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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 51872

Title: Impact of reactivation of the *GFRA1* gene by DNA demethylation on the prognosis of patients with metastatic colon cancer

Reviewer's code: 00631989
Position: Editorial Board
Academic degree: BSc
Professional title: Professor, Associate Professor, Research Associate
Reviewer's country: Italy
Author's country: China

Reviewer chosen by: Artificial Intelligence Technique
Reviewer accepted review: 2019-10-12 11:59
Reviewer performed review: 2019-10-18 12:07
Review time: 6 Days

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
[Y] Grade A: Excellent	[ ] Grade A: Priority publishing	[ ] Accept (High priority)	Peer-Review:
[ ] Grade B: Very good	[Y] Grade B: Minor language polishing	[ ] Accept (General priority)	[Y] Anonymous
[ ] Grade C: Good	[ ] Grade C: A great deal of language polishing	[Y] Minor revision	[ ] Onymous
[ ] Grade D: Fair	[ ] Grade D: Rejection	[ ] Major revision	Peer-reviewer's expertise on the topic of the manuscript:
[ ] Grade E: Do not publish		[ ] Rejection	[Y] Advanced
			[ ] General
			[ ] No expertise
			Conflicts-of-Interest:
			[ ] Yes
			[Y] No

SPECIFIC COMMENTS TO AUTHORS

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This study presents evidence that GFRA1 gene demethylation in colorectal cancer is associated with GFRA1 gene over expression, metastatic risk and decreased survival. The methods used are appropriate. The results and the abstract are clear and focused. Tables and figure are appropriate. The conclusions appear sustained by results. The subject is appropriate for the journal. The scientific content fits the standard for publication. I suggest the manuscript can be accepted pending minor revisions. Please find below two lists of points, accordingly with criteria checklist proposed by the World Journal of Gastroenterology. The first list includes aspects I think do not need revision. The second list includes my suggestions for minor revisions. The number corresponds to item numbering of WJG. Items that do not need revision. 4) The manuscript adequately describes the background, present status and significance of the study. 6) The research objectives are achieved by the experiments used in this study. 9) The statistical analysis seems appropriate. 10) The manuscript meets the requirements of use of SI units. 12) The manuscript is well, concisely and coherently organized and presented. The style, language and grammar are accurate and appropriate. 13) The Authors uploaded the STROBE Statement – observational study. Items that require revision. 1) The title reflect the main subject/hypothesis of the manuscript, but the name of the gene (GFRA1) is lacking…it should be "….reactivation of the GFRA1 gene…" 2) The abstract summarizes and reflects the work described in the manuscript. The abbreviation "CC" should be mentioned in extenso at the beginning of the abstract. 3) The key words are lacking. 5) The Methods section is sufficiently clear however, the bisulfite modification assay is not described. 7) The manuscript interprets the findings adequately and appropriately, highlighting the key points concisely, clearly and logically. The findings and their applicability/relevance to the literature are stated in a clear and definite manner. The discussion is accurate and discusses the paper's scientific significance and/or relevance to clinical practice sufficiently. Few points need to be

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adjusted: a) the only non-discussed aspect is related to the limitation of the methylation assay to the CpGs only. Evidence that CpN methylation can contribute to gene expression are published, as well as technical explanation for the frequent underestimation of both CpG and CpN methylation. It should be useful to add this aspect to the discussion and quote the following papers: - DNA Methylation Profiles of Selected Pro-Inflammatory Cytokines in Alzheimer Disease. J Neuropathol Exp Neurol. 2017 Jan 1;76(1):27-31. doi: 10.1093/jnen/nlw099; - Disclosing bias in bisulfite assay: MethPrimers underestimate high DNA methylation. PLoS One. 2015 Feb 18;10(2):e0118318. doi: 10.1371/journal.pone.0118318; - A reassessment of semiquantitative analytical procedures for DNA methylation: comparison of bisulfite- and HpaII polymerase-chain-reaction-based methods. Anal Biochem. 2006 Mar 1;350(1):24-31. In particular, the Authors should disclose whether they observed CpN methylation and discuss the possible limitation due to the use of PCR primers sensitive to CpN methylation status. b) since methylation/demethylation dynamics are not studied in the present work, the term “hypomethylated” should be more correctly used instead of “demethylated” throughout the manuscript. 8) The figures, diagrams and tables are sufficient, good quality and appropriately illustrative of the paper contents. They do not require labeling with arrows, asterisks, etc., nor better legends. Only two figures need some improvement: a) In figure 1B it is impossible to see the sequence or any other annotation due to the poor resolution b) In figure S2 some numbers and samples’ codes appeared to be superimposed; the numbers under the samples’ codes should be cancelled (or samples’ codes placed in another position); it should be explained why only certain clones are presented. 11) The manuscript cites appropriately the latest, important and authoritative references in the introduction and discussion sections. The Author do not over-, self-, omit or incorrectly cite. The 3 papers reported at point 7 could be usefully added to quotations in the Discussion. 14) The

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Authors state that no informed consent was necessary, but in the Methods they state that patients signed written consent. Please clarify.

INITIAL REVIEW OF THE MANUSCRIPT

Google Search:

[ ] The same title

[ ] Duplicate publication

[ ] Plagiarism

[Y] No

BPG Search:

[ ] The same title

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[Y] No

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 51872

Title: Impact of reactivation of the GFR Y gene by DNA demethylation on the prognosis of patients with metastatic colon cancer

Reviewer's code: 01573970
Position: Peer Reviewer
Academic degree: PhD
Professional title: Professor
Reviewer's country: South Korea
Author's country: China

Reviewer chosen by: Artificial Intelligence Technique
Reviewer accepted review: 2019-10-09 02:48
Reviewer performed review: 2019-10-22 04:10
Review time: 13 Days and 1 Hour

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish	[Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection	Peer-Review: [Y] Anonymous [ ] Onymous Peer-reviewer's expertise on the topic of the manuscript: [Y] Advanced [ ] General [ ] No expertise Conflicts-of-Interest: [ ] Yes [Y] No

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Dear, The manuscript entitled 'Impact of Reactivation of the Gene by DNA Demethylation and the Prognosis of Patients with Metastatic Colon Cancer' by Ma et al. describes that hypomethylation of GFRA1 is colon cancer patients is associated with the increased expression of GFRA1 and worse prognosis. They performed several in vitro and in vivo assays to observe the effects of GFRA1 over-expression. Overall, the manuscript is well written and the results are convincing. I have a few comments for the authors. Major comments 1. The definition (or criteria) demethylation of GFRA1 seems to be confusing among different assay platforms and data sets (MethyLight, DHPLC, bisulfite-sequencing, and 450K array). I would suggest the authors to make a short table to describe the definition of dmGFRA1, dmGFRA1-high and dmGFRA1-low groups for each of the assay platforms. Minor comments 1. The GFRA1 should be listed in the main title 2. P. 8, 2nd paragraph, 'dmGFRA1 level was significantly increased' => 'GFRA1 was hypomethylated', I would suggest avoiding the confusing expression of 'dmGFRA1 level was increased' and using the more direct expression such as 'GFRA1 was demethylated or hypomethylated'. 3. In Table 1, why the authors used two different statistical tests (chi-square test and Fisher's exact test) instead of using one test consistently? Please provide reasons. 4. In table S1, how did the authors obtained P < 0.001 for Age term? I find the number is bizarre. 5. P, 15, the p-value for Vessel embolus is written as 0.039, but it is written as 0.060 in Table S2 (p. 39)

INITIAL REVIEW OF THE MANUSCRIPT

Google Search:

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[ ] Plagiarism

[Y] No

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[Y] No