

Dear Editor and Reviewer:

We sincerely appreciate your letter and the reviewer's comments regarding our manuscript entitled " Novel insights into SLC16A8 in colorectal cancer" (NO: 112894). These comments are of great value and very helpful for revising and improving our work.

We have seriously considered the comments of the reviewer and have made corresponding corrections. All changes are highlighted in **Yellow** in the revised manuscript. The main corrections in the paper and the responses to the reviewer's comments are listed below:

Reviewer #1:

1. Comments: • *Title: concise and interesting.* • *Abstract: good, but can be expanded because it is not informative enough: - Suggestion: Briefly summarize: Why the topic is important & The key contribution of the original paper* • *Core tip: good and clear.*

1. Reply: I am truly grateful for your invaluable suggestions. In the revised manuscript, we have added the content of the abstract section to better highlight the key contributions of the original paper and emphasize the significance of this topic. The modified parts have been marked in yellow font.

2. Comments: • *Main text: I think it needs more references related to the topic.* • *Limitation: Add a sentence on how these limitations can be addressed in future studies.*

2. Reply: Thank you very much for your professional and detailed comments. To enrich the content of the article, we have added references related to the topic. In response to the limitations of the article, we have added the limitations of the original paper and also supplemented effective ways to address these limitations in future research.

3. Comments: • *Language and style: - Avoid phrases like "highly enlightening," "outstanding insights," which sound promotional rather than academic.* - *Replace with objective statements: "The study provides valuable evidence supporting..."*

3. Reply: I am sincerely and deeply appreciative of your invaluable comments regarding the introduction section. Based on your opinions, we have changed some subjective descriptions in the article to objective academic terms.

Reviewer #2:

1.Comments: *However, the manuscript requires revisions to enhance the depth and rigor of the commentary, especially in addressing the limitations of the original study. The commentary should delve deeper into the limitations of the original study, particularly its reliance on siRNA knockdown as the sole method for validating the findings. While siRNA is a common approach, it does not provide conclusive evidence of causality or comprehensive insights into the physiological roles of the gene in question. The manuscript should explore how these limitations might impact the reliability of the conclusions drawn, such as whether the observed effects are truly representative of the gene's function in CRC.*

1.Reply:I am truly and profoundly grateful for your highly constructive comments.In view of the limitation that only siRNA was selected in the article to verify the experimental results, we analyzed the deficiencies and limitations of the siRNA approach. Its transient inhibitory effect and potential off-target risk directly affect the reliability of the experimental results and the experimental conclusion. In the limitations section, we have marked this content in yellow.

2.Comments: *Additionally, the small sample size of the study poses a concern regarding the generalizability of the results. The authors should discuss how these factors may affect the broader applicability of the conclusions in clinical practice and the need for further validation in larger, more diverse cohorts.*

2.Reply:Thank you for your constructive comments. The small sample size of animal studies in the original paper may produce false negative results, and the single-center cohort study of CRC specimens cannot prominently reflect the molecular heterogeneity characteristics of the colorectal cancer population. We discussed the limitations of the original paper for this part and offered our opinions.

3.Comments: *Moreover, the structure and content should be expanded to incorporate the latest research advances in SLC16A8 and its role in other cancers or in metabolic processes outside of CRC. This would*

provide a more comprehensive context for understanding the broader implications of the findings. The manuscript's outline should be updated to reflect these new themes, ensuring the review aligns with the evolving scientific landscape.

3.Reply: Thank you very much for the heads up. To better demonstrate the broad significance of the SLC16A8 target, we have added a new study on the role of SLC16A8 in breast cancer tumors and clear cell renal cell carcinoma.

4.Comments: *Lastly, the "Core Tip" should be more concise and focused on the key takeaways of the commentary. It should succinctly summarize the main findings and their clinical relevance. Although the overall writing style is fluent, there is room for improvement in clarity and wording, particularly in sections that discuss complex molecular mechanisms. A comprehensive review and revision of the entire text is necessary to address these issues and improve the manuscript's overall quality.*

4.Reply: I sincerely appreciate the time and effort you have dedicated to this review. In the revised article, we simplified "Core Tip" and condensed it into two sentences, focusing on the dual mechanisms and clinical translational potential of SLC16A8. To enhance clarity: We reorganized the description of molecular mechanisms and used more straightforward language to explain the parts of complex molecular mechanisms.

Editorial Office's comments

(1) Science Editor:

1 Scientific quality:

1.Comments: *Summary of the Peer-Review Report: The subject is interesting. However, the following problems still need to be solved. (1) The commentary should delve deeper into the limitations of the original study; (2) The manuscript should explore how these limitations might impact the reliability of the conclusions drawn; (3) The structure and content should be expanded; and (4) Add a sentence on how these limitations can be addressed in future studies.*

1.Reply: We fully agree with your point of view. It is crucial to have an in-depth discussion on the limitations of the research and its impact on the conclusion. For this reason, we have added a new paragraph in the discussion section specifically to delve into the limitations of this study. The modified parts have been highlighted in yellow. This modification directly responds to your first and second opinions, not only listing the limitations but also deeply analyzing how they potentially affect the

reliability and extrapolation of our conclusion. Thank you for suggesting that we expand the structure and content of the manuscript. We have sorted out and expanded the full text. We have also polished the language throughout the text to ensure that the logic is clearer and the expression is more accurate. Regarding the fourth point of opinion, it makes our research more forward-looking. We have added sentences about future research directions at the end of the discussion section. This modification directly indicates the specific methods to address the current limitations, providing a clear roadmap for subsequent research.

2 Specific comments

1.Comments: *Country/Territory of origin: China.*

1.Reply: We confirm that the country of origin for this study is China. This information has been duly noted and is correctly reflected in our manuscript and submission system.

2.Comments: *Please provide the latest language certificate after Return the Manuscript to Author for Revision.*

2.Reply: We thank the reviewer for this note. Although the language was graded ‘B (Very good)’, we have taken further steps to ensure the highest linguistic standards. Our manuscript has been professionally edited by Wallace Academic Editing. The Certificate of Editing is provided along with this response.

3.Comments: *Except for capitalization of the first word, all other words are represented in lowercase.*

3.Reply: We have strictly followed this requirement. The title has been changed to: “Novel insights into SLC16A8 in colorectal cancer”.

4 & 5.Comments: *Author names (unabbreviated) should be given as first name, middle name initial (with no period) and family (sur)name, and typed in bold with the first letter of each capitalized. Author names should be written out first (as first name, middle name initial (with no period) and family (sur)name; with a hyphen included between the syllables of Chinese names) and typed in bold, followed by a comma and the complete name of the affiliated institution, city, province/state, postcode and country typed in non-bold.*

4 & 5.Reply: We have meticulously revised the format of all author names throughout the manuscript as instructed. All Chinese names now include a hyphen between syllables and are typed in bold. The affiliated institutions following the names are now in non-bold font. The format now matches the provided examples exactly.

6.Comments: *The 'Author contributions' passage describes the specific contribution(s) made by each author. The author's names will be listed in the following format: full family (sur)name, followed by abbreviated first and middle names.*

6.Reply: The 'Author contributions' section has been rewritten according to the specified format. Each author is now listed with their full surname followed by the initials of their given and middle names.

7.Comments: *The 'Key words' list will provide 5-10 keywords that reflect the main content of the study.*

7.Reply: We have revised the keywords. We now provide 6 keywords that accurately reflect the main content of our study.

8.Comments: *In order to attract readers to read the full-text article, we request that the first author make an audio file describing the final core tip. This audio file will be published online, along with the article. The author can invite English language editing company to assist in resolving the language issues of Audio Core Tip.*

8.Reply: We have complied with this request. We have worked with the English editing company to prepare and polish the script for the Audio Core Tip.

9 & 10.Comments: *The name of the author(s) of a reference is listed in the sentence, the reference number should be placed immediately after the author(s) of the reference. Please remove "[]" from the reference list number. Please provide the PMID numbers (<https://pubmed.ncbi.nlm.nih.gov/>) and DOI citation numbers (<https://doi.crossref.org/simpleTextQuery>) to the reference list and list all authors of the references. If a reference has no PMID and DOI, please provide the source website address of this reference.*

9 & 10.Reply: We thank the reviewer for these critical comments. We have checked the entire text to ensure that when an author's name is mentioned, the reference number is placed immediately after it. We have used the recommended "Edit References by Auto-Analyser" tool to re-format and check the entire reference list. The square brackets "[]" around the reference numbers in the list have been removed. We have added PMID numbers and DOI citation numbers for all applicable references.

11.Comments: *The WJGO article which this editorial discussed has not been listed in the references list. Please add the WJGO article which this editorial discussed into the main text and references list <Tian HP, Xiao ZX, Su BW, Li YX, Peng H, Meng CY. Impact of SLC16A8 on tumor microenvironment and angiogenesis in colorectal cancer: New therapeutic target insights. World J Gastrointest Oncol 2025; 17: 99188 [PMID: 40235880 DOI: 10.4251/wjgo.v17.i4.99188]>.*

11.Reply: We apologize for this oversight. We have now added the following critical reference to the reference list: Tian HP, Xiao ZX, Su BW, Li YX, Peng H, Meng CY. Impact of SLC16A8 on tumor microenvironment and angiogenesis in colorectal cancer: New therapeutic target insights. World J Gastrointest Oncol 2025; 17:99188 [PMID: 40235880 DOI: 10.4251/wjgo.v17.i4.99188] .Furthermore, we have now cited this article in the main text.

We believe that our manuscript has been significantly improved after addressing all these points. Thank you again for your constructive comments.

(2) Executive Editor-in-Chief:

1.Comments: *Manuscript title. The title will concisely summarize the main topic of the study, being not overly long (no more than 18 words). Words such as 'exploration', 'research', 'analysis', 'observation', and 'investigation' are to be avoided. The title should not start with 'A', 'An', or 'The' and will not include any Arabic numbers or abbreviations. Please include the core key word in the title. If a title contains a colon, please capitalize the first letter of the first word after the colon. For example: Unexplained fetal tachycardia: A case report*

1.Reply: Thank you for your suggestion. We have made the required revisions to ensure conciseness (<18 words), avoid prohibited words, do not start with articles, have no numerical abbreviations, and include core keywords. The first letter after the colon should be capitalized.

2.Comments: *Running title: A short running title of no more than 6 words should be provided. Abbreviations are permitted. For example: Losurdo G et al. Two-year follow-up of HCC*

2.Reply: Thank you for your suggestion. We have provided a short header title of no more than six words.

3.Comments: *Author list. Author names (unabbreviated) should be given as first name, middle name initial (with no period) and family (sur)name, and typed in bold with the first letter of each capitalized. A hyphen should be included between the syllables of Chinese names. For example: Yi-Fan Chang, Jia-Jing Li, Tao Liu, Chong-Qing Wei, Li-Wei Ma, Vladimir N Nikolenko, Wei-Long Chang*

3.Reply: Thank you for your suggestion. In the revised article, the authors' names have been listed in bold in the "first name - last name" format, and hyphens have been added between the syllables of the Chinese names.

4.Comments: *Authors and institution(s): Author names should be written out first [as first name, middle name initial (with no period) and family (sur)name; with a hyphen included between the syllables of Chinese names] and typed in bold, followed by a comma and the complete name of the affiliated institution, city, province/state, postcode and country typed in non-bold.*

4.Reply: Thank you for your suggestion. We have checked that the names of each author and their complete information about the affiliated institutions (unit, city, postal code, country) have all been accurately listed, and the format meets the requirements.

5.Comments: *Co-first authors and co-corresponding authors. Designation of co-first authors and co-corresponding authors is permitted.*

5.Reply: Thank you for your suggestion. We have marked the co-first authors and/or corresponding authors as required and provided the necessary contribution descriptions. Only one contact person is listed.

6.Comments: *Author contributions: The 'Author contributions' passage describes the specific contribution(s) made by each author. The author's names will be listed in the following format: full family (sur)name, followed by abbreviated first and middle names.*

6.Reply: Thank you for your suggestion. We have described the specific contributions of each author in the format of "surname + initials of given name".

7.Comments: *Supportive foundations. If the manuscript has supportive foundations, authors must provide and specify the complete name(s) of the supportive foundation(s) and identification number(s) of grants or other financial support. Insert a semicolon (;) between funds, and end with a period (.).*

7..Reply: Thank you for your suggestion. The full names and numbers of all supporting funds have been provided, separated by semicolons.

8.Comments: *Corresponding author. The corresponding author's contact information will be provided in the following format: written out first name (with a hyphen included between the syllables of Chinese names), middle name initial (with no period) and family (sur)name, and typed in bold and ending with a comma, followed by the corresponding author's relevant honorifics (such as PhD, MD, Chief of Surgery, Assistant Professor, etc.) in bold. This is followed immediately by the affiliation (non-bold text), written out as complete name of the institution, street address, city and postcode, province/state, and country, and ending with a period. Immediately following the terminal period and a single space will be the corresponding author's E-mail address; this E-mail address must be issued by his/her institution. All the letters in the E-mail address should be typed in lowercase.*

8.Reply: Thank you for your suggestion. The complete contact information of the corresponding author (name, honorary title, address of the institution, email) has been provided in the required format.

9.Comments: *Abstract. An informative, unstructured abstract of no more than 150 words should accompany each manuscript. Abbreviations should be avoided, but if used should be spelled out at first mention.*

9.Reply: Thank you for your suggestion. We have provided an unstructured summary of no more than 150 words and avoided using undefined abbreviations.

10.Comments: *Key words. The 'Key Words' list will provide 5-10 keywords that reflect the main content of the study. Please do not use abbreviations for the keywords (e.g., Ulcerative colitis, not UC).*

The first letter of each keyword will be capitalized, and each keyword will be separated by a semicolon, with no terminal period.

10.Reply: Thank you for your suggestion. We have provided 10 keywords that reflect the core content of the research, ensuring that the first letter is capitalized, separated by semicolons, and there are no abbreviations.

11.Comments: *Core Tip. The Core Tip is a short paragraph that is independent of the content of the Abstract. The 'Core Tip' will provide a succinct summary of the study that outlines its most innovative and important arguments. This section should be less than 100 words. Abbreviations must be defined upon first appearance in the Core Tip. Do not use non-standard abbreviations, unless they appear at least two times in the text preceding the first usage/definition.*

11.Reply: Thank you for your suggestion. We have provided a core prompt that is independent of the abstract and no more than 100 words, summarizing the most innovative and important arguments of the research.

12.Comments: *Audio core tip. In order to attract readers to read the full-text article, we request that the first author make an audio file describing the final core tip. This audio file will be published online, along with the article. Please submit audio files according to the following specifications:*

Acceptable file formats: .mp3, .wav, or .aiff

Maximum file size: 10 MB

To achieve the best quality, when saving audio files as an .mp3, use a setting of 256 Kbps or higher for stereo or 128 Kbps or higher for mono. Sampling rate should be either 44.1 kHz or 48 kHz. Bit rate should be either 16 bit or 24 bit. To avoid audible clipping noise, please make sure that audio levels do not exceed 0 dBFS.

12.Reply: Thank you for your suggestion. The first author has recorded and submitted audio files that meet the specifications as required.

13.Comments:*Main text. The main text contains TO THE EDITOR/CORRECTION/ RETRACTION NOTE. The first level subtitles should be fully capitalized, bolded and underlined. For example: "TO THE EDITOR" Under the first-level subtitle, there can be several second-level subtitles. For*

formatting, capitalize the first letter for the first word; the subtitles are all in bold and italicized. For example: “Statistical analyses”.

There can be several third-level subtitles under the second-level subtitles. For these, the first letter of the first word is capitalized, and the full subtitles are bolded followed immediately by a colon. For example: “Mechanism of liver cancer: ...”.

13.Reply: Thank you for your suggestion. The formats of the main text and the first, second and third-level headings have all strictly followed the requirements of the journal.

14.Comments: *Units. Use SI units.*

For example: body mass, m (B) = 78 kg; blood pressure, p (B) = 16.2/12.3 kPa; incubation time, t (incubation) = 96 h; blood glucose concentration, c (glucose) 6.4 ± 2.1 mmol/L; blood CEA mass concentration, p (CEA) = 8.6 24.5 g/L; CO₂ volume fraction, 50 mL/L CO₂, and not 5% CO₂, likewise for 40 g/L formaldehyde, not 10% formalin; and mass fraction, 8 ng/g; etc. Arabic numerals such as 23,243,641 (i.e. 23 million, 243 thousand, and 641) should be written as 23243641, with no commas and no spaces.

14.Reply: Thank you for your suggestion. The entire text has uniformly adopted SI units, and the formats of numbers and units comply with the regulations.

15.Comments: *Standard abbreviations should be defined in the abstract and in the main body of the manuscript upon first mention in the text. In general, terms should not be abbreviated unless they are used two times or more and the abbreviation is helpful to the reader. Permissible abbreviations are listed in Units, Symbols and Abbreviations: A Guide for Biological and Medical Editors and Authors (Ed. Baron DN, 1988) published by The Royal Society of Medicine, London. Certain commonly used abbreviations, such as DNA, RNA, HIV, LD50, PCR, HBV, ECG, WBC, RBC, CT, ESR, CSF, IgG, ELISA, PBS, ATP, EDTA and mAb, do not need to be defined and can be used directly.*

15.Reply: Thank you for your suggestion. The abbreviation was defined at the time of its first appearance, meeting the requirements of usage frequency.

16.Comments: *Acknowledgements. Brief acknowledgements of persons who have made genuine contributions to the manuscript but do not qualify for authorship and who endorse the data and*

conclusions should be included. The Acknowledgments section should not include funding source, language editing companies, and other biomedical institutions providing paid services.

16.Reply: Thank you for your suggestion. The acknowledgments in the article only include individuals who have made substantial contributions to the research but do not meet the qualifications of collaborators, and do not include the sources of funds or commercial institutions.

17.Comments: *Reference numbers in the main text. The author should number the references in Arabic numerals according to the citation order in the text.*

The format for in-text citation of references should be [References Number], which should be with no space between “[]” and the preceding word. Example: The pathophysiology is thought to be due to an increased arterial flow that leads to secondary hepatocellular hyperplasia[1,2].

If the name of the author(s) of a reference is listed in the sentence, the reference number should be placed immediately after the author(s) of the reference. Example: Mandal et al[8] proposed that retractor aponeurosis disinsertion is the most likely cause of congenital low lid entropion.

In addition, please verify the order and total number of references cited to ensure that all references in the list are cited and in a correct numeric order.

17.Reply: Thank you for your suggestion. The References cited in the main text have all been marked in sequence in the format of "[References Number]", and the positions are correct.

18.Comments: *Authors should cite the references adequately and reasonably. Please verify the reference list of the manuscript according to the following key points:*

(1) All of the references in the manuscript should be consistent with or closely related to the subject of the manuscript. The manuscript should appropriately acknowledge the surrounding literature for the topic. Authors cannot cite any references which are unrelated to the subject of the manuscript and/or the context in which it is cited.

(2) Authors cannot cite their own published articles that are not relevant to the subject of the manuscript. If it's found that the manuscript includes any non-relevant references, the manuscript will be rejected immediately.

(3) References to important relevant articles published within the last 3-5 years should be included in the manuscript. Authors should check if any important references are missing from the manuscript's references list.

(4) Authors have the right to refuse to cite articles recommended by peer reviewers, unless the authors deem it necessary to cite and the recommended articles are very important articles closely related to the subject of the manuscript.

18.Reply: Thank you for your suggestion. All the cited literature is closely related to the theme of the manuscript and includes key literature from the past 3 to 5 years. There is no irrelevant or inappropriate self-citation.

19.Comments: *Edit References by Auto-Analyser. Authors should edit the references in their paper using the Auto-Analyser at <https://www.f6publishing.com/Forms/main/ArticleReferenceTool.aspx> to ensure the correctness of all reference information.*

19.Reply: Thank you for your suggestion. All references have been edited, proofread and formatted through the designated Auto-Analyser tool to ensure the accuracy of information and uniformity of format.

20.Comments: *Approved Grant Application Form(s) or Funding Agency Proposal's Approval Document(s). If the manuscript has supportive foundations, authors are required to upload the primary version (PDF) of the Supportive foundation's official approval, prepared in the official language of the authors' country to the F6Publishing system; for example, authors from China should upload the Chinese version of the document, authors from Italy should upload the Italian version of the document, etc. If not, delete those without supporting documents.*

20.Reply: Thank you for your suggestion. The manuscript has no supportive foundations.

21.Comments: *Conflict-of-Interest Disclosure Form. Authors should click and download the fillable ICMJE Form for Disclosure of Potential Conflicts of Interest (PDF), and fill it in. The Corresponding Author is responsible for filling out and uploading this form to the F6Publishing system.*

21.Reply: Thank you for your suggestion. The ICMJE Form for Disclosure of Potential Conflicts of Interest has been completed and uploaded to the F6Publishing system by the Corresponding Author.

Thank you again for your attention and comments on our paper. We hope that the corrections will be approved and look forward to hearing from you soon.

Sincerely,

Dr. Yanqi Dang
Institute of Digestive Diseases
Longhua Hospital
China-Canada Center of Research for Digestive Diseases
Shanghai University of Traditional Chinese Medicine