Peer Review File

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Reviewer A

The paper titled "Long non-coding RNA DINO promotes cisplatin sensitivity in lung adenocarcinoma via the p53-Bax axis" is interesting. The lncRNA DINO regulates the sensitivity of lung adenocarcinoma to cisplatin by stabilizing p53 and activating the p53-Bax axis, and thus, may be a novel therapeutic target to overcome cisplatin resistance. However, there are several minor issues that if addressed would significantly improve the manuscript.

Comment 1: There are many lncRNAs that regulate the cisplatin sensitivity of lung adenocarcinoma. Why did the author choose lncRNA DINO for research? Please describe the reason.

Reply 1: LncRNA DINO is a novel lncRNA transcribed from human cells treated with doxorubicin. Cisplatin and doxorubicin are both DNA-targeting chemotherapeutic drugs. Our preliminary experiments showed that cisplatin can stimulate the expression of lncRNA DINO. Therefore, we started to study the effect of lncRNA DINO on cisplatin treated lung adenocarcinoma and further found that lncRNA DINO can increase the sensitivity of cisplatin treatment.

Comment 2: What is the relationship between the low expression of lncRNA DINO and poor differentiation, lymph node metastasis, tumor size and stage of lung adenocarcinoma? It is suggested to add relevant contents.

Reply 2: According to TANRIC (https://ibl.mdanderson.org/tanric/_design/basic/main.html), high lncRNA DINO expression is linked to longer overall survival. We do not have solid data about the relationship between the low expression of lncRNA DINO and poor differentiation, lymph node metastasis, tumor size and stage of lung adenocarcinoma now. We will collect clinical data to discover the relationship between LncRNA DINO and the pathological state in future study.

Comment 3: In view of the issue of cisplatin resistance, what are the current targeted therapy system therapies for lung adenocarcinoma? It is recommended to add relevant content in the discussion section.

Reply 3: Currently, targeted therapy is recommended as first line treatment for patient with sensitive mutation, for example, EGFR or ALK mutation. But all patients will be resistant to targeted therapy eventually. Then chemotherapy will be the treatment choice. Thus, the issue of cisplatin resistance will be problem for all patients, with or without sensitive mutation. These have been added to discussion.

Changes in the text: We changed discussion in line 383-384.

Comment 4: How does lncRNA DINO affect the progression, chemoresistance and eventual recurrence of lung adenocarcinoma? It is suggested to add relevant contents.

Reply 4: According to our experimental results, LncRNA DINO can inhibit the proliferation of lung adenocarcinoma cell lines, increase the drug sensitivity of cisplatin chemotherapy and effectively inhibit the proliferation of cisplatin-resistant lung cancer in animal experiments. The mechanism is that lncRNA DINO regulates the sensitivity of lung adenocarcinoma to cisplatin by stabilizing p53 and activating the p53-Bax axis.

Comment 5: What is the important clinical value of lncRNA DINO-p53-Bax axis in lung adenocarcinoma? What is its potential as a therapeutic target for lung adenocarcinoma? It is recommended to add relevant content to the discussion.
Reply 5: p53 is a tumor suppressor gene that can inhibit the onset and development of lung adenocarcinoma. Bax is a pro-apoptotic gene that can promote apoptosis of tumor cells. The activity of the p53-Bax axis can predict the sensitivity of patients with lung adenocarcinoma to chemotherapy, radiotherapy and immunotherapy. LncRNA DINO is a potential therapeutic target for lung adenocarcinoma, which needs further research to make conclusion.

Comment 6: The introduction part of this paper is not comprehensive enough, and the similar papers have not been cited, such as "LncRNA SNHG7 promotes non-small cell lung cancer progression and cisplatin resistance by inducing autophagic activity, J Thorac Dis, PMID: 36794139". It is recommended to quote the articles.
Reply 6: Thank you for the suggestion. We added this paper to the reference.
Changes in the text: We insert the new quote in line 536 - 538.

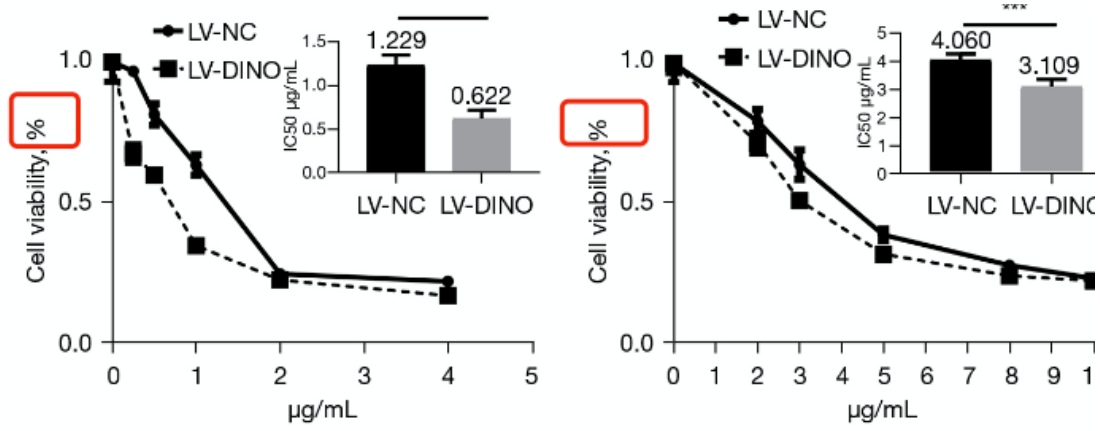
Comment 7: What are the problems and challenges that need to be overcome in the clinical application of lncRNA? It is recommended to add relevant content.
Reply 7: In the clinical application of lncRNA, the following problems and challenges need to be overcome： 1. Standardization of assay methods: The current lack of uniform assay methods and standardized analytical procedures makes it difficult to compare and reproduce results between different studies. Therefore, it is necessary to establish standardized detection methods and analytical procedures. 2. Analysis of biological functions: Although a large number of lncRNAs have been discovered, their biological functions are still poorly understood. Therefore, the biological function and mechanism of action of lncRNAs need to be further investigated. 3. Reliability and accuracy of clinical application: Although lncRNAs have been shown to play an important role in the development and progression of many diseases, further research and validation are needed to ensure their reliability and accuracy in clinical applications. 4. Safety and efficacy: Before lncRNA can be used in clinical treatment, a large number of safety and efficacy studies are needed to ensure their safety and efficacy in treatment. 5. Efficient gene delivering system in vivo. Currently we lack of efficient gene delivering system that makes gene therapy possible in clinic. We have added these to our discussion.
Changes in the text: We have added 1 sentence to discussion (see Page13, line 449-452).

Reviewer B

1. Figure 1: Please define “n.s.” in figure legends.

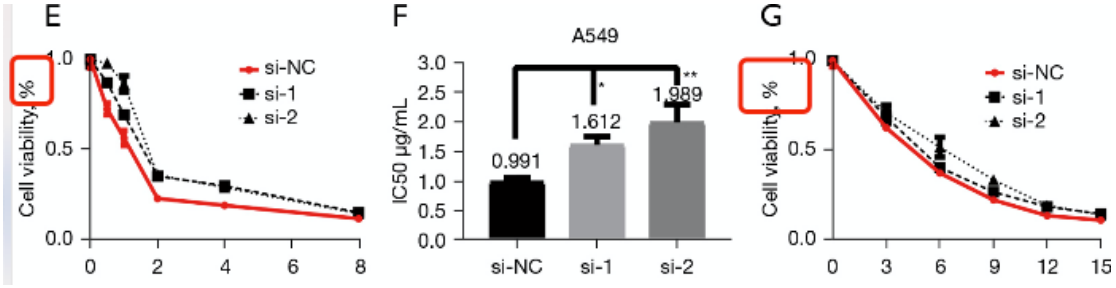
Reply: We insert the new definition of “n.s.” (see Page20, line 638).

2. Figure 2: It seems “%” should be removed since the numbers on the Y-axis are 0-1.0.



Reply: We removed the "%" in those images. (see Figure 2).

3. Figure 3: It seems “%” should be removed since the numbers on the Y-axis are 0-1.0.



Reply: We removed the "%" in those images. (see Figure 3).