Peer Review File

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Reviewer A

In this article the authors utilize ONCOMINE; UALCAN; HPA; Kaplan-Meier plotter; cBioPortal; STRING; Database for annotation, DAVID; TIMER; and Omics databases to evaluate CSE1L and XPO family expression in lung adenocarcinoma and LUSC. The authors show that transcriptional and protein expression levels of CSE1L and XPO1/5/6/7 were increased in patients with LUAD and LUSC. Interestingly the increased transcriptional levels of CSE1L and XPO5/6/7 were linked to worse prognosis. On the contrary, XPO1 over-expression was linked to better prognosis. High mutation rate was observed in the disease model tested with high mutation being linked to immune infiltration. Strengths and weaknesses are nicely covered.Specific comments:The authors must discuss the observation from other studies where XPO1 expression was linked to poor prognosis (Nagasaka et al Lung Cancer. 2021 Oct;160:92-98. doi: 10.1016/j.lungcan.2021.08.010. Epub 2021 Aug 27.)References should include newer articles on XPO1 family proteins and lung cancer and other cancersThere are several typos in the manuscript including the abstract and highlight box text.Legends to figures can be enhanced

Comment 1:The authors must discuss the observation from other studies where XPO1 expression was linked to poor prognosis (Nagasaka et al Lung Cancer. 2021 Oct;160:92-98. doi: 10.1016/j.lungcan.2021.08.010. Epub 2021 Aug 27.)
Reply 1: we have modified our text as advised (see Page 14, line 410-414).
Changes in the text: Nagasaka M et al.(44) retrospectively analyzed de-identified pathological and molecular information from 18,218 NSCLC samples to describe the prevalence of XPO1 mutations and amplifications in NSCLC. Their study found that presence of XPO1 pathogenic mutations was associated with a poor OS in both the entire NSCLC cohort and the adenocarcinoma subgroup.

Comment 2: References should include newer articles on XPO1 family proteins and lung cancer and other cancers.
Reply 2: The latest research on XPO2 and cancer did not have relevant research data in 2023 and 2022, and we also provided relevant research data in 2021 in the article. Simultaneously added the latest research data results of XPOT and XPO5 in recent years (see Page 15, line 451-457). Overall, there were relatively few studies on the relationship between exportins and

cancer in 2022 and 2023.

Changes in the text: In addition, Pan et al.(52) have found in recent years that knocking out XPOT through small interfering RNA can inhibit the proliferation and migration of neuroblastoma cells. However, the role of XPOT in lung cancer has not been previously explored. Regarding XPO5, Ozdas S et al.(53) found that the mRNA and protein levels of XPO5 were upregulated in metastatic cells of head and neck squamous cell carcinoma (HNSCC), and silencing XPO5 resulted in reduced cell proliferation, delayed wound healing, and increased Caspase-3 enzyme activity in HNSCC cell lines.

Comment 3: There are several typos in the manuscript including the abstract and highlight box text.

Reply 3: We have carefully read the abstract and highlight box text and made some minor modifications, but we hope you can point out the typos so that we can make accurate corrections.

Comment 4: Legends to figures can be enhanced.

Reply 4: We have all made modifications to the legends.

Reviewer B

The paper titled “Comprehensive bioinformatics analysis on exportins in lung adenocarcinoma and lung squamous cell carcinoma” is interesting. The study provides novel insights into the selection of prognostic biomarkers of exportins in LUAD and LUSC. However, there are several minor issues that if addressed would significantly improve the manuscript.

1) What is the relationship between exportins and disease microenvironment? How valuable is exportins in predicting the therapeutic effect and drug sensitivity of LUAD and LUSC patients? It is recommended to add relevant contents.
2) It may be more meaningful to add functional research on key genes.
3) What is the characteristic feature in a transformed phenotype of lung cancer? What role does exportins play in this process? It is recommended to add relevant contents.
4) The introduction part of this paper is not comprehensive enough, and the similar papers have not been cited, such as “Identification of potential key molecular biomarkers in lung adenocarcinoma by bioinformatics analysis, PMID: 35261899”. It is recommended to quote the article.
5) This study is based on bioinformatics analysis. It is recommended to increase in vivo and in vitro experimental studies, which may be more meaningful.
6) Please analyze the mechanism of exportins regulation in LUAD and LUSC based on the

results of this study and in combination with relevant literature.

Comment 1: What is the relationship between exportins and disease microenvironment? How valuable is exportins in predicting the therapeutic effect and drug sensitivity of LUAD and LUSC patients? It is recommended to add relevant contents.

Reply 1: We have added relevant content in the discussion section (see Page 17, line 493-498, see Page 13, line 375-381).

Changes in the text: Tumor-derived microbubbles (TMVs) are extracellular vesicles released from tumor cells, which are now understood to promote the communication between tumor and surrounding microenvironment. A research showed that the interaction between ARF6-GTP and XPO5 transporteda a pre-miRNA complex to sites of TMV biogenesis for inclusion as TMV cargo.This indicates that XPO5 is related to tumor microenvironment.

XPO1 knockout enhanced the sensitivity of SCLC cells to chemotherapy, and XPO1 inhibition showed synergistic effect with first-line and second-line chemotherapy. Selinur is a small molecule XPO1 inhibitor, which can significantly inhibit tumor growth in patients with SCLC in combination with cisplatin or iritinib.

Comment 2: It may be more meaningful to add functional research on key genes.

Reply 2: our research still has some limitations. Since all the datas in our study are from the public databases, there is no cellular function researchs or animal experiments in vivo and in vitro of exportins，and then we will start to carry out relevant experimental researchs to promote the clinical application of exportins as potential biomarkers of LUAD and LUSC (see Page 18, line 542-546).

Changes in the text: However, our research still has some limitations. Since all the datas in our study are from the public databases, there is no cellular function researchs or animal experiments in vivo and in vitro of exportins，and then we will start to carry out relevant experimental researchs to promote the clinical application of exportins as potential biomarkers of LUAD and LUSC.

Comment 3: What is the characteristic feature in a transformed phenotype of lung cancer? What role does exportins play in this process? It is recommended to add relevant contents.

Reply 3:We have added relevant content in the introduction section (see Page 4, line 97-102).

Changes in the text: A study showed that CRM1 is frequently over-expressed in NSCLC, especially in LUAD and LUSC. Furthermore, the study also found that after tobacco carcinogen, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) exposure or transfection with CRM1 vector, the overexpression of CRM1 in the lung epithelial cell line BEAS-2B led to cellular transformation, which suggests that the up-regulation of CRM1 may be an important pathway for malignant transformation of lung epithelial cells.

Comment 4: The introduction part of this paper is not comprehensive enough, and the similar papers have not been cited, such as “Identification of potential key molecular biomarkers in lung adenocarcinoma by bioinformatics analysis, PMID: 35261899”. It is recommended to quote the article.

Reply 4: We have cited related articles in the introduction section (see Page 5, line113-115)

Changes in the text: For example, Guo et al. analyzed the DEGs and hub genes that affect the development of LUAD through bioinformatics technology, providing potential diagnosis and treatment strategies for the treatment of LUAD.

Comment 5: This study is based on bioinformatics analysis. It is recommended to increase in vivo and in vitro experimental studies, which may be more meaningful.

Reply 5: our research still has some limitations. Since all the datas in our study are from the public databases, there is no cellular function researchs or animal experiments in vivo and in vitro of exportins，and then we will start to carry out relevant experimental researchs to promote the clinical application of exportins as potential biomarkers of LUAD and LUSC (see Page 18, line 542-546).

Changes in the text: Changes in the text: However, our research still has some limitations. Since all the datas in our study are from the public databases, there is no cellular function researchs or animal experiments in vivo and in vitro of exportins，and then we will start to carry out relevant experimental researchs to promote the clinical application of exportins as potential biomarkers of LUAD and LUSC.

Comment 6: Please analyze the mechanism of exportins regulation in LUAD and LUSC based on the results of this study and in combination with relevant literature.

Reply 6: We have added relevant content in the introduction section (see Page 4, line 97-102). There are also some related contents in the discussion section on page 14-15, lines 422-430.

Changes in the text: A study showed that CRM1 is frequently over-expressed in NSCLC, especially in LUAD and LUSC. Furthermore, the study also found that after tobacco carcinogen, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) exposure or transfection with CRM1 vector, the overexpression of CRM1 in the lung epithelial cell line BEAS-2B led to cellular transformation, which suggests that the up-regulation of CRM1 may be an important pathway for malignant transformation of lung epithelial cells.

Reviewer C

1. Please add the statement "The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).” **in both the “Methods” section of Main Text and the “Ethical Statement” section of Footnote.**

Reply 1: We have confirmed and modified it.

2. Please check if any more references need to be added in the below 3 sentences since you mentioned “Studies”, but only one reference was cited. If not, “studies” should be changed to “a study/a previous study”.

423 and lung cancer (12). Some studies have found that the stable overexpression of
424 *CRM1* in human bronchial epithelial cells leads to malignant cellular transformation
425 (14). XPO1 knockout enhanced the sensitivity of SCLC cells to chemotherapy, and

545 *EIF5A2*). Although the mechanism of *EIF5A1* causing cancers has not been fully
546 clarified, some studies have found that the *EIF5A1* and *EIF5A2* proteins are
547 overexpressed in some human tumors (55). At present, there are no more reports on

612 DNA-damage response, and apoptosis (65). Some studies have proven that *E2F1*
613 promotes EMT by regulating *ZEB2* in SCLC (66). In SCLC cells, *ILF2* interacts with

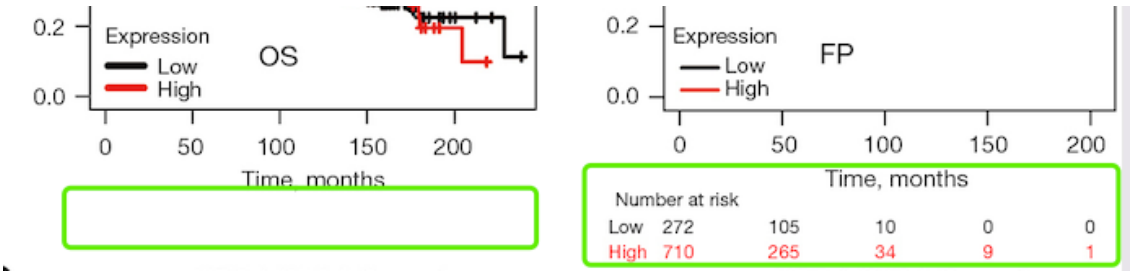
Reply 2: We have modified the above contents.

3. Table 2:
Please indicate the full name of "OS", "PFS" in Table 2 footnote.
Reply 3: We have modified it.

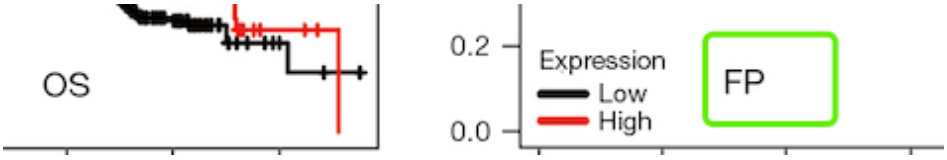
4. Table S2:
Please indicate the full name of "LUAD", "LUSC", “GO”, “KEGG” in Table S2 footnote.
Reply 4: We have modified it.

5. Figure 3:
1) The legend of Figure 3 should declare that the images are cited from the HPA database and corresponding URLs are needed.
Please consult the HPA's stipulation https://www.proteinatlas.org/about/licence and revise the description accordingly.
2) If available, please indicate the magnification for these cell maps in the legend.
Reply 5: We have modified Figure 3.

6. Figure 4:
1) “Number at risk” is missing in Figure 4B. Please check.



2) Should all “FP” be “PFS”? Please revise.

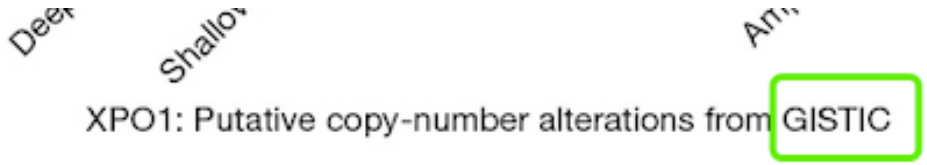


Reply 6.1: We have modified Figure 4B.

Reply 6.2: We have modified Figure 4.

7. Figure 6:

Please indicate the full name of "GISTIC" in the legend.

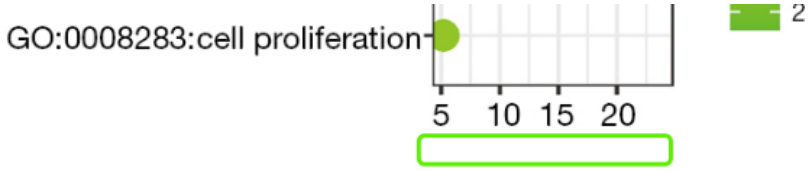


Reply 7: We have modified it.

8. Figure 7:

1) There are Figure 7A, B parts in your main text, but no letters A, B were marked in your Figure 7. Please add.

2) Please add the description of x-axis in Figure 7A and B.



3) Please indicate the full name of "BP", “CC”, “MF” in the legend.

Reply 8: We have modified it.