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ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology
ESPS manuscript NO: 17333
Title: IGF-1 promoted the growth and metastasis of hepatocellular carcinoma through inhibition of proteasome-mediated Cathepsin B degradation
Reviewer's code: 00698242
Reviewer's country: United States
Science editor: Yuan Qi
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CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	Google Search:	[ ] Accept
[Y] Grade B: Very good	[Y] Grade B: Minor language polishing	[ ] The same title	[ ] High priority for publication
[ ] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] Duplicate publication	[ ] Rejection
[ ] Grade D: Fair	[ ] Grade D: Rejected	[ ] Plagiarism	[Y] Minor revision
[ ] Grade E: Poor		[Y] No	[ ] Major revision
		BPG Search:	
		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

In this manuscript, the authors demonstrate that IGF-1 promotes proliferation, migration, and invasion of liver cancer lines by upregulating cathepsin B expression. Moreover, the liver cancer cells grow more readily in diabetic mice, which have been shonw to overexpress IGF-1, and form more metastases when injected in the tail vein of diabetic mice. The authors also show that the mechanism of cathepsin upregulation by IGF-1 appears to involve inhibition of cathepsin B degradation via the proteasome, although how IGF-1 inhibits the proteasome was not investigated. In general, the manuscript is interesting, and provides a new mechanism for how cathepsin B may be upregulated in tumor cells. However, the manuscript is sloppily written (detailed below), lacks page numbers which makes it difficult to read, and has run-on sentences and numerous grammatical errors. Moreover, there are several problems with the Methods, which shed doubt on the validity of some of the conclusions. Detailed comments are outlined below. Figure 1C. In the Methods section, the authors indicate that the scratch assays were performed for 48h in 10% serum, but the Figure/legend, indicates IGF or 1% FBS were utilized for the assays and that the assays proceeded for 24h. Obviously,

it is unclear how this experiment was performed. If it was done in 10% serum, the authors cannot conclude that there is an effect on migration, as the cells are likely to fill the wound via proliferation during this time period. Figure 1D. Cathepsins are present in proforms, intermediate and active forms. It is unclear which form is shown. The authors need to show the entire blot with MW markers indicating each form of the protein. This is a critical point because if the authors are visualizing the active band, they aren't observing an increase in expression, but instead are visualizing inhibition of activation. Figure 1E. The Figure Legend indicates the presence of a panel (E); however, there is no panel (E) in the figure. Perhaps they are referring to the right panel of Fig. 1D? Figure 2B, C are not referenced in text. Figure 3A. Although the data in the diabetic mice are interesting, there is no definitive data showing that the effect is mediated by IGF-1. Figure 4A. This RT-PCR experiment either needs to be quantitative (qRT-PCR) or semi-quantitative (actin primers within the same reaction, taking aliquots at various cycle#s). Without some sort of quantitative measure one can't be certain that the reaction isn't maxed out. In fact, the Method section does not even indicate how many cycles were utilized. Also, the authors indicate that there isn't a change in transcription, when, in fact, this isn't a transcriptional assay. The authors can only say there are no changes in mRNA levels (if they perform an quantitative experiment). Figure 4B,C,F. See comment for Fig. 1D. Figure 4C. The second upper panel is labeled CTS rather than CTSB. MG132 and baflomycin doses needed to be indicated either in the figure or in the figure legend. The authors also need to include a control to show that the baflomycin is working. Figure 5. A Figure 5 is shown, but there is no figure legend and it isn't referenced in the text. It appears to be a repeat of Figures 4D-F. This is very sloppy and indicates that the authors didn't reread the manuscript prior to submission.

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		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

In general, this is a good paper describing the effect of IGF-1 on HCC proliferation, migration, and metastasis. The authors found CTSB as a downstream target of IGF-1 I controlling the mechanism above. The mechanism of IGF-1 controlling CTSB level through protein degradation is pretty well demonstrated. There are 3 points I would like the authors to address: 1) expression level of IGF-1 receptor with CTSB knockdown, and also the level of IGFR on WT and Diabetic mice. 2) CTSB has been reported to be a Hedgehog target in pancreatic cancer. Does CTSB accumulation cause an upregulation in Hedgehog pathway (SHh, SMO, Patched receptor) etc , hence causing the increase migration and metastatic ability 3) Xenograft experiment showing decrease in tumour size after overexpression of PA28.