Answers to reviewer's opinions

To reviewer 1:

1. The authors review the roles of apoptosis in liver aging and age-related liver diseases. The article implicates that apoptosis and aging play a central role in the occurrence, development, and treatment of age-related liver diseases. It is suitable to the Journal and could be helpful in clinic application.

Thank you for the comments on our manuscript. Your confirmation to our review will encourage us to do better in future.

To reviewer 2:

1. Aging of other cell types than hepatocytes should be addressed. Especially the homing of immune cells in aging should be discussed.

Thanks for your valuable suggestions. We have consulted recent corresponding literature and found that immune cells such as natural killer cells congregate in the aged liver. The increased immune cells produce more inflammatory cytokines and chemokines. Please see this content in Paragraph 1 of Page 3.

2. References: first reference should be proofed.

We are sorry for this errors. We have corrected wrong references

accordingly and checked entire references again to avoid faulty references.

To reviewer 3:

1. Some more figures would make the reading easier and the understanding of the complicated pathways involved in the process of apoptosis and the development of the liver diseases more accessible to the non-expert reader.

Thank you for the comments. We have added another figure 3 to make the complicated pathways in the manuscript more clearly and easily. Figure 3 depicts and summarizes the cause of NAFLD and the ways to alleviate it.

2. The obvious ones would be the pathways leading to the development of the diseases mentioned in the review (NAFLD, liver fibrosis, cirrhosis, liver cancer) but the mitochondrial fusion and fission and its involvement in apoptosis in the liver could also be considered for inclusion.

Mitochondrial fusion and fission have already been discussed in detail in our previous paper（Zhong H-H, et al,2017）. Here, mitochondrial fusion and fission are associated with mitochondrial dysfunction, and mitochondrial dysfunction is discussed in Page 6, Paragraph 2. In

addition, after consulting more recent literatures, we found that mitochondrial dynamics were associated with metabolic stress closely. Caloric restriction can slow down the aging process via the regulation of mitofusion and fission. Furthermore, mitofusion and fission are involved in the development of NASH. Therefore, we discussed the detailed role of mitochondrial fusion and fission in “calorie restriction” (Page 10, Paragraph 1) and “NASH” (Page 14, Paragraph 2; Page 16, Paragraph 1) parts of the manuscript.

3. The future directions section needs to be expanded.

In the future directions section, we have added new insights and directions to treat age-related liver diseases. More accurate ways to detect apoptosis and how to adjust apoptosis-related genes to alleviate liver diseases are important to be explored in the future.

4. Some pathways are explained in extensive detail but some others are mentioned briefly (ER stress, UPR, Sirt7).

You are right. That is true. It is because some apoptosis pathways such as ER stress, UPR and Sirt7, etc. have been discussed in detail in our previous paper（Zhong H-H, et al,2017）.

5. Minor grammatical errors throughout the review should be

corrected.

In order to deal with this problem, we have read the manuscript many times to find out and correct those grammatical errors. In addition, we have also employed an English-language editing service to polish our wording to improve the interpretation of entire manuscript.

To reviewer 4:

1. "However, polyploid cells exhibited less survival opportunity compared with liver cells. If excessive polyploid cells are present, and renewing cells are lacking, failure may occur during liver damage. Given that polyploid cells are eliminated through apoptosis to avoid liver failure, apoptosis is deemed to protect liver aging."(page 7, first paragraph) This is a very interesting statement. Add the reference or if this is their own theory, explain more.

Thank you for the comments. The statement you mentioned above is associated with the experiment result of Giorgadze et al. They got such a conclusion according to the experiment results. However, up to now we havn't consulted more references related to the statement.

2. Brown atrophy (senile atrophy) is usually not associated with liver dysfunction. Does the authors insight explain this phenomenon from the stand point of apoptosis and polyploidy?

This is very interesting topic worthy of exploring. But our aim of mentioning brown atrophy is just to introduce age-related morphological changes in the liver. Furthermore, considering the word limit and length of manuscript, trying to explain this phenomenon from the stand point of apoptosis and polyploidy remain to be done in the further.

3. Non-alcoholic fatty liver seems to be related to aging. Any epidemiological data on that ?

Yes, it is. Non-alcoholic fatty liver is correlated with aging tightly. Detailed epidemiological data can be found in the previous literatures below. (“Nonalcoholic fatty liver disease and aging: Epidemiology to management”, “Prevalence of nonalcoholic fatty liver among administrative officers in Shanghai: an epidemiological survey”)

4. You do not include massive hepatic necrosis (such as so called fulminant hepatitis or acute yellow atrophy, classical example of expensive apoptosis related disease process).

Thanks for your opinion. In the injured liver, cell death modes include necrosis, necroptosis, autophagy, and apoptosis, and those death modes are different. Apoptosis is programmed cell death or to commit suicide, but necrosis is a premature death of cells. Apoptosis covers physiological response and pathological conditions, whereas necrosis is a pathologic

process that is often caused by external factors to the cell or tissue. Characteristics of apoptosis and necrosis are distinctly identified. In this review we mainly discuss apoptosis, but not include massive hepatic necrosis.