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ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology
ESPS manuscript NO: 17394
Title: HuR mediated post-transcriptional regulation as a new potential adjuvant therapeutic target in chemotherapy for pancreatic cancer
Reviewer's code: 03057875
Reviewer's country: Japan
Science editor: Jing Yu
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CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	Google Search:	[ ] Accept
[ ] Grade B: Very good	[Y] Grade B: Minor language polishing	[ ] The same title	[ ] High priority for publication
[Y] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] Duplicate publication	[ ] Rejection
[ ] Grade D: Fair	[ ] Grade D: Rejected	[ ] Plagiarism	[ ] Minor revision
[ ] Grade E: Poor		[Y] No	[Y] Major revision
		BPG Search:	
		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

The manuscript by Jakstaite and colleagues described a study demonstrating a role of HuR in chemoresistance of pancreatic cancer. The authors found that treatment with GEM induced HuR expression and its translocation from nuclear to cytoplasm, affecting COX-2 and HO-1 protein expression. They also revealed that knockdown of HuR sensitized pancreatic cancer cells to GEM treatment. Finally, they concluded that HuR would regulate the posttranscriptional modification of cytoprotective molecules including COX-2 and HO-1, and be a key molecule for induction of chemoresistance in pancreatic cancer. Although this study presents some interesting results, there are some critical points that need to be clarified and some additional information are required. Major points; 1. The authors showed that expression levels of HuR mRNA and protein were decreased in PDA tissues compared to normal tissues. However, expressions of COX-2 and HO-1, well-known targets of HuR, were increased in PDA. These results strongly suggested that HuR would not be main cause of COX-2 and HO-1 overexpression observed in pancreatic cancer tissues. In other word, HuR could modulate these expressions only under stress condition, because

GEM-induced HuR modulated COX-2 and HO-1 expression in pancreatic cancer cells as the author shown in this manuscript. To clarify that HuR could modulate COX-2 and HO-1 expression only after GEM treatments, they need to show that treatment with HuR siRNA alone do not affect on these expressions in Fig 6. Same approaches should be taken in Fig 7, 8 and 9. Moreover, they had better to investigate the expression of HuR, COX-2 and HO-1 in PDA tissues treated or untreated with GEM by immunohistochemistry. These approaches will be useful to prove their hypothesis. 2. It is hard to compare the intensity of immunoblot across the different membranes. In Fig 2, the authors need to apply protein samples from normal pancreas, pancreatic cancer, and colon cancer on same membrane. Same approaches should be taken in Fig 6A. 3. In this study, usage of beta-actin for loading control is inappropriate, because it has been reported that HuR binds to beta-actin mRNA and regulates its expression (Dormoy-Raclet et al. Mol Cell Biol. 2007). The authors need to use other internal control, such as GAPDH, and re-evaluate their results. 4. While the effects of HuR-knockdown in sensitivity to GEM were much in MiaPaca2 and SU.86.86 compared to Capan-1 and -2 cells, the activation levels of caspases 3 and 7 after HuR siRNA plus GEM-treatments looks quite similar in all cells. The results of fluorescence microscopy analysis, as presented in Fig 10, are hard to evaluate. Quantitation of caspase activation using luminescent assay is required. The authors also need to examine the effects of HuR-overexpression on chemoresistance in pancreatic cancer cells, in addition to HuR knockdown experiments. Minor points: 1. In Fig 3, the authors need to show the HuR expression of each tissue sample. 2. In Fig 9, it is hard to distinguish the morphological changes of cancer cells. The authors should show the photomicrographs with appropriate brightness and contrast. Same approaches should be taken in Fig 10. 3. In Fig 11, it is difficult to distinguish translocation of HuR from nuclear to cytoplasm. The authors need to show photomicrographs with high magnification. Furthermore, they need to show the images merged with DAPI stain and HuR expression. 4. I do not understand the explanation (“Study showed that HuR silencing sensitized pancreatic cancer cells to GEM, but didn’t have an effect on cell viability.”) since HuR knockdown further decreased cell viability in GEM-treated cells (Fig 7).