Response Letter

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What are the Changes in the Hotspots and Frontiers of miRNA in Hepatocellular Carcinoma Over the Past Decade

Lu Zhang, Zu-Yuan Chen, Xiao-Xian Wei, Jian-Di Li, Gang Chen*
Department of Pathology, First Affiliated Hospital of Guangxi Medical University, 6 Shuangyong Road Nanning, Guangxi Zhuang Autonomous Region 530021, PR China.
*Corresponding author: Gang Chen, chengang@gxmu.edu.cn

Dear editors:
We would like to sincerely thank you and the reviewers for reviewing our manuscript. The suggestions are all valuable and very helpful for improving our paper, as well as the important guiding significance to our researches. We have studied comments carefully and have made corrections which we hope meet with approval. Below are the point-by-point responses to each comment. Our responses are italicized and in blue.

Reviewer #1:
Scientific Quality: Grade B (Very good)
Language Quality: Grade B (Minor language polishing)
Conclusion: Minor revision
Specific Comments to Authors: In this manuscript, the authors aimed to perform a comprehensive analysis of recent research concerning miRNAs in hepatocellular carcinoma (HCC). All relevant publications were retrieved and, overall, a total of 9,426 publications on this topic were selected. According to the keywords analysis, the researches of miRNAs focused on their expression level, the effects and mechanisms on the biological behavior of HCC. Keywords bursting analysis showed that in the early years (2013–2017), “microRNA expression”, “gene expression”, “expression profile”, “functional polymorphism”, “circulating microRNA”, “susceptibility” and “mir 21” et al. started to raise attention. In the latest phase (2018–2022), the hot topics were “sorafenib resistance”, “tumor microenvironment” and so on. They thus concluded that the study would provide a comprehensive overview for the researches of miRNAs in HCC based on bibliometric analysis ranging from miRNAs expression level, the effects, and mechanisms on the biological behavior of HCC, to sorafenib resistance, tumor microenvironment and so on. The study is of interest, however, in my opinion, the authors should tried to focus their research on the topic now of

major clinical impact. miRNA in HCC development as well as treatment response/resistance, have been extensively studied. However, with the recent increasing development of systemic treatments, the authors should disucss the recent evidence supporting the higher anti-tumor efficacy of combination treatment strategy based on the combination of tyrosine kinase inhibitor plus immune checkpoint inhibitors as well-described in a recent comprehensive review addressing the improved efficacy and overall survival and safety profile of combination (TKI plus ICI) treatments, as recently reported (TKIs in combination with immunotherapy for hepatocellular carcinoma. Expert Rev Anticancer Ther. 2023 Mar;23(3):279-291).

Reply: *We are very grateful to your professional review work on our research. According to your valuable suggestion, we have added to the discussion on this topic on page 14 as follows:*

At present, systemic therapy has become the standard therapy for unresectable HCC in the middle and late stages. Small molecule antiangiogenic targeted drugs (TKIs) and immune checkpoint inhibitors (ICIs) are the main systemic therapy options. The combination of the two often has a synergistic effect and improves the prognosis of HCC patients. During the use of these systems for treatment, changes in miRNA expression profiles and levels in HCC patients may have important value in predicting drug efficacy, drug-related adverse events and prognosis[66].

-To improve the clinical significance I would suggest to recall and discuss the following 2 topics both related to miRNA: 1) recent studies addressed the different miRNA profile in hepatocarcinogenesis according to the underlying liver disease which are now changing in the changing scenarion of HCC as recently demonstrated in a largen cohort of HCC patients (). This important epidemiological issue should be recalled and discussed.

Reply: *Thank you very much for your suggestions. We have added to the discussion on the different miRNA profile in hepatocarcinogenesis on page 12 as follows:*

Existing preclinical studies and clinical trials have discovered different miRNA profiles in hepatocarcinogenesis. For example, miR-122 and miR-34a play important roles in hepatic lipid metabolism, which is associated with HCC[39, 40]. miR-122 also has important roles in hepatic inflammation, as do miR-132 and miR-155[41-43]. miR-21 can mediate the activation of hepatic stellate cells via the PTEN/AKT pathway during hepatic fibrosis[44]. Hepatitis B virus (HBV) is the most common cause of HCC in China, and the miR-99 family can promote HBV replication, while miR-199-3p and miR-201 can suppress HBV replication[45, 46]. A cohort study suggested that miR-221 and miR-222 play pivotal roles in the progression of liver

fibrosis due to persistent hepatitis C virus (HCV) infection[47]. Another study demonstrated that miR-182 is associated with alcoholic hepatitis[48].

2) regarding the resistance to sorafenib and the safety profile, the authors should discuss the clinically relevant topic related to the need of predicitve marker able to identify patients responding to sorafenib and other systemic therapies as well as marker able to predict treatment-related adverse events since it has been recently demonstrated that optimal management od adverse events and improvements of theri managment translates into longer patient overall survival, as recently demonstrated (Management of adverse events with tailored sorafenib dosing prolongs survival of hepatocellular carcinoma patients. J Hepatol. 2019 Dec;71(6):1175-1183.).

Reply: *Thank you very much for your kind suggestions, which are helpful in improving our study. We have added to the discussion on this topic on page 14 as follows:*

Studies have explored various relationships between miRNAs and sorafenib. For example, miR-23a-3p contributes to sorafenib resistance in HCC by regulating ferroptosis[62]. miR-10b-3p can be a biomarker for predicting sorafenib efficacy[63]. miR-494-3p promotes sorafenib resistance in HCC cells by targeting PTEN[64]. Wang et al. found that compared with patients with HCC treated with sorafenib, patients treated with lenvatinib developed 3 differentially expressed miRNAs, including miR-548ah, miR-888 and miR-196a-1[65]. Wang et al. further investigated the adverse events of sorafenib and lenvatinib and found that the patients in the sorafenib group and lenvatinib group developed different frequent symptoms, such as hypertension, diarrhoea and hand-foot skin reactions[65].

We sincerely thank you once again for your valuable suggestions on our manuscript. Your suggestion has greatly improved our research. Thank you very much for your time and consideration.

Yours Sincerely,
From: Prof. Gang Chen MD, PhD
Department of Pathology
First Affiliated Hospital of Guangxi Medical University
6 Shuangyong Road
Nanning, Guangxi Zhuang Autonomous Region, China 530021
Tel: 0086-771-5356534
Fax: 0086-771-5356534
E-mail: chengang@gxmu.edu.cn