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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 35758

Title: PXR and CAR modulate differently CYP3A-mediated metabolism in early- and late-stage cholestasis

Reviewer's code: 02855928

Reviewer's country: Japan

Science editor: Ze-Mao Gong

Date sent for review: 2017-08-07

Date reviewed: 2017-08-11

Review time: 3 Days

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input checked="" type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input checked="" type="checkbox"/> No	<input checked="" type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		BPG Search:	<input type="checkbox"/> Major revision
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input checked="" type="checkbox"/> No	

COMMENTS TO AUTHORS

Data of regulation/ blocking of PXR and/or CAR should be shown. This data seems to be important for their suggestion.



PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 35758

Title: PXR and CAR modulate differently CYP3A-mediated metabolism in early- and late-stage cholestasis

Reviewer's code: 02447901

Reviewer's country: Taiwan

Science editor: Ze-Mao Gong

Date sent for review: 2017-08-07

Date reviewed: 2017-08-15

Review time: 7 Days

Table with 4 columns: CLASSIFICATION, LANGUAGE EVALUATION, SCIENTIFIC MISCONDUCT, CONCLUSION. It contains checkboxes for various review criteria like 'Grade A: Excellent', 'Priority publishing', 'Google Search', 'Accept', etc.

COMMENTS TO AUTHORS

In this manuscript, the authors ascertained whether cholestasis affected the expression of CYP3A1, CYP3A2, PXR, and CAR in bile duct ligated rodents. When comparing with sham, 2-week of bile duct ligation increased hepatic PXR, CAR, and CYP3A1 expression and 4-week of bile duct ligation downregulated PXR, CAR, and CYP3A1 expression. Hepatic nuclear receptors such as PXR and CAR and corresponding effectors such as CYP3A are crucial to cholesterol and bile acid metabolism and have substantial roles in the pathogenesis of cholestasis. Therefore, their altered expression during the course of cholestasis is expected. Advanced study designs and experiments are required. 1. A course of two week and four week was defined as mild and severe state of cholestasis. Although histological examination and hepatic biochemical findings revealed changes in hepatic tissues of wild cholestasis, data of common serum biochemical failed to



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demonstrate liver injury. Generally, 2-week of bile duct ligation was enough to cause liver injury in rodents. 2. The levels of bile acids should be monitored. 3. In addition to measurement of PXR, CAR, and CYP3A expression, parameters behind these nuclear receptors and enzymes should be examined for comparison.



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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 35758

Title: PXR and CAR modulate differently CYP3A-mediated metabolism in early- and late-stage cholestasis

Reviewer's code: 00004925

Reviewer's country: Austria

Science editor: Ze-Mao Gong

Date sent for review: 2017-08-07

Date reviewed: 2017-08-16

Review time: 9 Days

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input checked="" type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input checked="" type="checkbox"/> No	<input checked="" type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		BPG Search:	<input type="checkbox"/> Major revision
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input checked="" type="checkbox"/> No	

COMMENTS TO AUTHORS

This is a well written paper demonstrating that early and late cholestasis affect the expression of the drug metabolizing enzymes CYP3A1 and CYP3A2 differently. The findings are of scientific and clinical relevance. I have the following questions and comments. 1. Since the focus of the paper is on drug metabolism it would be of interest to include data on the expression of CYP3A4. 2. Strictly speaking, the authors only demonstrated a correlation between the changes in PXR and CAR expression, not a cause effect relationship. Please change the wording in the discussion on page 12, lines 19-20. 3. In discussing the cross-talks of NRs in the regulation of intermediate metabolism, FXR should be mentioned. 4. Discussion, last sentence: BA elimination was not a topic of this paper and the relevant transporters have not been studied. Please modify. 5. Abstract: Consider to modify the conclusions. Promoting drug metabolism



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may be a target better related to the topic of this paper. There are no data in this paper on BA elimination