

June 24, 2014

Dear Editor,

Thank you for your invitation to contribute to the World Journal of Gastroenterology (ID 02807991). Please find enclosed the revised topic highlight in Word format (file name: 10417-review.docx).

Title: Mechanistic links between gut microbial community dynamics, microbial functions and metabolic health.

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Name of Journal: *World Journal of Gastroenterology*

ESPS manuscript no: 10417

All requested revisions from the Editor have been made. In addition we have responded to all reviewers' suggestions. In the edited manuscript responses to explicit requests from the reviewers are underlined. Additional minor changes that improve the overall quality of the manuscript are highlighted. The manuscript is co-authored by native English speakers with extensive editorial experience who have carefully checked all grammar and spelling.

Reviewer 02907177:

The three main criticisms of this reviewer (below) suggest an unrealistic expectation for a manuscript that is focussed on human clinical applications. This is not realistic for the microbiome in metabolic disease since definitive microbial markers for metabolic dysbiosis are still lacking and outside the scope of the review plan we submitted to the journal in response to the invitation.

- 1) *The diagnostic and therapeutic aspects related to gut microbiota would be more useful.*
- 2) *It is not a systematic review, limited to a narrative review.*
- 3) *The evidence used to sustain the article is poor, with many studies in animals, "in vitro", about microbiology, physiology and pathology.*

In order to distinguish this manuscript from other reviews on gut microbiome and metabolic health, we balanced the evidence for host-microbe linkages in metabolic dysbiosis with a critique on the factors that complicate the process of identifying diagnostic markers (pages 3-8). The focus of this manuscript is to dissect the mechanisms by which host-microbiome interactions contribute to metabolic dysbiosis. Mechanistic studies in humans are scarce due to ethical concerns and thus, the majority of the proof-of-concept findings are derived from experiments conducted in animals. Approximately 25% of the references are examples that then relate this primary evidence from animal models to associations observed in cross-sectional and intervention studies in humans.

We have further focussed the review by reducing the extent of narrative sections. Some sections of any review inevitably have a narrative style because supporting evidence needs to be described with sufficient detail to systematically address the main theme. In this case sections on host

response have been rephrased and added (page 4, underlined text) to extend our evaluation of the interdependent relationship between host system, diet and gut microbiome. The whole review, especially Table 1 and our hypothesised drivers and triggers of diet-induced dysbiosis (pages 14 and 15), is a unique synthesis of the present knowledge of the gut microbiome and its functions in metabolic health.

Reviewer 02946383 did not make any suggestions.

Reviewer 00072815:

1) *The association of the microbiome and central nervous system should be mentioned.*

We thank the reviewer for this suggestion. We have addressed this suggestion by including additional references and expanded our discussion on the gut-brain axis (underlined text in pages 3 and 12). Since the focus of the review is on microbial dynamics we feel further detail would be out of the scope.

2) *Though Paneth cells are mentioned in Figure 2, but the role of beta defensins should be discussed.*

We introduce the subject of antimicrobial peptides to illustrate a mechanism by which the host animal exerts control on microbial distribution within the intestinal tract and may also influence community structure. We make a brief generic statement in this regard and have included a further reference that clarifies the role of beta defensins in this regard. We feel the specific examples given of alpha defensins and RegIIIy (underlined text in page 8) are sufficient and more appropriate to support the main point and have not included further specific discussion of beta defensins (nor did we think the reviewer was asking for this).

Regards,



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