Dear editor,

On behalf of my co-authors, we thank you very much for giving us an opportunity to revise our manuscript. We appreciate you and reviewers very much for your positive and constructive comments and suggestions on our manuscript entitled "Comprehensive multi-omics analysis identified core molecular processes in esophageal cancer and revealed GNGT2 is a potential prognostic marker". We have addressed the comments raised by the reviewers, and the amendments are showed in the revised manuscript.

Response to the reviewer's comments:

Reviewer #1: it is a well written and documented manuscript

Answer: Thank you for your comment, which encourages us and values our work.

Reviewer #2: This is a very interesting genomic study about the broad relationships of the esophageal cancers my multi-omic analysis with the possible pathogenesis, their relations with the clinical progression and the prognosis of these tumors I hope this study will open new ways for a better knowledge of these tumors that will conduct in the near future to get an early diagnosis and a better prognosis.

Answer: Thank you for your comment. We will try our best to continue related word for early diagnosis and better prognosis in the future.

Reviewer #3: The Authors compared samples from 40 patients with esophageal cancer with samples of normal esophageal mucosa in 40 volunteers. Differential expression analysis was performed to identified differentially expressed genes in different stages of esophageal cancer from TCGA data. Then exacting gene interaction modules and identifying hub genes in module interaction network. Further, though survival analysis, methylation analysis, pivot analysis and enrichment analysis, some important molecules and related

function or pathway were identified to elucidate potential mechanism in esophageal cancer. A total of 7457 differentially expressed genes (DEGs) and 14 gene interaction modules were identified. These module genes were significantly involved in the positive regulation of protein transport, gastric acid secretion, insulin-like growth factor receptor binding and other biological processes, as well as p53 signaling pathway, ERBB signaling pathway and EGFR signaling pathway. Then, TFs (including HIF1A) and ncRNAs (including CRNDE and hsa-mir-330-3p) significantly regulate dysfunction modules were identified. Further, survival analysis showed that GNGT2 was closely related to survival of esophageal cancer. The paper is very interesting and it deserves publication. Few notes, which probably can help in future publications or in perfecting the one I read.

1-The introduction is probably too long.

Answer: We have shortened the introduction according to your suggestion.

2- A reader will be much interested to know about the action of the genes correlated to esophageal cancer occurrence and progression in this study. Namely GNGT2. For example, it is evident that the majority of the genes found in this study to be correlated to esophageal cancer, are related to inflammation. In this setting, are they a primary or a secondary event in the history of esophageal cancer? In vitro, inhibition of specific genes and its correlation to growth of cancer cells, could be to elucidate this matter.

Answer: Thank you for your reminding. In vitro experiment in cell lines such as knockdown, overexpression, phenotype experiment is performed by our colleague and will be published in the future, but not in this study, which focus on in silico analysis to reveal potential prognostic marker for esophageal cancer.

3-Probably, the Authors should specify if the 40 volunteers were matched for age and sex with patients with esophageal cancer.

Answer: Thank you for your reminding. We have corrected this issue according

to your suggestion.

4- It is evident that matched patients had normal esophageal mucosa. It might be more interesting to compare findings in patients with esophageal cancer with those of patients with esophagitis related to gastroesophageal reflux. In both situations we will have inflammation, and we can differentiate genes involve just in inflammation from those involved in cancer proliferation. We could find explanations why in some patients' inflammation may lead to cancer and in other does not imply cancer formation.

Answer: Thank you for your suggestion, which inspired us for the further study. However, the relationship between inflammation and cancer is not the scope of this study. We are appreciated for your suggestion that we will compare esophageal cancer patients with those of patients with esophagitis related to gastroesophageal reflux to explore the relationship between inflammation and cancer in our next study.

5-Genes involved in cancer formation and proliferation may have a significant role according to the development of the cancer itself. In the initial stages the changes from normal mucosa to metaplasia are correlated with many genes. The progression from metaplasia to cancer cells probably involves more specific genes. In other words, I suggest the Authors to continue their interesting study trying to correlate different genes expression to the time related, sequential biological progression from normal cells to cancer cells

Answer: Thank you for your suggestion. We have correlate different genes expression to the time related, sequential biological progression from stage I to IV. However, it is not appropriate to compare normal cells with cancer cells because of the different genetic background of cancer cells. In other words, we believe that normal cell lines and cancer cell lines are not comparable to verify this issue.

We tried our best to improve the manuscript and made some changes in the manuscript. After English editing, there are some changes in the manuscript. These changes will not influence the content and framework of the paper. And here we did not list the changes in revised paper.

Looking forward to hearing from you.

Yours sincerely.

Yun-Gang Luo