

## First review

**Scientific Quality:** Grade B (Very good)

**Language Quality:** Grade B (Minor language polishing)

**Conclusion:** Minor revision

The author has discussed a very important point which is the role of transforming growth factor-beta (TGF- $\beta$ ) in pro-oncogenic processes, such as invasion, epithelial-mesenchymal transition, promotion of angiogenesis, and immunomodulatory effects. Activation of TGF- $\beta$  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 $\beta$ 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

## Response to the 1st review

We thank the reviewer for the excellent review of our manuscript as well as insightful critiques that helped us improve the manuscript. We have considered all comments and made changes with the 'highlighted text' in the manuscript.

1. Throughout the text, the abbreviation „T $\beta$ R” has been corrected to the universally used abbreviation „TGF- $\beta$ R”. The authors are not aware that the abbreviations MSI, CIN, and CIMP are not universal.
2. and 7. References have been added after each paragraph
3. Individual types of SMADs were listed in Table 2, and only selected SMADs were described in the text
4. and 5. The SMADs paragraph was revised, focusing mainly on CRC
6. The phrase „pro-oncogenic response” has been changed to a „pro-oncogenic process”.

## **2nd review**

**Scientific Quality:** Grade D (Fair)

**Language Quality:** Grade B (Minor language polishing)

**Conclusion:** Major revision

Thank you for inviting me to evaluate the review titled "Transforming growth factor- $\beta$  (TGF- $\beta$ )/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?

## **Response to the 2nd review**

We thank the reviewer for the excellent review of our manuscript as well as insightful critiques that helped us improve the manuscript. We have considered all comments and made changes with the 'highlighted text' in the manuscript.

1. Core tip has been rewritten. The role of granulocytes in antitumor immunity was clarified in the conclusion.
2. A chapter on targeted therapies and immune checkpoint inhibitors was added

## **3rd review**

**Scientific Quality:** Grade C (Good)

**Language Quality:** Grade B (Minor language polishing)

**Conclusion:** Major revision

Thank you for the opportunity to review a manuscript No: 77346 entitled " Transforming growth factor- $\beta$  (TGF- $\beta$ )/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- $\beta$ /SMAD pathway in

colorectal cancer. Transforming growth factor-beta (TGF- $\beta$ ) 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.

### **Response to the 3rd review**

We thank the reviewer for the excellent review of our manuscript as well as insightful critiques that helped us improve the manuscript. We have considered all comments and made changes with the 'highlighted text' in the manuscript.

1. The language of this review article has been checked.....
2. Relationship between TGF-beta and EMT for tumors was summarized in Fig.2
3. Fibrosis was discussed in more detail in the chapter TGF- $\beta$  AND ITS ROLE IN TUMOR PROMOTION
4. Figure 5 about inhibition strategies of TGF- $\beta$  signaling pathway for CRC treatment and also Table 3 about clinical trials of drugs for the treatment of colorectal cancer were added
5. A chapter on recent non-coding RNAs that play an important regulatory role in CRC has been added.

批注 [M1]: DOPLNIŤ!!!!

6. Tab. 2 about SMAD1/5/8 was added to the article and Fig. 2 was expanded to include this part of the signaling pathway
7. The running title has been changed

#### **4th review**

**Scientific Quality:** Grade C (Good)

**Language Quality:** Grade B (Minor language polishing)

**Conclusion:** Major revision

This paper is a well-written review article describing Transforming growth factor- $\beta$ /SMAD pathway in colorectal cancer. TGF- $\beta$  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- $\beta$ /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- $\beta$  works in opposite directions.
3. Are there any clinical trials of TGF- $\beta$  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.

#### **Response to the 4th review**

We thank the reviewer for the excellent review of our manuscript as well as insightful critiques that helped us improve the manuscript. We have considered all comments and made changes with the 'highlighted text' in the manuscript.

1. This paragraph has been changed.

2. In Figure 2, we described both effects of the TGF- $\beta$  signaling pathway
3. Figure 5 about inhibition strategies of TGF- $\beta$  signaling pathway for CRC treatment and also Table 3 about clinical trials of drugs for the treatment of colorectal cancer were added and were also described in the main text
4. Information on the percentage of CIN positive cases, MSI cases, and CIMP has been added to the main text

#### 5th review

**Scientific Quality:** Grade C (Good)

**Language Quality:** Grade B (Minor language polishing)

**Conclusion:** Minor revision

The TGF- $\beta$ /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- $\beta$ /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- $\beta$  signaling pathway is very important.” However, in the main text, the description of TGF- $\beta$  signaling pathway modulator is far from enough.
- 2: The study of noncoding RNAs on TGF- $\beta$ /SMAD signaling should also be discussed, as some circRNAs such as circPTEN1 have been reported to suppress the TGF- $\beta$ /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- $\beta$ /SMAD pathway. Chemically synthesized small molecule drugs, such as the Smad3 inhibitor SIS3, also need to be discussed.

#### Response to the 5th review

We thank the reviewer for the excellent review of our manuscript as well as insightful critiques that helped us improve the manuscript. We have considered all comments and made changes with the ‘highlighted text’ in the manuscript.

1. Figure 5 about inhibition strategies of TGF- $\beta$  signaling pathway for CRC treatment and also Table 3 about clinical trials of drugs for the treatment of colorectal cancer were added and were also described in the main text
2. A chapter on REGULATION OF TGF- $\beta$  SIGNALING PATHWAY BY NON-CODING RNAs was added
3. A chapter on SMALL MOLECULE INHIBITORS OF SMAD EXPRESSION AND PHOSPHORYLATION was added