Response letter

Dear reviewers and editor-in-chief,

Thanks for your consideration and reviewing our manuscript. We appreciate your work which will contribute to improve our manuscript. According to the comments, we have made serious modification. We hope the revised manuscript will be accord with the requirement. The following is our response to the comment.

Reviewer #1: Dear Editor, Dear Authors, It is promising to have a nice structured review article to summarize the role of IL-33 / ST2 in colorectal cancer prevention, carcinogenesis, progress and their therapeutic potential based on a number of update evidence and studies. However, there are still some major points, which have to be further concerned. 1. It is suggested to incorporate better graphic figures to illustrate both the structure of IL-33 and its ligand ST2 as well as the role of IL-33 / ST2 in CRC carcinogenesis and progression if applicable. For the therapeutic potentials, a comprehensive table to sum up the therapeutic strategies targeting IL-33 / ST2 will be more informative. 2. It is highly important to ask the author to check all the references cited in the manuscript properly. For instance: #In particular, it is worth mentioning that several risk factors are related CRC development, including lack of exercise, smoking, red meat and alcohol consumption [3, 4]. Reference 4 doesn't mention this point. #Combining radiation with conventional chemotherapy can exacerbate mucositis, leading to chemotherapeutic dose reductions or inevitable cessation of such treatments [49, 50]. It is rather hard to find the correlated description in the reference 49 and 50. 3. In the title there is a focus on colorectal carcinogenesis, progress….but in the content, there is only a part for IL-33 / ST2 and CRC progression, the structure need to be better organized. 4. There are already IL-33 antibody clinical trials, for instance, SAR440340 (Anti-IL-33 mAb) or other blockade strategies could be further discussed in the part of: Diversified therapeutics based on IL-33 / ST2 signaling in CRC. 5. The potential role of IL-33 in regulating tumor initiating cells has been reported, as well as the impact on stem cell– niche interactions. (Taniguchi et al Science 2021), this new highlight could be further integrated into the review, linking to CRC prospects. Minor pointes: 1. There

are still some mistakes about language and typos, the authors are suggested to optimize the manuscript completely The expression like: ‘Generally speaking’, ‘type-II disbetes’, ‘Recent research progress seem to provide’ …. in the context, has to be avoided 2. Be consistent with the space before the citation, some have, some did not have, please update that accordingly. 3. A summary of abbreviations will be appreciated

Response:

We appreciate your work for our manuscript. You suggestions are pertinent and benefit to our manuscript. We made the modification according to your suggestions.

Major points:

1. It is suggested to incorporate better graphic figures to illustrate both the structure of IL-33 and its ligand ST2 as well as the role of IL-33 / ST2 in CRC carcinogenesis and progression if applicable. For the therapeutic potentials, a comprehensive table to sum up the therapeutic strategies targeting IL-33 / ST2 will be more informative.

Response: Thanks for your suggestion. According to your suggestion, we add one figure in the manuscript as Figure 1 The structure of IL-33, and activation and the role of IL-33/ST2 in CRC promotion and prevention.

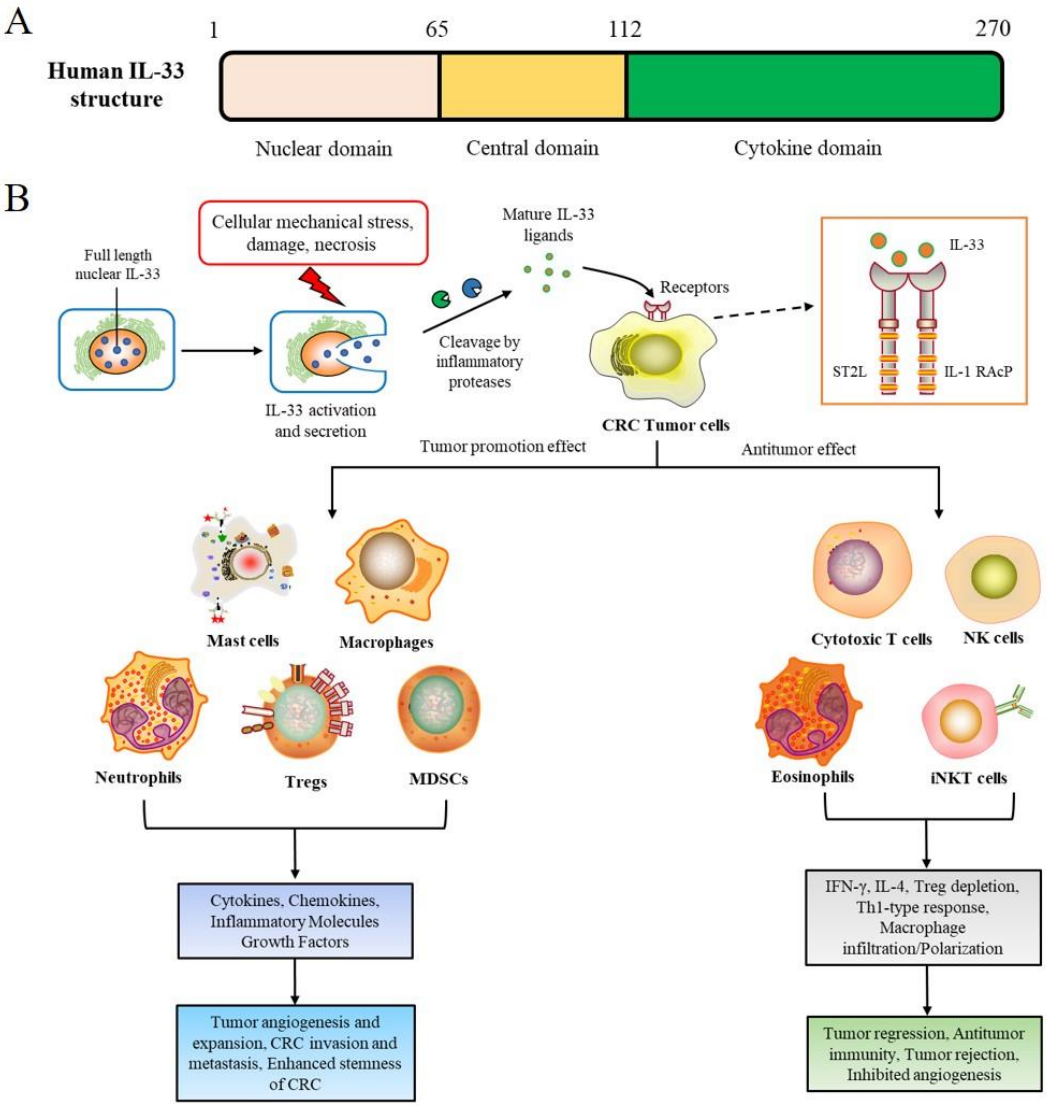

Figure 1 The structure of IL-33, and activation and the role of IL-33/ST2 in CRC promotion and prevention. A. The structure of human IL-33 Protein. IL-33 is constituted with two evolutionary conserved nuclear domain and cytokine domain separated by the highly divergent central domain. B. The role of IL-33/ST2 in CRC. The full length IL-33 is cleaved by inflammatory proteases under cellular stress, damage and injury, and is activated and secreted into mature IL-33 ligands. Then, active IL-33 binds to the receptor ST2L and coreceptor IL-1 RAcP on target cell surface such as CRC tumor cells, and plays a dual role in cancer including tumor promotion effect and antitumor effect through diversified cells in tumor microenvironment and the molecules they secrete.

In addition, we also added a table summing up the therapeutic strategies targeting IL-33 / ST2. Please see the following table 1.

Table 1 Diversified therapeutics based on IL-33/ST2 signaling in CRC

Type of Therapeutic strategies	Pattern of IL-33/ST2 signaling involved	Drugs or cells used	Antitumor effects or mechanisms	References
Conventional Therapy	Blockade of IL-33/ST2 signaling	Irinotecan, SN-38	Alleviated mucositis, reduced tumor growth	55, 59, 60
Blockade of immune checkpoint	Exogenous IL-33 or its overexpression, ST2 depletion	PD-1 antibody	Activated $CD8^+$ T cell cytotoxicity, tumor regression	66, 67
Lymphocyte immunotherapy	Enhanced IL-33 expression	Tumor-infiltrating $CD8^+$ T, IFN-γ^+ $CD4^+$T cells, eosinophils, ILC2	Upregulation of IFN-γ, antitumor immunity, Inhibition of tumor expansion/metastasis	69, 71, 73, 76
Cancer gene therapy	Overexpression of IL-33	Oncolytic adenovirus, vaccinia virus	Oncolysis, Inhibition of tumor growth, migration and tumor stem-cell activity	77, 78

2. It is highly important to ask the author to check all the references cited in the manuscript properly. For instance: #In particular, it is worth mentioning that several

risk factors are related CRC development, including lack of exercise, smoking, red meat and alcohol consumption [3, 4]. Reference 4 doesn't mention this point. #Combining radiation with conventional chemotherapy can exacerbate mucositis, leading to chemotherapeutic dose reductions or inevitable cessation of such treatments [49, 50]. It is rather hard to find the correlated description in the reference 49 and 50.

Response: We have appreciated your review for the references cited in the manuscript. According to your suggestions, we deleted the reference 4 and 49, 50, and cited and added the related reference. In addition, we checked the references through the manuscript, and renewed the reference including the added paragraph according to the journal style. Please check the revised manuscript.

3. In the title there is a focus on colorectal carcinogenesis, progress….but in the content, there is only a part for IL-33 / ST2 and CRC progression, the structure need to be better organized.

Response: We have appreciated your suggestion. According to your suggestion, we have reorganized the Part 3. The roles of IL-33/ST2 in CRC. We have added one section 3.1 IL-33/ST2 and CRC carcinogenesis, and also modified the 3.2 IL-33/ST2 and CRC progress. Please see the revised manuscript.

4. There are already IL-33 antibody clinical trials, for instance, SAR440340 (Anti-IL-33 mAb) or other blockade strategies could be further discussed in the part of: Diversified therapeutics based on IL-33 / ST2 signaling in CRC.

Response: Thanks for your suggestion. We searched the website: clinicaltrials.gov, and found at least two anti-IL-33 monoclonal antibodies in clinical trials at Phase I/II. We added the description in the last paragraph of 4.4 part: To be noted, there are at least two anti-IL-33 antibodies (SAR440340 and MEDI3506) being developed to treat Chronic Obstructive Pulmonary Disease, moderate-to-severe asthma, and chronic bronchitis in clinical phase I and II trials (NCT03387852, NCT03546907, NCT04751487, NCT04570657, NCT04701983, and NCT04631016). Thus, it suggests that the blockade strategy using anti-IL-33 antibodies will has the potential and the

prospect for treatment of human cancer including CRC where IL-33 plays the pro-tumorigenesis role.

5. The potential role of IL-33 in regulating tumor initiating cells has been reported, as well as the impact on stem cell– niche interactions. (Taniguchi et al Science 2021), this new highlight could be further integrated into the review, linking to CRC prospects.

Response: Thanks for your suggestion. We read the highlighted paper published in Science (Taniguchi S, Elhance A, Van Duzer A, Kumar S, Leitenberger JJ, Oshimori N. Tumor-initiating cells establish an IL-33-TGF-beta niche signaling loop to promote cancer progression. *Science* 2020) and learnt the new knowledge about IL-33. We added the description in the part 3.1: More importantly, Taniguchi et al. reported that the potential role of IL-33 in regulating tumor initiating cells (TIC), as well as the impact on stem cell-niche interactions, which is necessary for tumor progression, and highlight the new role of IL-33 in promote CRC stemness and carcinogenesis.

Minor pointes:

1. There are still some mistakes about language and typos, the authors are suggested to optimize the manuscript completely The expression like: 'Generally speaking', 'type-II disbetes', 'Recent research progress seem to provide' …. in the context, has to be avoided.

Response: Thanks for your suggestions. We revised these mistakes about language and typos throughout the manuscript.

2. Be consistent with the space before the citation, some have, some did not have, please update that accordingly.

Response: We have appreciated your work. We checked the format of the citation, and update the space before the citation. There is not a space between the word and the citation. Please check the revised manuscript.

3. A summary of abbreviations will be appreciated.

Response: Thanks for your suggestion. We listed the summary of abbreviations. Please check the revised manuscript.

To Science Editor:

(1) The "Author Contributions" section is missing. Please provide the author contributions;

Response: Thanks for your remind. We provide the author contributions. Please check the revised manuscript.

(2) The authors did not provide the approved grant application form(s). Please upload the approved grant application form(s) or funding agency copy of any approval document(s);

Response: We upload the approved grant application form.

(3) The authors did not provide original pictures. 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;

Response: We provide the original figure and the PowerPoint files.

(4) PMID and DOI numbers are missing in the reference list.

Response: We updated the reference PMID and DOI, and renewed the reference list according to the journal style.