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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 59059

Title: What could microRNA expression tell us more about colorectal serrated pathway carcinogenesis?

Reviewer's code: 05194997
Position: Peer Reviewer
Academic degree: MD

Professional title: Professor

Reviewer's Country/Territory: Italy

Author's Country/Territory: Bulgaria

Manuscript submission date: 2020-08-29

Reviewer chosen by: AI Technique

Reviewer accepted review: 2020-08-31 13:07

Reviewer performed review: 2020-09-04 12:10

Review time: 3 Days and 23 Hours

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [Y] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

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SPECIFIC COMMENTS TO AUTHORS

Summary: Thank you for inviting me to review the manuscript entitled: "What could microRNA expression tell us more about colorectal serrated pathway carcinogenesis?" by Peruhova M and colleagues. Overall, it is an interesting study addressing an important interest regarding the involvement of the microRNAs in the serrated pathway. The manuscript is well structured. The background evidences concisely and adequately the major points concerning the molecular and histological characteristics of serrated polyps. Concerning microRNAs and serrated pathway in colorectal cancer, the authors evidence the most recent investigations. This field is rapidly advancing, and there have been a variety of recent published reviews on the same argument. However, the authors included some information (i.e. the mucosal immunity) that makes it different from the other published reviews. There are several changes (major and minor revisions) that authors need to address to complete this manuscript, which has a high potential of interest. Moderate English changes are required. Major: 1) The title of the review clearly asks if the microRNA expression could tell us more about colorectal serrated pathway carcinogenesis. I would really appreciate if the Authors could better highlight, stress more and critically answer to this question, as well as discuss the potential clinical role of miRNAs in serrated CRC pathway along all the text and particularly in the conclusion. Moreover, they should summarize what we can conclude from the literature search. What do the authors think of summarizing the results within a table (for instance, evidencing microRNAs deregulated expression in specific serrated lesions and when available by comparing it with the one in normal mucosa?); 2) Authors included some information that makes this review different from the other already published reviews. However, adding some recent findings concerning also the role of fecal miRNAs in this field would further distinguish this manuscript from the others. Minor: 1) In

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Abstract, Core tip and Introduction verify the plural of some words (i.e. replace "non-coding-RNA" with "non-coding-RNAs", or "the pivotal role of miRNAs"). 2) In "MORPHOLOGICAL ASPECTS OF SERRATED POLYPS": a. Ascribing 25% of all CRCs to the serrated neoplastic pathway is not completely correct. Based on the literature, the percentage prevalence of serrated pathway bears really a high variability, ranging from 15 up to 30% of all CRCs; b. "TSAs are extremely rare <1%, while HPs are the most common, comprising approximately 75% of all serrated polyps….". TSA represent 1% of all CRC polyps, not of all serrated lesions. Authors should specify that 1% refers to all CRC lesions, as they did subsequently in the text. c. Authors should describe SAC. 3) In "EPIGENETIC AND GENETIC ASPECTS IN SERRATED PATHWAY": a. "Methylation" as well as "promotors" are not the right terms, replace them with "methylator and "promoters". b. Along the text "Methylation is an epigenetic process where a methyl group (CH3) is added to the cytosine nucleotide in a CpG dinucleotide settings", authors would say at CpG dinucleotide group? 4) In "Microsatellite Instability Mechanism in CRC": a. Authors should also add atypical MSH3 and epCAM mutations, as well as the mutational frequency in HNPCC patients; b. MSI tumors can also be subclassified. Authors could briefly descibe their subclassification (MSS, MSI-H, MSI-L); c. Authors should better clarifiy this point. 3–15% of all CRCs are represented by sporadic forms with MSI, and that about 80% of MSI CRCs are characterized by the hypermethylation of MLH1, while 20% of MSI CRCs by mutations in MMR genes. 5) In "BRAF / KRAS Gene Mutations": a. Concerning the title "BRAF / KRAS Gene Mutations", authors should evidence that they are overviewing these mutations in relationship with the serrated pathway. It could be replaced with "BRAF / KRAS Gene Mutations in serrated CRC"; b. Add reference of the work of Catherine E. Bond and Vicki L. J. Whitehall (2018, Gastroenterology Research and Practice). This is a comprehensive and an interesting review that clearly summarize the role of BRAFV600E

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mutation in CRC; c. Authors should also discuss the conflicting results that recently emerged on the association between BRAF mutation and female sex among serrated adenomas (Ref 44 of the manuscript, Travaglino et al. 2019 hystopathology); d. Authors should better clarify the difference between serrated tumors driven by BRAF or KRAS mutation. For instance serrated polyps emerging from the KRAS mutant pathway evolve into carcinomas that are characterized by low levels of CIMP. 6) In "The Role of miRNA-31 in Carcinogenesis": a. Replace the title with "The Role of miRNA-31 in Carcinogenesis of serrated pathway of the colorectum" or "… serrated CRC carcinogenesis"; b. Authors should cite the paper of Aoki et al on miR-31 in serrated progression (World J of Gastr. 2014) and the recent paper of Nobuhito Kubota et al. (Oncology Letters 2020) in which upregulation of miR-31 is associated with poor prognosis in patients with advanced colorectal cancer. 7) In "The Involvement of miRNA-21 in CRC": a. Recent investigations on miR-21 as novel non-invasive biomarker for early detection and prognosis of CRC patients should be cited and/or discussed (i.e. Ghareib et al. Journal of Gastrointestinal Cancer 2020, or the one of Monteleone et al. scientific report 2019). Moreover, what the authors think about the recent findings on faecal miR-21, miR-92a and their combination as promising non-invasive biomarkers for faecal-based CRC screening (scientific reports 2019, Tung on Yau et al.)? b. Add reference. The down-regulation of PTEN protein by miR-21 in CRC xenografts nude mice has been also demonstrated by Wu Y and collaborators in Cell Physiol Biochem, 2017. c. The oncomiR-21 predicts recurrence and poor survival in patients with CRC. Authors should include this information (Chen et al Onco Targets Ther. 2016) 8) Concerning the title "The Role of miRNA-181a-2 in Cancer Development", should be more appropriated to specify the correlation of this miRNA with serrated CRC. Authors are not refferring to the role of the miRNA-181a-12 overall in cancer. It could be modified as: "The Role of miRNA-181a-2 in the development of

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serrated pathway in CRC" 9) In "HUMAN GUT MICROBIOTA, MUCOSAL IMMUNITY, AND miRNA IN SERRATED PATHWAY", authors should discuss the recent investigation of Nakanishi et al (Immunity 2018) and cite the recent and intersting review of the same author (Trends cancer 2019). Moreover, they should also discuss the particular capacity of SAC in avoiding the immune response. Figures general comment: verify abbreviations at the end of the legends; 1) Figure 1: a. "CD" stands for citological dysplasia. Miss the abbreviations in the legend (as well as for "WHO"); b. Authors could also add the % of each subtype and in addition range HP subtypes from the higher to the lower %. 2) Figure 2: a. Describe briefly your scheme on the serrated pathway progression in the legend; b. Add the color-code explaination in the legend; c. Authors could also specify that TSA tumors with KRAS mutations could be caused by MGMT loss. 3) Figure 3: a. Authors should clarify the color-code of the figure in the legend. b. Why the direction of the figure goes from the left to right and not vice versa?

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RE-REVIEW REPORT OF REVISED MANUSCRIPT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 59059

Title: What could microRNA expression tell us more about colorectal serrated pathway carcinogenesis?

Reviewer's code: 05194997
Position: Peer Reviewer
Academic degree: MD
Professional title: Professor
Reviewer's Country/Territory: Italy
Author's Country/Territory: Bulgaria

Manuscript submission date: 2020-08-29
Reviewer chosen by: Pan Huang
Reviewer accepted review: 2020-09-25 08:50
Reviewer performed review: 2020-09-26 13:41
Review time: 1 Day and 4 Hours

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[Y] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [ ] Major revision [ ] Rejection
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

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Dear Editors and "The World Journal of Gastroenterology", Thank you for inviting me to review the manuscript entitled: "What could microRNA expression tell us more about colorectal serrated pathway carcinogenesis?" by Peruhova M and colleagues. I have revised the new version of the submitted manuscript. The Authors addressed my suggestions, responded properly to my queries and present a much improved manuscript. I have nothing more to add/revise for this paper. With Best regards and wishes.