References:

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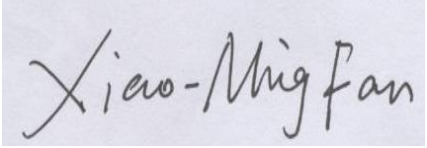
3 References and typesetting were corrected

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

Sincerely yours,



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