

Reviewer#1:

Manuscript NO 64603

Title "**Gut microbiota-derived metabolites as key modulators in obesity**"

The authors have taken on an important task in the present manuscript: to elucidate the mechanisms by which several relatively well-studied microbial metabolites can influence intestinal mucosal homeostasis and discuss how they might affect metabolic diseases. Pathogenic mechanisms of microbiota involved in metabolic syndrome remain elusive. This topic is indeed a very interesting one. The subject would be of general interest to the community of obesity researchers besides to the clinicians. It is well organized and easy to read. The manuscript is a comprehensive review and references are numerous and of recent data.

However, I have some suggestions to make in order to improve the clarity of the manuscript:

1. The title is quite general and it does not reflect with precision the content of the review.

Answer:

The title has changed to "Gut microbiota-derived metabolites as key mucosal barrier modulators in obesity". This modification can reflect the fact that this review is focused on microbial metabolites on mucosal homeostatic regulation.

2. I suggest a short reminder of gut barrier homeostasis in the Introduction section.

Answer:

We have added this information in the introduction part accordingly.

3. In other way, the first paragraph of the point 2 when the authors describe the different types of free fatty acids can be obviated because is rather known and focused only in short fatty acids. The origin of this fatty acids in the gut could be specified.

Answer:

We have deleted the unnecessary description of long- and medium-chain FAs accordingly.

4. The heading 5. “Dietary derived microbial metabolites in regulating mucosal homeostasis” could be the heading 2 because all (SCFA, tryptophan-derived, tyrosine-derived ...are of dietary origin and produced by bacteria). The heading could be “Other dietary-derived....”

Answer:

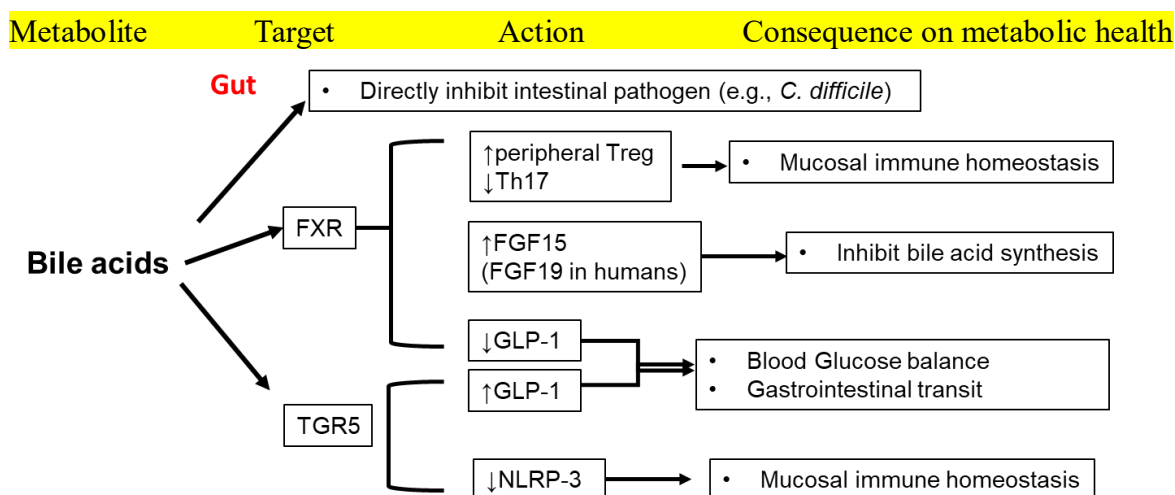
The heading has been modified accordingly.

5. Figures are rather confused. First, the legend of the figures must be sufficiently explanatory by itself, without having to resort to the text (there is not a legend at all). The legends should be modified at this regard. It lacks the definitions of the abbreviations. It should be specified if the metabolite activates or decreased the action of the target.

(our response is on the next page)

I propose that should have four explicative points in the three figures: The metabolite in question. A column with the target of the metabolite, a column with the molecular effect and the action produced in mucosal homeostasis and a column with the consequences on metabolic health (carbohydrate intolerance, blood hypertension, dyslipidemia, inflammation ...). In this sense, the known effect of GPR41 activation on blood pressure is not mentioned.

For example, in Figure 3:



In the current format the information is variable in the three figures, is mixed the effect produced in mucosal homeostasis and the consequences on metabolic health. It is not clear regarding if the metabolite stimulates or inhibits the target, mainly in figure 1 is notorious this aspect. There is information in the text not reflected in the Figures (action of SFA on the activation of G-coupled receptors GPR43 and GPR109)

Answer:

Thanks for the reviewer's great suggestions.

1) We have modified all the figures accordingly. The exact effects of the metabolites in stimulating or inhibiting their targets are indicated accordingly. Actions of SCFAs on GPR43/GPR109 have been added to the figure accordingly.

2) We have added detailed descriptions of the figure legends accordingly.

3) We have not added the references regarding GPR41 regulation of blood pressure, considering the fact that the manuscript is majorly focused on intestinal barrier functions, but not the systemic effects of SCFAs per se. If the reviewer insists, we will be happy to add the information accordingly.

Minor remarks

Please, explain the abbreviation the first time in the text (DCs?)

Answer:

We have added the full name accordingly.

Reviewer #2:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: "Gut microbiota-derived metabolites as key modulators in obesity" is an interesting paper. Authors have well summarized and explain the role of many metabolites on mucosal homeostasis. I have really appreciated the summary figures.

Answer:

Thanks for the positive review.