

Dear Peer-viewers:

Thank you very much for your busy time to review my manuscript and put forward valuable comments. We have read all the comments carefully and through deep thinking , we are going to reply the comments below now.

Firstly, we have given the detailed information about wortmannin in the discussion section and showed it by red font. Specific as follows:

“Wortmannin, which half inhibition concentration was 0.004 microns, was firstly extracted from the Fungus Penicillium Wortmanni in 1957. It was also the ATP uncompetitive irreversible PI3K inhibitors. The specific mechanism of wortmannin was combined with PI3K gamma and result in the irreversible modification of lysine in 833 loci, which was the active site of PI3K^[29]. Wortmannin had different inhibiting ability on the family of PIKK such as mTOR, DNA-PK, ATM and ATR at high concentration^[30,31]. ”

Secondly, we have explained the clinical practice significance about the result of this study in the summary section and also showed it by red font. Specific as follows:

“This study will contribute to seek for the effective treatment strategy of tumor cells in hypoxia environment and provide strong evidence and new thoughts for the diagnosis and treatment of cancers. It also afford the direction on the research for the exploitation of new antitumor drugs and thus give more reasonable and individualized therapeutic schedules to the cancer patients in

clinic.”

Thirdly, we have described correlation of other risk factors such as carbonic anhydrase (CA) and monocarboxylate transporters (MCTs) in the discussion section and also showed it by red font. Specific as follows:

“In addition to involving the glucose transport and the glycolysis process, the relevant proteins about glycolysis in tumor cells also included the glycolysis products such as carbonic anhydrase (CA) , monocarboxylate transporters (MCTs) and so on. Studies had already confirmed that CAIX and MCT4 gene promoter sequences existed the binding sites of HIF-1 α , which can promote the transmembrane transport of lactic acid and hydrogen ion through enhancing the expression and activity of CAIX and MCT4 and then to ensure the smooth progress of glycolysis^[24,25,26,27]. It suggested that HIF-1 α , as the key factor in the process of regulating the tumors glycolysis, may involve in the enhanced glycolysis process of tumor cells by the level of glucose transport, glycolysis activation and lactic acid transport.”

Fourthly, we have carefully corrected the spelling mistakes in the whole manuscript.

Finally, we have corrected the references according to the journal's rules.

Thank you again for your review.

Best regards,

Ling Zeng.