

PEER-REVIEW REPORT

Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 74090

Title: Tumor microenvironment involvement in colorectal cancer progression via Wnt/ β -catenin pathway: providing understanding of the complex mechanism of chemoresistance

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05128663

Position: Editorial Board

Academic degree: BSc, MD, MSc, PhD

Professional title: Academic Research, Attending Doctor, Postdoc, Research Associate, Research Fellow

Reviewer's Country/Territory: Greece

Author's Country/Territory: Argentina

Manuscript submission date: 2021-12-21

Reviewer chosen by: AI Technique

Reviewer accepted review: 2021-12-28 15:23

Reviewer performed review: 2022-01-08 10:13

Review time: 10 Days and 18 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 Grade E: Do not publish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 checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input type="checkbox"/> Yes <input checked="" 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

Comments to the authors The article with the title “Tumor microenvironment involvement in colorectal cancer progression via Wnt/ β -catenin pathway: providing understanding of the complex mechanism of chemoresistance” is well done, but I would offer these comments to the investigators: 1) Several words throughout the manuscript appear to be merged. Please correct it. 2) Some minor grammatical errors occur. The manuscript contains significant language-related issues. Please correct these types of grammatical errors throughout the paper. 3) It will be an interesting topic for your work to mention the association of Wnt/ β -catenin pathway with autophagy. Autophagy is a basic catabolic process with TME development and the cross-presentation of neo-antigen. 4) Many references are considered old, and it is needed to be updated

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Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05914859

Position: Peer Reviewer

Academic degree: MD, PhD

Professional title: Lecturer

Reviewer's Country/Territory: Romania

Author's Country/Territory: Argentina

Manuscript submission date: 2021-12-21

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-01-02 17:49

Reviewer performed review: 2022-01-20 01:15

Review time: 17 Days and 7 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 checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection

Re-review	<input type="checkbox"/> Yes <input checked="" 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

I've read with great interest the paper "Tumor microenvironment involvement in colorectal cancer progression via Wnt/ β -catenin pathway: providing understanding of the complex mechanism of chemoresistance" by María B Novoa Díaz et al. It is a very exhaustively elaborated review regarding the complex topic the authors dealt with, that I will hardly call as a mini review. The paper is quite long. All the molecular mechanism involved in the topic are evocated and of course this needs a lot of space. I would suggest to reduce the point 2 to just the last part starting with I 2015. Probably the point 3 also may be included in point 4 and reduced to just one sentence. There are some abbreviation that are not mentined in the table. The english has to be reviewed. Summarizing, the paper is very complex and offers a detailed vision on the mollecular mechanisms involved in colorectal cancer evolution and their impliction on the oncology treatment. However it is very extensive so an effort to summarise the text would be of great benefit for the readers.

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Title: Tumor microenvironment involvement in colorectal cancer progression via Wnt/ β -catenin pathway: providing understanding of the complex mechanism of chemoresistance

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05224033

Position: Editorial Board

Academic degree: PhD

Professional title: Director

Reviewer's Country/Territory: China

Author's Country/Territory: Argentina

Manuscript submission date: 2021-12-21

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-01-17 04:00

Reviewer performed review: 2022-01-23 05:03

Review time: 6 Days and 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 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="checkbox"/>] Anonymous [<input type="checkbox"/>] Onymous Conflicts-of-Interest: [<input type="checkbox"/>] Yes [<input checked="" type="checkbox"/>] No

SPECIFIC COMMENTS TO AUTHORS

In this review, the author described the cross-communication between Wnt/ β -catenin pathway and cancer microenvironment in carcinogenesis, progression, and chemoresistance in CRC. It is a comprehensive review, and the prospective sight is the development of the pathway inhibitor in the disease. In the introduction, I think the more precise description of CRC, tumor microenvironment, and the pathway is better in the introduction. Point 2, is it ok for illustrating the cross-communication between Wnt/ β -catenin pathway and cancer microenvironment in colorectal carcinogenesis? Point 3 and 4 can be combined as a integral part demonstrating integration of them in CRC progression. The most important is the application of pathway inhibitor in CRC, I think this part can be considered as an important section in the review. The author shall be more comprehensively described the development and usage of the inhibitor in CRC, the clear mechanism diagram shall be provided.

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Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 06045450

Position: Peer Reviewer

Academic degree: MD

Professional title: Assistant Professor

Reviewer's Country/Territory: Iran

Author's Country/Territory: Argentina

Manuscript submission date: 2021-12-21

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-01-22 17:55

Reviewer performed review: 2022-01-28 13:12

Review time: 5 Days and 19 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 checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection



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Re-review	<input type="checkbox"/> Yes <input checked="" 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

How many patients did you examine in your study?

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Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05081392

Position: Editorial Board

Academic degree: MD, PhD

Professional title: Chief Physician, Professor

Reviewer's Country/Territory: China

Author's Country/Territory: Argentina

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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

This manuscript aimed at investigating the mechanism of chemoresistance of colorectal cancer. Tumor microenvironment is the “soil” for tumor breeding, the frequent interaction between tumor cells and other components in the microenvironment is considered to be the key factor leading to tumor progression and chemoresistance. Although there are some merits in this study, several issues should not be ignored. 1.

Previous studies have demonstrated that the mechanism of T cell exhaustion in the TME is critical to improve cancer immunotherapy, and that the Wnt/ β -catenin pathway has been identified as one of the most important oncogenic signaling pathways associated with immune evasion. Thus, I suggest the authors add specific content on the role of WNT signaling on the immune evasion in the TME, including effects on cells, i.e, natural killer (NK) cells, Treg cells, myeloid-derived suppressor cells (MDSC) and cytotoxic T lymphocytes (CTLs), rather than the simple content in part 6. 2.

Immunotherapy targeting TME is an important treatment for CRC. It is a promising strategy for cancer therapy. Authors can add the effect on Wnt / β - Catenin signaling pathway regulates immune cells (such as CD8+ T cells, Tregs, DC) in TME to mediate the resistance of CRC to immunotherapy. 3. Can the gut bacteria and their metabolites enriched in CRC's TME affect the Wnt/ β -catenin pathway? 4. “Recently, studies have shown that these vesicles can carry several proteins, lipids”. What proteins and lipids can be carried by vesicles? 5. TLR signaling wide expression within the TME of CRC, but TLR signaling did not shown in the Table 1. 6. Revise the reference format of the sixth line from the bottom on page 6. 7. The research on the influence of



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tumor microenvironment on chemoresistance has attracted great attention. At present, there are similar articles to summarize this content. This paper only includes the recent researches, authors does not put forward new ideas and lack of novelty. 8. Hypoxia is a key feature of tumor microenvironment, authors need to add some relevant studies about the correlation between Wnt/ β -catenin signaling pathway and hypoxia signaling pathway. 9. The transfer of Wnt ligands or β -catenin via Extracellular Vesicles (EVs) has been proposed as a Wnt signalling activation mechanism. They have great impact on proliferation, motility, EMT, migration, invasion, immune evasion, chemoresistance, and TME reprogramming. A more detailed introduction to EVs may make the article more comprehensive.