

Peer Review File

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Reviewer Comments

Comment 1: Minor editing of English language required.

Reply 1: Thanks for your valuable comments. We have made revisions to the manuscript through the editage website (<https://www.editage.cn/>).

Changes in the text: We have marked the modified parts in red.

Comment 2: The author claim that VA cannot only reduce RIBE via inhibiting TGFβRI but also enhance the killing effect of radiation on tumor. Please discuss this point with more previous findings.

Reply 2: Thanks for your valuable comments. We added some data in Figure 5 (see Figure 5F) to illustrate our findings and discussed our research results with previous findings in the manuscript (see Page 9-10, line 247-259)

Changes in the text: The details are on page 9-10, line 247-259.

Comment 3: Figs. 5C and D, please provide more information about the low level of TGFβRI expression in Co+IR+VA group compared to control group. In addition, please provide example to support your discussion.

Reply 3: Thanks for your valuable comments. The focus of this study was on the damage response of bystander BMSCs after radiation of A549 cells, and the highly expression of TGFβRI on BMSCs led to the reduced cell viability. Under this premise, the effect of VA in reducing the damage on BMSCs was observed. However, the BMSCs in the Ctrl group were neither co-cultured with A549 cells nor irradiated with 2 Gy X-rays, so we did not compare the Co+IR+VA group with Ctrl group.

Changes in the text: We add some data in Figure 5 (see Figure 5F)

Comment 4: I don't understand the results of Fig. 5E. Please address these issues to improve the manuscript further.

Reply 4: Thanks for your valuable comments. We apologize for not clearly labeling the groups in Figure 5E (The newly modified version of Fig 5G). We have relabeled the image and will upload the revised Figure 5. (See revised Figure 5G, the groups are Tumor, IR, IR+VA, respectively.)

Changes in the text: We have relabeled the image in Figure 5 (see Figure 5G)

Comment 5: What are the limitations in this study?

Reply 5: Thanks for your question. Although it was found that the increase of CTSB in A549 cells after radiation can lead to an increase in TGF-β1, we also used the CTSB inhibitor CA-074Me to verify the correlation between the two. However, the specific mechanism by which CTSB regulates the increase in TGF-β1 expression still needs further exploration.

Changes in the text: The details are on page 11, line 298-303.

Comment 6: Abstract, please provide the full name of CTSB and TGF-β1 in the method section not in results section.

Reply 6: Thanks for your valuable comments. We have modified our text as advised (see Page 2, line 35, 36, and 46).

Changes in the text: The details are on page 2, line 35, 36, and 46.

Comment 7: Consider providing information and discuss about the results from Fig.4A-E in the revised manuscript. In addition, how to obtain the concentration of VA (based on the results of Fig.4A-E) for the study?

Reply 7: Thanks for your valuable comments. We apologize for not providing a detailed description of the screening process for the VA concentration in Figure 4. We have supplemented and revised the text based on your comments.

Changes in the text: The details are on page 9, line 229-237.