

1 Details of your submission

Journal title: World Journal of Gastroenterology

Manuscript NO: 39970

Title: Metabolomic alterations and chromosomal instability status in gastric cancer

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Received Date: 2018-05-22

Date sent for review: 2018-05-23

Date reviewed: 2018-05-31

Reviewer ID: 03317069

Review time: 7 Days

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2 Peer-review report

The authors would like to thank the Editor and Reviewers for their efforts to improve this manuscript. Please find below the point-to-point responses.

Reviewer #1 :

The study attempts to combine information regarding a new molecular classification of gastric cancer (GC), in particular the CIN GC subtype, and the metabolites produced at the tumor tissue level. However, results are descriptive and the discussion is not sufficiently coherent with the results (While VIT B?? it is not consequent to the metabolite that authors found). Thus the conclusion of the study could be improved to allow sufficient significance and relevance for clinical practice.

Response: Thanks for your kind comment. The previous reports on gastric cancer were mostly focusing on either genomics or metabolomics. Indeed the novelty of this study is to combine information regarding a new molecular classification of gastric cancer (GC), in particular the CIN GC subtype, and the metabolites produced at the tumor tissue level. We added: “To our knowledge, the present study is the first report combining the CIN status of gastric cancer with the metabolomics data.” Please refer to Page 16, Line 10-11. In the future, the relationship between the identified mutated genes and metabolites (or pathways) is the next step in our research. To demonstrate the relevance for clinical practice, we further discussed that vitamin B is critical in different pathways, especially on carbon metabolic pathway. If the chemical also affects the replication, repair, and methylation of DNA, it will probably have therapeutic impacts. We modified the sentence as: “Vitamin B has essential roles in carbon metabolism providing critical metabolites for DNA methylation, DNA repair, and nucleic acid synthesis^[29], although not significantly change in our study. Adjustment of vitamin B levels and genetic polymorphisms of related key enzymes in one carbon metabolism pathway might govern the bioavailability of metabolites and therefore cause changes in CIN phenotypes.” Please refer to Page 18, Line 1-6.

Ref 11 is not for laren classification instead for colorectal cancer.

Response: Thank you for the reminder. We modify that ref 11 to the previous sentence: “By definition, CIN tumors have a high degree of somatic copy-number variation, and they account for nearly half of all GCs, making them the predominant cancer subtype in the gastroesophageal junction or cardia^[11].” Please refer to Page 6, Line 20-22.

The sentence " in addition, thus valid and easy-to use cin....." must be revised.

Response: Thank you for advice. We rephrase the sentence as "In addition, an easy-to-use biomarker for CIN is still not available." Please refer to Page 6, Line 24-25.

Metabolomics offer an alternative to the traditional methods for GC, not solutions at today. Sohn demonstrated that CIN GC had a better OS than GC NOT with non-CIN GC

Response: We agree with the reviewer's comment. We clarify the sentence as: "Sohn et al.^[27] demonstrated that patients with CIN GC had better overall survival than those with non-CIN GC. Metabolomics might offer an alternative way for stratification that could help to select more appropriate adjuvant chemotherapy." Please refer to Page 17, Line 15-17.

Figure 1 showed not the triangles that instead was indicated in the legend

Response: Thanks for your kind comment. We modified to the correct marks. "(a) and (b) Tumor (green, n = 19) vs. healthy tissue (red, n = 19). (c) and (d) Tumor between CIN type (red, n = 9) and non-CIN type (green, n = 10). (e) and (f) Tumor (green, n = 9) and healthy tissue (red, n = 9) in the CIN type. (g) and (h) Tumor (green, n = 10) and healthy tissue (red, n = 10) in the non-CIN type." Please refer to Page 26, Figure 1.

Title of Tables could be revised (NOT healthy but non-CIN tissues, Table 4) or incomplete (compared to healthy , table 5)

Response: Thanks for your kind comment. We clarify the title of Table 4 to "Alteration metabolites with statistical significance between tumor and non-cancerous tissue." Please refer to Page 32, Table 4. We also modified the title of Table 5 to "Alteration metabolites with statistical significance between CIN and non-CIN types." Please refer to Page 33, Table 5.

Reviewer #2:

The authors explored the correlation of metabolomics profiles of gastric cancer (GC) with its chromosomally instability (CIN) status. This is a carefully done study and the

findings are of considerable interest. For the benefit of the reader, however, a number of points need modifying. These are given below.

Comments 1. (RESULTS, Patient demographics) How did the authors select these 19 patients? Sample size was too small to explore the correlation of metabolomics profiles of gastric cancer. In addition, the authors should show the statistical analysis in Table 1. There might be difference in age, sex and tumor size.

Response: Thanks for your kind comment. We added “We prospectively enrolled these 19 patients in a continuous cohort”. Please refer to Page 12, Line 5-6.

The statistical analysis for difference in age, sex and tumor size was added to Page 29, Table 1. We added “One of the study limitations was a small number of participants undergoing operation who were willing to contribute their tissue samples in each category, therefore, we did not correct for multiple comparisons.” Please refer to Page 18, Line 12-14.

2. (Discussion) The authors mentioned novel therapeutic possibilities regarding GC from their data. However, this study showed only the correlation of metabolomics profiles of gastric cancer with its chromosomally instability status. It seems to be difficult to connect novel therapeutic possibilities with only these results. Moreover, the authors showed many kinds of Metabolic alterations in GC tumors. In fact, what metabolites can affect cancer progression or patient’s prognosis?

Response: Thanks for your kind comment. The article was the first to propose the relationship between gastric cancer gene and metabolite changes. We will continue to work on what metabolites can affect cancer progression or patient’s prognosis. We added: “In future works, we would like to collect more patient survival data to understand what metabolites can affect cancer progression or patient’s prognosis.” Please refer to Page 18, Line 22-24.

Reviewer #3:

This work investigated to explore the correlation of metabolomics profiles of gastric cancer (GC) with its chromosomally instability (CIN) status. Classification of CIN and non-CIN type was based on 409 oncogenes and suppressor genes sequenced. And the aqueous metabolites were identified by liquid chromatography–mass spectrometry.

As a result, authors found that metabolomic profiles of GC tumors and the adjacent healthy tissue are distinct, and the CIN is associated with downstream metabolic alterations in GC. The relationship between metabolic profiles and the occurrence of GC has always been a matter of great concern. This manuscript provides novel evidence for the metabolism profiles and GC. It also provides novel evidence for the relationship between metabolic status and CIN. In the future, the relationship between specific metabolite changes and specific CIN will be further studied. In conclusion, this study provides a basis for the prevention and treatment of GC. In addition, the manuscript was well written. The set of data presented look convincing, solid and support the conclusions drawn. I recommend accepting this manuscript.

Response: [We appreciate Reviewer's effort and comments. Thank you very much indeed.](#)