Response letters

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Manuscript title: Bile acids and their receptors: potential therapeutic targets in inflammatory bowel disease

Dear Editors and Reviewers：

Thank you for the reviewer's comments concerning our manuscript entitled " Bile acids and their receptors: potential therapeutic targets in inflammatory bowel disease ". Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied comments carefully and have made corrections which we hope to meet with approval. Revised portions are marked in yellow on the paper. The main corrections in the paper and the responds to the reviewer's comments are as follows:

Reviewer 1:

Comments to the Author

1.Table 1 is not referred in the body of the text.

Reply: Thank you very much for your advice. We have inserted references to the Table 1 in the appropriate place in the text.

2. The text does not refer to the Figures. The authors must insert references to the Figures in the appropriate place in the text.

Reply: Thank you very much for your advice. We have inserted references to the Figures in the appropriate place in the text.

3. “inflammatory bowel disease” is not contracted to its abbreviation IBD on several occasions.

Reply: Thank you very much for your advice. We have carefully checked and revised the irregular abbreviations in the article.

4. Rewrite following sentences: .-Sentence in “2.1. Bile acid in the liver” when introducing HSD37. .-First sentence in “2.2 Bile acid metabolism in the intestine” when mentioning “micellar micelles”. .-“Interestingly, similar to isolithocholic acid (isoLCA), isoLCA can also…” .-“The absence of Pak2 in Th17 cells Genetic deletion of Pak2 in Th17 cells decreases…” .-“ ILC3 in intestinal draining lymph nodes expressed numerous significant class II histocompatibility complexes, according to a recent study (MHCIIs).” .-“Akagbosu” et al. .-Akkermansia muciniphila. .-“PXR and CAR have the typical modular nuclear receptor structure, which consists of a hinge, a DNA-binding domain (DBD), a ligand-binding domain, activation function 1 (AF-1), and activation function 2 (AF-2) (LBD).”
Reply: Thank you very much for your advice. We have modified the above phrases.

5. Suppress following sentences: .-“RORγt is a main transcription factor for Th17 cells.” Before “In paradox,…” .-“Paneth cells, which are positioned at the base of small intestinal crypts, release -defensins and play a crucial role in regulating intestinal flora and preserving intestinal homeostasis” is repeated.
Reply: Thank you very much for your advice. We have modified the above phrases.

Reviewer 2:
Comments to the Author
1. There is no figure citation in the main text, although there are only citations for Table 2. Please indicate citations for figures and Table 1 in the main text.
Reply: Thank you very much for your advice. We have inserted references to the Tables and the Figures in the appropriate place in the text.

2. The section "2.2 Bile acid metabolism in the intestine", 1st paragraph. "Changes in the intestinal epithelium of individuals with IBD decrease the reabsorption of bile acids by ASBT and increase the number of bile acids discharged in teh feces." Is this phenotype

related to changed nuclear recdeptor function(s)?

Reply: Thank you very much for your comments. The expression of ASBT can be regulated by nuclear receptors (FXR, CAR, PXR, VDR)[1, 2]。For example, reabsorbed bile acids can activate the FXR/ FGF axis, thereby negatively feeding back to inhibit ASBT expression and maintain the balance of the bile acid pool. Several previous studies have shown that intestinal inflammation significantly reduces FXR activation, thereby decreasing the activation of the FXR/ FGF axis and inhibiting ASBT expression. [3, 4]. Using real-time polymerase chain reaction to assess mRNA expression in intestinal mucosal biopsies from IBD patients, researchers found that ASBT expression was suppressed and accompanied by increased levels of inflammatory factors [5]。However, the underlying mechanisms of reduced ASBT levels in IBD are still not fully understood, and autochthonous diseases or drugs may also induce or inhibit transporter expression, leading to disturbances in the feedback mechanism[6, 7]。

3. The section "2.2 Bile acid metabolism in the intestine", 3rd paragraph. "This alteration reduces depolymerization and 7α-dehydroxylation, strongly decreasing the conversion capacity of the microbiota, resulting in a decrease in SBAs (DCA, LCA) and an elevation in primary and conjugated bile acids (CA, CDCA, TCA, GCA)." How does this phenotype influence receptor functions?

Reply: Thank you very much for your comments. In the terminal ileum, most conjugated BAs are reabsorbed and the others go through the deconjugation mediated by colonic microbiota. In colon, the unconjugated BAs are further transformed into secondary BAs (DCA and LCA) via 7α-dehydroxylation and finally excreted in feces. In IBD, gut dysbiosis affects the metabolism and mainly reduces the deconjugation and 7α-dehydroxylation, leading to the depletion of secondary BAs. On the one hand， Increased primary and conjugated bile acids will inhibit hepatic bile acid synthesis by activating the FXR-SHP/FGF axis. On the other hand, in section "3. The impact of bile acids and their receptors …", we described that some secondary bile acids can affect the pathophysiological mechanisms of IBD by acting on bile acid receptors in the intestine. The decrease in secondary bile acids reduces the activation of bile acid receptors in the

intestine, thus affecting the regulatory role of secondary bile acids.

4. The section "3.2 RORγt" "Interestingly, similar to isolithocholic acid (isoLCA), isoLCA can also de-suppress Th17 cells differentiation by inhibiting RORγt." This sentence does not make sense. Is "similar to isoLCA" correct? Is "de-suppress" correct? IsoLCA suppresses Th17 cells differentiation, doesn't it?

Reply:Thank you very much for your comments. We have modified the above phrases in the manuscript.

5. The section "4.3 UDCA". Please discuss what receptors are involed in the UDCA activity

Reply:Thank you very much for your comments. We have added a discussion on the activation of bile acid receptors by UDCA in IBD. However, studies in this area are still in their infancy and need to be further explored.

1 Chen ML, Huang X, Wang H, Hegner C, Liu Y, Shang J, Eliason A, Diao H, Park H, Frey B, Wang G, Mosure SA, Solt LA, Kojetin DJ, Rodriguez-Palacios A, Schady DA, Weaver CT, Pipkin ME, Moore DD, Sundrud MS. CAR directs T cell adaptation to bile acids in the small intestine. Nature 2021; 593(7857): 147-151 [PMID: 33828301 PMCID: PMC8862117 DOI: 10.1038/s41586-021-03421-6]

2 Van den Bossche L, Borsboom D, Devriese S, Van Welden S, Holvoet T, Devisscher L, Hindryckx P, De Vos M, Laukens D. Tauroursodeoxycholic acid protects bile acid homeostasis under inflammatory conditions and dampens Crohn's disease-like ileitis. Laboratory investigation; a journal of technical methods and pathology 2017; 97(5): 519-529 [PMID: 28165466 DOI: 10.1038/labinvest.2017.6]

3 Gadaleta RM, Oldenburg B, Willemsen EC, Spit M, Murzilli S, Salvatore L, Klomp LW, Siersema PD, van Erpecum KJ, van Mil SW. Activation of bile salt nuclear receptor FXR is repressed by pro-inflammatory cytokines activating NF-κB signaling in the intestine. Biochimica et biophysica acta 2011; 1812(8): 851-858 [PMID: 21540105 DOI: 10.1016/j.bbadis.2011.04.005]

4 Nijmeijer RM, Gadaleta RM, van Mil SW, van Bodegraven AA, Crusius JB, Dijkstra G, Hommes DW, de Jong DJ, Stokkers PC, Verspaget HW, Weersma RK, van der Woude CJ, Stapelbroek JM, Schipper ME, Wijmenga C, van Erpecum KJ, Oldenburg B. Farnesoid X receptor (FXR) activation and FXR genetic variation in inflammatory bowel disease. PloS one 2011; 6(8): e23745 [PMID: 21887309 PMCID: PMC3161760 DOI: 10.1371/journal.pone.0023745]

5 Jahnel J, Fickert P, Hauer AC, Högenauer C, Avian A, Trauner M. Inflammatory bowel disease alters intestinal bile acid transporter expression. Drug metabolism and disposition: the biological fate of chemicals 2014; 42(9): 1423-1431 [PMID: 24965812 DOI: 10.1124/dmd.114.058065]

6 Zhu Q, Iwai R, Okaguchi T, Shirasaka Y, Tamai I. Apple juice relieves loperamide-induced constipation in rats by downregulating the intestinal apical sodium-dependent bile acid transporter ASBT. Food & function 2023 [PMID: 37129213 DOI: 10.1039/d3fo00510k]

7 Liu S, Liu M, Zhang ML, Wang CZ, Zhang YL, Zhang YJ, Du CY, Sheng SF, Wang W,

Fan YT, Song JN, Huang JC, Feng YY, Qiao W, Huang JL, Li YH, Zhou L, Zhang J, Chang YS. Transcription factor Klf9 controls bile acid reabsorption and enterohepatic circulation in mice via promoting intestinal Asbt expression. Acta pharmacologica Sinica 2022; 43(9): 2362-2372 [PMID: 35105957 PMCID: PMC9433408 DOI: 10.1038/s41401-021-00850-x]