Dear Editors and reviewers,

Firstly, we thank you sincerely for your review our manuscript. We read the comments of the reviewers and searched the related reference paper. Then, we modified and revised the manuscript according the comments, and added some discussion through referring to some papers. We submit the revised manuscript, thanks.

Comments:

1. This is an interesting article that reviewed CDKN1A (p21, CIP1) in cancer. It is very important to better characterize molecular mechanisms of carcinogenesis. Hence, this review is important. Overall, the paper can have significant impact with following revisions. Please write “CDKN1A (p21, CIP1)”, “TP53 (p53)”, etc. because those are CDKN1A and TP53 gene products. The first appearance should be “CDKN1A (p21)” and thereafter CDKN1A (p21) or CDKN1A should be used. We need to use standardized names. Please see www.genenames.org. p21 is non-specific name, and can mean many proteins such as CDKN1A: cyclin dependent kinase inhibitor 1A Gene symbol alias P21 TCEAL1: transcription elongation factor A like 1 Gene symbol alias p21 H3P16: H3 histone pseudogene 16 Gene symbol alias p21 NSG1: neuronal vesicle trafficking associated 1 Gene symbol alias P21.

Response:

Thank you for your suggestions about the gene name of p21. According to your suggestions, we searched the website www.genenames.org and the related paper (p21 is a universal inhibitor of cyclinkinases. Nature 1993; p21 in cancer: Intricate networks and multiple activities. Nat. Rev. Cancer 2009; Less understood issues: p21(Cip1) in mitosis and its therapeutic potential.Oncogene 2015), and found the nomenclature of p21 is consistent with your suggestion. Thus, we wroteCDKN1A (p21) at its first appearance and then use the name of p21.

2. There are many environmental and microenvironmental factors that influence molecular mechanisms of carcinogenesis. When discussing CDKN1A expression variable, the authors can also discuss influence of those factors, eg, smoking, diet, microbiome, etc.

Response:

Thanks for your suggestion. According to your suggestion, we added the description about "environmental and microenvironmental factors that influence molecular mechanisms of carcinogenesis with p21" in the part "p21 AND CARCINOGENESIS" through citing the related reference [Gut 2011: 397-411; J Pathol. 2019, 247: 615-628]。

3. In this context, as a future direction, research on cancer risk factors, microbiome, immunity, and molecular tissue biomarkers is needed.

Response:

Thanks for your suggestion. According to your suggestion, we added the description "*In addition, further studies should be focused on MPE and investigate cancer risk factors, microbiome, immunity, and molecular tissue biomarkers, which was related with molecular pathologies in normal or diseased tissue.*'' *Please check the revised manuscript.*

4. In these contexts, the authors should discuss molecular pathological epidemiology (MPE), which can investigate those factors in relation to molecular pathologies in normal or diseased tissue. MPE, its strengths and challenges have been discussed in Gut 2011, Annu Rev Pathol 2019, etc. I believe MPE research can be a promising direction. Please describe strengths and challenges of MPE.

Response:

Thanks for your suggestion.We added the description about MPE in the part "p21 AND TUMOR THERAPY" according to your suggestion through citing the related

publication [J Gastroenterol. 2017, 52:265-275; Annu Rev Pathol. 2019]. Please check the revised manuscript.