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Molecular biosignatures and gut-barrier alterations in inflammatory bowel diseases

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i hörsal Arvid Carlsson, Medicinaregatan 3, Fredagen den 16 September, klockan 9:00

av **Luiza Moraes Holst**

Fakultetsopponent:

Dr. Michael Eberhardson

Karolinska Institutet, Sweden

Avhandlingen baseras på följande delarbeten

I. **Moraes Holst L**, Magnusson MK, Mavroudis G, Polster A, Jonefjäll B, Törnblom H, Sundin J, Simrén M, Strid H, Öhman L. *Systemic inflammatory protein profiles distinguish irritable bowel syndrome (IBS) and ulcerative colitis (UC), irrespective of inflammation or IBS-like symptoms*
Inflammatory Bowel Diseases 2020; 26(6): 874–884

II. **Moraes Holst L,** Halfvarson J, Carlson M, Hedin C, Kruse R, Lindqvist CM, Bergemalm D, Almer S, Bresso F, Lundström ML, Repsilber D, D'Amato M, Keita ÅV, Hjortswang H, Söderholm J, Sundin J, Törnblom H, Simrén M, Strid H, Magnusson MK and Öhman L. *Downregulated mucosal autophagy, alpha kinase-1 and IL-17 signaling pathways in active and quiescent ulcerative colitis*
Clinical and Experimental Gastroenterology, volume 2022: 15 129–144

III. **Moraes Holst L**, Iribarren C, Sapnara M, Isaksson S, Savolainen O, Wettergren Y, Törnblom H, Strid H, Simrén M, Magnusson MK and Öhman L. *Effects of luminal factors on the epithelial barrier in gastrointestinal diseases*
Submitted manuscript

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Molecular biosignatures and gut-barrier alterations in inflammatory bowel diseases

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Avdelning för Mikrobiologi och Immunologi, Institutionen för Biomedicin, Sahlgrenska akademin, Göteborgs universitet, Sverige, 2022.

Abstract

Inflammatory bowel diseases (IBD) are chronic immune-mediated disorders affecting the gastrointestinal tract. The multifactorial pathophysiology of IBD is commonly explained as an abnormal interplay between genetic, immune, environmental and microbial factors. However, the understanding of the mechanisms behind IBD pathogenesis is far from complete, which limits the assessment of disease phenotypes and the identification of optimal therapy choices for an effective individualized care.
This thesis has advanced the understanding of disease specific immune features on systemic as well as mucosal level, allowing for improved characterization of disease activity and phenotypes. Analyses of systemic protein profiles and mucosal gene expression identified sustained alterations in Th17 axis and barrier function during active disease and in remission, which suggest that the dysregulation of these mechanisms is involved in the relapse and remitting disease pattern observed in IBD. Further, we demonstrated that the intestinal microenvironment harbors disease specific metabolite profiles and induces distinct effects on epithelial cells *in vitro*. Hence, fecal supernatants, here considered as a proxy for the luminal microenvironment, from patients with colon cancer, IBD and irritable bowel syndrome induced distinct gene expression patterns in intestinal epithelial cell cultures. This indicates that the experimental setup may be an approach to study the crosstalk between the gut epithelium and the luminal content.

In conclusion, the results of this thesis have improved the immunological knowledge of disease activity and phenotypes, thereby guiding future studies of how to treat and prevent flares for optimal individualized therapy. Further, a promising strategy for exploring how the luminal content interacts with the epithelial barrier and contributes to the presentation of disease pathogenesis.

Keywords: Inflammatory bowel diseases, ulcerative colitis, Crohn's disease, immunopathogenesis, IBD.

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