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ESPS Peer-review Report
Name of Journal: World Journal of Gastroenterology
ESPS Manuscript NO: 10285
Title: Inhibition of KL-6/MUC1 glycosylation limits aggressive progression of pancreatic cancer
Reviewer code: 02446370
Science editor: Yuan Qi
Date sent for review: 2014-03-24 21:06
Date reviewed: 2014-04-01 22:43

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A (Excellent)	[ ] Grade A: Priority Publishing	Google Search:	[ ] Accept
[ ] Grade B (Very good)	[Y] Grade B: minor language polishing	[ ] Existed	[ ] High priority for publication
[Y] Grade C (Good)	[ ] Grade C: a great deal of language polishing	[ ] No records	[ ]Rejection
[ ] Grade D (Fair)	[ ] Grade D: rejected	BPG Search:	[ ] Minor revision
[ ] Grade E (Poor)		[ ] Existed	[Y] Major revision
		[ ] No records	

COMMENTS TO AUTHORS

In this paper, the authors have studied the presence of KL-6/MUC1 epitope on two types of pancreatic cancer, PDAC and IPMN. They found that KL-6 is expressed in PDAC but not in IPMN. Then they inhibited O-glycosylation and N-glycosylation to try to correlate a type of glycosylation to biological properties of pancreatic cancer cells. They found differences that suggest that targeting glycosylation may be useful to control aggressive behavior of the tumor. Despite very interesting data, the paper can not be published as it is and would be greatly enhanced with a few additional experiments listed in the major points. In general, authors' conclusions are too fetched forward and often have to be modulated as they do not have the real proof for what they conclude. For example when they compare data in the two pancreatic cancer cell lines, they often conclude that the effects are the same in both cell lines when we can see clear differences. Major points: 1- The paper is on KL-6/MUC1 glycosylation (it is stated as early as in the title) but nowhere there is data on MUC1 to correlate with KL-6 stainings. It is important as KL-6 motifs may be found on other membrane glycoproteins. MUC1 immunohistochemical staining must be added in figure 1 to correlate with KL-6 and eventually show co-localization. In figure 1B, KL-6 positive staining is shown at the apical pole of normal epithelial cells. It is important to show MUC1 staining is there as well to be able to conclude that KL-6 staining corresponds of MUC1 peptide staining. 2- Figure 2: What are the controls to compare the effects of tunicamycin and BAG? Are cells incubated with solvent used to dissolve tunicamycin or BAG? This is not stated. Without the control we can not conclude to any effect since it is a comparative study. Add this information both in the material and methods section (proliferation assays) and in figure 1. 3- Figure 3E: conclusion that KL6/MUC1 staining decreased in both cell lines

must be modulated. It is not clear that there is a decrease in figure 3E. Same remark in figure 4. Inhibition following BAG treatment is quite clear whereas that following tunicamycin is more subtil (B and E), all cells are not spherical and individualized as shown for BAG (C and F). These differences between tunicamycin and BAG effects (figures 3, 4) should be discussed in the discussion section. It is clear from these experiments that inhibition of N-glycosylation does not alter cell properties as does inhibition of O-glycosylation with BAG. 4- Figure 6: again effects of tunicamycin on KL6 expression (decrease?) are not as clear cut as those with BAG. Moreover, there is no precise calculation of the number of cells expressing or not KL6 after the treatments. This should be done to give some depth to the conclusion. Observation on one field shown to the reader is not sufficient. Figure 6B: showing Ecadherin and vimentin expression by western-blotting is quite preliminary data to talk about EMT process. More is needed. Again modulate the conclusions. Especially increase of Ecadherin and decrease of vimentin in Panc-1 treated with tunicamycin is difficult to see/believe. It is the inverse that we see. Please explain/discuss. 5- Discussion should emphasize the differences between the two inhibitors that target either O- or N-glycosylation, it is obvious that the consequences are not the same. Make a parallel with oligosaccharidic structures present on MUC1/mucins in general? Discuss. Minor points: 1- Figures 4 and 5: What are the control groups? Please define. We do not know what control corresponds to. 2- Manuscript must be proofread by a native speaker to correct grammatical errors here and there. 3- Be careful with the terms used: to conclude at the end of the discussion that KL6 plays an important role… is a bit too fetched forward as no mechanistic is shown is the paper. Keep the conclusions to "possible involvement/implication" but certainly not a role.

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COMMENTS TO AUTHORS

WJG Reviewer report This is an interesting study on the role of MUC1 glucosylation in pancreatic malignancies. Nevertheless in general the investigation lacks convincing depth that could be improved by for example a second method for confirmation of claimed effects in each case. Some specific points/ questions: - The finding that all pancreatic ca cases were positive for the glucosylation ab (albeit in different degrees) is quite interesting. More details should be provided regarding the intensity of staining and if any quantitative measurement was applied. Also whether the pathologist grading was blinded on the patients' diagnosis. Were there any controls with benign pancreatic tissue diagnoses studied? If not it would be advisable to study and present such controls. Was any attempt of clinical prognostic correlation undertaken? - The part on EMT is particularly interesting but authors have presented only very initial data. Immunoflorescence data on vimentin should also be presented. In fig 6b, in contrast to what the authors claim, e-cadherin seems to be down-regulated and vimentin up-regulated with tunicamycin in Panc-1 cells. Also presenting quantification of the western data would be of help. - No attempt has been made for a mechanistic clarification of the seen effects, i.e. what are the intra-cellular pathways affected. - Addition of in vivo experiments would be a major asset for the paper. - Some language polishing is needed. This is particularly required for the abstract.