

PEER-REVIEW REPORT

Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 91833

Title: Necroptosis contributes to non-alcoholic fatty liver disease pathoetiology with promising diagnostic and therapeutic functions

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: 2024-01-06

Reviewer chosen by: AI Technique

Reviewer accepted review: 2024-01-13 17:16

Reviewer performed review: 2024-01-13 18:00

Review time: 1 Hour

Scientific quality	<input checked="" type="radio"/> Grade A: Excellent <input type="radio"/> Grade B: Very good <input type="radio"/> Grade C: Good <input type="radio"/> Grade D: Fair <input type="radio"/> Grade E: Do not publish
Novelty of this manuscript	<input checked="" type="radio"/> Grade A: Excellent <input type="radio"/> Grade B: Good <input type="radio"/> Grade C: Fair <input type="radio"/> Grade D: No novelty
Creativity or innovation of this manuscript	<input checked="" type="radio"/> Grade A: Excellent <input type="radio"/> Grade B: Good <input type="radio"/> Grade C: Fair <input type="radio"/> Grade D: No creativity or innovation

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

SPECIFIC COMMENTS TO AUTHORS

In this review manuscript, the authors aimed to review the types of non-apoptotic regulated cell deaths (RCDs), in particular pyroptosis, ferroptosis, and necroptosis in the occurrence of Nonalcoholic fatty liver disease (NAFLD) and its progression towards steatohepatitis and cancer, with potential impact in diagnostic and therapeutic approaches. The review is well-written and presented. However, in my opinion, the potential clinical/therapeutic impact should be improved by discussing the potential improvement of available and under investigation systemic treatments for hepatocellular carcinoma (HCC). In particular, it has been previously demonstrated that Metronomic capecitabine promotes ferroptosis (Int Immunopharmacol. 2023 Nov;124(Pt A):110810. doi: 10.1016/j.intimp.2023.110810.) which can be an adjunctive antitumor therapeutic mechanism to further investigate in hepatocellular carcinoma. In this regard, the authors should recall the recently published cohort studies demonstrating both anti-tumor efficacy and safety of metronomic capecitabine in HCC patients unresponsive to the tyrosine kinase inhibitor sorafenib or intolerant to first-line sorafenib, as previously demonstrated (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). Importantly, the authors should recall the recent development of combination treatment strategies for HCC patients based on the combination of tyrosine kinase inhibitors and/or anti-VGFR agents plus immune checkpoint inhibitors, as well-described in a recent comprehensive review (TKIs in combination with immunotherapy for hepatocellular carcinoma. Expert Rev Anticancer Ther. 2023 Mar;23(3):279-291. doi: 10.1080/14737140.2023.2181162.), to explore which combined treatment have more favorable effect on pyroptosis, ferroptosis, and necroptosis.