

ESPS manuscript NO: 22913

Title: Therapeutic strategies for metabolic syndrome via bile acid signaling pathway

We are grateful to the editor and reviewers for their comments and suggestions; they have helped us improve our paper considerably. As indicated in the following responses, we have taken all of these comments and suggestions into account in the revised version of our paper.

Editor's comment 1

Please only keep one address for the correspondence author.

Response 1

We have removed the address of "Department of Internal Medicine, Keio University School of Medicine, Shinjuku, Tokyo, 160-8582, Japan." and kept one address.

Editor's comment 2

Please add PubMed citation numbers and DOI citation to the reference list and list all authors. Please revise throughout. The author should provide the first page of the paper without PMID and DOI.

PMID (<http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=PubMed>) DOI
(<http://www.crossref.org/SimpleTextQuery/>)

Response 2

We added PubMed citation numbers and DOI citation.

Editor's comment 3

Please provide all the figures in PPT format (primary version).

Response 3

I will submit all the figures in PPT format.

Reviewer 1:

Reviewer's code: 00009616

Comment 1:

good review

Reply1:

Thank you.

Reviewer 2:

Reviewer's code: 02445706

Comment 1

I do recommend the publication of this paper in its present form

Reply 1:

Thank you for your comment.

Reviewer 3:**Reviewer's code: 02861055** □

The submitted manuscript by Taoka et al. is a detailed review of current literature about the emerging roles of bile acids as signaling molecules. In particular, the paper focuses on the role of bile acids in metabolic pathways and on how the manipulation of these pathways could become a strategy to treat metabolic syndrome in humans. The manuscript is of interest. A number of minor issues are listed below.

Comment 1

The title of the manuscript does not reflect the main subject of the paper. The paper mainly deals with the role of bile acids in the regulation of the metabolic pathways, rather than with current therapeutic strategies for metabolic syndrome based on bile acids. The title should be changed accordingly.

Response 1:

We agree. We have changed the title from “Therapeutic strategies for metabolic syndrome via bile acid signaling pathway” to “Role of bile acids in the regulation of the metabolic pathways”. We also changed the running title from “Bile acid and metabolic syndrome” to “Bile acid and metabolic regulation”.

Comment 2

The paragraph “Novel roles of bile acids in the gastrointestinal tract” includes too many different notions, which are not necessarily “new” (e.g. bariatric surgery and BARR). The Authors should decide the message of this paragraph and avoid redundancy.

Response 2:

We agree and have changed “Novel roles of bile acids in the gastrointestinal tract” into “Roles of bile acids in the gastrointestinal tract”. We removed the word “Novel”.

Comment 3

The paragraph “Bile acids and autophagy” would find a better allocation later in the manuscript. Priority should be given to glucose, lipid and energy metabolism.

Response 3:

We agree, and have assigned the paragraph “Bile acids and autophagy” later in the manuscript and also allocated the figure “Autophagy regulation by the FXR” to the latter part.

Comment 4

In the paragraph “Bile acids in glucose metabolism” the Authors should briefly mention the current clinical use of GLP-1 agonist in the treatment of diabetes.

Response 4:

Thank you for your comment. We have added the plain mention of GLP-1 current clinical use of GLP-1 agonist in the paragraph “Bile acids in glucose metabolism”.

Comment 5

The manuscript should be revised by an English native speaker for spelling and grammar errors.

Response 5:

We have submitted this manuscript to Native Speakers of English editing and revised the language of our manuscript.

