

Responses to reviewer #1:

Comment 1. In my opinion the title need some further modification, because it is confusable and mostly corresponds to a research article rather than to a review study.

Response 1. We appreciate your time and efforts on reviewing our manuscript! We noticed that the ambiguity of the paper title which could not clarify the theme clearly. As your suggestion, we changed the title of our manuscript to “**Current knowledge on the multiform reconstitution of intestinal stem cell niche**” (supporting reference: [https:// 10.1146/annurev-cellbio-100814-125218](https://doi.org/10.1146/annurev-cellbio-100814-125218)). Thanks again for your kind reminding!

Comment 2. In pages 4-6 section 2.1 Biochemical Signaling within the ISC Niche. I think it would be better the specific signaling pathways should not be seperated as different subsections. If the authors insist to present seperately the different signaling pathways more information need to be added

Response 2. Biochemical signaling is vital to the self-renewal property of the ISCs. However, the reconstitution of ISC niche *in vitro* entails more requirements including niche cells and mechanical cues, which are always ignored in studies before. So, we made an adjustment to the contents regarded to biochemical signaling properly to balance the arrangement.

Comment 3. The authors should add before the section 5 Future Development and Challenges, a section describing the potential applications of the presented methodology. Are there any clinical trials that are now performing using the described methodologies.

Response 3. This is an important point. We have been watching the application of organoid technique into clinical use. But this step is limited due to biosafety concern and unverified validity. Organoid technique still serves as disease model or drug screening platform described in the manuscript.

Comment 4. Also the authors should add the interplay between Intestinal Mesenchymal Stromal Cells and Intestinal cells, their role and their potential contribution in immunity.

Response 4. We noticed that we made the contents about niche cells around ISCs a bit simple. As you suggestion, we make further efforts to explain the role of different cell types within ISC niche. (supporting reference: 10.1242/dev.104976)