Cover Letter

Dear Editors and Reviewers,

Thank you very much for taking the time to review this manuscript. We truly appreciate all your valuable comments and suggestions. We hereby submit the revised manuscript to be considered for publication in the World Journal of Gastroenterology. We have addressed all the questions and provided a point-by-point reply, which is attached to the end of this letter.

Here, I confirm that all authors who contributed significantly to the work have read and approved the manuscript and that the manuscript has not been published and is not being considered for publication elsewhere. Thank you again for your consideration. Looking forward to your reply.

Sincerely,

Shukun Yao

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Replies to Editors' Comments

#Company editor-in-chief:

I have reviewed the Peer-Review Report, the full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Gastroenterology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. Before final acceptance, uniform presentation should be used for figures showing the same or similar contents; for example, "Figure 1Pathological changes of atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ...". Please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file. Please authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content. Please check and confirm whether the figures are original (i.e. generated de novo by the author(s) for this paper). If the picture is 'original', the author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2023. Before final acceptance, when revising the manuscript, the author must supplement and improve the highlights of the latest cutting-edge research results, thereby further improving the content of the manuscript. To this end, authors are advised to apply a new tool, the Reference Citation Analysis (RCA). RCA is an artificial intelligence technology-based open multidisciplinary citation analysis database. In it, upon obtaining search results from the keywords entered by the author, "Impact Index Per Article" under "Ranked by" should be selected to find the latest

highlight articles, which can then be used to further improve an article under preparation/peer-review/revision.

Reply: Thank you very much for your helpful suggestions. In the revised manuscript, we have revised the abstract, main text, tables and figures according to the revision requirements.

#Science editor:

Language Quality: Grade B (Minor language polishing)

Scientific Quality: Grade B (Very good).

Reply: Thank you very much for your helpful support.

Replies to Reviewers' Comments

#Reviewer 1:

Q1. Wang and colleagues report on LILRB2 as a promising therapeutic target and noninvasive screening biomarker for colorectal cancer. The manuscript assesses the presence of the LILRB2 protein and its ligand ANGPTL2 in CRC tissue along with the impact of overexpression on differentiation metastasis and prognosis in CRC. The manuscript also highlights the potential of LILRB2 for screening purposes. The manuscript subject is novel, and the paper is well written, with clear objectives, methods, discussion and conclusions supported by the data presented.

R1. We truly appreciate your help comments. Thank you.

Q2. My main concern involves the figures, specifically figures 1, 3 and 4. Consistent use of asterisks between figures should be encouraged and they should represent the same across figures. For example, 3 asterisks appear to represent a significance of p <0.001 in figures 1 and 4. However, the 2 asterisks represent 2 different values in figures 4C and 4D. An explanation of what the asterisks stand for in Figures 4A-D would add clarity for the reader.

R2. We apologize for the missing explanation of what the asterisks stand for in the figures. ***P<0.05, **P<0.01, *P<0.05. We have added corresponding notes at the end of Figure 1 and Figure 4. Please refer to the revised manuscript with tracked changes.

Q3. Another item in the discussion needs to be mentioned. At the end of the 3rd paragraph of the discussion the final sentence mentions that LILRB2 is overexpressed hepatocellular and breast cancer. This finding needs to be addressed as a limitation as then LILRB2 levels could be confounded by the presence of 2 tumors concurrently. The point about further study of LILRB2 in both hepatocellular and breast cancer is well taken.

R3. Thank you very much for your valuable suggestion. We have further

explained this limitation in the discussion part as suggested:

- Discussion: "Furthermore, LILRB2 levels could be confounded by the presence of other tumors concurrently, such as NSCLC, hepatocellular and breast cancer, which needs to be excluded."

#Reviewer 2:

Q1. The study of Wang QQ et al. investigated LILRB2 and its ligand, ANGPTL2 in CRC patients, healthy controls and adenoma patients. The study is well designed, the language of the article is very good, the presentation of data and figure quality is excellent.

R1. Thank you very much.

Q2. Correlation is used very often in Results to present relationships/associations. The reviewer suggests that the authors use other terms and use the word correlation only for the Spearman and Pearson tests.

R2. Please accept our apology for inappropriate words and misunderstanding caused. We have replaced "correlation" with "association", and the "correlation" is used only for the Spearman or Pearson analysis. Please refer to the revised manuscript with tracked changes.

Q3. "Confirming that serum LILRB2 level is associated with tumour burden in CRC." This statement should be a refined. To prove this claim, the authors should have performed several measurements after the surgical removal of the tumor, including when progression, recurrence, etc. occurs.

R3. Thank you very much for your suggestion. This is indeed important for our results. We have revised the discussion part as suggested, please refer to the revised manuscript with tracked changes.

Q4. "Another source is hypothesized to be CRC-associated immune cells because tumorigenesis is closely related to the chronic inflammatory state in

the body and during tumour development, chemotaxis and infiltration of myeloid cells, including neutrophils, dendritic cells, and tumour-associated macrophages, which are common cell types with LILRB2 expression." Similar to the above, please refine. Authors collected postoperaitve blood within 24 hours of the surgery. This time is not enough for the immune cells to be properly "cleared" from the circulation.

R4. Thank you very much. Similar to above Q3 comment, we have revised the discussion part as suggested:

- Discussion: "However, considering the half-life of protein, the time is not long enough to detect the serum LILRB2 concentration only 24 hours after operation, and this is also not long enough for the immune cells to disappear gradually from circulation. Therefore, follow-up after the surgical removal, including measurements of the serum LILRB2 concentration, circulating tumor cell load and immune cell infiltration, is necessary. It is more meaningful that the serum LILRB2 decreases after 2 weeks or longer of follow-up and increases when the tumor progresses or recurs."

Q5. In Table 1, percentages should be calculated for the subgroups (columns), and not for the rows. E.g., in the case of age, instead of this: 4(44.4%) 5(55.6%) 15(30.6%) 34(69.4%) calculate this: 4(4/19 in %) 5(5/39 in %) 15(15/19 in %) 34(34/39 in %) The prevalence rates of the parameters in each group are more useful information for a clinician than the data presented by the authors in the current version.

R5. We really appreciate your comment. This has greatly improved the article. We have recalculated and revised the percentages in Table 1. Please refer to the revised manuscript with tracked changes. Thanks again.