Dear Editor,

Thank you for your letter with comments on our manuscript "Understanding the role of PIN1 in hepatocellular carcinoma", and for the opportunity to submit a revision of the manuscript. We would also like to thank the reviewers for the valuable comments and suggestions to strengthen this manuscript. The changes that have been incorporated in the revised manuscript were highlighted in RED for ease of reference. We have also addressed all the queries raised by the editorial board and reviewers as detailed below.

We look forward to hearing from you soon.

Yours faithfully,

Eric Tse, on behalf of all authors

REVIEWER 1:

1. Introduction on PIN1 with surgical specimens or clinical data should be propagated with more literatures. This part would show the rationale for the investigation of PIN1 aiming at treatment of HCC.
   Author reply: *Thank you for your comment. As suggested, relevant information and the related references have been added in the section "PIN1 overexpression in hepatocellular carcinoma" to highlight the findings of PIN1 over-expression in HCC surgical samples.*

2. Table would present the drugs targeting PIN1 for the treatment of HCC.
   Author reply: *Thank you for your comment. We have now created a table to summarize the potential PIN1 inhibitors for cancer treatment (Table 1).*

REVIEWER 2:

1. I suggest the authors to include in the introduction a schematic cartoon of PIN1 protein showing the different parts and the relative functions.
   Author reply: *Thank you for your comment. We have now included a schematic diagram of PIN1 protein (Figure 1), illustrating the structure of the 2 functional domains of the protein.*

2. In the section: "Roles of PIN1 in hepatocarcinogenesis" I suggest to briefly explain the role of Rb in relation to E2F.
   Author reply: *Thank you for your comment. We have elaborated the role of Rb in relation to E2F in the section: "Regulation of PIN1 expression and activity. Furthermore, Figure 2 and the legend (PIN1 dysregulation and targets in hepatocellular carcinoma) have been updated to include the Rb-E2F pathway.*

3. In the section: "PIN1 as a new drug target for hepatocellular carcinoma treatment" the authors write: "Therefore, it remains uncertain whether PIN1 inhibitors would have any adverse effect on normal tissues. Preclinical or clinical studies are necessary to examine the safety and effectiveness of the PIN1 inhibitors in cancer treatment". It may be useful to write a sentence reminding the readers that the use of HCC targeted delivery systems may overcome the detrimental effects on normal cells.
   Author reply: *Thank you for your comment and we have revised accordingly.*

4. In the section: "PIN1 as a new drug target for hepatocellular carcinoma treatment" the author mention the fact that sorafenib may exert its therapeutic effects in HCC also via indirect impairment of PIN1. I recommend the author to mention another examples of drug able to down regulate HCC growth via direct/indirect impairment of PIN1, namely bortezomib (Farra et al, Biochimie. 2015 May;112:85-95)
   Author reply: *Thank you for your comment. As suggested, we have discussed the negative effect of bortezomib on HCC proliferation via direct/indirect impairment of PIN1 function in*

the last paragraph of the section: "PIN1 as a new drug target for hepatocellular carcinoma treatment."

REVIEWER 3:

1. In the Introduction Section, the authors demonstrated that 'PIN1 is mainly localized in the nucleus.' In my understanding, PIN1 ubiquitously exists in both nucleus and cytoplasm. Is the sentence true? If yes, please provide the reference which mentioned about that.
   Author reply: *Thank you for your comment and several references have been included to support that 'PIN1 is mainly localized in the nucleus.'*
   1. *Lu et al. (Nature. 1996 Apr;380:544-547) have demonstrated that ectopically expressed HA-tagged PIN1 was almost exclusively localized to the nuclei in HeLa cell.*
   2. *Lu et al. (Journal of Biological Chemistry. 2002 Jan;277:2381-2384) have also shown that GFP-PIN1 was localized to the nuclei in HeLa cells.*
   3. *Lee et al. (Molecular Cell. 2011 Apr;42(2):147-159) further verified that endogenous PIN1 was mainly localized in the nuclei of NIH3T3 cells.*
   4. *Our study (Cheng et al. American journal of pathology. 2013 Mar;182:765-775) also showed an intense immunohistochemical staining of PIN1 in the cell nuclei of human HCC.*

2. In the Introduction Section, the authors introduce NF-κB as one of the PIN1-interacting partners. It is better to change 'NF-κB' to 'NF-κB-p65'.
   Author reply: *Thank you for your comment and we have revised accordingly.*

3. In the section about 'Regulation of PIN1 expression and activity', they explained E2F, NOTCH1, miRNAs, as important factors to regulate PIN1 expression. A previous report by Wang J, et al. have demonstrated that FOXC1 negatively regulates PIN1 expression and function of human basal-like breast cancer cell. Why don't you add the explanation about FOXC1.
   Author reply: *Thank you for your comment. As suggested, we have discussed the effect of FOXC1 on regulation of PIN1 expression in the first paragraph of the section: "Regulation of PIN1 expression and activity."*

4. In the section about 'PIN1 and ?-catenin/ cyclin D1 signaling pathway', the author demonstrated the following sentence 'In the presence of TNF-a, PIN1 binds the phosphorylated ~ ' for the explanation of the reference 20. I believe that TNF-a is not necessary for PIN1 to bind to NF-kB-p65. Therefore, the words 'In the presence of TNF-a' should be deleted. Moreover, it might be better to add the fact that Ser276 of NF-kB-p65 is phosphorylated after binding of PIN1.
   Author reply: *Thank you for your comment and we have revised accordingly.*

5. EMT is reported to promote tumor cell invasion and metastasis in many cancers including HCC. Several reports have shown that Pin1 might be involved in the increase of EMT-mediated tumor invasiveness in several cancers including HCC. Therefore, I recommend to add the section about 'Roles of PIN1 in EMT-mediated tumor invasiveness'.
   Author reply: *Thank you for your comment. We have added a new section: "Roles of PIN1 in tumour invasiveness" to review the role of PIN1 in tumor cell invasion and metastasis.*