Göteborg, 2017

Immunological and Microbiological perspectives on Irritable Bowel Syndrome

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i Karl Isaksson, Medicinaregatan 16, Göteborg, fredag den 15 december, klockan 13:00

av **Sean Bennet**

Fakultetsopponent:

Professor Stephen Vanner

Depts. of Medicine, and Biomedical and Molecular Sciences,

Queen's University, Canada

Avhandlingen baseras på följande delarbeten

I. **Multivariate modelling of faecal bacterial profiles of patients with IBS predicts responsiveness to a diet low in FODMAPs**
Bennet SMP, Böhn L, Störsrud S, Liljebo T, Collin L, Lindfors P, Törnblom H, Öhman L and Simrén M. *Gut 2017 Apr 17. [Epub ahead of print]*.

II. **Global cytokine profiles and association with clinical characteristics in patients with irritable bowel syndrome**
Bennet SMP, Polster A, Törnblom H, Isaksson S, Capronnier S, Tessier A, Le Nevé B, Simrén M and Öhman L. *Am J Gastroenterol 2016;111:1165-76.*

III. **Systemic cytokines are elevated in a subset of patients with irritable bowel syndrome (IBS) but largely unrelated to symptom characteristics**
Bennet SMP, Palsson O, Whitehead WE, Barrow DA, Törnblom H, Öhman L, Simrén M and van Tilburg MAL. *Submitted*

IV. **Altered intestinal antibacterial gene expression response profile in irritable bowel syndrome is linked to bacterial composition and immune activation**
Bennet SMP#, Sundin J#, Magnusson MK, Strid H, Tap J, Derrien M, Le Nevé B, Doré J, Törnblom H, Simrén M* and Öhman L*. *Submitted*

SAHLGRENSKA AKADEMIN
INSTITUTIONEN FÖR MEDICIN

GÖTEBORGS UNIVERSITET

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Sean Bennet

invärtesmedicin och klinisk nutrition, Institutionen för medicine, Sahlgrenska akademin, Göteborgs universitet, Sverige, 2017.

Abstract

Irritable bowel syndrome affects ~11% of the population in the Western world and is characterised by altered bowel habits and abdominal pain. The range of additional symptoms between subjects makes the group of IBS patients heterogeneous. Increased immune activity, altered gut microbiota and diet are implicated in symptom generation though the mechanisms are poorly understood. Moreover, gut microbiota and immune activity interplay in relation to symptoms requires elucidation and while dietary intervention is effective in some patients its impact on gut microbiota is unclear. Most likely, all patients do not share the same symptom generating mechanisms, and thus better means to stratify patients for both research and treatment is required.This thesis aimed to demonstrate how gut microbiota, the immune system and their crosstalk result in symptom generation in IBS patients. Furthermore, we aimed to demonstrate how dietary intervention affects microbiota of the gut and if patient responsiveness to intervention therapy could be predicted by gut microbiota profiles.This thesis demonstrates that a diet low in poorly absorbed carbohydrates (FODMAP) changes the gut microbiota composition and reduces beneficial bacteria in IBS patients. Moreover, the composition of gut microbiota can be used to discriminate patients whose IBS symptoms improved or not after a low FODMAP diet. Additionally, serum or mucosal cytokines cannot be used alone to diagnose IBS. However, a subset of immuno-active patients had comparatively raised serum levels of pro-inflammatory cytokines to healthy subjects and immuno-normal IBS patients, although no major associations between cytokines and symptoms were found. Further, IBS patients had an altered mucosal expression of genes associated with an innate antimicrobial response compared to healthy subjects. The antibacterial gene expression response profiles as well as faecal and mucosal bacterial profiles were different between immuno-active and immuno-normal IBS patients, but were not associated to symptoms. In conclusion, a subset of IBS patients has altered immune activity, deemed by cytokine and innate antimicrobial response profiles, which do not seem to be associated with any specific symptom profile. Further, faecal microbial profiles may be used to identify responders to low FODMAP diet therapy but negative impact of the diet on beneficial bacteria requires further investigation. Thus, this thesis has identified novel subgroups of IBS patients based on underlying mechanisms which may guide development of innovative therapy options.

Keywords: IBS, Microbiota, Immune system, FODMAPs

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