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Subject: Response to Reviewer's comments, WJGE Manuscript No. 40077

Dear Professor Wang,

Thank you very much for your letter detailing the reviewers' comments to our invited manuscript No 40077 at World Journal of Gastroenterology ("The Calcium-Sensing Receptor in colorectal inflammation and cancer: current insights and future perspectives").

We also want to thank you for providing the edited / annotated version of our manuscript, which we have used as a basis for making the adaptations according to the editor's and reviewers' comments.

With regards to the titles, we would like to point out that we purposely reversed the deletions of the article "The" accompanying "Calcium Sensing Receptor" or "CaSR". The use of the definitive article to denominate the receptor is very common and widely used in the CaSR field, compare. e.g. the titles of references ^[1-5].

Here we now send you the revised manuscript which incorporates all the changes made based on the reviewers' comments and the editorial changes that were already in the edited version, as well as some minor corrections for spelling and clarification. Detailed answers to the reviewers' comments are below. We have recorded our audio core tip and edited the title page as required. References, figures and tables were formatted as per the supplied instructions. Figures are provided both in the manuscript and separately in high resolution.

Yours sincerely,

Dr. Martin Schepelmann
Corresponding author

Point by point response to the Reviewer's comments:

Comments by Reviewer 1: (Scientific quality: C, Good; Language Quality: B, Minor polishing; Conclusion: Major revision; Peer-Review: Anonymous; Expertise: General; Conflict of Interest: No)

- *The authors have written a review on an interesting topic of CaSR and colorectal cancer and inflammation. I have following comments for the authors:*

Response:

Thank you very much for your evaluation of the topic of our review being of interest.

- *1. A large part of the manuscript is discussing the role of CaSR in other cancers due to which the manuscript becomes unnecessarily lengthy. It would be desirable to focus only on the relation between CaSR and colorectal cancer and inflammation in this review.*

Response:

Thank you very much for your comment. As also detailed for a similar comment by reviewer 2, we have now substantially shortened the section of the manuscript on the role of the CaSR in other cancers (by about 1/3rd).

- *2. Several important following articles on the topic of the manuscript have not been quoted: a. Zhu Y et al. Br J Cancer. 2017 Sep 5;117(6):898-906. b. Fetahu IS et al. Int J Cancer. 2016 Jan 1;138(1):137-45. c. Singh N, et al. Mol Carcinog. 2015 Jul;54(7):543-53. d. Mahmoudi T, et al. Asian Pac J Cancer Prev. 2014;15(15):6035-9. e. Jenab M, et al. Cancer Epidemiol Biomarkers Prev. 2009 Sep;18(9):2485-91.*

Response:

Thank you very much for pointing out these missing articles.

We have now added the references *Zhu Y et al. Br J Cancer. 2017 Sep 5;117(6):898-906 (now ref # 107)*, *Singh N, et al. Mol Carcinog. 2015 Jul;54(7):543-53 (now ref #120)*, *Mahmoudi T, et al. Asian Pac J Cancer Prev. 2014;15(15):6035-9 (now ref #108)* and *Jenab M, et al. Cancer Epidemiol Biomarkers Prev. 2009 Sep;18(9):2485-91 (now ref #109)* to the appropriate sections in the manuscript.

The article Fetahu IS et al. Int J Cancer. 2016 Jan 1;138(1):137-45 was already referenced in our manuscript (reference # 61).

Comments by Reviewer 2: (Scientific quality: C, Good; Language Quality: B, Minor polishing; Conclusion: Minor revision; Peer-Review: Anonymous; Expertise: General; Conflict of Interest: No)

- *The review by Luca lamartino et al has described the pathophysiological roles of the extracellular calcium-sensing receptor (CaSR). In addition to the detail description of CaSR in colorectal inflammation and cancer, this review provided extensive knowledge about the distinct roles of CaSR in diverse organs and cells. This review is well organized and written.*

Response:

Thank you very much for your high opinion on the organisation and writing style of our manuscript.

- *Major comment: The role of CaSR in cancers as well as other benign lesions is not a new topic and several reviews have addressed the different facets of CaSR signalling and Pharmacology. Although this review aimed to describe the role of CaSR in colorectal inflammation and cancer, the authors described the effects of the molecule in many other organs; as a result, the review is very long while short of novelty.*

Response:

Thank you very much for your comment. In accordance with your suggestion and the suggestion of reviewer 1 (see above), we have shortened the sections on the effects of the CaSR in the other organs and have re-written other parts of the CaSR in colorectal cancer section to be more concise. However, as reviewer 3, who by his own definition is an advanced expert in the field, rated our review to be of excellent quality and did not remark on any surplus topics, we did not want to completely remove these sections or change them too extensively, so that the essence of the review – which apparently was highly appreciated by reviewer 3 and reviewer 1 – is not impaired.

- *Minor comment: The author should give the full name of CaSR in the title.*

Response:

Thank you very much for your suggestion. We have now provided the full name of the CaSR in the title: “The Calcium-Sensing Receptor in colorectal inflammation and cancer: current insights and future perspectives”.

Comments by Reviewer 3: (Scientific quality: A, Excellent; Language Quality: A, Priority publishing; Conclusion: Accept (High priority); Peer-Review: Anonymous; Expertise: Advanced; Conflict of Interest: No)

- *The extensive revision of CaSR in inflammation and cancer highlights in a clear way all important issue regarding this receptor in health and in disease.*

Response:

We thank the reviewer very much for his high opinion of our work, both scientifically and language-wise, especially as he categorizes himself as being of advanced knowledge in the field.

Example references (for use of the definitive article “the” in conjunction with “Calcium-Sensing Receptor”)

1. Leach K, Sexton PM, Christopoulos A, Conigrave AD. Engendering biased signalling from **the** calcium-sensing receptor for the pharmacotherapy of diverse disorders. *Br J Pharmacol* 2014;**171**:1142–55 [PMID: 24111791 DOI: 10.1111/bph.12420]
2. Conigrave AD. **The** calcium-sensing receptor and the parathyroid: Past, present, future. *Front Physiol* 2016;**7** [PMID: 28018229 DOI: 10.3389/fphys.2016.00563]
3. Lopez-Fernandez I, Schepelmann M, Brennan SC, Yarova PL, Riccardi D. **The** calcium-sensing receptor: One of a kind. *Exp Physiol* 2015;**100**:1392–9 [PMID: 26105576 DOI: 10.1113/EP085137]
4. MacLeod RJ. A new role for **the** extracellular calcium-sensing receptor demonstrated by using CCK-eGFP BAC mice. *Am J Physiol Gastrointest Liver Physiol* 2011;**300**:G526–7 [PMID: 21311025 DOI: 10.1152/ajpgi.00029.2011]
5. Sparks SM, Spearing PK, Diaz CJ, Cowan DJ, Jayawickreme C, Chen G, Rimele TJ, Generaux C, Harston LT, Roller SG. Identification of potent, nonabsorbable agonists of **the** calcium-sensing receptor for GI-specific administration. *Bioorg Med Chem Lett* 2017;**27**:4673–7 [PMID: 28916340 DOI: 10.1016/j.bmcl.2017.09.008]