Dear editors

We would sincerely thank the editor and reviewers for your careful review. We have revised the manuscript according to the reviewers' valuable comments. We also added several novel therapeutic targets published during the review period. In addition, the title was modified according to the editors' suggestion. The point-by-point responses are listed below.

Yours sincerely,

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Responses to reviewers' comments

Reviewer #1:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: This review focuses on recent researches reporting the mechanism underlying the pathogenesis of NASH. This research also tries to compile signaling pathways targeting key mechanisms that contribute to NASH development. The authors try to open new insights into explored the mechanism of NASH and its novel therapeutic targets. This study focused on basic cellular and molecular mechanisms and did not discuss subsequent pathological and also therapeutic outcomes in every research. However, it seems that approaches target signaling pathways driving disease development can use to inform new treatments for precision medicine. Therefore, it may provide a novel platform to identify and prioritize novel targets for NAFLD and NASH, creating a path for drug developers towards a first-in-class treatment.

Response: Thank the reviewer for the valuable comments. Our manuscript is focused on the novel therapeutic targets reported in basic research filed in recent years. Thus, evidence of therapeutic outcomes, especially side effects, was lacking in some studies we discussed in the manuscript. In the revised manuscript, we provide the therapeutic effects of these emerging novel targets on the development and progress of NAFLD based on preclinical studies in various animal models, which are summarized in Table 1.

Reviewer #2:

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Minor revision

Specific Comments to Authors: The manuscript was reviewed for publication in the journal. The

manuscript was designed to review emerging novel targets for NASH treatment. It is the reviewer's opinion that the review is quite interesting and easy to follow. However, it appears that there are a couple of minor concerns in the manuscript. 1) The authors discussed the potential targets outside the liver. How about other targets such as the systemic or metabolic effects? The authors should discuss the issue. 2) The authors have discussed the cell specific effects for NASH treatment. How about the specific effects of liver immune cells such as lymphocytes, neutrophils, and other cells? The authors should discuss the issue.

Response: We highly appreciate the comments and suggestions. It has been reported that the GLP1 receptor agonists and FGF21 analogues show potential to treat NASH by improving systemic energy metabolism, which are in phase II/III clinical trials. Some recent basic studies also report novel approaches for NAFLD treatment that target systemic metabolic homeostasis. The extrahepatic organs can influence liver function by releasing hormones or inflammatory factors or by regulating systemic metabolic homeostasis such as energy expenditure and insulin sensitivity. As an example, anti-Gremlin 1 antibody and the small molecule SN-401 ameliorate NAFLD by increasing insulin sensitivity and regulating systemic metabolic homeostasis. In the revised manuscript, we added these new findings.

As the reviewer suggested, in the revised manuscript we discussed the targets on neutrophils and macrophages in the section "Approaches targeting the inflammatory pathway to treat NASH". In addition, we added approaches targeting dendritic cells and lymphocytes to treat NAFLD.