

PEER-REVIEW REPORT

Name of journal: *World Journal of Gastrointestinal Oncology*

Manuscript NO: 67296

Title: EFN Y in gastrointestinal cancer: expression, regulation and clinical significance

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 06036960

Position: Peer Reviewer

Academic degree: BSc, MSc

Professional title: Academic Research, Research Scientist

Reviewer's Country/Territory: Poland

Author's Country/Territory: China

Manuscript submission date: 2021-04-20

Reviewer chosen by: AI Technique

Reviewer accepted review: 2021-07-28 05:46

Reviewer performed review: 2021-08-07 21:06

Review time: 10 Days and 15 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 Grade E: Do not publish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 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	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous

SPECIFIC COMMENTS TO AUTHORS

Dear Authors, A very comprehensive review with special attention on molecular aspects (great work with possible mechanisms of angiogenesis and therapeutic aspects or perspective for the future). Overall, the article can be recommended but not without proper revisions. My suggestions/concerns/questions are below: 1. Abstract, the second sentence. It is quite long and please consider rephrasing it a little. What I also suggest is to change “and” words to something else since there is quite a few of them. For example: “The ephrins and EPH-related receptors comprise the largest subfamily of receptor protein-tyrosine kinases WHICH play an indispensable role in normal growth and development OR in the pathophysiology of various tumors” 2. Introduction, all sentences up to first (“[1]”) reference. Are all these data from one citation? 3. Introduction, sentence “Studies have shown that the EphA2 receptor and its ligand ephrin-A1 are expressed in a variety of malignant tumors, and the interaction between the two promotes the migration of tumor vascular endothelial cells [4]”. I suggest changing the last “the” word to “these”. 4. Add hyphen in “EphrinB” (page 5), since you use it for all other cases (e.g. Ephrin-A). 5. Figure 1. I suggest to split subfigure A into subfigure A and B to underline changes between EFNA and EFNB (at first glance I was unable to spot it). The current subfigure B would be subfigure C in that case. 6. The last sentence on page 6. I would add “through” or “by” after “activated” in “When EphA2 is activated ephrin-A1 binding, (...)”. 7. Table 2. Is the symbol “(-)” represents lack of data? 8. Third sentence in “Gastric cancer” section. The end of this sentence is hard to understand. If I am not mistaken, will this version work? “EFNA1 is highly expressed in GC tissues, but is low or not expressed in benign GC lesion; its expression increases with malignant status.” 9. The sentence starting with “Increases in EFNA1

expression parallel increases" is hard to understand, please rewrite it. I do have suggestion for the beginning of this sentence e.g. "EFNA expression increases with both clinical stage and lymph node metastasis (...)". 10. The last sentence in "Gastric cancer" section. The part after the last comma would be better if it sounds like "(...) and metastasis of GC cells; up-regulation of GMAN is also associated with poor prognosis of GC." 11. This sentence is hard to understand, please rewrite it. "Among them, from adenoma to cancer tissue, the copy number and mRNA expression of EFNA1 increased, indicating that EFNA1 may be a driver gene that promotes rectal adenocarcinoma-rectal cancer". 12. The sentence starting with "A study by Rosenberg et al. showed that the CRC epithelial cell line Caco-2" is very long. Consider splitting it to two separate sentences or add semicolon somewhere. 13. The sentence starting with "Kataoka et al. detected the expression of EFNA1 in CRC specimens and found that 62.5% (25/37)". I suggest changing the second part of it to "62.5% (25/37) expressed ephrin-A1 in greater extend which correlated with low survival rate and poor prognosis" 14. The last sentence in "Colorectal cancer" section. Just my curiosity, but are you able to perform such multi-center clinical study in the future? 15. Citation "[57,58]" on page 10 is not upper indexed. 16. The sentence starting with "A study by Lida et al. [57] showed that ephrin-A1". In terms of cell cycle, are there any other proteins than p21 which were regulated by ephrin-A1? 17. Section "Esophageal cancer". Abbreviation "ESCC" is explained in the third sentence while it should be in the second one. 18. The sentence starting with "The results showed that 84.4% (146/173) positively expressed". Are the values in brackets represents number of tissue samples? If so, please add "sample" or "specimen" somewhere in this sentence, as this could be not clear for all readers at first glance. 19. The sentence starting with "Univariate analysis showed that a high level of EFNA1 protein expression". Is the high level of EFNA1 also independently associated with metastasis, grade or stage? Or this is only with OS? 20. The sentence starting with

“In addition, studies have also shown that ephrin-A1 and EphA2 often co-localize”. I feel something might be missing in this sentence, or the ending “related to co-localize” should be “related to co-localization”. 21. The first reference in “Role of EFNA1 in gastrointestinal cancers” section. Is the first sentence of this section really summarized citations from no. 28 to 61? 22. Change “a” to “an” before “increase” in sentence “Potla et al. [42] found that in three- dimensional spheroid cultures of HT29 colon cancer cells, a increase of EFNA1”. 23. The last sentence of “Regulation of gastrointestinal cancer cell growth” could be rewritten, especially the end of it. I suggest “its abnormal expression in cancers can affect tumor growth and formation”. 24. Sentence starting with “In addition, studies have shown that the density of ephrin-A1”. What do you mean by “density” here? Maybe the “amount” would fit better? 25. To the entire manuscript: if you use EFNA1 for gene, remember to use italics. Please double-check if you have it properly done. Also, “in vitro” and “in vivo” should also be italicized. 26. RT-PCR abbreviation was explained on page 13 while it should be at least on page 11. 27. First sentence in “EFNA1 AND TUMOR ANGIOGENESIS” section. “tumor process” could be changed to “carcinogenesis” to avoid using triple “tumor” in the same sentence. 28. Sentence with “new blood vessels can be used as a metastasis channel”. I think there should be “metastasis channelS” since you have “blood vesselS”. Also, I would go for “metastatic channels” to avoid “metastasis” repetition. 29. Sentence starting with “In 2000, Ogawa et al”. I would add “that” after “showing”. 30. Figure 3. Change “cell membrane” to “cell membrane”. Also, I would standardize the size of lipid bilayer for both cells and add some text to clearly indicate that we have one bilayer from one cell and second from another. 31. Table 1, column “Encoding mRNA and protein”. Delete space between comma and “NP_004419.2”. 32. Could you add some information about one of gastrointestinal cancers which is pancreatic cancer? I think making the subsection in the main section “EFNA1 AND GASTROINTESTINAL CANCERS” would do the job.

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Reviewer's code: 05776309

Position: Peer Reviewer

Academic degree: MSc, PhD

Professional title: Doctor, Research Scientist

Reviewer's Country/Territory: Egypt

Author's Country/Territory: China

Manuscript submission date: 2021-04-20

Reviewer chosen by: AI Technique

Reviewer accepted review: 2021-07-29 06:30

Reviewer performed review: 2021-08-10 18:44

Review time: 12 Days and 12 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
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Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
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 manuscript is well written but the abstract and introduction can be summarized