Peer Review File

Article information: http://dx.doi.org/10.21037/tcr-20-2827.

Reviewer Comments

Lung adenocarcinoma (LUAD) accounts for the largest proportion of lung cancer patients and has the highest morbidity and mortality worldwide. In the manuscript "Identification of immune-associated lncRNAs as a prognostic marker for lung adenocarcinoma", authors constructed a risk signature of immune-associated lncRNAs and clustered LUAD samples into low- or high-risk based on this signature, and validated the signature's prognostic and clinical value.
Couple questions are required to be answered before accepted.

(1) There were several similar reports about immune-associated lncRNAs in cancers (Mol Carcinog. 2019 Apr;58(4):544-553) and (Mol Cancer. 2017 Jan 19;16(1):16) in the PubMed. What is the novel idea in the paper? Please elaborate in the introduction.
Reply1: We thank the reviewer's advices. And the introduction of the original manuscript did not make it clear about the novel and importance of this article. In view of this, we have strengthened the introduction to highlight innovation.
Changes in the text: Page 4, line 70-81

(2) Why to validate risk model by PDAC, not LUAD?
Reply2: We thank for you reminding, we apologize for the confusion caused by insufficient explanation. Actually, the internal validation of LUAD was performed for the risk model (see Page 5, line 91-92; Page 8, line 163-172). We randomly chose 70% of the 499 LUAD patients as the training group and 30% as the testing group. The risk model generated from the training group was then validated in the testing group. We found that "KEGG_PANCREATIC_ CANCER" ($p = 0.01$, NSE = 1.77) was also significantly enriched in the high-risk group when we used the GSEA analysis, so the PDAC dataset was not performed to validate the risk model, but rather to explore whether models can be applied to other cancers. Now we revise it and add some explanation in the introduction.
Changes in the text: Page 4, line 70-81

(3) Why to focus on 7 lncRNAs in the paper? Please illustrate clearly in the introduction.
Reply3: We thank for you reminding, we apologize for the confusion caused by insufficient explanation. Now we revise it and add some explanation in the introduction.
Changes in the text: Page 4, line 70-81

(4) Please supplement the role of tumor microenvironment in LUAD in the introduction.

Reply4: We thank the reviewer's advices. Some previous studies and views on tumor microenvironment and LUAD have been added to the introduction.

Changes in the text: Page 3, line 47-52 and line 57-59.

(5) It is must to test the effect of a representative lncRNA in lung cancer microenvironment. The experimental data was missing in the paper.

Reply5: We thank the reviewer for the great point. We consider this part outside the scope of our purpose. The main purpose of this paper is to construct a new risk model for LUAD, and the basic mechanism of the 7 lncRNAs is not clear, which we also mentioned in the original manuscript(see Page 11, line 302-305). The mechanism of action of these lncRNAs and their role in LUAD tumor microenvironment deserve further study. Actually, We read some published articles similar to this one (Aging (Albany NY) . 2018 Sep 11;10(9):2356-2366. ; Aging (Albany NY). 2019 Jan 19;11(2):467-479. and J Cell Biochem. 2019 Sep;120(9):15730-15739. in PubMed), we found that such articles were more focused on clinical value, while experimental data of genes or lncRNAs related to predictive models were missing. This is also the reason why we put forward corresponding views on the deficiencies of this research at the end of the article(see Page 17, line 364-367).

(6) Which results were indicated these lncRNAs were involved in immune response?

Reply6: Firstly, we obtained the lncRNAs which were co-expressed with the immune-related mRNAs, and we construct a risk model with these lncRNAs. Then we used ssGSEA with 29 immune-associated gene sets, ESTIMATE and GSEA to verified the relationship between the immune response and different risk groups clustered by the risk model. We should point out that our focus is to prove that different LUAD populations divided by these lncRNAs have different immune responses, which is well illustrated in Figure 4

(7) Why not to validate the risk model by the data from your hospital? Why not to explore the role of the inflammatory factors in LUAD microenvironment?

Reply7: We agree with the reviewer that it would be nice to validate the risk model by the current data from our hospital. Unfortunately, however, the preservation of intact tumor tissues for accurate pathological diagnosis which made sample collection of LUAD particularly difficult. Hence we are lacking the specimens of LUAD and normal tissues now. We appreciate the reviewer for the insightful comments, but feel that such studies could be subjects of future reports. And considering the main purpose of this article is to construct a new risk prediction model for LUAD. We think that it

might be inappropriate to spend a lot of time exploring the role of inflammatory factors in the tumor microenvironment.

(8) Please illustrate clearly the functions of these lncRNAs in LUAD microenvironment, respectively.

Reply8: We thank the reviewer's advices. We should acknowledge that this is a weakness of our research, as we point out at the end of the original manuscript (see Page 14, line 304-307; Page 17, line 364-367). In this article, we can only illustrate what we have figured out, that is, the populations differentiated by these lncRNAs behave differently in the immune response and LUAD microenvironment. And we have added some explanation in the revised manuscript.

Changes in the text: Page 15, line322-328.

(9) Whether the prognostic value of 7 immune-associated cancer is applicable for other cancer, except PDAC?

Reply9: In the GSEA analysis, we also found that "KEGG_THYROID_CANCER" (p = 0.012, NSE = 1.66) was also significantly enriched in the high-risk group. We have attempted to perform the risk model in the thyroid cancer. However, due to the good prognosis of thyroid cancer, the number of patients with follow-up endpoint in TCGA data was small, so although the trend was the same as that of LUAD and PDAC, there was no statistical difference. Considering the main focus in this article is to to construct a new risk prediction model for LUAD. we did not discuss these results in our manuscript.