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PEER-REVIEW REPORT

Name of journal: *World Journal of Gastrointestinal Oncology*

Manuscript NO: 90602

Title: LncRNA HAND2-A ultrasound microbubbles suppress hepatocellular carcinoma progression by regulating the miR-873-5p/TIM axis

Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 06195974
Position: Editorial Board
Academic degree: MD, PhD
Professional title: Assistant Professor
Reviewer's Country/Territory: United States
Author's Country/Territory: China

Manuscript submission date: 2023-12-08

Reviewer chosen by: AI Technique

Reviewer accepted review: 2023-12-09 00:34

Reviewer performed review: 2023-12-20 19:24

Review time: 11 Days and 18 Hours

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Novelty of this manuscript	[Y] Grade A: Excellent [ ] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No novelty
Creativity or innovation of this manuscript	[Y] Grade A: Excellent [ ] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No creativity or innovation

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Scientific significance of the conclusion in this manuscript	[Y] Grade A: Excellent [ ] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No scientific significance
Language quality	[Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous
	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

This is an interesting study investigating the role of UTMB-mediated HAND2-AS1 in hepatocellular carcinoma (HCC) progression. Qiang Zou and colleagues delivered HAND2-AS1 into HeGp2 HCC cells by UTMBs and found that UTMBs carrying HAND2-AS1 suppressed the cell invasion, proliferation and EMT. Their findings would indicated that HAND2-AS1 suppressed the MMP2/MMP9 signalling pathway and then suppressed tumour progression by upregulating TIMP2 via targeting miR-873-5p. Of interest, in vivo results demonstrated that tumour formation was inhibited in xenograft mice injected with HAND2-AS1-bearing UTMBs. The study has merit since it explores novel hepatocarcinogenesis-related mechanisms, potentially providing an additional source for the treatment of HCC. The study is of current interest since HCC is one of the most letal and frequent cancer worlwide. However, to make the study of clinical impact, the authors should discuss and try to link the study findings with the efficacy of available systemic therapies for the treatment of HCC. In particular, in the current scenario of increasing number of systemic therapies, we urgently need to identify prognostic markers to identify patients who better respond to tyrosine kinase inhibitors

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(TKI) such as sorafenib, lenvatinib, regorafenib, cabozantinib, and immune checkpoint inhibitors (ICI) such as anti-PD1, PDL1, CTLA-4 agents. In fact, it has been recently demonstrated that combination treatment strategy based on TKI plus ICI significantly enhance treatment response as well-described in a comprehensive review addressing the improved efficacy of TKI-ICI combination treatments (Expert Rev Anticancer Ther. 2023 Mar;23(3):279-291. doi: 10.1080/14737140.2023.2181162). Importantly, there are also other systemic treatments that have demonstrated both good efficacy and safety profiles in patients progressing under first-line TKI agent or intolerant to sorafenib as capecitabine, a safe and unexpensive therapy, as recently demonstrated in cohort real-life/clinical practice studies (Dig Liver Dis. 2015 Jun;47(6):518-22. doi: 10.1016/j.dld.2015.03.010; J Cancer Res Clin Oncol. 2018 Feb;144(2):403-414. doi: 10.1007/s00432-017-2556-6). The authors should suggest future studies investigating the prognostic role of lncRNAs to select the best systemic treatment in the era of precision medicine.