

PEER-REVIEW REPORT

Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 77346

Title: Transforming growth factor- β (TGF- β)/SMAD pathway in colorectal cancer

Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 06266265

Position: Peer Reviewer

Academic degree: MD

Professional title: Doctor

Reviewer's Country/Territory: China

Author's Country/Territory: Slovakia

Manuscript submission date: 2022-05-12

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-05-15 07:29

Reviewer performed review: 2022-05-26 02:46

Review time: 10 Days and 19 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 Grade E: Do not publish
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 checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous

statements

Conflicts-of-Interest: [] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

The TGF- β /SMAD signaling pathway has a dual effect; during tumor initiation and early stages, it stops the cell cycle and triggers apoptosis and in later stages, it promotes tumorigenesis and increases tumor progression and invasiveness. In the current manuscript, the author systematically summarized the latest research progress of the TGF- β /SMAD pathway on the regulation of colorectal cancer. However there are several major points below that need to be improved. 1: In the abstract section, the author emphasize “knowledge of the activation and inhibition of factors that affect the TGF- β signaling pathway is very important.” However, in the main text, the description of TGF- β signaling pathway modulator is far from enough. 2: The study of noncoding RNAs on TGF- β /SMAD signaling should also be discussed, as some circRNAs such as circPTEN1 have been reported to suppress the TGF- β /SMAD signaling by disrupting the formation of Smad complex in colorectal cancer. 3: This paper mainly discusses the regulatory effect of natural drugs on TGF- β /SMAD pathway. Chemically synthesized small molecule drugs, such as the Smad3 inhibitor SIS3, also need to be discussed.

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Title: Transforming growth factor- β (TGF- β)/SMAD pathway in colorectal cancer

Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 04062289

Position: Peer Reviewer

Academic degree: MD, PhD

Professional title: Academic Research, Surgeon, Surgical Oncologist

Reviewer's Country/Territory: Japan

Author's Country/Territory: Slovakia

Manuscript submission date: 2022-05-12

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-05-12 12:21

Reviewer performed review: 2022-05-27 00:32

Review time: 14 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
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

statements

Conflicts-of-Interest: [] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

This paper is a well-written review article describing Transforming growth factor- β /SMAD pathway in colorectal cancer. TGF- β and SMAD are broadly known as key molecules for carcinogenesis, cancer progression and drug-resistance acquisition in various kinds of cancer. However, their molecular functions within tumor cells are diverse and can lead to various confusions and misunderstandings about their oncological implications. From this point of view, this review article is very useful in advancing basic research on colorectal cancer. However, there are several points to be described and to be revised. Major Comments; 1. In the third paragraph of Introduction, the author described that patient with 18qLOH have a higher survival rate. However, the previous text describes the opposite fact, is there a contradiction? 2. The TGF- β /SMAD pathway acts in a tumor suppressive mechanism in early carcinogenesis, however, it acts in a tumor-promoting mechanism in later stages of carcinogenesis. Please explain in detail in Figure how TGF- β works in opposite directions. 3. Are there any clinical trials of TGF- β or SMAD inhibitors? If there are, please summarize and describe them. 4. Please provide a brief summary of the percentage of CIN positive cases, MSI cases, and CIMP high cases among all colorectal cancer cases.

PEER-REVIEW REPORT

Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 77346

Title: Transforming growth factor- β (TGF- β)/SMAD pathway in colorectal cancer

Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05198253

Position: Peer Reviewer

Academic degree: MD, PhD

Professional title: Academic Research, Chief Doctor, Doctor, Research Scientist

Reviewer's Country/Territory: China

Author's Country/Territory: Slovakia

Manuscript submission date: 2022-05-12

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-05-27 11:12

Reviewer performed review: 2022-06-06 03:06

Review time: 9 Days and 15 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
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

statements

Conflicts-of-Interest: [] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

Thank you for the opportunity to review a manuscript No: 77346 entitled " Transforming growth factor- β (TGF- β)/SMAD pathway in colorectal cancer" by J. Maslankova et. al. in World Journal of Gastroenterology. This paper is a well-written review article describing Transforming growth factor- β /SMAD pathway in colorectal cancer. Transforming growth factor-beta (TGF- β) plays an important role in pro-oncogenic response processes, such as invasion, epithelial-mesenchymal transition, promotion of angiogenesis, and immunomodulatory effects. The topic of this article is very interesting and important. However, the current manuscript has several problems and needs to be revised. 1. The language of the article needs further revision; 2. Figure 2 does not summarize the relationship between TGF-beta and EMT for tumors; 3. A large number of literatures support that fibrosis will provide armor for tumors, drug resistance. TGF-beta and fibrosis are strong related. The article needs to further deepen the discussion in this direction; 4. Authors need to add a figure or table to list related drugs related to TGF-beta/Smad and their mechanism of action; 5. A prospective section required to be added to improve the meaning of the article, and the authors need to try their best to summarize the shortcomings of the existing research and provide conjectures to guide future research; 6. Although Smad1/5/8 is rarely reported in CRC, the article also needs to briefly mention their function and summarize them in Figure 2; 7. Running Title should be changed properly.

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Manuscript NO: 77346

Title: Transforming growth factor- β (TGF- β)/SMAD pathway in colorectal cancer

Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05469117

Position: Editorial Board

Academic degree: PhD

Professional title: Adjunct Professor, Chief Physician, Deputy Director

Reviewer's Country/Territory: China

Author's Country/Territory: Slovakia

Manuscript submission date: 2022-05-12

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-05-30 16:03

Reviewer performed review: 2022-06-06 19:06

Review time: 7 Days and 3 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input checked="" 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 type="checkbox"/> Yes <input checked="" type="checkbox"/> No
Peer-reviewer	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous

statements

Conflicts-of-Interest: [] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

Thank you for inviting me to evaluate the review titled “Transforming growth factor- β (TGF- β)/SMAD pathway in colorectal cancer”. It is an interesting paper, which describe that the TGF-/SMAD signaling pathway has a dual effect; during tumor initiation and early stages, it stops the cell cycle and triggers apoptosis and in later stages, it promotes tumorigenesis and increases tumor progression and invasiveness. Some suggestions on personalized diagnosis and treatment are given. The provided figures are well composed and understandable, and the quality of language of the manuscript is quite acceptable for me. But the language is poor and it makes it difficult for the reader to follow the flow of the manuscript. There are some advices for author: 1) “Core Tip: Antitumor immunity is mediated by macrophages, natural killer cells, granulocytes, T cells, and antibodies. ”Can you explain how granulocytes participate in Antitumor immunity? 2) Why are targeted therapies and immune checkpoint inhibitors not discussed?

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Manuscript NO: 77346

Title: Transforming growth factor- β (TGF- β)/SMAD pathway in colorectal cancer

Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 03856292

Position: Peer Reviewer

Academic degree: PhD

Professional title: Associate Professor

Reviewer's Country/Territory: Egypt

Author's Country/Territory: Slovakia

Manuscript submission date: 2022-05-12

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-06-01 10:31

Reviewer performed review: 2022-06-07 22:48

Review time: 6 Days and 12 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 checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous

statements

Conflicts-of-Interest: [] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

The author has discussed a very important point which is the role of transforming growth factor-beta (TGF- β) in pro-oncogenic processes, such as invasion, epithelial-mesenchymal transition, promotion of angiogenesis, and immunomodulatory effects. Activation of TGF- β signaling is associated with drug resistance in CRC. They discussed the receptors and their roles too. However, I have few comments to the author:

1. Some used abbreviations are not universal as CIMP, MSI, CIN, T β R. 2. A lot of paragraphs are mentioned without references. 3. The precise role of each receptor or SMAD should be mentioned in the 1st paragraph then mention the studies which agree or disagree with clarification of this point. 4. There are a lot of contradictory sentences on the role of each SMAD and not mentioned is it in CRC or other types of cancer (please specify) 5. There are many conflicting sentences that need rephrasing in the introduction, SMAD7. 6. It is a pro-oncogenic process not response process. 7. The main limitation of this study is the lack of citation in many paragraphs

RE-REVIEW REPORT OF REVISED MANUSCRIPT

Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 77346

Title: Regulation of transforming growth factor- β signaling as a therapeutic approach to treating colorectal cancer

Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05198253

Position: Peer Reviewer

Academic degree: MD, PhD

Professional title: Academic Research, Chief Doctor, Doctor, Research Scientist

Reviewer's Country/Territory: China

Author's Country/Territory: Slovakia

Manuscript submission date: 2022-05-12

Reviewer chosen by: Yu-Lu Chen

Reviewer accepted review: 2022-07-22 05:57

Reviewer performed review: 2022-07-22 06:03

Review time: 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 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 checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Peer-reviewer	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous



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statements

Conflicts-of-Interest: [] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

Well done.

RE-REVIEW REPORT OF REVISED MANUSCRIPT

Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 77346

Title: Regulation of transforming growth factor- β signaling as a therapeutic approach to treating colorectal cancer

Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 04062289

Position: Peer Reviewer

Academic degree: MD, PhD

Professional title: Academic Research, Surgeon, Surgical Oncologist

Reviewer's Country/Territory: Japan

Author's Country/Territory: Slovakia

Manuscript submission date: 2022-05-12

Reviewer chosen by: Yu-Lu Chen

Reviewer accepted review: 2022-07-21 04:50

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Review time: 1 Day and 5 Hours

Scientific quality	<input checked="" type="radio"/> Grade A: Excellent <input type="radio"/> Grade B: Very good <input type="radio"/> Grade C: Good <input type="radio"/> Grade D: Fair <input type="radio"/> Grade E: Do not publish
Language quality	<input checked="" type="radio"/> Grade A: Priority publishing <input type="radio"/> Grade B: Minor language polishing <input type="radio"/> Grade C: A great deal of language polishing <input type="radio"/> Grade D: Rejection
Conclusion	<input type="radio"/> Accept (High priority) <input checked="" type="radio"/> Accept (General priority) <input type="radio"/> Minor revision <input type="radio"/> Major revision <input type="radio"/> Rejection
Peer-reviewer	Peer-Review: <input checked="" type="radio"/> Anonymous <input type="radio"/> Onymous



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statements

Conflicts-of-Interest: [] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

The quality of the papers has improved very much, with appropriate responses and corrections to the reviewers' suggestions. This paper summarizing the role of TGF- β and SMAD in colorectal cancer will be very useful for further development of basic research and clinical application of molecular targeted drugs. No further revisions or supplements to this paper are deemed necessary. Congratulations on a great work!