Korea Research Institute of Bioscience and Biotechnology

Dear Dr. Jing Yu

Re: *World Journal of Gastroenterology #18470*

Title: "Genomic and epigenomic heterogeneity in molecular subtypes of gastric cancer"

September 8, 2015

We thank you and the reviewer who made positive evaluations on our manuscript. We completely agree with the reviewer's comments and appreciate very much for the pertinent comments. We made our best to address all the concerns raised. Please see the point-by-point answers with corrections and additions. The requested revisions are marked in red in this revised manuscript (some English editorial changes are not marked).

(1) Reviewer *00291404*' Comments

In this review, the authors have done a superb job in summarizing research progress leading to the molecular subtyping of gastric cancer into four subgroups. The new classification may help develop novel personalized medicine for the treatment of gastric cancer. The manuscript is well written and data are well presented.

(2) Reviewer *02438565*' Comments

I think that authors reviewed the comprehensive data about the molecular subtype analyses of gastric cancer, on which the subtly promising markers for prognosis of gastric cancer are basing. The language and grammar are fluent.

Our response to (1)~(2):

Thanks for the appreciation and generous comments.

(3) Reviewer *01939435*' Comments

The authors review the genomic and epigenomic heterogeneity of the four molecular subtypes of gastric cancer. They also describe a mutational meta-analysis and a reanalysis of DNA methylation that were performed using previously reported gastric cancer datasets. In general, the manuscript is written well and clear. I suggest that the authors could summarize all the abbreviation for genes used in this paper, such as ARID1A and BCOR.....

Our response to (3):

Thanks for your comments. According to your comments, we added complete description of genes next to the abbreviated gene symbols in this revision.

(4) Reviewer *03018260'* Comments

This manuscript describes the categorization of gastric cancer (GC). It is been traditionally classsified into two major groups (intestinal and diffuse type). They use 4 types. Overall, this is an extensive review. 1) It is verbous. It needs to be succinct. 2) It is long. It should be shorter. (it was not interesting to read it through)

Our response to (4-1)~(4-2):

We agree your comments. So, we tried to revise our manuscript more succinctly in this revision. As a result, the total number of words including references was decreased from 9,195 (original manuscript) to 8,426 (revised manuscript).

3) Helicobacter pylori causes GC. They need to add address bacterial causes of GC. HP is known to survive much longer than previously reported outside stomach. 4) Can they analyze the GC types using 'gene tpye profiles'? Not only by big causing

types such as MSI, virus, chromosome stability, etc.

Our response to (4-3)~(4-4): As your comments, Helicobacter pylori infection and the expression of specific cancer-associated genes are well-established drivers for gastric cancer development. However, the purpose of this review is to summarize and discuss the four molecular subtypes of gastric cancer that were recently demonstrated from the Cancer Genome Atlas (TCGA) network. In fact, unsupervised clustering of multi-dimensional data sets including mRNA, miRNA, exome, whole-genome, and CpG methylation from the TCGA did not reveal the evident molecular signature of Helicobacter pylori infection. Therefore, we think that bacterial causes by Helicobacter pylori and gene-type profiles, which you pointed out, may be out of scope of this review.

5) Conclusion is weak. They described a lot and it is so much in detail, it will be good to summarize the main text in conclusion again. 6) There any many speculative suggesions such as "miRNAs may potentially serve as useful markers ..". It will be better to state conclusively.

Our response to (4-5)~(4-6):

We agree your comments. Thus, we revised Conclusion section to shortly summarize the main text and removed speculative phrases in this revision.

With all these changes, we hope the revision is now acceptable for publication.

Sincerely yours,

Seon-Young Kim, Ph.D.

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