FACULTY OF HEALTH AND MEDICAL SCIENCES
UNIVERSITY OF COPENHAGEN

Editor
World Journal of Gastroenterology

30 SEPTEMBER 2014

DEPARTMENT OF VETERINARY DISEASE BIOLOGY

AXEL KORNERUP HANSEN
PROFESSOR,
DR.MED.VET., DVM, DIP.ECLAM

EXPERIMENTAL ANIMAL MODELS
THORVALDSENSVEJ 57, ST
DK-1871 FREDERIKSBERG C
TEL DIR +45 35 33 27 26
akh@sund.ku.dk

Dear editor

I hereby submit

The impact of the gut microbiota on rodent models of human disease

Manuscript No 9783

after revision.

I thank the reviewers for their valuable comments and I have the following replies to the points raised:

Reviewer No 1

This is a very interesting review article on the role of the gut microbiota composition on rodent models of human diseases. The topic is very interesting and very original. The manuscript is well written and the figures very clear.

Thank you.

Reviewer No 2

General Comments

In the introductory pages containing the Introduction, General Mechanisms Behind Gut Microbiota Impact, and Examples of the Impact of the Overall Composition of the Gut Microbiota sections, I think subheadings could be useful. For example, the mechanisms that you have discussed include immune-mediated mechanisms, metabolic mechanisms, etc. I think including these types of subheadings would help to organize the section.

Good point. Subheadings has been inserted.

It would be useful if in the Introductory sections, there was an expanded view of the symbiotic relationship between the host and its gut microbiota. Is it mutualism or commensalism? What might be the benefit of the symbiotic relationship to the microbe?

A section with the subheading 'The host-microbiota relationship' has been inserted into the introduction.

In the sections pertaining to animal models of IBD, it would be helpful if the authors were sure to point out which model of IBD is being used in the discussed studies. This is important, because there are multiple animal models for IBD, including IL-10-/- mice, C. rodentium-challenge, DSS administration, etc. It is also important to make sure that it is clear that these are models of colitis and not actually inflammatory bowel disease (in some instances the model is referred to as IBD in mice).

This has been done. It is furthermore explained in Table 1.

It is interesting to note that there was no discussion of overall diversity measures and how they may pertain to health/disease. Can the authors comment on whether alpha diversity can have detrimental effects for health?

It is now described as 'In both man and mouse a microbiota with a low diversity is indicative of an increased risk of developing inflammatory disease' (Section 'The complexity of microbial impact on the host').

In the Discussion, the authors make the point that the same microbes can have different effects on different diseases. The example is given of SFB protecting against Type 1 diabetes, but also enhancing colitic inflammation. Is there evidence that the levels of the microbes, and not just absence vs. presence, are important?

This is now described as 'For most of these bacteria it is the abundance of them rather than it is the qualitative presence or absence of them, which are responsible for their impact on the host' (Section 'The complexity of microbial impact on the host'). Examples of this are also given under the specific bacteria.

I am not sure what the last two sentences of the Discussion mean. Are the authors implying that we should not screen/eradicate pathogens in our laboratory mice? If so, how would one control for the presence of these diseases in experiments?

I admit that the sentence concerning getting resources by reducing the amount of ordinary bacteriological quality control is irrelevant here, and it has been omitted.

Specific Comments:

The first sentence of the abstract is too long and needs to be broken up into smaller sentences.

Thank you. This has been done.

In general, there are several sentences that are too long and need to be revised. There are also several spelling and grammatical errors that should be corrected.

I am sorry. This has been checked.

Is there are reference for the statement that because of the huge accumulation of lymphatic tissue the microbiota is not very diverse in the upper gut?

The references 4-10 all deal with the microbiota in various parts of the gut. The sentence has now been divided into two, and it has been made clear that these references covers both parts of the statement (upper and lower part of the gut).

It is stated that the LPS from Proteobacteria are important MAMPs to stimulate the immune system. While I agree with this, LPS is found on all Gram-negatives, not just the Proteobacteria.

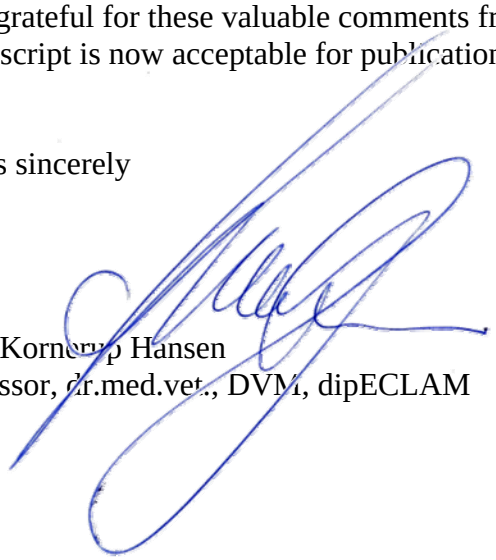
LPS is widely found in Gram negative cell walls, but not all forms stimulate the innate immunity. This has now been clarified by modifying the sentence to 'An important example of a MAMP is lipopolysaccharides (LPS), which are important parts of the cell wall of Gram negative bacteria [27]. This is most frequently found in its active form in Proteobacteria [28] from which it is known to stimulate TLR 4'.

In addition, what about other MAMPS, such as peptidoglycan and flagella? The TLR2 and TLR5 are shown in the figure, but there is not much discussion on these other TLR ligands/MAMPS.

This has now been inserted into the text in the section 'The window of opportunity'.

I am grateful for these valuable comments from the reviewers, and I hope the manuscript is now acceptable for publication.

Yours sincerely



Axel Kornerup Hansen
Professor, dr.med.vet., DVM, dipECLAM