Dear Prof. Lian-Sheng Ma,

Re: Manuscript ID 76325

Please find attached a revised version of our manuscript "P2X7 Receptor as the regulator of T-cell function in intestinal barrier disruption".

Your comments were highly insightful and enabled us to greatly improve the quality of our manuscript. We have carefully checked the article and fixed linguistic errors. Revisions in the manuscript are shown by using the track changes mode in MS Word or by using colored text, for example, "~~Foxo3~~", "FOXO3". We will offer two manuscripts with or without modifications.

We shall look forward to hearing from you at your earliest convenience.

Sincerely yours,

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Answers to reviewers:

Reviewer #1:

1. Comment: "1. Please explain more about the role of the P2X7 receptor in infections; for example, in recent years, multiple SNPs of the P2X7 receptor have been found in patients with bacterial sepsis. In addition, the P2X7 receptor of dendritic cells derived from healthy individuals is found to have similar SNPs to those of patients with bacterial sepsis. Systemic administration of BzATP (the agonist of the P2X7 receptor) increases the inflammatory response, while systemic blocking the P2X7 receptor with A740003 reduces the level of pro-inflammatory cytokines in intestinal mucosa after cecal ligation and puncture (CLP)."

Response: Thank you for your comments. According to your advice, we have clarified with more explanation in page 6, line 210-220; page 9, line 334-337.

2. Comment: "2. Please cite more recent publications: Grassi F. The P2X7 receptor as regulator of T cell development and function. Frontiers in Immunology. 2020; 11: 1179."

Response: Thank you for your comments. The reference has been added in page 25, line 870-872.

3. Comment: "3. There are 31 repeated references below in the manuscript. Please omit them!"

Response: Thank you for your comments. We were sorry that we forgot to delete these 31 repeated references. We have corrected this mistake.

Reviewer #2:

1. Comment: "1. Since this review proposed about P2X7R as the potential target for treatment of inflammation of the intestine, the authors generally should review and discuss about the intracellular signaling pathway, perhaps for example, about the MAPK, ERK1/2, and other signaling molecules of the T cell known to date that are associated with the function of P2X7R. This is because the signaling pathway may be one of the many important factors for research and development of novel drug with specific molecular targeting such as P2X7R in T cells. In addition, different subsets of T

cells may also have differential sensitivities of the same receptor. Other previous reviews found in the literature have already mentioned most of the information currently stated in this manuscript. The authors should try to provide their insights specifically into the role of T cell expressing P2X7R in intestinal barrier disruption as a potential drug target for modulating T cell responses in particular, as proposed in the title."

Response: Thank you for your comments. More details about the signaling pathways related to P2X7R have been provided, and we provided more evidence associated with the role of P2X7R in T cells in page 4, line 151-158; page 4, line 210-220; page 6, line 267-269; page 8, line 304-307; page 8, line 334-342.

2. Comment: "2. The letters depicting components within figure 1 are too small."

Response: Thank you for your comments. According to your advice, the letters in figure 1 have been resized.