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Summary of PhD thesis

# Effect of gut microbiota on intestinal integrity

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# Summary

In the human gut the complex microbial community termed the gut microbiota reside. In the present work the bacterial part of the gut microbiota is in focus. It interacts with the host and is considered to have impact on host health. The gut microbiota specifically interacts directly and indirectly with the intestinal epithelial cells that together with a mucus layer functions as the final barrier between the luminal content and the underlying host tissue. Maintenance of this barrier is extremely important, as impairment may lead to inflammation and bacterial translocation resulting in adverse effects on host health. The intestinal integrity is here considered to be mainly maintained through the mucus layer covering the epithelial cells, and the epithelial cells, which forms the barrier through interactions by tight junction proteins. Alterations of the intestinal integrity may arise based on loss or altered proliferation of epithelial cells, alterations in the mucus layer as well as altered permeability at the tight junctions. This may lead to inflammation, hence causing more impairment of the barrier.

The gut microbiota is considered to be able to affect the intestinal integrity. Specifically some bacterial strains have been shown to affect barrier function both *in vitro* and *in vivo*, and some studies have correlated specific bacterial groups with markers for intestinal integrity. Therefore modulations of the gut bacterial composition may have an effect on the intestinal integrity. In general an increase in barrier function is considered beneficial, as it must limit translocation of lumen content to the underlying intestinal tissue. In the present work the effect of modulating the gut bacterial community on the intestinal integrity was evaluated by application of the *in vitro* setup the trans-epithelial electrical resistance (TER) assay and by determination of FITC-dextran permeability *in vivo* as well as gene expression analysis of genes relevant for intestinal integrity. Changes in bacterial community were determined using culture-independent methods as quantitative PCR and high-throughput sequencing of the V3-region in the 16S rRNA encoding gene.

Changes in the faecal bacterial composition of postmenopausal women following a dietary intervention with whole-grain or refined wheat and effects of faecal water on TER were initially examined (manuscript 1). Whole grain wheat was shown to increase the relative abundance of *Bifidobacterium* spp. during the intervention while refined wheat reduced *Bacteroides* spp. Faecal water collected from both dietary intervention groups increased TER, but no difference was found between the groups. However the effect of faecal water on TER tended to correlate negatively with relative abundance of *Bifidobacterium* spp.

Previous studies have connected modulation of the gut microbial composition by prebiotics to pathogen translocation, therefore the effect of modulating the gut bacterial composition with prebiotics and the subsequent effects on intestinal integrity were examined. Initially human faecal bacterial community was modulated by *in vitro* batch fermentations with prebiotics (manuscript 2). Effects of this modulation on TER were hence to be determined. This work is still ongoing. The effect of the putative prebiotic Xylo-oligosaccharides (XOS) on intestinal permeability of FITC-dextran was determined in rats (manuscript 3). In the same study the effects of increasing the abundance of commensal *Bifidobacterium* spp. by supplementation of such a commensal strain (*B. pseudolongum*) on intestinal permeability was examined. This was done as *Bifidobac-*

*terium* are stimulated by prebiotics, and based on the correlation previously determined in the work. Neither XOS nor *B. pseudolongum* affected intestinal permeability of 4 kDa FITC-dextran or the effect of caecal water on TER. In the study only gene expression of the tight junction protein occludin was affected by XOS supplementation. This was connected to only minor alterations of the gut microbial composition, potentially causing the lack of alterations in the intestinal integrity.

In order to modulate the gut microbial composition extensively rats were dosed with antibiotics and permeability for FITC-dextran was determined (manuscript 4). These treatments resulted in both increased as well as decreased intestinal permeability. Specifically cefotoximin and vancomycin decreased FITC-dextran permeability and modulated the gut bacterial composition. Metronidazole was not shown to modulate the gut bacterial composition, but it increased intestinal permeability. Finally, amoxicillin modulated the gut microbiota extensively but it did not affect FITC-dextran permeability.

Conclusively the present work shows that modulation of the gut microbiota may affect the intestinal integrity. However, it can, as of yet, not be concluded in which direction the gut microbiota should be modulated to increase or decrease intestinal integrity. In conclusion the present work has led to results that extend knowledge within the research field of intestinal integrity, but more research should be done in order to clarify which bacteria or community structure have an effect on intestinal integrity.