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Reviewer's code: 00225318

Answer We thanks the reviewer very much for the support of our hypothesis. We have emphasized the risk of targeting autophagy in the real clinical application in the last paragraph of discussion part as following:

These results suggested that ATG5-ATG12 is important for the survival of HBV-associated HCC during states of limited tumor nutrients. However, as mentioned previously that autophagy has a dual-function in cancer. Despite its role as tumor promotion in the later phase, it can act as a tumor suppressor during cancer initiation. Therefore, the therapeutic intervention that target autophagy has to take this information into consideration too.

The only significant limitation is the determination of levels of RNA using commercial (2X) Power SYBR Green. In this sense it must be confirmed positive cases and their levels by using specific Taqman probes or FRET type.

Answer In this study, the levels of RNA were confirmed by western blotting for detection of the protein expression instead.

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Reviewer's code: 00506552

Answer We have revised the manuscript according to your comments.

Fig. 1, 2 and 3 can be combined in one figure. such as Fig. 1.

Answer Thanks very much for your suggestion. We have combined figure 1 and figure 2, which were both experiments in the cell line as one figure as suggested. However, figure 3 is a protein expression from patient tissues, we decided to present it separately.

In Fig. 3, it would be nice to see the real protein bands, at least one or two representative samples compare to the adjacent non tumors and non HBV-HCCs.

Answer Thanks very much for your suggestion, the protein bands, which were representatives of each group (HBV-associated HCC and non-HBV HCC) were now shown.

Fig. 5 and 6 can be combined in one figure.

Answer We have revised manuscript according to your comments.

The quality of Fig. 6A needs to be improved since the percentage in the fig. are not recognizable. Especially, it need to make clear that it was not the reuse of their data from their previous publication by Kunanopparat et al., 2016 from Asian Pac J Allergy Immunol.

Answer Thanks very much for your kind suggestion of this point. For apoptosis assays in normal condition, we have previously reported this result in Kunanopparat et al., 2016. In this study, we repeated the experiment in normal condition compared to the additional experiment in starvation condition. We have clarified this point in the manuscript and clearly added a reference from Kunanopparat et al., 2016 from Asian Pac J Allergy Immunol. The figure that we showed here is not the same that have been published previously.

In Fig. 7 and 9, the open bar was HepG2 and the closed bar was HepG2.2.15 as Fig. 6 and 8??

Answer We apologized for missing of the label. We already added the label in this figure.

Most importantly, it would be nice to demonstrate that effect of HBV replication by over-expression and knock-down of ATG12 since they used HBV replicating HepG2.2.15 cells for their experiments.

Answer We already reported the effect of ATG12 knock down on HBV replication in HepG2.2.15 in the publication of Kunanopparat et al., 2016 from Asian Pac J Allergy Immunol.