

Dear Dr. Editor

Thanks a lot for valuable suggestions of all reviewers. We did corrections required by reviewers and highlighted the corrected parts in Yellow color.

Reviewer 1:

This is good and comprehensive review about Cytokine gene polymorphism in hepatitis-related HCC. The manuscript is well organized and well constructed.

1. In Table 1, as a summary of the review, the authors should add one more column about correlation of respective gene polymorphism and HCC. If the correlation is still not clear, the authors can state " no clear correlation".

Answer: Done

Table one (Pages 9-10) has been corrected and results were categorized into 3 columns: Risk factor, protective factor and no association.

2. In addition, the English in this manuscript should be improved.

Answer: Done

English has been checked for both spelling and grammar errors.

Reviewer 2:

Authors comprehensively reviewed the molecular epidemiological association between HCC risks and genetic polymorphisms on the cytokine genes. In general, this review included the most important studies published in the last two decades and summarized these studies by genes and risks. The credit of doing such a large amount of work by authors should be given and appreciated; however, several concerns need to be addressed.

1. The authors only listed and simply stated the results (risks or protective effects of polymorphisms) from many studies, but they did not dig into the reasons for those contrary findings. To review molecular epidemiology studies (using genetic variants as markers), authors should analyze confounding factors, such as the sample size, the ethnicity of the study population, the disease stage, and the genotyping method, etc. I suggest authors re-visit the publications and summarize/explain above factors in the revised manuscript.

Answer: It is too hard to comment on each study enrolled on this review article (more than 200 studies) on sample size, the ethnicity of the study population, the disease stage, and the genotyping method, etc.. and discuss the results based on these factors. This simply may reach

with the review article to one hundred pages. I think this could be done by meta analysis for each cytokine.

If you implies to statistical analysis of confounders (such as described in this manuscript: How to control confounding effects by statistical analysis, Gastroenterol Hepatol Bed Bench 2012;5(2):79-83) this is not the subject of this review article. We were gatering informations about what have been done till today in cytokine polymorphism in HCC patients. Although, I think it will be a very good idea to make a statistical analysis to have a deep view about what is really affecting the disease.

2. There are many grammatical errors and typos in the manuscript, for which authors should correct and improve.

Answer: Done

English has been checked for both spelling and grammar errors.

3. Authors believed that the expression of cytokines has an important effect on the HCC incidence; therefore, the association between the copy number variation of cytokine genes and HCC risk should be mentioned/reviewed in the manuscript.

Answer: We found around 50 articles deal with copy number variation (CNV) on HCC. They did not study CNV in cytokine genes in Hepatitis related HCC; only genes related to HCC as oncogenes, tumor suppressor genes either in HCC patients or HCC cell line. We check the most relevant review articles on this topic and we found nothing about CNV in cytokine genes

1. Target genes discovery through copy number alteration analysis in human hepatocellular carcinoma World J Gastroenterol. 2013 Dec 21;19(47):8873-9]
2. Genetic Landscape and Biomarkers of Hepatocellular Carcinoma. Gastroenterology. 2015 Oct;149(5):1226-1239.e4.

4. Table I is not informative enough. Author should include the odd ratio and confidence interval for each study to clearly demonstrate the risk or protective effect.

Answer: Table one (Pages 9-10) has been corrected and results were categorized into 3 columns: Risk factor, protective factor and no association. Adding odd ratio and confidence interval will add no more information as Risk factor means Odd ratio value higher than 1 and protective factor means Odd ration less than 1. Moreover, each gene has at least 3 genotypes and 2 alleles, it will be too much data on the table to add OR and CI for each of them (5 parameters at least for each studied cytokines). I think the table with its new correction is more informative and if anyone is interested on one specific manuscript, it is easy to get it from reference list.

5. In some places, the style for presenting SNP is not appropriate. For example, IL-1 β -31 should be IL-1 β -31C or IL-1 β -31T.

Answer: Done (page 11-12)

Reviewer 3:

Dondeti MF et al. read many relevant references about the association of cytokine gene polymorphisms with hepatitis-related hepatocellular carcinoma, and give us a comprehensive review for the achievements of this field. The title is interesting enough to attract reader's attentions.

1. Authors should add introduction part in the beginning and summary at the end of the manuscript.

Answer: Done

Introduction in Page 3 and summary in Pages 22-23

2. The English language needs to be carefully checked and edited, there are many mistakes in grammar, sentence structure, and word spelling.

Answer: Done

English has been checked for both spelling and grimmer errors.

3. Try to make the content more concise and clear.

Answer: Done

We have checked the whole manuscript.

Reviewer 4:

1. The data under title: Roles of cytokines in the hepatitis viruses infections is not mentioned the role of cytokines in HCV in details. It showed only some basic data. I suggest rewriting this part.

Answer: Done

We added a paragraph about the most important cytokine in HCV infection (Pages 6-7)

2. The data under the title: Cytokines' gene polymorphisms as the protagonist of hepatitis-related HCC is also basic information, could you delete the paragraphs about the definition and types of the polymorphisms.

Answer: Done

This part is deleted, we just mentioned to 3 types of polymorphisms (Page 8)

3. When the authors studied the individual cytokines with HCC, I think they should study more meta analyses studies than case controls' and discuss them in details.

Answer: Done

Meta analysis studies have been added (Pages 12, 14, 16, 21, 22)

4. Rewrite the title of table 1 to become meaningful

Answer: Done

The new title is: Associations between Cytokine Gene Polymorphisms and HCC

5. Figure 1 should be uploaded again as it is not obvious.

Answer: Done

More clearly colored figure has been uploaded