

Specific Comments To Authors

05927046 Conclusion: Minor revision

Scientific Quality: Grade D (Fair)

Language Quality: Grade B (Minor language polishing)

1. In this manuscript, the authors reviewed intestinal WNT pathway in the transition from physiology to oncology. In the canonical Wnt/ β -catenin signaling, it consists of the transmembrane complex (Lrp5/6 and Frizzled), a destruction complex (Axin, APC, GSK3, CK1, PP2A) and β -catenin. In introducing of WNT signaling in intestinal mucosal physiology, whether the transmembrane complex, destruction complex or β -catenin are relative to stomach, small intestine and colon, please describe the detailed mechanism or the current research progress.

Following your recommendation, we revised the paragraph and added especially recently published references.

2. In the part" HYPERACTIVATION OF WNT SIGNALING DRIVES PATHOPHYSIOLOGY AND ONCOLOGY" Oncology should be a type of pathophysiology? Choose one of them maybe better.

Thanks for the suggestion. The title is changed to "HYPERACTIVATION OF WNT SIGNALING DRIVES PATHOPHYSIOLOGY"

3. In the Figure 4, the experiment was conducted by the author? Or are they from other references? Please illustrate in the legend.

The figure contains previously unpublished experiments done by the author J. Swoboda. We added this information in the author contribution.

02523682 Conclusion: Major revision

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

This manuscript reviewed the Wnt/ β -catenin signaling pathway, the regulatory mechanism of this pathway and its role in intestinal homeostasis, the molecular mechanisms and the histomorphological features of Wnt hyperactivation, and the central role of Wnt signaling pathway in intestinal carcinogenesis as well as its clinical relevance in colorectal carcinoma. Although the manuscript is well organized and descibed, the novelty of this manuscript still need to be considered

because there are published papers including review about Wnt signaling pathway and intestine.

1. The title is "Intestinal WNT in the transition from physiology to oncology". However, this manuscript seems to focus on the physiology of Wnt while describing oncology role of Wnt signaling in a slightly simpler way. The author should reinforce the the transition from physiology to oncology and the clinical cancer relevance of Wnt activation.

Following your recommendation, we revised the paragraphs, especially the "CLINICAL RELEVANCE OF WNT ACTIVATION" intensively and added especially recently published data.

2. In the Section "THE NECESSITY OF WNT SIGNALING IN INTESTINAL MUCOSAL PHYSIOLOGY", the authors mentioned three organs: Stomach, Small intestine, and Colon. However, in the Section "Clinical relevance of Wnt activation in colorectal cancer", the authors only described the prognostic value of Wnt activation and as a potential target in colorectal cancer. How about the roles and status of Wnt activation in stomach?

We added a paragraph about Clinical relevance of Wnt activation in the stomach and in the small intestine.

3. In the Section "CLINICAL RELEVANCE OF WNT ACTIVATION IN COLORECTAL CANCER", the authors only focus on the role of APC in CRC prognosis, 5-ASA and WNT-induced chemoresistance. In fact, there are many protein factors in the Wnt pathway that are associated with tumors, including colon cancer, and many therapeutic targets and drugs are available for the treatment of colon cancer such as A PROTAC peptide (Cell Discov. 2020 Jun 9;6:35. doi: 10.1038/s41421-020-0171-1), Oncolytic adenovirus (Biomedicines. 2020 Dec 11;8(12):593. doi: 10.3390/biomedicines8120593; Biochem Biophys Res Commun. 2017 Sep 16;491(2):469-477. doi: 10.1016/j.bbrc.2017.07.041) and An aggregon (Nat Commun. 2019 Sep 18;10(1):4251. doi: 10.1038/s41467-019-12203-8) et al. This Section is the important section in this manuscript. The authors also draw the figure or list a table about the potential target in Wnt/ β -catenin signaling for the prevention and treatment of colorectal cancer.

Thank you very much for the appropriate references. We intensively revised the section "CLINICAL RELEVANCE OF WNT ACTIVATION" and "WNT/ β -CATENIN

SIGNALING AS A POTENTIAL TARGET IN THE PREVENTION AND TREATMENT OF INTESTINAL CANCER". We made detailed additions with the proposed references and further references. Furthermore, we have created a table with possible therapeutic targets in Wnt/ β -catenin signaling.

02523682 Conclusion: Accept (General priority)

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

I reviewed the revised manuscript, the authors have well done the issues that the reviewers questioned. The language is great. I think it is fit to accept it.

Thanks for your comments.