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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology
Manuscript NO: 32406
Title: The cytoplasmic domain of Tissue Factor promotes liver fibrosis in mice
Reviewer's code: 01027885
Reviewer's country: United States
Science editor: Jing Yu
Date sent for review: 2017-01-09
Date reviewed: 2017-01-28

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 paper by Knight et al describes that genetic ablation of the intracellular portion of tissue factor or of PAR2 downstream to tissue factor both reduce in a non-additive fashion fibrosis in the liver induced by treating mice with CCL4. Some insights in the mechanism of action of the two manipulations were provided by histological data indicating that they both reduce the frequency of activated smooth muscle cells and activated macrophages and the levels of TGF-beta, a known profibrotic factor, in the liver. The results are interesting in view of the fact that liver fibrosis is an unmet clinical need which involves a large number of patients and that drugs targeting tissue factor have been developed and are currently in clinical trials for treatment of thrombosis. Major Comments 1) Although the results were obtained on a robust number of mice, it is unclear how many times the experiments were repeated. Also, only male males were investigated. Given the gender-biased effects of TGF-beta, the experiments should be repeated also on female mice. 2) Representative histological data should be presented. In addition, the computer method used for their quantification

requires a better definition. What HPF means in Figure 2? Is this the same than hpf used in the result section? 3) The data are counterintuitive and provide limited mechanist insights. In fact, both deletion of the intracytoplasmic domain of tissue factor, which supposedly activated PAR2 because it is a PAR2 inhibitor, and PAR2 deletion prevented development of liver fibrosis. The authors should check the baseline levels of PAR2 in the tissue factor deficient mice to address this contradiction. In addition, they should take into consideration that the intracellular domain of tissue factor may repress liver fibrosis by activating an alternative pathway that is dominant over that of PAR2. This dominance may also explain why it is not possible to suppress further liver fibrosis by combining tissue factor and PAR2 deletion. The hypothesis of two distinctive pathways would also explain the additional paradox mentioned in the paper. That is that deletion of the entire tissue factor protein, by activating thrombosis, induces heart fibrosis, while deletion of the sole intracellular portion of the protein reduced liver fibrosis (this manuscript). Overall however, I suggest deleting the discussion about heart fibrosis. Fibrosis in the liver and in the heart may be determined by distinctive mechanisms anyhow. 4) The authors should carefully revise the manuscript to avoid over-interpretation. As an example, on page 13, line 24, the authors state that they have shown a reduction in macrophage recruitment in the liver of knock out mice following induction of liver fibrosis. Since the livers were stained only with an antibody that identified activated macrophages, the paper does not provide any data on the frequency of the total macrophage population in this organ. The discussion few lines below on PDGF-BB induced chemotaxis is also not supported by determinations of PDGF-BB expression. 5) Efforts should be made to reduce the extensive speculations made in the Discussion. A way to achieve this would be to move the first paragraph of the discussion which provides the rationale for the study in the Introduction and to delelete the lines 5-8 on page 14 which deal with breast cancer and not with fibrosis. 6) Ablation of tissue factor and PAR-2 reduces but does completely prevent development of liver fibrosis in this model. The absence of data indicating that these levels of reduction have therapeutic significance is a major drawback of the paper. Also unclear is whether it is possible to achieve by pharmacological means levels of tissue factor or PAR-2 inhibition similar to those achieved by deleting the genes. Pharmacological inhibitors of TF should not only be discussed but also investigated in this model. Minor comments 1) Figure captures. All the Figure captures shou