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# PEER-REVIEW REPORT

**Name of journal:** *World Journal of Hepatology*

**Manuscript NO:** 83944

**Title:** Ductular reaction in non-alcoholic fatty liver disease: When Macbeth is perverted

**Provenance and peer review**: Invited manuscript; Externally peer reviewed

**Peer-review model:** Single blind

**Reviewer's code:** 03294368
**Position:** Editorial Board
**Academic degree:** DSc, MD, PhD
**Professional title:** Dean, Professor
**Reviewer's Country/Territory:** Georgia
**Author's Country/Territory:** China

**Manuscript submission date:** 2023-02-27

**Reviewer chosen by:** AI Technique

**Reviewer accepted review:** 2023-03-06 07:24

**Reviewer performed review:** 2023-03-12 16:30

**Review time:** 6 Days and 9 Hours

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[ ] Grade D: Fair [ ] Grade E: Do not publish |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

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|---|---|
| **Scientific significance of the conclusion in this manuscript** | [ ] Grade A: Excellent [ Y] 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** | [ ] Yes [ Y] No |
| **Peer-reviewer statements** | Peer-Review: [ ] Anonymous [ Y] Onymous |
| | Conflicts-of-Interest: [ ] Yes [ Y] No |

**SPECIFIC COMMENTS TO AUTHORS**

The paper focuses on a very important pathology that affects billions of people worldwide, but there are still many unanswered questions about it. The paper is well-written and contributes to our understanding of Non-alcoholic Fatty Liver Disease (NAFLD) and its association with Ductular Reaction (DR). The title is well-designed and the reference to Macbeth is impressive. The abstract provides an adequate summary of the manuscript. The use of subheadings makes the paper easy to follow. The illustrations are informative and help to clarify the content. However, the classification of ductular reactions given under the subheading "Overview of Ductular Reaction" is superficial and could be more detailed. It is also important for the authors to clarify their position on the types of ductal reactions that develop in MAFLD. Additionally, the authors could highlight the differences between the DR revealing in humans and animal models of MAFLD. On page 8, where the mechanisms of development of centrilobular DR are discussed, it is important to note whether such a response may develop as a result of activation of the Herring ductuli (as a niche for hepatic progenitor cells) that extend far from the portal tracts into the hepatic lobules.

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It would also be useful to note whether the concept proposed by Desmet, that DRs develop in the form of embryonic ductal plates, including in the setting of NAFLD, is shared. Overall, the article is interesting and with some minor revisions, I support its publication.

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**Reviewer's code:** 05346014
**Position:** Editorial Board
**Academic degree:** MD

**Professional title:** Associate Professor

**Reviewer's Country/Territory:** Brazil

**Author's Country/Territory:** China

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**Reviewer chosen by:** AI Technique

**Reviewer accepted review:** 2023-03-13 00:53

**Reviewer performed review:** 2023-03-25 23:59

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

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| **Conclusion** | [ ] Accept (High priority) [ ] Accept (General priority) [ Y] Minor revision [ ] Major revision [ ] Rejection |
| **Re-review** | [ ] Yes [ Y] No |
| **Peer-reviewer statements** | Peer-Review: [ Y] Anonymous [ ] Onymous |
| | Conflicts-of-Interest: [ ] Yes [ Y] No |

**SPECIFIC COMMENTS TO AUTHORS**

Ductular Reaction in Non-alcoholic Fatty Liver Disease: When Macbeth is perverted Recently, several studies have shown that the extent of ductular reaction (DR) is parallel to the stages of NASH and fibrosis. DR is a common compensatory reaction in a liver injury involving hepatic progenitor cells (HPCs), hepatic stellate cells (HSCs), myofibroblasts, inflammatory cells (such as macrophages), and their secreted substances. This review summarises previous research on the correlation between DR and NASH, the potential interplay mechanism of HPC differentiation, and NASH progression. My specific queries and comments are below: 1. A detailed English review should be provided. 2. While the current review has merit, the ductular reaction is undermined by a poorly articulated and an under-elaborated topic – An overview of ductular reaction. 3. Regarding the mechanisms involved in the ductular injury, are the studies presented restricted only to animal models? 4. The sentence "Of note, DR may play a favourable role in NASH in promoting liver regeneration and injury repair but may unfavourably contribute to the occurrence and progression of inflammation and fibrosis in NASH" should be written more clearly. 5. The ductular injury was centred on the

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age difference in the "Correlation between NASH and DR" session. What could other factors be involved? 6. In the section "NKT cells and HPC differentiation fate in NASH", the authors must make it clear if the alterations are identified only in animal models or if there is a study in humans included. Minor revision