

PEER-REVIEW REPORT

Name of journal: *World Journal of Gastrointestinal Oncology*

Manuscript NO: 77761

Title: Overexpression of ELL-associated factor 2 suppresses invasion, migration, and angiogenesis in colorectal cancer

Provenance and peer review: Unsolicited manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 03252941

Position: Editorial Board

Academic degree: MD

Professional title: Doctor, Professor

Reviewer's Country/Territory: Japan

Author's Country/Territory: China

Manuscript submission date: 2022-05-19

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-05-20 23:02

Reviewer performed review: 2022-05-22 23:34

Review time: 2 Days

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" 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 Grade E: Do not publish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="radio"/>] Anonymous [<input type="radio"/>] Onymous Conflicts-of-Interest: [<input type="radio"/>] Yes [<input checked="" type="radio"/>] No
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SPECIFIC COMMENTS TO AUTHORS

Feng et al. investigated the role of EAF2 in colorectal cancer. They revealed that EAF2 suppresses cell motility and angiogenesis via the stat3/TGF- β 1 pathway. This is a well planned and performed study. Also, the paper is relatively well written. I have some minor comments on it. 1. Statistical analysis in materials and methods is not described sufficiently. Applications of Wilcoxon signed-rank test and ROC analysis are not explained. What is the outcome (dependent variable) for determining the cut-off of EAF2 as an independent variable in the ROC analysis? 2. Method of multivariate analysis is not explained. How did you select variables subject to multivariate analysis from univariate analysis? P values of histologic type and CA19-9 are both 0.378, but the former was entered into multivariate analysis but the latter was not. Please explain the reason. 3. (ll.259-260 & Table 2) According to my calculation, p value of distant metastasis is not 0.025 but 0.466 by chi-square test or 0.709 by chi-square test with Yates' correction. P value of CEA is not 0.038 but 0.728 by chi-square test or 0.943 by chi-square test with Yates' correction. Please review the Table 2. 4. ITH in l.364 should be spelled out. 5. There are some grammatical errors. Please revise English.

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Provenance and peer review: Unsolicited manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 00070916

Position: Editorial Board

Academic degree: PhD

Professional title: Senior Researcher, Senior Scientist

Reviewer's Country/Territory: Germany

Author's Country/Territory: China

Manuscript submission date: 2022-05-19

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-05-20 12:15

Reviewer performed review: 2022-05-24 12:44

Review time: 4 Days

Scientific quality	<input 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 checked="" type="checkbox"/> Grade E: Do not publish
Language quality	<input 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 checked="" type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input checked="" type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No



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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

In its current form the manuscript cannot be properly reviewed since the quality of the English language is in parts not good enough to prevent misunderstandings and wrong judgement. However, the research itself might be of interest. This is why I will suggest to reject but recommend resubmission after language check.

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Title: Overexpression of ELL-associated factor 2 suppresses invasion, migration, and angiogenesis in colorectal cancer

Provenance and peer review: Unsolicited manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 03478911

Position: Associate Editor

Academic degree: PhD

Professional title: Chief Technician, Executive Vice President, Research Assistant Professor

Reviewer's Country/Territory: South Korea

Author's Country/Territory: China

Manuscript submission date: 2022-05-19

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-05-19 20:47

Reviewer performed review: 2022-05-25 06:21

Review time: 5 Days and 9 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" 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 type="checkbox"/> Grade B: Minor language polishing <input checked="" 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="checkbox"/>] Anonymous [<input type="checkbox"/>] Onymous Conflicts-of-Interest: [<input type="checkbox"/>] Yes [<input checked="" type="checkbox"/>] No

SPECIFIC COMMENTS TO AUTHORS

This study investigated the relationship between EAF2 and colorectal cancer progression. All results indicate an increased risk of colorectal cancer due to decreased EAF2 expression, and it is also well verified in the analysis of clinical samples. However, there are major and minor issues to address. 1. In table 1, the expression of EAF2 did not show any correlation with clinicopathologic characteristics. It should be focused more on the association with tumorigenesis, but did not. 2. In figures 3 and 5, a heterogeneous expression pattern of GAPDH was shown between the groups. The bar graphs for the RKO and HT29 groups in Figure 3 and the EAF2-OA-T group in Figure 5 are unreliable. 3. Information on the conditioned media utilized in the study in figures 7 and 8 is missing. Producing method and the purpose of its use should be described in detail. 4. It should be clarified whether the increase in the risk of CRC is due to a decrease in EAF2 expression or a decrease in detection due to an EAF2 mutation when using an ordinary antibody. The progression of CRC induced by EAF2 mutation is well established, and the authors' point of view is the same as that according to the described background. 5. Depending on the results, decreased expression of EAF2 increases the risk of CRC. If so, it is wondering how to increase the EAF2 in patients with CRC? It must be discussed because the authors argued that EAF2 is possible to consider as a therapeutic target. 5. It needs a great deal of English correction.

PEER-REVIEW REPORT

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Provenance and peer review: Unsolicited manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 04738361

Position: Peer Reviewer

Academic degree: PhD

Professional title: Director, Research Scientist

Reviewer's Country/Territory: France

Author's Country/Territory: China

Manuscript submission date: 2022-05-19

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-05-20 14:39

Reviewer performed review: 2022-06-01 19:16

Review time: 12 Days and 4 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" 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 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="checkbox"/> Anonymous <input type="checkbox"/> Onymous
	Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

Manuscript ID 77761 describes the role of EAF2 in several biological functions of CRC cells including their angiogenesis, proliferation, and invasion. Although very interesting the following points should be clarified: * In the introduction section, the authors used future tense for their aims. Please change all of them to past tense. * The authors have mentioned that they used DMEM for culturing HUVECs and other endothelial cells. This medium is the correct choice for endothelial cells since it does not contain all the necessary growth factors including VEGF, IGF, EGF, FGF and etc. The classic medium is EGM2. This can significantly impact the results. (Please refer to PMID: 33344453 and <https://doi.org/10.1016/j.jocit.2018.09.004>) * Concerning the wound healing test with RKO cells, it is not clear why the authors did not continue the experiment in order to have a closed wounded area? * Please mention how many times each experiment was performed. * In lines 322 and 323 are the authors sure about the figure citation? * The representative images in figure 7 are not acceptable. Please use some better-quality photos. Moreover, it is not clear what have the authors measured in the tube formation test? Please refer to PMID: 33344453 for a better analysis of networks. * I am not sure if the HUVECs are the best endothelial model in this experiment knowing that endothelial progenitor cells (EPCs) are involved in cancer angiogenesis. I suggest the authors comment on this. PMID: 33627177 * It has been shown that TGF- β 1 treatment can induce long non-coding RNA expression mostly through regulation of FOXP1-IT1 and RAD21. It would be interesting to discuss the role of lncRNA in CRC as it is a hot topic. PMID: 35194111

RE-REVIEW REPORT OF REVISED MANUSCRIPT

Name of journal: *World Journal of Gastrointestinal Oncology*

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Peer-review model: Single blind

Reviewer's code: 03478911

Position: Associate Editor

Academic degree: PhD

Professional title: Chief Technician, Executive Vice President, Research Assistant Professor

Reviewer's Country/Territory: South Korea

Author's Country/Territory: China

Manuscript submission date: 2022-05-19

Reviewer chosen by: Jing-Jie Wang

Reviewer accepted review: 2022-07-27 00:05

Reviewer performed review: 2022-07-27 00:09

Review time: 1 Hour

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" 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 checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection



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Peer-reviewer statements	Peer-Review: [Y] Anonymous [] Onymous Conflicts-of-Interest: [] Yes [Y] No
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SPECIFIC COMMENTS TO AUTHORS

All concerns have been well addressed. There is no issue to raise.

RE-REVIEW REPORT OF REVISED MANUSCRIPT

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Reviewer's code: 00070916

Position: Editorial Board

Academic degree: PhD

Professional title: Senior Researcher, Senior Scientist

Reviewer's Country/Territory: Germany

Author's Country/Territory: China

Manuscript submission date: 2022-05-19

Reviewer chosen by: Jing-Jie Wang

Reviewer accepted review: 2022-07-26 12:16

Reviewer performed review: 2022-07-28 13:05

Review time: 2 Days

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input checked="" 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 type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Peer-reviewer	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous

statements

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

SPECIFIC COMMENTS TO AUTHORS

The revised version is now in an English language quality which allows reviewing it. However, in order to gain overall quality, several points have to be addressed to justify publication:

1. The authors refer to MSI-H in the background/introduction, but do not give these data for the 70 cases included.
2. A Table of all data available for the cases included should be given as Supplementary information. It should explicitly also include the expression levels obtained by immunohistochemistry and - where applicable - W-Blot analysis. Also highlight these cases in order to allow the potential reader to easily follow your case selection.
3. Speaking of - all original W-Blots must be provided for review.
4. All cell line experiments must be performed with at least two cell lines - this is now a general rule and not a cruel argument. At best with cell lines in known, low passage numbers.
5. In the conclusion: "recombination of proteins, transfection of overexpressed genes," - it is not clear what exactly this should mean. Either re-phrase or delete.
6. In the Table 2, please modify by dividing the colon cancer cases into right-sided and left-sided cases. Also: please define what is "normal" for those cases where this term is used (CEA, CA19-9, P53 and CDX2).

Minor points:

1. All sentences used in the abstract are re-used somewhere in the manuscript body - this must be changed!
2. Style for mentioning the suppliers should be Company name, City, Country - at first mentioning and Company name subsequently. Please do everywhere.
3. There is sometimes a problem with "°C" - I see it sometimes as "a" please check.
4. Introduction of abbreviations is only recommended when used subsequently at least two more times.
5. Legend of Figure 9: GAPDH mentioned - but cannot be found in the scheme.

RE-REVIEW REPORT OF REVISED MANUSCRIPT

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Professional title: Director, Research Scientist

Reviewer's Country/Territory: France

Author's Country/Territory: China

Manuscript submission date: 2022-05-19

Reviewer chosen by: Jing-Jie Wang

Reviewer accepted review: 2022-07-29 13:19

Reviewer performed review: 2022-07-29 13:29

Review time: 1 Hour

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 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 type="checkbox"/> Anonymous <input checked="" type="checkbox"/> Onymous



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statements

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

SPECIFIC COMMENTS TO AUTHORS

The authors have addressed my concerns and questions. I have no further comment.

Regards Sina NASERIAN