Dear Editors and Reviewers:

Thank you for your letter and for the reviewers' comments concerning our manuscript entitled "Obesity and cancer stem cells: roles in cancer initiation, progression and therapy resistance" (Manuscript NO.: 81896). These comments are all valuable and very helpful. I have studied the comments carefully. After reading these comments carefully, we revised our manuscript. The main responses to the reviewer's comments are as follows:

Reviewer #1:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: The review by Xie is discussing an important and novel topic, however, it seems the hypotheses which are proposed by the authors are not based on robust evidence and is only based on a few in-vitro or animal studies, or personal inferences of the authors.

Response:

Thank you for pointing out this limitation, which is also the aim of this review. Although the association between obesity and cancer has been robustly established and the important roles of CSCs in the initiation and progression of cancer have been investigated comprehensively, reports on the links between obesity and CSCs are still limited, and many of them are in vitro or animal studies. Therefore, we conducted this review not only to discuss the links between obesity and CSCs but also to point out the research status of this field for future considerations. Thus, we listed many personal inferences in this review. Is not that the purpose of this review, even some of them may be demonstrated to be incorrect in future studies?

Nevertheless, considering the importance of the topic, I agree with the publication of the paper after the following corrections:

1- Please add a definition of "cancer stem cells" and also explain "cancer stem

cells theory" in the introduction section.

Response:

Thank you for your suggestion. Although it is difficult to define the CSCs exactly, based on your comments, we described the attributes of CSCs in slightly more detail but avoided too much space to discuss a topic that has been reviewed elsewhere.

2- In the "OBESITY AND CSCs IN CANCER INITIATION" section and table 1, most of the cited references are discussing high-fat diets and not obesity. Although high-fat diet can be a risk factor for obesity, it is not equal to obesity and the results of these studies should not be mixed up.

Response:

As stated in the first response, data on associations between obesity and CSCs in cancer initiation are lacking not only in human cancers but also in other obesity models, such as the *ob/ob* model and obesity models induced by other diet styles. As a reliable and commonly used method to establish obesity models, HFD has naturally become the focus of this review. Therefore, we added a sentence "Currently, the majority of obesity models are induced by HFD; however, other dietary patterns, such as a high-sugar diet and Western-styled diet, have also been shown to be obesogenic, and the effects of these dietary patterns on the initiation of cancer warrant further studies. " to clarify this confusion.

3- Some sentences repeated along the text and should be removed (e.g. "The key roles of obesity in the activation of stem cell programs have attracted much attention in recent years"

Response:

Thank you for your comments. We have rechecked our writing of this manuscript to avoid describing the same meanings repeatedly. However, it may be difficult for the authors to find these flaws in manuscript wrote by themselves, as in their minds, they always write what they think is necessary. Therefore, if some type of such flaws is still retained, we hope you can accept

them if the didn't confuse the meanings of the content, thanks.

4- In many cases, the authors had a straightforward approach, and they ignored different discussions and points of view about a topic that should be corrected. Just a few examples: "obesity is always accompanied by hyperlipidemia" obesity is not always accompanied by hyperlipidemia, and many obese people are metabolically healthy (MHO). Or "surgical intervention does not guarantee the recovery of obese patients to a normal state and is typically a harmful method". Also, HFDs are not the only obesogenic diets and many studies show that high-carbohydrate diets are more obesogenic than HFDs and even low-carb HFDs (ketogenic diets) are widely used for weight loss. Moreover, regarding leptin and adiponectin different discussions exist.

Response:

Thank you for your comments. First, we need to discuss the different obesity-related diets. As stated previously, although the dietary behavior is far more complex in humans, in experimental conditions, we need to simplify them; therefore, many dietary methods have been established for obesity induction or weight loss, such as HFD, high-sugar diet, Western-styled diet, ketogenic diets, caloric restriction and fasting. However, as current available evidence on topic of this review is mainly from animal models induced by HFD, making HFD nearly equal to obesity in this review. Therefore, we added more discussion in the manuscript to clarify this confusion. Second, for topics without robust evidence or even discrepancies, such as leptin and adiponectin, it is difficult to delineate a comprehensive and accurate picture of them; thus, we only cited the findings related to this manuscript, letting these uncertainties as questions listed in the final section. Third, regarding the straightforwardness when some topics are expressed, some may result from the reasons listed in the "second", and some may result from nonnative English speakers of the authors. We have rechecked the manuscript and revised some of them, hoping that these revisions may meet the requirements. For example, "obesity is always accompanied by hyperlipidemia" was expressed as "the incidence of

hyperlipidemia is higher in obese populations".

5- It seems there are some spelling mistakes in the text and the revision of the paper is recommended (e.g. " Substantial studies have reported that obesity or HFD markedly affects the composition of the commercial microbiota, especially in the intestine").

Response:

Thank you for your valuable comment. We have revised the manuscript carefully and sent it for editing by AJE, a professional English language editing company.

Reviewer #2:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: It was very rewarding for me reading your review. I had almost no comments until the last two paragraphs. Please consider my comments there. I have tried to rewrite some of it. I suggest adding a short paragraph about the newer GLP-1 and GIP/GLP-1 medications. Both the content and layout as well as the language is great.

Response:

Thank you for your valuable comment. However, after searching the literature comprehensively, we did not find any reports on the effects of GLP-1 and GIP/GLP-1 medications on CSCs.

EDITORIAL OFFICE'S COMMENTS

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. Please visit the following website for the professional English language editing companies we recommend:

Response:

We have revised the manuscript carefully and sent it for editing by AJE, a professional English language editing company.

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. Please visit our RCA database for more information at: https://www.referencecitationanalysis.com/.

Response:

Based on this suggestion, we searched for related articles using the key words of this review, and we found no new reports that need to be supplemented.

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 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) 2022.

Response:

As the figures were created with BioRender.com, when they were transformed

into ppt, only the text portions were editable, and we hope that this format will meet the requirements. In addition, the publication and licensing rights of the figure were obtained and have been submitted with the figure.

We tried our best to improve the manuscript and made some changes in the manuscript. These changes will not influence the content and framework of the paper. We appreciate for Editors/Reviewers' warm work earnestly, and hope that the correction will meet with approval.

Once again, thank you very much for your comments and suggestions.

Yours sincerely,

Wenjie Xie, Jian Li