PEER-REVIEW REPORT Reviewer's code: 03836930

Major comments:

1/ The term "atypical regeneration" is not a term that is used in the Hepatology scientific literature. Although I understand the phenomenon to which the authors refer, it would be best to focus on normal liver regeneration and describe how the damaged liver attempts to regenerate. More detailed and description of signaling pathways during different phases of atypical liver regeneration could be added.

Answer: Since liver regeneration involving liver stem cells is still understudied, different terms (such as stem cells/progenitor-dependent regeneration, alternative regeneration, etc.) are used in various articles on this topic since there is no generally accepted term for this phenomenon. The term atypical liver regeneration has appeared in several articles and has been used to simplify the understanding of the term versus typical liver regeneration. This term will be changed in the article.

2/The review is not very well divided between typical and atypical liver regeneration. The majority of the review extensively describes molecular pathways controlling different phases of typical liver regeneration.

Answer: Unfortunately, atypical liver regeneration, which involves liver stem cells, is understudied, unlike normal liver regeneration; thus, this article contains an unequal amount of information on normal and progenitor-dependent liver regeneration.

3/ The description of signaling pathways in three different phases is dense and the reader easily gets lost. It would be good to have more detailed figures summarizing how these signaling pathways collaborate during these different phases.

Answer: We have tried to make the pictures as accessible and intelligible as possible for the readers of this article by dividing all the stages into separate pictures. The large number of different molecular factors makes it difficult to put these stages in a single picture because the result is a picture overloaded with information.

3/ The authors should provide further details in the paragraph dedicated to miRNAs, which miRNAs play a role in the typical and/or atypical liver regeneration, and which cell type is particularly affected by these miRNAs.

Answer: This article indicates that the data on miRNA expression are based on studies that were performed after a partial hepatectomy, which activates normal regeneration. Thus, all miRNAs listed affect hepatocytes. Unfortunately, no data on miRNA expression in cases of alternative regeneration pathways are available at this time.

4/ A paragraph describing actual drugs used to modulate positively liver regeneration based on the knowledge of molecular pathways can be added.

Answer: Pharmacological treatment of insufficient liver regeneration is lacking. A paragraph describing experimental studies on liver regeneration stimulation was added.

Minor comments:

1/ The last paragraph of the Introduction section might be better explained, and the term liver regeneration better defined.

Answer: Based on our analysis of the literature data, we tried to show that the term "liver regeneration" is widely used in the literature and includes many processes that occur with the functional unit of the liver – hepatocyte – against the background of various injuries. At the same time, the restoration of liver function is associated not only with compensatory hypertrophy of the parenchyma but also with many molecular aspects. Many different factors are involved, including inflammatory cytokines, growth factors, bile acids, mature hepatocytes, resident stem cells called “hepatic progenitor cells” and others. This allowed us to analyze various aspects and types of liver repair and to reflect on the most significant biomolecular pathways involved in these processes and, in our opinion, there are enough data for the introduction of the article.

2/ The authors should provide details regarding whether the signaling pathways described are in murine model or in human.

Answer: The described signaling pathways are specifically attributed to humans; those pathways that are attributed to mice have a corresponding labeling or are described using murine genes.

3/ There are many inconsistencies in the abbreviation of genes or proteins in the entire review. The authors might refer to human and mouse gene and protein nomenclature.

Answer: The abbreviations were carefully checked and corrected if needed.

4/ the authors might underline from the beginning that typical liver regeneration is specific for healthy liver and occurs among liver donors. Liver regeneration in liver transplant recipient is classified in typical or atypical liver regeneration?

Answer: The information was added in the beginning. Liver from living liver donors regenerates in the typical manner, as was stated in this article.

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Question: As the medicine is moving towards patient tailor therapies, we need to include how gender, hormones and ethnicity would affect the outcomes of liver regeneration. This data is limited in the literature.

Answer: We absolutely agree that gender, age and hormonal status determine the conditions for the regenerative potential of the liver in various organ injuries. Biomolecular pathways of typical and atypical liver regeneration according to the literature data are currently mostly studied in animal models with subsequent extrapolation of the results to humans. The purpose of this review article was to analyze the molecular pathways and generalize cellular factors that determine the stimulation or inhibition of the liver parenchyma regeneration processes. In the future, we plan to conduct a comparative analysis of the results of liver volume recovery after resection among different sex and age groups and to compare data of the world's leading clinics located on different continents to approximately assess the impact of ethnicity on the process of organ volume recovery.