Peer Review File

Article information: https://dx.doi.org/10.21037/tcr-23-1450

Reviewer A

The manuscript concerns a review that sheds light on LOXL1-AS1 functions in multiple cancers. This is an informative review addressing the role of LOXL1-AS1 in multiple cancers as a diagnostic and therapeutic biomarker. There are some issues that need to be addressed before this manuscript can be accepted for publication.

1. The title of the paper is not accurately expressed, and I think it needs to be rewritten.

Reply 1: I am very grateful to the reviewers for their valuable comments. I've revised and replaced it with a more appropriate title.

Changes in the text: I replaced the title with something more appropriate. (See Line 1-2)

2. Paper is replete with spelling mistakes. Please, edit the manuscript regarding word mistakes.

Reply 2: I am very grateful to the reviewers for their valuable comments. I've corrected the spelling errors in the article.

3. Some references missing. For example, “novel diagnostic and prognostic biomarkers for early identification of 66 cancer are particularly important for developing cancer treatment strategies and reducing mortality.”; “Extensive human genome analysis shows that 90% of eukaryotic genomic DNA is actively transcribed into RNA, but only 2% is actually mRNA that can be encoded for subsequent biological functions of proteins.”; “lncRNA is the most dominant type of ncRNA, named because it is usually more than 200 nt in length.”

The following references may increase the reader's comprehension:

a. Sheykhhasan M, Tanzadehpanah H, Ahmadieh Yazdi A, Mahaki H, Seyedebrahimi R, Akbari M, Manoochehri H, Kalhor N, Dama P. FLVCR1-AS1 and FBXL19-AS1: Two Putative lncRNA Candidates in Multiple Human Cancers. Noncoding RNA. 2022 Dec 22;9(1):1. doi: 10.3390/ncrna9010001. PMID: 36649030; PMCID: PMC9844485.

b. Sheykhhasan M, Ahmadyousefi Y, Seyedebrahimi R, Tanzadehpanah H, Manoochehri H, Dama P, Hosseini NF, Akbari M, Eslami Farsani M. DLX6-AS1: a putative lncRNA candidate in multiple human cancers. Expert Rev Mol Med. 2021 Nov 26;23:e17. doi: 10.1017/erm.2021.17. PMID: 34823630.

Reply 3: I am very grateful to the reviewers for their valuable comments, I have added multiple appropriate references in the locations suggested by the reviewers, and this

includes the literature suggested by the reviewers.

Changes in the text: I've added the missing references. (See Line 73, 77, 79)

4. In order to make the review more interesting to read, I suggest the authors divide the manuscript under headings based on types of cancers such as " LOXL1-AS1 in carcinomas" or " LOXL1-AS1 in sarcomas" and " LOXL1-AS1 in other solid cancers". Other types of classifications such as " LOXL1-AS1 in epithelial cancers" or " LOXL1-AS1 in mesenchymal cancers" or " LOXL1-AS1 in endometrial cancers" etc would also be an interesting touch to the review.

Reply 4: I am very grateful to the reviewers for their valuable comments, I have categorised the titles by cancer type as suggested by the reviewers to make the article clearer in its presentation.

Changes in the text: I've categorized the changes by tumor title. (See Line140, 311, 322)

5. In order to make the paper more interesting to read, I suggested that the authors could add one graphical abstract to the manuscript.

Reply 5: I am very grateful to the reviewers for their valuable comments, I have added a graphic summary to the article, which is a great idea.

Changes in the text: I've added a graphical summary. (See Line 30-31)

6. I suggest including clear limitations of the study in the discussion.

Reply 6: I am very grateful to the reviewers for their valuable comments, I have added the clear limitations of the study in the last part of the discussion.

Changes in the text: I added to the obvious limitations of the study. (See Line 449-453)

Reviewer B

1. As required in the reporting checklist, please identify the report as a Narrative Review or Literature Review in the title.

Reply 2: Dear Editor, We have indicated in the title that the report is a narrative review.

Changes in the text: See Line 1-2.

2. In the Abstract, the search keywords mentioned in the Methods seems to miss a word "neoplasm". Please check and revise.

Reply 8: Dear Editor, The term "neoplasm" has been added to the section of search terms mentioned in "Methods".

Changes in the text: See Line 42

3. Citations:

1) The citations of ***Ref 2-3, 78-79*** are missing in the text, please check and revise.
2) References should be cited consecutively in the main text. For example, the first citation of ***Ref 60*** should be after ***Ref 59***, and ***Ref 65*** after ***Ref 64.*** Please check through and revise.
3) It is suggested to cite the corresponding reference since you mentioned author's name:
   - Sun and Li et al. detected the expression level of LOXL1-AS1 in 84 and 89 gastric cancer pathological tissues, respectively, and the expression level of LOXL1-AS1 was increased compared with that in normal tissues.
4) The authors mentioned in below sentences are inconsistent with the relative references, please check and revise.
   - Fang et al.[27] selected tissue samples from 45 OC patients and 4 ovarian cancer cells for LOXL1-AS1 expression verification, and the results showed that the expression level of LOXL1-AS1 was increased.

     [27] Xue F, Xu Y H, Shen C C, et al. Non-coding RNA LOXL1-AS1 exhibits oncogenic activity in ovarian cancer via regulation of miR-18b-5p/VMA21 axis [J]. Biomed Pharmacother, 2020, 125109568.
   - Li et al.[72] obtained 45 pairs of ESCC and normal paracancerous tissue samples to detect LOXL1-AS1 expression levels.

     [72] Morgan E, Soerjomataram I, Rumgay H, et al. The Global Landscape of Esophageal Squamous Cell Carcinoma and Esophageal Adenocarcinoma Incidence and Mortality in 2020 and Projections to 2040: New Estimates From GLOBOCAN 2020 [J]. Gastroenterology, 2022, 163(3) 649-658.e642.
   - Zhao et al.[45] found that in ESCC cells, the expression level of LOXL1-AS1 had a strong positive correlation with the proliferation ability of ESCC cells, and further studies showed that when LOXL1-AS1 was silenced, the apoptosis program of ESCC cells was significantly induced.

[45] Li H, Chu J, Jia J, et al. LncRNA LOXL1-AS1 promotes esophageal squamous cell carcinoma progression by targeting DESC1 [J]. J Cancer, 2021, 12(2) 530-538.

5) Please check if more/any reference should be cited since you mentioned "studies":

- Many in vivo and in vitro experimental studies have shown that LOXL1-AS1 can bind to miRNA as competitive endogenous RNAs (ceRNA), that is, the regulatory mechanism of miRNA sponge, targeting a variety of specific genes or signaling pathways, regulating the malignant biological behavior of tumor cells, and promoting tumor growth[23]
- Studies have confirmed that LOXL1-AS1 can regulate the proliferation and migration ability of GC cells, promote the process of EMT and upregulate the stem expression of gastric cancer cancer stem cells (CSCs).
- Studies have shown that LOXL1-AS1 expression is upregulated in laryngeal cancer cells such as Tu-177, M4E, SNU-899, SNU-46, and AMC-HN-8, and it is proved that LOXL1-AS1 can enhance the proliferation and migration ability of laryngeal cancer cells and promote the epithelial-mesenchymal transformation (EMT) process[33].
- Several studies have shown that the expression level of LOXL1-AS1 in various LC cell lines and lung cancer tissues is upregulated, and this expression degree is more correlated with tumor advanced and metastasis[38].
- Studies have pointed out that LOXL1-AS1 is also overexpressed in medulloblastoma tissues and is associated with the degree of advanced malignancy of tumors[36].
- Studies have shown that overexpressed LOXL1-AS1 is an important cancer-promoting factor in CRC, and LOXL1-AS1 can promote tumor cell proliferation and inhibit apoptosis by regulating the miR-1224-5p/miR-761/HK2 signaling axis[30].
- Studies have shown that knocking down the expression level of LOXL1-AS1 in ESCC cells can increase the percentage of G1 phase in the ESCC cell cycle, while reducing the proportion of S phase, causing cell cycle

arrest[45].

- Numerous tumor-related studies have pointed out that LOXL1-AS1 is generally overexpressed in cancer tissues, which can distinguish tumor tissues from normal tissues more specifically, making it have obvious advantages in early diagnosis of tumors.

Reply 3.1: Dear Editor, the problem here has been fixed.
Changes in the text: See Line 61 and 336.

Reply 3.2: Dear Editor, the problem here has been fixed.

Reply 3.3: Dear Editor, I have added the appropriate references here, but since one reference has been withdrawn, I have modified the corresponding article content.
Changes in the text: See Line 139-146.

Reply 3.4: Dear Editor, I have corrected the inconsistency between the authors and the relevant references.
Changes in the text: See Line 159-160, 243, 334.

Reply 3.5: Dear Editor, I have corrected the inconsistency between the authors and the relevant references.
Changes in the text: See Line 103, 144-146, 199-202, 216,290-291, 327-330, 387-390, 401.

4. Tables and Figures

1) Please check through and make sure that **all abbreviations in each figure and table have been defined in each legend**. For example, please provide the full names of **"TNM" "FIGO" "MSI**" in the foot of Table 2.
2) Table 1: Please check the date. January 6th, 2023?

3)

Items	Specification
Date of search	1/6/2023

4) Please specify the selection process in detail (who conducted the selection, whether it was conducted independently, how consensus was obtained, etc.) in Table 1.

5)

Selection process	Two authors selected studies together

6) Table 2-3: please uppercase the first letter.

Type of disease	Expression	Clinical features
breast cancer	upregulates	TNM stage, lymp
gastric cancer	upregulates	tumor size, lympl
		metastasis, TNM
		post-progression s
endometrial cancer	upregulates	menstruation, pat
		metastasis, FIGO

7) Please confirm if the elements of Figure 2 are original or not. If not, permission from the copyrighter is required.

Reply 4.1-4.4: Dear Editor, I have revised the contents of the form accordingly, as detailed in Tables 1-3.

Reply 4.5: On behalf of all the authors, I would like to declare that the creation of the images is based on the graphic site Biorender, of which we are paid members, and there is no lack of copyright.