

PEER-REVIEW REPORT

Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 72414

Title: Forkhead Box q1 promotes invasion and metastasis in colorectal cancer by activating the epidermal growth factor receptor pathway

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 04232981

Position: Editorial Board

Academic degree: MD, MSc, PhD

Professional title: Assistant Professor

Reviewer's Country/Territory: Bangladesh

Author's Country/Territory: China

Manuscript submission date: 2021-10-18

Reviewer chosen by: AI Technique

Reviewer accepted review: 2021-10-18 11:39

Reviewer performed review: 2021-10-29 19:44

Review time: 11 Days and 8 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No

Peer-reviewer statements	Peer-Review: [<input type="checkbox"/>] Anonymous [<input checked="" type="checkbox"/>] Onymous Conflicts-of-Interest: [<input type="checkbox"/>] Yes [<input checked="" type="checkbox"/>] No
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SPECIFIC COMMENTS TO AUTHORS

Manuscript Number: 72414 Title: FOXQ1 promotes invasion and metastasis in colorectal cancer by activating the HB-EGF/EGFR pathway Journal: World Journal of Gastroenterology Minor comments: The author appraised this paper by evaluating the mechanism that FOXQ1 promotes the invasion and metastasis of Colorectal cancer by activating the HB-EGF/EGFR pathway. However, your article is inadequately presented. Furthermore, there are many problems in the different sections as well. Although the article has scientific rigor, several minor flows need to be improved before publication. 1. The abstract section can improve—add a focus point in the abstract section. 2. Rewrite the methods, results and conclusion (in the abstract) in a more straightforward form. 3. FOXQ1 regulated the expression of HB-EGF, which initiated a cascading effect on multiple important node genes in the EGFR pathway. What does it mean? 4. HB-EGF expression levels and EGFR pathway activation states were detected by Western blot before and after recombinant human HB-EGF (rhHB-EGF) protein was added to DLD1-shFOXQ1 cells. What does it mean? 5. Authors are suggested to use the full form when used for the first time throughout the manuscript. 6. The introduction section looks good. Authors can try to include the existing research limitations also, how the present research unravels those limits. 7. Aim of the study should need to add as the last paragraph in the introduction. 8. Material and methods also look good. Need a logical flow of the writings with enough references. 9. Check all the symbols. 10. Cutoff values for the scoring system were assigned as follows: high expression of FOXQ1 and HB-EGF were defined as an IRS of ≥ 4 (4, 6, 8, 9 and 12); and low expression was defined as an IRS of < 4 (0, 1, 2 and 3). Any references? 11. Exogenous recombinant HB-EGF



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protein at a final concentration of 50 ng/mL was added to the cell culture medium when the cell density reached 80%. Why is so? 12. The results section can improve by adding significant results. 13. The writing of results is good. Need to maintain a logical flow of the writings. 14. Figures presentation is up to mark. 15. Figure legends are self-explanatory. Need to confirm without the repetition of the results and discussion in the figure legends. 16. The discussion is good. The discussion section can improve by including the data from other sources about related works. 17. The conclusion needs to address future perspectives. 18. Novelty of the work should be added by the author in the conclusion section. 19. Many spacing, punctuation marks problem found in the tables. 20. Spacing, punctuation marks, grammar, and spelling errors should be reviewed thoroughly. I found so many typos throughout the manuscript.

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Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05387405

Position: Peer Reviewer

Academic degree: MSc, PhD

Professional title: Research Scientist

Reviewer's Country/Territory: Hungary

Author's Country/Territory: China

Manuscript submission date: 2021-10-18

Reviewer chosen by: AI Technique

Reviewer accepted review: 2021-11-13 10:09

Reviewer performed review: 2021-11-17 10:49

Review time: 4 Days

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No

Peer-reviewer statements	Peer-Review: [<input checked="" type="radio"/>] Anonymous [<input type="radio"/>] Onymous
	Conflicts-of-Interest: [<input type="radio"/>] Yes [<input checked="" type="radio"/>] No

SPECIFIC COMMENTS TO AUTHORS

Authors of the article investigated FOXQ1 and HB-EGF in CRC. The article is well written, easy to follow, results are clear. However, the following issues should be resolved prior publication: 1. A better Discussion is needed. Most of the Discussion is basically the repeat of results. Comparison of new findings with previous ones are a must. Reference to figures and p-values should be removed from Discussion unless the result is so significant that it needs to be re-referenced. 2. Did authors applied any p-value correction? 3. On figures, use the conventional */**/** signs to represent significance of $p < 0.05$ / 0.01 / 0.001 instead of a/b/c. 4. Within the main text, exact p-values must be presented with 4 digit decimals. 5. In Discussion authors wrote: "In our previous studies, we found that the mRNA...". Citation must be included! 6. First two paragraph of Discussion can be megerged in my oppinion. 7. Please include the vulcano plots as well if they are mentioned witin the text. 8. As per their position within the manuscript, the ordering of Table 2 and 3 should be changed. 9. A new table about the clinicohystopathological details of the 65 patiens must be included.

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Title: Forkhead Box q1 promotes invasion and metastasis in colorectal cancer by activating the epidermal growth factor receptor pathway

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05774721

Position: Peer Reviewer

Academic degree: PhD

Professional title: Research Assistant

Reviewer's Country/Territory: Argentina

Author's Country/Territory: China

Manuscript submission date: 2021-10-18

Reviewer chosen by: AI Technique

Reviewer accepted review: 2021-11-14 16:59

Reviewer performed review: 2021-11-24 18:35

Review time: 10 Days and 1 Hour

Scientific quality	<input checked="" type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No

Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous
	Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

This work reports the role of FOXQ1 in colorectal cancer progression through HB-EGF/EGFR pathway. The research work is clear, well organized, easy-to-read and mostly conclusive. Some concerns on the part of this reviewer should be resolved prior to the article publication.

- 1- EGFR should be defined in the abstract and in the manuscript text.
- 2- Sections should be numbered.
- 3- In the Introduction, "Forkhead Box Q1 (FOXQ1) is a member of the fork head transcription factor family[4], and it promotes tumor genes by activating cell proliferation, invasion and apoptosis[5]." What do the authors mean by "tumor genes"? Tumorigenesis? Tumor genes transcription?. Also in the Introduction "There is evidence that poor efficacy and survival in CRC are associated with abnormally activated signaling pathways, including the EGFR signaling pathway[17]." The poor efficacy is referred to the treatments? this should be stated.
- 4- I observe that MAPKs are evaluated. Which one of them? ERK 1/2 MAPK? This should be stated in the text and figures. As a suggestion, beta-Catenin modulation by FOXQ1 through HB-EGF/EGFR pathway could be also studied, since this protein is relevant for CRC progression and chemoresistance.
- 5- Cell proliferation should be assessed with more than one test. For example Neutral red uptake, trypan blue, MTT, MTS.
- 6- In "Expression and prognosis of FOXQ1 and HB-EGF in CRC and normal colorectal tissues" Section of the Results. The authors state that "FOXQ1 was also associated with worse overall survival (Figure 1C)". From what is observed in the Figure, it should be clarified that is FOXQ1's increased expression.
- 7- In the figures, the statistical comparison between two samples should be indicated with asterisks. Also noted that the authors use two criteria, simultaneously expressing two values of probability of error when only the



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smallest error value should go. For example, $P = 0.01$. Also, To show consistency throughout the text, they should unify the criteria

9- Section “FOXQ1 inhibition induces HB-EGF suppression and EGF/PDGF signaling pathway blockade in vitro”. I think this section is very interesting, however, these results only suggest what they show, that FOXQ1 is involved in the modulation of the mentioned pathways. It is known that there are many cross signals at the intracellular level. To be able to suggest that the EGFR receptor is involved, tests should be carried out by inhibiting the activity or blocking EGRF (with antibodies) with subsequent treatment of exogenous FOXQ1 and finally see how the signaling pathways are modulated. Colocalization assays by immunocytochemistry can also be performed. Otherwise, the direct involvement of EGFR can only be argued in the discussion section.

9- In the final section of the results. Not my expertise, but the analysis of the colorectal tumors tissue looks scant. More details about the selected patients should be included and further analyzed in the results, (age, tumor stage, tumor classification, treatment)

RE-REVIEW REPORT OF REVISED MANUSCRIPT

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Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05387405

Position: Peer Reviewer

Academic degree: MSc, PhD

Professional title: Research Scientist

Reviewer's Country/Territory: Hungary

Author's Country/Territory: China

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Reviewer chosen by: Jia-Ru Fan

Reviewer accepted review: 2022-01-21 07:15

Reviewer performed review: 2022-01-22 11:18

Review time: 1 Day and 4 Hours

Scientific quality	<input checked="" type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Peer-reviewer	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous



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statements

Conflicts-of-Interest: [] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

Manuscript improved significantly. There are a few typos here and there, which should be checked prior publication. In Table 3, "(mm)" is missing from size of tumor.