

## List of responses

Dear Editors and Reviewers:

Thank you for your letter and for the reviewers' comments concerning our manuscript entitled "FoxM1 regulates VEGF-A expression to promote the angiogenesis and tumor cell growth of gallbladder cancer". Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied comments carefully and have made correction which we hope meet with approval. The main corrections in the paper and the responds to the reviewer's comments are as flowing:

Responds to the reviewer's comments:

Reviewer #1:

1. Response to comment: No information is given in the "materials and methods section" on patients

**Response:** Thank you for the comments on the paper. From line 117, we added "Patient tissues and information".

2. Response to comment: Methods used are described with little precision and lack important details.

**Response:** On line 145-165, we perfected the important details of the experimental method

3. Response to comment: The legend of each figure should be more informative, indicating the corresponding method for each data.

**Response:** Thank you for your comment. Your opinions inspired us and we revised the manuscript accordingly. In each figure legend, we added the corresponding method.

4. Response to comment: Images with immunohistochemical or HE staining should be shown with scale bars. The quality of images with HE staining (Fig.6) should be improved

**Response:** Thank you for reminding us the improper description on the study. In figure.1,3,4,5,6, we added the scale bars and improved the quality of images with HE staining (Fig.6).

5. Response to comment: The statement in the text "the tumors of mice transfected with lenti-FoxM1-shRNA were smaller than the control group" does not correspond to that observed in figure 6D.

**Response:** We are very sorry for our negligence of the correct marking of the annotation. The mistake in fig.6 was fixed.

6. Response to comment: For data relating to tumor foci and microvascular density (Fig. 6E-G), the number of fields counted per sample, the number of samples and animals evaluated should be indicated.

**Response:** The number fields counted per sample and samples and animals evaluated were added in figure legend of figure6.

7. Response to comment: The number of patients evaluated with Kaplan-Meier analysis should be indicated.

**Response:** In figure legend of figure7, we added the number of patients evaluated with Kaplan-Meier analysis.

Reviewer #2:

1. Response to comment: The article does not have page and line numbers, which makes it very difficult for reviewers to provide comments.

**Response:** Thank you for the comments. We added page and line numbers according to your advice.

2. Response to comment: Abstract: “Which lacks diagnosis and therapeutic targets”. This sentence needs to be revised. How was gallbladder cancer diagnosed if there are no diagnostic targets? Do you mean biomolecular markers?

**Response:** Your suggestion is greatly appreciated. According to your suggestion, we revised the sentence to “which lacks effective therapeutic targets”.

3. Response to comment: BALB/C nude mice were performed. This needs to be revised. It should be BALB/C nude mice were used to establish the xenograft tumor model.

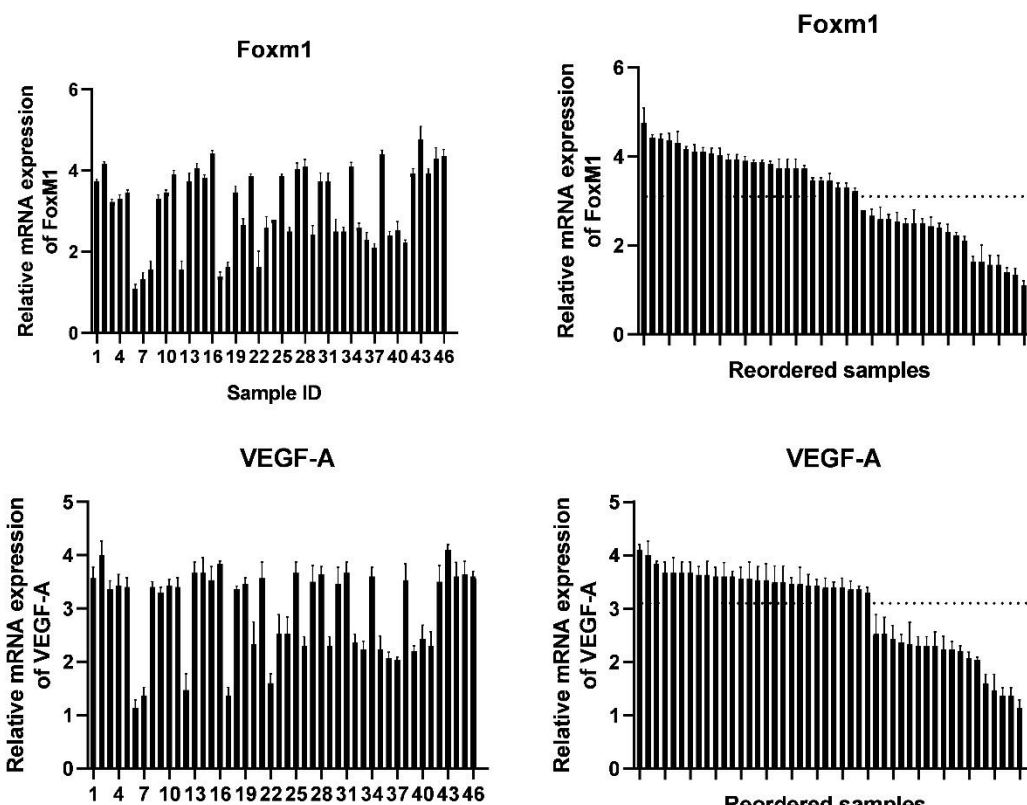
**Response:** Thank you for your suggestion, we revised the sentence as “BALB/C nude mice were used to establish the xenograft tumor model.” of line 48.

4. Response to comment: Last paragraph of the introduction “We found that both upregulation and downregulation of FoxM1 are involved in the growth and inhibition of GBC cells, with the possibility of a direct regulatory relationship.” This is confusing. Are both upregulation and downregulation of FoxM1 involved in the inhibition of GBC cells? “Tumor cell migration and invasion were also examined to measure the effects of FoxM1 regulation. We aim to explore the mechanism by which FoxM1 regulates VEGF-A in GBC”. If this is your aim, please specify in the conclusion what mechanisms have you found?

**Response:** On line 109-111, we revised the paragraph. Function of overexpression and downregulation of FoxM1 were explained separately, we believe it should illustrate our findings more clearly. We found that FoxM1 could combine with VEGF-A and activate the transcription, led to GBC progression, and we added the description on line 111-114.

5. Response to comment: Figure 7: The authors used “high” and “low”. What are criteria to define “high” and “low”?

**Response:** We used qPCR to detect the mRNA expression of FoxM1 and VEGF-A in patient samples. As showed in the figure below, according to the mean of “Relative mRNA expression”, we divided those samples into high and low groups.



Response to editor:

1. Response to comment: I found the authors did not provide the approved grant application form(s). Please upload the approved grant application form(s) or funding agency copy of any approval document(s);

**Response:** Thank you for the comments. We uploaded the approved grant application form on the website.

2. Response to comment: I found the authors did not provide the original figures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor;

**Response:** We are very sorry that we didn't provide the original figures. We uploaded the PowerPoint which included all the figures.

3. Response to comment: I found the authors did not add the PMID and DOI in the reference list. Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references. Please revise throughout;

**Response:** Thank you for the comments on the paper. We corrected the reference lists according to the author guideline.

4. Response to comment: I found the authors did not write the "article highlight" section. Please write the "article highlights" section at the end of the main text; and

**Response:** We are very sorry that we didn't write the "article highlight" section. We added the "article highlights" section on line 395-445.

5. Response to comment: please don't include any \*, #, †, §, ‡, ¥, @....in your manuscript; Please use superscript numbers for illustration; and for statistical significance, please use superscript letters. Statistical significance is expressed as  $aP < 0.05$ ,  $bP < 0.01$  ( $P > 0.05$  usually does not need to be denoted). If there are other series of P values,  $cP < 0.05$  and  $dP < 0.01$  are used, and a third series of P values is expressed as  $eP < 0.05$  and  $fP < 0.01$ .

**Response:** Thank you for the comments. We corrected it according to the guideline in the manuscript, each figure and each figure legend. Please notice that we did not remove the # symbol in author list which indicated the equally contributed authors because we did not know how to mark these authors. Please feel free to edit # symbol as your standard.