

Reviewer 1: 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.

1. The classification of ductular reactions given under the subheading "Overview of Ductular Reaction" is superficial and could be more detailed.

Response: Thanks for the reviewer's comments. We feel sorry not to describe the classification of ductular reactions clearly enough. Following the reviewer's advice, we have described the classification of ductular reactions in original paragraph (Page 4, Lines 5-24).

2. The authors could highlight the differences between the DR revealing in humans and animal models of MAFLD

Response: Thanks for the reviewer's comments. Following the reviewer's advice, we have added more details about the differences between the DR revealing in humans and animal models of MAFLD (Page 7, Lines 31-32; Page8, Lines 1-6).

3. 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. 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.

Response: Thanks for the reviewer's comments. We should be consider whether centrilobular DRs were a result of migrating HPCs form Hering canals into hypoxic centrilobular zones, but such mechanism would not explain the increasing numbers of hepatocytes showing the described progressing changes in a centripetal gradient⁽¹⁾.

Reviewer 2: 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 summarizes previous research on the correlation between DR and NASH, the potential interplay mechanism of HPC differentiation, and NASH progression.

1. A detailed English review should be provided.

Response: Thanks for the reviewer's comments. We have re-edited the whole manuscript and improved some detail in the revised manuscript.

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.

Response: Thanks for the reviewer's comments. Subheading overview of ductular reaction has been modified to **Overview of Ductular Reaction and correlation between HPC and DR** (Page 3, Lines 32).

3. Regarding the mechanisms involved in the ductular injury, are the studies presented restricted only to animal models?

Response: Thanks for the reviewer's comments. Following the reviewer's suggestion, we added some the mechanisms involved in the ductular reaction in human. (Page 5, Lines 31-32; Page10, Lines 8).

4. The sentence "Of note, DR may play a favorable role in NASH in promoting liver regeneration and injury repair but may unfavorably contribute to the occurrence and progression of inflammation and fibrosis in NASH" should be written more clearly.

Response: Thanks for the reviewer's comments. We have re-edited the sentence more clearly. Of note, during the course of chronic liver disease, when the capacity for liver regeneration is impaired, concomitant with HPC activation and differentiation, DR assists in the repair of liver injury, but in some specific cases this differentiation promotes the progression of NASH and liver fibrosis. (Page 6, Lines 28-32).

5. The ductular injury was centred on the age difference in the "Correlation between NASH and DR" session. What could other factors be involved?

Response: Thanks for the reviewer's comments. We added other factors involved DR location in NASH. Perhaps there are more factors involved in this difference. (Page 9, Lines 8-12).

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.

Response: Thanks for the reviewer's comments. Following the reviewer's suggestion, we found some study that show difference relationship in NKT cells and HPC differentiation fate in HBV patients. But we did not find another research in NASH patient. (Page 16, Lines 17).

1. Desmet VJ. Ductal plates in hepatic ductular reactions. Hypothesis and implications. I. Types of ductular reaction reconsidered. Virchows Arch. 2011;**458**(3):251-9. [PMID: 21287200 DOI:10.1007/s00428-011-1048-3]