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Dear editor,

We thank you very much for giving us an opportunity to revise our manuscript, we appreciate editor and reviewer very much for their constructive comments, criticisms and suggestions on our manuscript entitled “Roles of the $\text{Na}^+/\text{Ca}^{2+}$ exchanger 1 in digestive system physiology and pathophysiology”. All these comments about the contents and structure of my paper are most helpful.

We have studied the reviewer's comments point to point carefully and have made revision in this manuscript. We have tried our best to revise our manuscript including figures according to the comments. We would like to express our great appreciation to you and reviewer for comments on our paper. We hope the changes we have made in this revised version of our paper resolve all the concerns from the reviewer.

Looking forward to hearing from you.

Thank you and best regards.

Yours sincerely,

Rui Xie

Rui Xie, MD, PhD.

Professor

Department of GASTROENTEROLOGY

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We thank the reviewers for their thoughtful comments. We have followed their suggestions point by point and have made all the corrections to our best ability. Below are our point by point responses (in blue) to their concerns.

2 Peer-review report

Reviewer #1: Minor revision

We thank the reviewer for this kind suggestion. We have modified the manuscript. Now its much better than before.

Reviewer #2: This review intends to explore the role and possible regulatory mechanisms of NCX1 in digestive physiology and pathophysiology to support the NCX1-based therapeutic potentials of digestive diseases. In this manuscript, authors summarized the NCX1 structure and its biochemical features in the gastrointestinal system, several regulatory signal pathways and mechanisms of action of NCX1 in GI. Although the manuscript is well written, some references cited in this review are old, such as reference 5,6,25 and 26, please make sure to update these references. Moreover, the texts on the figures are too small to read, in figure 2, TGF-beta was replaced with TGF- β in the figure Legend. Please keep a consistent description. In discussion, I suggest to summarize some possibilities for drug development and clinical treatments by targeting NCX1 or calcium channels.

We thank the reviewer for this kind suggestion. We have added several new references. TGF-beta was replaced with TGF- β in the whole manuscript, and make sure everything the same.

Reviewer #3: In this review, the authors reports the role of NCX1 in digestive system physiology and pathophysiology to guide an eventual clinical treatments. The paper is informative and interesting. All the step of the paper are clearly written. The discussion argues and the conclusion indicates that the NCX1 channel protein regulates the Ca²⁺ signaling pathway via its forward/reverse modes in the digestive system and regulates the cell function. This point is interesting in particular in digestive pathophysiology. In introduction, the authors must add one or two sentences showing the role of immune system and inflammation in digestive pathologies such as IBD or gastric ulcer (Soufli et al, 2016; Boutemine et al, 2018). In Discussion, the authors must add one sentence about the clinical relevance and indicate some possibilities for drug development for early intervention in inflammation-associated tumors.

We thank the reviewer for this kind suggestion. We have added the new sentences in both introduction and discussion. Some conceptual sentences and summative sentences are repeatedly scrutinized and expressed more clearly and clearly. All changed sentences with "marked in red" in the whole manuscript.