Reviewer 1:

Liver is the transfer station of nutrition and one of the main organs of lipid metabolism. It is of great value to elucidate the relationships between lipid metabolism and oncogenesis, progression and drug-resistance of hepatocellular carcinoma, which help to search for therapeutic targets. This manuscript summarized involvement of lipid metabolism-related molecules and signaling pathways in the occurrence and development of hepatocellular carcinoma and their impacts on tumor immune environment, and reviewed progress of researches combining lipid metabolism targeted reagents with tyrosine kinase inhibitors or immunotherapy, providing fresh light for subsequent further studies. This is one of the few reviews on lipid metabolism influencing target therapy and/or immunotherapy for hepatocellular carcinoma, and worth publishing.

We appreciate the affirmation and important comments from this reviewer. The lipid metabolism of HCC cells has undergone significant reprogramming, which affects tumors in different aspects such as energy metabolism and tumor immunity. Targeted therapy combined with immunotherapy is currently the first-line treatment for unresectable HCC in advanced stage[1]. From this review, we know that lipid metabolism has a significant impact on targeted therapy represented by lenvatinib and immunotherapy represented by anti-PD-1/PD-L1 drugs. It is a therapeutic strategy worth exploring to combine the drugs targeting lipid metabolism with existing treatment. We will carry out experimental and clinical research later to further explore the changes of lipid metabolism in HCC and its potential value in combined treatment of HCC.

Reviewer 2:

The article takes a look at the specific changes in HCC metabolism reprogramming lipid metabolism in hepatocellular carcinoma (HCC) and their implications for both HCC therapeutic approaches. Therapeutic strategies for HCC targeting lipid metabolism and how they can be rationally combined with targeted therapy or immunotherapy are also described. Of some value.

1 . As the metabolic pathways are very complex, it is suggested that some of the metabolic processes could be shown in diagrams

We appreciate the insightful suggestions of the reviewer. To improve the clarity of the metabolic pathways involved in this review, we drew two new simple metabolic flow charts, fatty acid metabolic pathway diagram (figure1a) and cholesterol metabolic pathway diagram (Figure 2a). In fact, the pathways discussed in this review also exist in the figure we originally drew, and the changes in these metabolic processes in HCC are also marked (Figure 1b, 2b). Thanks again for the valuable suggestion from this reviewer, which makes our review more organized.

2. and that the specific sites of action of the relevant drugs could be labelled on the diagrams for greater clarity.

We appreciate the important comments from this reviewer. We highly agree with the suggestion. Marking the action sites of drugs or reagents in the figure can make our review clearer. We

previously marked the sites of action in the figure drawn to describe the changes in lipid metabolism, which may not be obvious because of the elements we used. We have adjusted it to improve the clarity of action sites (Figure1b, 2b). Of note, to avoid redundancy, we did not show the action sites in the metabolic pathway diagram (Figure1a, 2a).

Reviewer 3:

In the manuscript (Manuscript ID: 82027) by Xiaochen Feng and colleagues entitled "Lipid metabolism of hepatocellular carcinoma impacts targeted therapy and immunotherapy", the authors summarized that the abnormal lipid metabolism in HCC and their prognostic impact on HCC patients. Furthermore, this manuscript reviewed the impacts of lipid metabolism on the current main drug treatment for HCC such as sorafenib, Lenvatinib, and cabozantinib. The topic is very interesting. However, the combination of atezolizumab and bevacizumab is currently the standard of care as first-line treatment for advanced HCC.

1. ***The authors should discuss as much as possible the impact of aberrant lipid metabolism on bevacizumab.***

We appreciate the quite important comments from this reviewer. This review discusses the impact of lipid metabolism on targeted therapy, mainly focusing on sorafenib and lenvatinib. At first, we thought about discussing the impact on the anti-angiogenesis drug bevacizumab, However, there is no research specializing in the impact of lipid metabolism on the efficacy of bevacizumab in the treatment of HCC. Some studies reported that bevacizumab can lead to the upregulation of the fatty acid transport related gene FABP when treating other types of tumors, which promotes the uptake and utilization of lipids by cancer cells. When FABP is inhibited, the tumor growth rate decreases more significantly[2]. Interestingly, another study reported that FABP5 can promote the angiogenesis of HCC by activating VEGF related pathways[3]. Therefore, targeting lipid metabolism related genes such as FABP may improve the therapeutic effect of bevacizumab on HCC. These contents are shown in detail from line 13 to line 24 on page 10 of the manuscript.

2. ***The authors should discuss as much as possible the impact of aberrant lipid metabolism on atezolizumab.***

We appreciate the quite important comments from this reviewer. This review discusses the impact of lipid metabolism on immunotherapy, mainly focusing on the impact of anti-PD-1 therapy. This review mentioned that the combination of FASN inhibitor and anti PD-L1 therapy doesn't have significant efficacy[4], but did not discuss the impact of other aspects of lipid metabolism on anti-PD-L1 therapy represented by atezolizumab. In HCC, FABP5 on tumor-derived monocytes activates the expression of PD-L1 on Treg cells through JNK-STAT3 pathway, thereby inhibiting tumor immunity. Therefore, FABP5 is negatively related to the prognosis of HCC patients[5]. In addition, other studies have shown that the combination of atezolizumab and bevacizumab has a good effect in the treatment of HCC with hepatic steatosis, which is related to the upregulation of PD-L1 induced by high palmitic acid in TME[6]. These contents are shown in detail from line 7 to line 16 on page 14 of the manuscript. In addition, to avoid repeated discussion, we deleted some original contents. Thank you again for this valuable suggestion, which makes our review more comprehensive.

EDITORIAL OFFICE'S COMMENTS

Authors must revise the manuscript according to the Editorial Office's comments and suggestions, which are listed below:

(1) Science editor:

The manuscript has been peer-reviewed, and it' s ready for the first decision.
Language Quality: Grade B (Minor language polishing)
Scientific Quality: Grade C (Good)

We appreciate the evaluation of our review from the science editor. The manuscript has been carefully modified. To improve the language quality of the review, we polished the language of the review, using more fluent sentences to make the manuscript more concise, clear and organized. In addition, we contacted a professional English language editing company for further polishing. The materials submitted this time are attached with a new polishing certificate. To improve the scientific quality of the review, we supplemented and polished the content of the article. According to the suggestions put forward by the review, we added some contents to discuss the influence of lipid metabolism on the current first-line treatment and its potential therapeutic value. To make the content clearer, we also drew a metabolic pathway diagram (Figure1a, 2a) for the metabolic process involved in the review, and modified the previously drawn figures of changes in HCC lipid metabolism, making the important action sites more obvious.

(2) Company editor-in-chief:

I have reviewed the Peer-Review Report and the full text of the manuscript, all of which have met the basic publishing requirements of the World Journal of Gastrointestinal Oncology, 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.

1. ***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: https://www.wjgnet.com/bpg/gerinfo/240.***

We appreciate the quite important comments from the editor-in-chief. The quality of the English language is very important for a manuscript. Firstly, we carefully polished the language of the manuscript by ourselves, using more proper vocabulary and coherent sentences to make the review more concise and comprehensive. Then, we also contacted a professional English language editing company to help us further polish the language. The materials we submitted this time include a new English Language Certificate.

EDITORIAL CERTIFICATE.pdf

2. ***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/.***

We appreciate the kindly suggestion from the editor-in-chief. To make the content of our manuscript more abundant and novel, we discussed more cutting-edge research results: (1) from line 13 to line 24 on page 10 of the manuscript (2) from line 7 to line 16 on page 14, and cited more high-quality literature (reference 65-67, 93-95). We also appreciate your recommended database, the Reference Citation Analysis (RCA). This database is very powerful and practical. It not only helps us download some articles conveniently, but also automatically rank them in order of importance, which greatly saves our time. We will recommend this useful database to other researchers, hoping them also benefit from it.

3. ***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: ...".***

We appreciate the kindly suggestion from the editor-in-chief. We checked the description part of the figures to make sure that uniform presentation was used. In addition, we checked the body part of the manuscript to ensure the consistency of the contents. Thank you for your reminding.

4. ***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.***

We appreciate your suggestion and detailed explanation. We provide composable Figures according to your requirements. Of note, the drawing software we originally used can only export the final complete figure, and cannot provide separate components. Therefore, we used Adobe Illustrator to carefully split the elements of the figure, and rearrange them in PowerPoint (PPT). All figures are original, and we have added the copyright information to the bottom right-hand side of the picture in PPT.

Reference

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