We are pleased to see a high level of enthusiasm for our paper. We thank the reviewers and the editor for their valuable comments and insightful suggestions. We have considered each of them carefully and made extensive modification of the original manuscript accordingly. Moreover, we have gone through the paper thoroughly to ensure clarity of language and correct all the grammatical errors.

Reviewer #1:

It is a decent review. There are a few suggestions for enhancing the manuscript.

1. Minor 1. Please correct grammar and formatting throughout the manuscript.

We have gone through the paper thoroughly and corrected all the typos and grammatical errors.

2. Major: 1. Please include this article in the discussion Chen Yang et al. Metabolism-associated molecular classification of hepatocellular carcinoma, Mol Oncol. 2020 Apr; 14(4): 896–913.Published online 2020 Jan 29. doi: 10.1002/1878-0261.12639. PMCID: PMC7138397; PMID: 31955511

We have cited the work of (Chen et al., 2020) by adding a new paragraph to discuss the utility of metabolism to classify HCC into subclasses.

Page 13, line 13-18: "Apart from tumor diagnosis and treatment, the metabolism can also be used to classify HCCs into subtypes. A study proposed three subclasses of HCC with active, intermediate, or exhausted metabolic activities, which not only verified the heterogeneity of HCC from the metabolic landscape, but also implied possible prognosis and potential response toward metabolic therapies"

3. Does the scope of review include the component of Proteogenomics impacting Metabolomics? If yes then it may be included in the discussion and plenty of data is available regarding the same

Our current review maintains a specific focus on metabolomics and metabolism related basic research, and consequently the discussion of Proteogenomics impacting Metabolomics is a little beyond the scope of the current review. But it would be a major focus in our next work.

Reviewer #2:

This paper presents a review of metabolic traits of Hepatocellular carcinoma (HCC) with a focus on alterations on glycolysis, lipid metabolism and glutamine addiction. It then highlight some routes to develop biomarkers and therapies. This is a well-written and very informative paper that reaches its goal with regards to the specific HCC characteristics.

We thank the reviewer for the positive comments and careful read of our manuscript.

1. page 6, line 4: the use of the expression "metabolic reprogramming" is more and more debated in the very recent literature, for example in Medina, BioEssays 2020 (https://onlinelibrary.wiley.com/doi/10.1002/bies.202000058) or Jacquet et al. Biology 2021 (https://www.mdpi.com/2079-7737/10/2/129). One reason is that this expression is used to cover many different meanings. Instead of "metabolic reprogramming", "metabolic alterations" might be a good alternative.

We agree with the reviewer, and have now replaced "metabolic reprogramming" with "metabolic alterations".

2. page 6, line 7: it is wrong to associate the "Warburg effect" to "aerobic glycolysis". This is not the definition originally given by Otto Warburg in his 1956 paper since he only noted an enhanced production of

lactate independently of the presence of oxygen. The original observation by Warburg has progressively drifted with time to be limited to “aerobic glycolysis” due to the propagation of this shortcut. page 6, line 5: replace “Warburg effect” by “aerobic glycolysis” if this is what you mean to avoid any confusion. And also replace “suitable environment” by “suitable mechanism” (or something similar). page 12, line 3: I would replace “metabolic reprogramming” by “metabolic alteration” page 13, line 14: what is AAD ? page 24, line 2: trials instead of trails (2 occurrences) page 27, line 11: I would replace “energy reprogramming” by energy alteration or changes page 29, line 4: the field instead of filed ?

We agree with the reviewer, and have now replaced “Warburg effect” with “aerobic glycolysis”, and replaced “suitable environment” with “suitable mechanism”.

Typos have been corrected.