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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology
Manuscript NO: 36962
Title: Autoimmune liver diseases-related autoantibodies in patients with biliary atresia
Reviewer's code: 03011144
Reviewer's country: India
Science editor: Ke Chen
Date sent for review: 2017-11-22
Date reviewed: 2017-11-22
Review time: 1 Hour

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] Grade A: Excellent	[Y] Grade A: Priority publishing	Google Search:	[Y] Accept
[Y] Grade B: Very good	[ ] 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	[ ] Minor revision
[ ] Grade E: Poor		[ ] No	[ ] Major revision
		BPG Search:	
		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[ ] No	

COMMENTS TO AUTHORS

Further focus on clinical outcome - jaundice clearance vs ab titre would be interesting. Was maternal sera also analyzed to co-relate the ab titre in the children?

Response to Reviewer 1(03011144);
We sincerely thank you for your kind view and positive comments on our manuscript. We were sorry to tell you that the correlation of maternal serum antibody titre to the children was failed to be analyzed in our present study, for the difficulty to obtain the mothers'serum samples of the children. Considering the clinical significance of titre and the source of autoantibodies in biliary atresia, an elaborated enlarged study would be necessary. The clinical outcome-jaundice clearance vs antibody titre would also be included in future investigation, as you kindly suggested.

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology
Manuscript NO: 36962
Title: Autoimmune liver diseases-related autoantibodies in patients with biliary atresia
Reviewer's code: 01553680
Reviewer's country: Japan
Science editor: Ke Chen
Date sent for review: 2017-11-22
Date reviewed: 2017-11-22
Review time: 8 Hours

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		[ ] No	[ ] Major revision
		BPG Search:	
		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[ ] No	

COMMENTS TO AUTHORS

In this study, the authors tried to evaluate the utility and specificity of autoimmune liver disease (ALD)-related autoAbs in patients with biliary atresia (BA). They found that anti-BPO Ab and ANCA were more frequently detected in BA patients than in controls. Interestingly, ANCA positivity was closely associated with the appearance of post-operative cholangitis. This study is well-controlled retrospective one and the authors successfully provide evince that a significant population of patients with BA were positive for ALD-related autoAbs. Please address the following points to strengthen their conclusion. 1) If BA is characterized by autoAb production, then how the autoAbs are produced? Autoimmune-diseases are usually associated with pro-inflammatory cytokine responses. Please examine the serum levels of pro-inflammatory Th1 and Th2 cytokines with the ability to enhance autoAb production. 2) Neutrophil activation is associated with ANCA production. Is there any evidence that

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neutrophils are activated in BA? Please examine the number of peripheral blood neutrophils in patients with BA. 3) Please discuss the mechanisms accounting for high prevalence of anti-BPO Ab in BA patients. 4) Immune responses to intestinal microflora underlie the immuno-pathogenesis of several autoimmune disorders including ALD. Is there any evidence that dysbiosis is involved in the immune-pathogenesis of BA? Please discuss.

Response to reviewer (01553680**);**

1) If BA is characterized by autoAb production, then how the autoAbs are produced? Autoimmune-diseases are usually associated with pro-inflammatory cytokine responses. Please examine the serum levels of pro-inflammatory Th1 and Th2 cytokines with the ability to enhance autoAb production.

Response： Thank you very much for your comments.
AutoAbs production is a common phenomenon in BA. We suppose that molecular mimicry should be the main mechanism to explain the onset of the autoimmune response and production of autoAbs in BA. A recent study provided evidence for this assumption. In the study, they reported that viral RRV peptides mimicing self-peptides led to a break in immune tolerance and development of autoantibodies [α-Enolase Autoantibodies Cross-Reactive to Viral Proteins in a Mouse Model of Biliary Atresia].Some other unidentified exogenous proteins which shared similar antigenic motifs with self-proteins might also participate in the process of autoAbs production in BA.

In your review, you mentioned that the serum levels of proinflammatory Th1 and Th2 cytokines with the ability to enchance autoAb production.We agreed very much to your opinion on this. However, we did not examine the serum levels of Th1 and Th2 cytokines in the current study, for the limited amount of sera available in our experiments. Nevertheless, there are bunch of studies in mice, as listed in the references, reported that not only Th1 and Th2 cells increased in BA but also the serum levels of their produced cytokines (eg, IFN-γ、IL-2 and IL-13) rose up.[①Armed CD4+ Th1 effector cells and activated macrophages participate in bile duct injury in murine biliary atresia. Clin Immunol, 2005, 115(2): 200-209. ②Obstruction of extrahepatic bile ducts by lymphocytes is regulated by IFN-gamma in experimental biliary atresia. J Clin Invest, 2004, 114(3): 322-329. ③Biliary atresia is associated with CD4+ Th1 cell-mediated portal tract inflammation. Pediatr Res, 2004, 56(1): 79-87. ④Genetic induction of proinflammatory immunity in children with biliary atresia. Lancet, 2002,360(9346): 1653-1659. ⑤Th2 signals induce epithelial injury in mice and are compatible with the biliary atresia phenotype. J Clin Invest, 2011, 121(11): 4244-4256. ⑥Cellular and humoral autoimmunity directed at bile duct epithelia in murine biliary atresia. Hepatology, 2006, 44:1231–1239.]

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2) Neutrophil activation is associated with ANCA production. Is there any evidence that neutrophils are activated in BA? Please examine the number of peripheral blood neutrophils in patients with BA.

Response: Thank you very much for your comments.
There are several evidence supported that the neutrophils are activated in BA. Lu et al has reported that α-enolase, one of the minor antigen targets of antineutrophil cytoplasmic antibodies present in BA [alpha-enolase autoantibodies cross-reactive to viral proteins in a mouse model of biliary atresia. *Gastroenterology* 2010; 139: 1753-1761]. Studies also showed that the accumulation of neutrophils to the site of biliary injury attracted by release of IL-8/Cxcl-8 by macrophages [Macrophages are targeted by rotavirus in experimental biliary atresia and induce neutrophil chemotaxis by Mip2/Cxcl2. Pediatr Res. 2010; 67(4):345–51], and confirmed the wide distribution of neutrophils in biliary atresia, occurring as a result of bile duct obstruction. [Neutrophils in biliary atresia. A study on their morphologic distribution and expression of CAP37. Pathol Res Pract. 2010; 206(5):314-7.]

As you suggested, the number of peripheral blood neutrophils in patients with BA has been added in supplemental materials (**Supplemental Table 1).** The data showed that the number of leukocyte, neutrophil, and neutrophil % in ANCAs-positive biliary atresia was slightly higher than the ANCA-negative group; however, there was no statistical significant differences between both groups.

3) Please discuss the mechanisms accounting for high prevalence of anti-BPO Ab in BA patients.

Response: Thank you for your comments. The mechanisms accounting for the high prevalence of anti-BPO autoantibody in BA may explain as following:
Liver is particularly rich in mitochondrion organelles. Persistent cholestasis in BA often leads to hepatocyte injury, the exposed mitochondrion to immune cells will induce the production of autoantibodies,i.e. anti-AMA (mainly consists of anti-BPO), which is the serological hallmark of primary biliary cirrhosis (PBC) with unclear pathogenetic significance. In this study, the positivity rate of anti-BPO showed no difference in short-term outcomes of follow-up BA (Page 12). There was also no correlation between anti-BPO and PBC in the period and severity of the diseases, and the effects of treatments. Our findings suggested that anti-BPO be a potential biomarker emerging in the humoral autoimmune response against live damage.

4) Immune responses to intestinal microflora underlie the immuno-pathogenesis of several autoimmune disorders including ALD. Is there any evidence that dysbiosis is

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involved in the immune-pathogenesis of BA?

Response：Thank you for your comments. Immune response to intestinal microflora does underlie the immuno-pathogenesis of several autoimmune disorders including ALD. However, the involvement of dysbiosis in the immune-pathogenesis of BA was not included in our present study for it is beyond the scope of this paper. Interestingly, a recent study on animals suggested that the postnatal development of the intestinal microbiota is an important susceptibility factor for experimental BA. [Cxcr2 signaling and the microbiome suppress inflammation, bile duct injury, and the phenotype of experimental biliary atresia. PLoS On, 2017 Aug 1; 12(8): e0182089.] The data also form the rationale for future human-based studies to investigate the microbiome profiles at diagnosis and following hepatoportoenterostomy. So I think that it is worth exploring dysbiosis of intestinal microflora in the immune-pathogenesis of BA.

Response to editor's suggestion;

We thank the editor for carefully reading our manuscript and for giving detailed suggestions. We did the following tasks according to editor's suggestion:

1. We provided language certificate letter by professional English language editing company (*Filipodia Publishing, LLC*).

2. Our work described in the manuscript was partially supported by grants from the Guangdong Provincial Science and Technology Planning Projects (No. 2014A020212520) and the Guangzhou Science and Technology Project (No. 201707010014). We also provided the approved grant application documents.

3. We made an audio file describing our final core tip.

4. We finished this part of the ARTICLE HIGHLIGHT.

5. We checked the references and found that there were no repeated references. Meantime, we added PubMed citation numbers and DOI citation to the reference list and list all authors.

6. We revised the figure 2 according to the editor's suggestion.