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7901 Stoneridge Drive, Suite 501,
Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
https://www.wjgnet.com

PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 42817

Title: Biomarker identification and trans-regulatory network analyses in esophageal adenocarcinoma and Barrett's esophagus

Reviewer's code: 03259445

Reviewer's country: Japan

Science editor: Xue-Jiao Wang

Date sent for review: 2018-10-19

Date reviewed: 2018-10-28

Review time: 9 Days

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection	[ ] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [Y] Major revision [ ] Rejection	Peer-Review: [ ] Anonymous [Y] Onymous Peer-reviewer's expertise on the topic of the manuscript: [ ] Advanced [Y] General [ ] No expertise Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

Thank you for giving me the chance to review this interesting manuscript. The authors investigated the transcriptome changes in the progression from normal esophagus to esophageal adenocarcinoma and Barrett's esophagus. I enjoyed reviewing this

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manuscript. The theory and data of this article were very interesting and persuasive,

Thank you so much for your positive remarks.

but I am not sure the readers of this journal, gastroenterologists, will read this article with much interest. This article is too basic and gemomics for this journal. I recommend the authors to add data or persuasive theories to attract the readers of this journal.

Thank you for your advice. That's a good suggestion. The datasets used in our study are retrieved from NCBI GEO Database. We used "Barrett's esophagus" and "esophageal adenocarcinoma" as the key words to search related datasets in the Database. After reading the whole result items, we then selected the most adequate two datasets with the largest sample sizes, which also consist of NE, BE and EAC groups of patients. The data presented in our manuscript is what we got after a series of bioinformatics analyses. In this study, comprehensive bioinformatics analyses of the DEGs from two datasets were performed, and the genes and biomarkers potentially involved in the progression of BE and EAC were identified. After trans-regulatory network prediction, ROC evaluation and DAVID annotation, an association between COL1A1 and EAC was found. Similarly, an association between MMP1 and BE was also predicted. This study might provide a novel perspective on the molecular mechanisms involved in the development of BE and EAC to the clinical gastroenterologists. It is better to perform and validate our analyses on a cohort with larger sample sizes. And the results and conclusions will be more valuable, and the theories will be more persuasive. At this very moment, we are planning to do multi-omics analyses on the same subjects to acquire more information and the sample sizes are larger than the datasets we retrieved online. That is to say, the validation groups will be introduced in our future study and further validation is going on right now. We totally agree with your advisements and thanks a lot.

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 42817

Title: Biomarker identification and trans-regulatory network analyses in esophageal adenocarcinoma and Barrett's esophagus

Reviewer's code: 00182114

Reviewer's country: Japan

Science editor: Xue-Jiao Wang

Date sent for review: 2018-10-31

Date reviewed: 2018-11-08

Review time: 8 Days

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish	[Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection	Peer-Review: [Y] Anonymous [ ] Onymous Peer-reviewer's expertise on the topic of the manuscript: [ ] Advanced [Y] General [ ] No expertise Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

Author concluded that the results of MMP-1 and Col1A1 expression were comparable with the higher expression levels of adenocarcinomas from BE. I agree to author's conclusion.

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Thank you so much for your positive remarks.

I ask some questions to author.

1. How about SCC in MMPI and COL1A1 level?

Thank you for your questions. In this study, our research group has mainly focused on Barrett's esophagus (BE) and esophageal adenocarcinoma (EAC). After a series of bioinformatics analyses, we found the association between MMP1 and BE, and the association between COL1A1 and EAC. As to the expression levels of MMP1 and COL1A1 in esophageal squamous cell carcinoma (ESCC), I'm sorry that we could not give you a final conclusion because of the lack of experiments and bioinformatics analyses of ESCC. However, we attached great importance to your valuable questions and searched on the PubMed in order to give you a satisfactory reply. The expression of MMP1 was markedly increased in ESCC samples and was closely associated with lymph node metastasis and advanced TNM stages, and it could be an independent factor for overall survival in ESCC patients (PMID: 27130665). MMP1 may also have a higher expression in cutaneous SCC, neck SCC, nasopharyngeal SCC and lung SCC (PMID: 28209530; 29290801; 24063540; 15688379; 18661521; 25789706). COL1A1 was showed to have a higher expression and associated with tumor metastasis in ESCC patients compared to controls (PMID: 19082484). Moreover, COL1A1 was also found to have a higher expression in oral SCC, head and neck SCC (PMID: 28569392; 27128408; 29254802; 27123054). I hope that our replies are useful. Thank you!

2. Please tell me the carcinogenesis of esophageal adenocarcinoma from barrett esophagus.

The mechanisms and factors related to the progression of EAC from BE are still unclear. In our study, we aimed to explore the changes in the transcriptome, and to determine

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https://www.wjgnet.com

the differentially expressed genes and their roles in the multistep morphological progression of BE and EAC based on two GEO datasets. We screened for potential genes and determined their diagnostic values, and a number of potent genes and their underlying mechanisms could be identified and clarified. The results in our study are obtained mainly based on bioinformatics analyses. And the sample sizes in each group of patients are not large enough. In other words, it is difficult to reveal the carcinogenesis of EAC in just one study. To our knowledge, some factors, including gastroesophageal reflux disease, male, central obesity and smoking, have already been identified as risk factors of EAC, and long-segment BE is also an important factor. Moreover, BE is the only known precursor of EAC, and patients with BE have a persistent and excessive risk of EAC over time.

The carcinogenesis of EAC is quite a complex molecular mechanism, involving multiple genes and pathways, and it is a typically multistep progress as well. Meanwhile, the interactions between genetics and environments are playing important roles, as well as various carcinogenic factors. Many studies have indicated that chromosomal abnormalities, telomerase abnormalities, and the abnormalities of cyclins and signal transduction pathways are related to the progression from BE to EAC. Although abnormal expressions of some genes/factors have been confirmed and predicted to be related to EAC carcinogenesis, their exact roles in precise stages are still not clear. Biomarkers of EAC with great sensitivity and specificity are under exploration, and certain genes/factors haven't been widely recognized. Therefore, identification of potent biomarkers in the early stage of EAC carcinogenesis is still a hot spot.

Furthermore, more experiments are been carried on, so are ours. We hope that our future studies would provide more detailed information. Thank you for your questions.

Moreover, please tell me the etiology of SCC and ADC in esophagus.

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Thank you for your questions. Esophageal carcinoma is a malignant tumor located in the esophagus, including squamous cell carcinoma (ESCC) and adenocarcinoma (EAC). ESCC has a higher incidence than EAC. To date, the etiology of both ESCC and EAC are still not clear. Some risk factors of ESCC are listed as follows: nitrosamine compounds, certain toxins produced by some fungus, lack of trace elements, certain diet and habits such as drinking and smoking, long-term stimulation including reflux, genetics and infection of HPV. As to EAC, Some factors including gastroesophageal reflux disease, male, central obesity and smoking have already been identified as risk factors of EAC, and long-segment BE is also an important factor. Moreover, BE is the only known precursor of EAC, and patients with BE have a persistent and excessive risk of EAC over time. Thank you!