

ANSWERING REVIEWERS



December 6, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 6855-Review.doc).

Title: CCN Family Proteins in Gastric Carcinogenesis

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Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 6855

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) **Response to the Reviewer 00502831's comments:** We want to thank the Reviewer for his/her valuable comments. We feel that his/her insightful suggestions have helped us improved our manuscript to meet the high standard required for publication in *World Journal of Gastroenterology*. The following are our responses to the specific comments raised. All revisions are red-marked.

1). Why is CCN family protein up-regulated in some cancers, but down-regulated in other some cancer?

Response 1: We appreciate the comments of the reviewer. We've added some statements for this phenomenon in the 2nd paragraph of the page 2 as follows. "The expression of CCN family proteins is dependent on cell type and context. CCN family proteins can act both positively and negatively in carcinogenesis for different tumor types. The positive or negative effect depends on whether angiogenic factors are limiting and whether conditions that favor apoptosis or senescence prevail".

2). How is the relationship between CCN1 and VEGFA, VEGFC?

Response 2: We appreciate the comments of the reviewer. We've added some statements for the relationship among CCN1, VEGF-A and VEGF-C in the 2nd paragraph of the page 3 as follows. "CCN1 promotes angiogenesis either directly by effects on endothelial cells or indirectly by regulating the angiogenic factors VEGF-A and VEGF-C. However, there are no data illustrating the relationship among CCN1, VEGF-A and VEGF-C in GC".

3). The authors reported "CCN1 contribute to peritoneal dissemination of GC by promoting

tumor-cell adhesion ability” and “Down regulation of CCN2 in GC cells would reduce peritoneal dissemination in nude mice“. This means CCN1 and CCN2 are related to the adhesion of cancer cells to the peritoneum?

Response 3: We appreciate the comments of the reviewer. CCN1 is related to peritoneal dissemination of GC with increased tumor cell adhesion ability, while CCN2 is related to peritoneal dissemination of GC with increased matrix metalloproteinase activity. We've added one more figure, Figure 2, to illustrate the relationship among CCN1, CCN2, and the peritoneal dissemination of GC.

4). How is the difference of prognosis between high expression of CCN1 and low expression of CCN1 in same stage in GC?

Response 4: We appreciate the comments of the reviewer. In patients with GC, high expression of CCN1 correlates with early recurrence. On stage-stratified analysis, the Kaplan-Meier survival estimates are less reliable for patients with stage I or II GC because there is a high censoring rate in the low CCN1 expression group. High CCN1 expression correlates with early recurrence in stage III GC patients. There is a similar trend of correlation but without statistically significant difference in stage IV GC patients (data unpublished).

5). Which is more contribute to the prognosis of GC, CCN1 or CCN2?

Response 5: We appreciate the comments of the reviewer. There is no data available now for comparison between CCN1 and CCN2 in GC prognosis.

6). Is CCN4 related to the peritoneal dissemination of GC?

Response 6: We appreciate the comments of the reviewer. Though CCN4 may act in concert with CCN1 and CCN2 proteins in peritoneal dissemination of GC, there is currently no related report.

7). How about clinical trial of targeting for CCN family proteins in GC?

Response 7: We appreciate the comments of the reviewer. We've added some statements in the 1st paragraph of the page 7 as follows. " For cancer therapy, there is only one ongoing phase I study evaluating FG 3019 therapy in combination with gemcitabine and erlotinib for patients with locally advanced or metastatic pancreatic cancer (ClinicalTrials.gov identifier: NCT01181245). There are currently no clinical trials of CCN-targeted therapy in GC".

8). The authors had better to explain the relationships between CCN1, CCN2 and peritoneal dissemination from GC using figure.

Response 8: We appreciate the comments of the reviewer. We've added one more figure, Figure 2, to illustrate the relationship among CCN1, CCN2 and the peritoneal dissemination of GC.

(2) Response to the Reviewer 02535288's comments: We want to thank the Reviewer for his/her valuable comments. We feel that his/her insightful suggestions have helped us improved our manuscript to meet the high standard required for publication in *World Journal of Gastroenterology*. The following are our responses to the specific comments raised. All revisions are red-marked.

1). Does CCN family protein have any role in the initiation? Authors are encouraged to address this question if there is any data available.

Response 1: We appreciate the comments of the reviewer. We've added some statements in the paragraph 2 of the page 2 as follows. "Of the CCN family proteins, only CCN2 has been reported to be involved in *Helicobacter pylori*-associated chronic gastritis. There is a positive correlation between the density of CCN2-producing mononuclear cells and the severity of chronic gastritis. The actual role of CCN family proteins in the initiation stage of GC carcinogenesis will be clarified with future studies".

2). A flow chart or figure, in addition to the Figure 1, to indicate how the CCN protein directly or indirectly involved in GC may be more helpful to readers to understand its role in GC.

Response 2: We appreciate the comments of the reviewer. We've added one more figure, Figure 3, to indicate the CCN family proteins involved in different stages of GC carcinogenesis.

3). English language needs to be improved, in page 3-4 as well as in the text, a lot of past tense are used in the statements, for instance, "would, could, might," are very frequently applied, this is very rare style for a review paper.

Response 3: We appreciate the comments of the reviewer. We've corrected the past tense to present tense. And the manuscript has been edited by the English language editing company (AJE).

4). In page 5, 2nd paragraph, references are needed for the middle sentence.

Response 4: We appreciate the comments of the reviewer. We've added one reference for the middle sentence as mentioned.

5). Page 6, lines 4-5, the statement is confusing and I find it hard to understand the CCN3 and its functions, please modify the sentence.

Response 5: We appreciate the comments of the reviewer. We've modified the statement as follows. "CCN3 can mediate its various activities through interaction with integrins, such as $\alpha v\beta 3$, $\alpha v\beta 5$, $\alpha 5\beta 1$, $\alpha 6\beta 1$ ".

6). In page 7, lines 11-12, you are in the middle of discussing CCN6, but add CCN5 in the middle, this may need to be placed in CCN5 discussion.

Response 6: We appreciate the comments of the reviewer. We've corrected the typo and changed "CCN5" to "**CCN6**" in page 7.

7). In page 20, "Table. 1" should be "Table 1."

Response 7: We appreciate the comments of the reviewer. We've changed "Table. 1" to "**Table 1.**" in page 20 according to your kind comments.

8). CCN-targeted therapy part are weak, the content needs to be strengthened.

Response 8: We appreciate the comments of the reviewer. We've strengthened this part by adding more statements as follows. "With the greater understanding of the molecular biology of carcinogenesis, more targeted agents have been developed and are associated with improved outcomes in some advanced cancers. Trastuzumab, the first and only targeted agent approved for the treatment of GC, has shown clinical benefits in response rates and survival in combination treatment with chemotherapy for HER-2 positive advanced GC.....Further phase II clinical trials for evaluating its efficacy are underway. For cancer therapy, there is only one ongoing phase I study evaluating FG 3019 therapy in combination with gemcitabine and erlotinib for patients with locally advanced or metastatic pancreatic cancer (ClinicalTrials.gov identifier: NCT01181245). There are currently no clinical trials of CCN-targeted therapy in GC".

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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