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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 47414

Title: Identification of differentially-expressed genes regulated by methylation in colon cancer based on bioinformatics analysis

Reviewer's code: 03001816

Reviewer's country: United States

Science editor: Jia-Ping Yan

Reviewer accepted review: 2019-03-24 14:24

Reviewer performed review: 2019-03-24 14:33

Review time: 1 Hour

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[ ] Grade E: Do not publish		[ ] Rejection	[ ] Advanced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

SPECIFIC COMMENTS TO AUTHORS

This is an excellent study. I find no significant problems. There are a few minor text formatting that can be dealt with in copy editing. I therefore recommend acceptance of this manuscript, which provides new information on the role of methylation in color

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cancer.

INITIAL REVIEW OF THE MANUSCRIPT

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 47414

Title: Identification of differentially-expressed genes regulated by methylation in colon cancer based on bioinformatics analysis

Reviewer's code: 02856239

Reviewer's country: United States

Science editor: Jia-Ping Yan

Reviewer accepted review: 2019-03-25 13:41

Reviewer performed review: 2019-03-25 14:53

Review time: 1 Hour

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[ ] Grade E: Do not publish		[ ] Rejection	[Y] Advanced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

Overall, this is an interesting study. Analyses were generally well performed. The authors should improve the paper on following points: The authors should emphasize the need for a larger validation cohort to replicate findings. This study does

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not address tumor microenvironment or macro-environment surrounding patients. In this context, it is worth discussing molecular pathological epidemiology (MPE), integration of molecular pathology and data science, which can use tumor markers as surrogate of disease pathologies. MPE deeply studies environmental exposures, intermediate variables (such as plasma markers), and molecular changes in cancer. MPE helps precision medicine. These epigenomic and epigenetic markers can be useful. MPE has been discussed previously. Eg, I can see Gut 2011; Mod Pathol 2013; Annu Rev Pathol 2019, etc in the website.

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 47414

Title: Identification of differentially-expressed genes regulated by methylation in colon cancer based on bioinformatics analysis

Reviewer's code: 00070916

Reviewer's country: Germany

Science editor: Jia-Ping Yan

Reviewer accepted review: 2019-03-28 09:54

Reviewer performed review: 2019-04-02 13:05

Review time: 5 Days and 3 Hours

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

SPECIFIC COMMENTS TO AUTHORS

The authors used an in silico strategy taking advantage of public data sets to identify genes differentially expressed due to epigenetic (i.e. methylation) modifications in place in CRC cells. This is a well-known, excepted approach with clear advantages but also

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several weak points which should be taken into consideration. Overall, the data are presented in a suited form and have the potential to contribute to the overall knowledge in the field. Several points should be cosidered to improve the manuscript further; some are critical: Major: - it is of highest importance to compare the presented data from the "303 tumor tissues and 19 normal tissues" with the results of the subgroup analysis of the pairs of the 19 normal tissues + matching tumor tissues from the very same patients. Only if there is no major difference, the overall results can be considered as reliable. Alternatively (or preferrably in addition), the strategy should be used to analyse a second independent set of data (for example from the clinic of the authors). - a short look into PubMed makes clear that this analysis is not the first of his kind (see also minor point 3). Thus, it would definitely help to put a little effort into "making a difference" - for example is the pure listing of enriched pathways not of relevance for most researchers. Identifying genes with roles in several cancer-related pathways would for example be of higher interest. - the part of the discussion dealing with MLH1 methylation is really bad. It is clear that this is a prerequisite for microsatellite-instability also associated with aberrant general methylation - among other features. Together with the non-MSI CpG island methylated CRCs, the MSI+ CRCs will be most likely represent the hypermethylated cases. This point has to be made clear to the readers showing the moleculat features of the CRC cases included into the final analysis. - In line with this argument goes my comment on the overall results concerning GDNF and RELN: if my understanding is correct, a big part of the better prognosis for the CRC cases with hypermethylation might be contributable to the fact that this is a side-effect of MSI - and there, it has been clearly shown that the reason of better prognosis lies in the hypermutated state which has not much and not directly to do with the hypermethylation - a co-incidence and not a correlation. This might be wrong - thus, the authors should adjust for MSI when performing the survival analysis (Figure 4). - the

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discussion would clearly benefit from a reduction in the amplitude and more focus. For example: "Vodenkova et al.[50] indicated that “base excision repair” capacity is a potential prognostic biomarker, applicable for prediction of therapy response. The “cell cycle” pathway is a critical mechanism in regulating cell proliferation." is not really giving information to the reader. Minor: - in the abstract, MeDEG should be introduced properly - "Functional analysis of MeDEGs" is misleading, since there are no experiments described. Maybe "In silico functional analysis of MeDEGs" fits already better - in the results part, "MeDEGs related to the prognosis of GC patients" must be replaced - a little bit to sloppy copy- and-pasting is here obvious again

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 47414

Title: Identification of differentially-expressed genes regulated by methylation in colon cancer based on bioinformatics analysis

Reviewer's code: 00044333

Reviewer's country: South Korea

Science editor: Jia-Ping Yan

Reviewer accepted review: 2019-03-31 23:01

Reviewer performed review: 2019-04-14 10:14

Review time: 13 Days and 11 Hours

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) [Y] Accept (General priority) [ ] Minor revision [ ] Major revision [ ] Rejection	Peer-Review: [Y] Anonymous [ ] Onymous Peer-reviewer's expertise on the topic of the manuscript: [ ] Advanced [Y] General [ ] No expertise Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

The authors presented well-organized analysis on differentially-expressed genes regulated by methylation in colon cancer by utilizing bioinofrmatics tools like GO and KEGG pathway, GSEA and PPI, using TCGA public data. Especially, detailed analysis

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were performed on GDNF and RELN, including survival analysis. Minor typo: In 'MeDEGs related to the prognosis of GC patients' of Results, (Figure 5A, B) --> (Figure 4A, B) In legend of Figure 4, gastric cancer --> colon cancer

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