

**December 25, 2020**

**Dear Editors,**

Manuscript ID: 60449

Title: Could Gastrointestinal Tumor Initiating Cells Originate from Cell-Cell Fusion *In Vivo*?

We are glad that editors and reviewers have provided some valuable comments to our manuscript. We have read the peer review comments carefully, revised the manuscript according to the comments and marked the revised words in red. A point-to-point response of the comments is provided below in this response letter. We also polished the whole text including the abstract to improve the English language and style in the revised manuscript. Here we provide an English Language Certificate issued by a professional English language editing company.

With best regards,

Yours sincerely,

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**Reviewer #1**

**Questions 1:** In Introduction, the mutation introduction and cell-cell fusion may be discussed more in detail.

**Reply to reviewer #1:** we added “Wild-type p53 can be experimentally replaced with a mutant version of p53 via PCR, CRISPR/Cas9, and knock-in techniques. When a related gene mutation occurs,” on the line 53 to 56 “The absence of APC is rare and APC is commonly found in gastrointestinal cells, including normal populations of

gastrointestinal stem cells,” on the line 64 to 65 (That APC study did not introduce the mutation, but found the mutation), “ZEB1, a transcription factor known to be involved in EMT, is necessary for the conversion of non-TICs to TICs.” on the line 86 to 87 (Explain the role of ZEB1), “Cell fusion is an essential physiological process, which plays a role in fertilization, virus entry, muscle differentiation, and placenta development. It was also reported to be closely associated with the occurrence and development of cancer.” on the line 92 to 94.

**Questions 2:** In “Cell fusion between colorectal cancer cells and stem cells”, how the fusion of intestinal epithelial cancer cells and macrophages from bone marrow-derived cells in vivo leads to nuclear reprogramming may be described more in detail.

**Reply to reviewer #1:** we added “play a role in giTIC formation by introducing endogenous reprogramming, as cell fusion hybrids retain transcripts from both parental cells and also express a unique subset of transcripts[50].”. on the line 103 to 105.

**Questions 3:** Proofreading is needed.

**Reply to reviewer #1:** The modification and proofreading have been completed. Here we provide an English Language Certificate issued by a professional English language editing company.

### **Science editor**

**Questions 1:** I found no “Core tip” section. Please provide the core tip;

**Reply to science editor:** We added “Core tip: Currently, there are many controversial hypotheses concerning the generation of gastrointestinal tumor-initiating cells (giTICs). Here, we mainly reviewed the current advances in the understanding of giTIC origination from the cell-cell fusion of cancer cells and bone marrow-derived cells..” on line 27 to 30.

**Questions 2:** I found the authors did not provide the approved grant application form(s).

**Reply to science editor:** Please check the file “approved grant application forms or funding agency copy of any approval documents”.

**Questions 3:** I found the authors did not provide the original figures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by

the editor;

**Reply to science editor:** Please check the original figure documents in this revision. We prepared figures using PPT to ensure all graphs or arrows or text portions can be reprocessed by the editor. The files are named “60449-Figures.pptx” and “60449-Figures.AI”.

**Questions 4:** I found the authors did not add the full PMID and DOI in the reference list. Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references. Please revise throughout;

**Reply to science editor:** Citations content has been modified accordingly. Authors lists, PMID and DOI citation numbers has been provided in the reference.

**Questions 5:** the author should number the references in Arabic numerals according to the citation order in the text. The reference numbers will be superscripted in square brackets at the end of the sentence with the citation content or after the cited author’s name, with no spaces.

**Reply to science editor:** Citation content has been modified using “World J Gastroenterology.ens” format.

**Editorial office director**

**Questions:** I have checked the comments written by the science editor.

**Reply to editorial office director:** OK, thank you.

**Company editor-in-chief**

**Questions:** The quality of the English language of the manuscript does not meet the requirements of the journal. Before final acceptance, the author(s) must provide the English Language Certificate issued by a professional English language editing company.

**Reply to company editor-in-chief:** The language has been edited to ensure that it meets the requirements. Here we provide an English Language Certificate issued by a professional English language editing company.