

Please provide specific point-to-point replies to each reviewer's comments.

Response to Reviewer #1:

[Comment 1] In the introduction section, the authors described that liver cancer mainly includes hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC), and the two types of liver cancers may have different tumor microenvironments (TMEs). However, the article showed the TME and its roles in HCC progression. Therefore, the authors should describe these findings on ICC.

[Answer 1] This is a valuable comment. Thank you for raising the question of the proportion of different types of liver cancer in this manuscript. Indeed, there are several pathological types of liver cancer sharing the same liver microenvironment despite of the different origins of cancer cells, which leads to lots of similarities among these types. In addition, HCC accounts for more than 90% of liver cancer. That's why we spent much time in describing the characteristics of this representative type of liver cancer. However, the manuscript still contains some special issues for ICC, such as IDHs and FGFR mutations, to help readers understand the possibly distinct TME characteristics of ICC.

[Comment 2] In the introduction section, on line 5, HCC is an abbreviation.

[Answer 2] Thank you for your careful work. We have modified the mistake in the revised manuscript.

[Comment 3] In the reference section, ref number 138, there was no name of journal.

[Answer 3] We are sorry for this careless mistake. The journal name has been added in the revised manuscript.

Response to Reviewer #2:

[Comment 1] The paper too detailed for the average reader and I would encourage the authors to make efforts in order to summarize and to avoid repetition of some pathophysiology concepts.

[Answer 1] Thank you for this comment. We realized that some parts of the manuscript, *e.g.*, the macrophages immunometabolism part, are redundant to

some extent. Hence we make some efforts on simplification and hope the revised manuscript can be a concise and informative version.

[Comment 2] In addition, the authors may consider to emphasize on what are the most attractive molecules to be further investigated as therapeutic drug targets, as well as if any of them are already under investigation in randomized trials. A dedicated table would be welcomed here to delineate future directions.

[Answer 2] We sincerely appreciate this valuable suggestion. A table (Table 1) about immunometabolic therapies for cancers has been added in the revised manuscript. These molecules are currently most attractive ones, and some of them have been under preclinical or clinical investigations.

Response to Reviewer #3:

[Comment 1] minor grammatical/typographical errors

[Answer] Thank you very much to point out the grammatical and typographical errors. We have corrected the error in the revised manuscript. In addition, we have applied professional scientific editing for language polishing of our manuscript.