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Intestinal microenvironment, epithelial barrier interactions and human milk oligosaccharide supplementation in irritable bowel syndrome

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i hörsal Arvid Carlsson, Medicinaregatan 3, Torsdagen den 9 Juni, klockan 9.00

av **Cristina Iribarren Gómez**

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Avhandlingen baseras på följande delarbeten

I. Ahluwalia B†, **Iribarren C**†, Magnusson MK, Sundin J, Clevers E, Savolainen O, Ross AR, Törnblom H, Simrén M, Öhman L. *A distinct faecal microbiota and metabolite profile linked to bowel habits in patients with irritable bowel syndrome.* Cells 2021; 10(6): 1459.

II. **Iribarren C**†, Nordlander S†, Sundin J, Isaksson S, Savolainen O, Törnblom H, Magnusson MK, Simrén M, Öhman L. *Fecal luminal factors from patients with irritable bowel syndrome induce distinct gene expression of colonoids.* Neurogastroenterology & Motility 2022; 00:e14390 [Published online].

III. **Iribarren C**, Törnblom H, Aziz I, Magnusson MK, Sundin J, Vigsnæs LK, Amundsen ID, McConnell B, Seitzberg D, Öhman L, Simrén M. *Human milk oligosaccharide supplementation in irritable bowel syndrome patients: A parallel, randomized, double-blind, placebo-controlled study.* Neurogastroenterology & Motility 2020; 32(10): e13920.

IV. **Iribarren C**, Magnusson MK, Vigsnæs LK, Aziz I, Amundsen ID, Šuligoj T, Juge N, Patel P, Sapnara M, Johnsen L, Sørensen N, Sundin J, Törnblom H, Simrén M, Öhman L. *The effects of human milk oligosaccharides on gut microbiota, metabolite profiles and host mucosal response in patients with irritable bowel syndrome.* Nutrients 2021; 13(11): 3836.

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Intestinal microenvironment, epithelial barrier interactions and human milk oligosaccharide supplementation in irritable bowel syndrome

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Abstract

Alterations of the microbiota-host interactions at the mucosal border may be of importance in symptom generation in irritable bowel syndrome (IBS), a disorder of gut-brain interaction. Hence, microbiota-targeted interventions may benefit some patients by beneficially modulating the intestinal microenvironment. This thesis aimed to determine the importance of the intestinal microenvironment for the intestinal immune activity and barrier function in IBS, as well as to assess the effects of human milk oligosaccharide (HMO) supplementation in IBS patients. First, we describe that the IBS patients have a distinct intestinal microenvironment, in particular metabolites, that is linked to bowel habits. Second, we present an *in vitro* model using patient-derived fecal supernatants and healthy-derived epithelial colonoids for exploring the interactions between the intestinal microenvironment and the epithelial barrier in IBS. Third, we show that a HMO mixture of 2'-O-fucosyllactose and lacto-N-neotetraose (4:1 ratio) (2'FL/LNnT) increases the abundance of bifidobacteria, with no risk of symptom deterioration. Finally, we demonstrate that supplementation with 2'FL/LNnT modulates the gut microbiota, increasing bifidobacteria, and fecal and plasma metabolites, but it does not influence the intestinal immune activity and barrier function.

In conclusion, the results of this thesis support the importance of the intestinal microenvironment and the microbiota-host interactions at the mucosal border in IBS, which might be modulated by HMO supplementation. Future studies are warranted to provide a better insight into the cross talk at the mucosal border as well as the mechanisms of action of HMO supplementation for the management of IBS symptoms.

Keywords: colonoids, epithelium, gut microbiota-host interaction, human milk oligosaccharides, intestinal milieu, irritable bowel syndrome, metabolites, microbiota, mucosal border.

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