

# Early Stage Inflammation and Cancer as Reflected in the Gastrointestinal Mucus Composition

## Implications for Diagnosis, Prognosis and Pathogenesis

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademien, Göteborgs universitet, kommer att offentlig försvaras i hörsal Arvid Carlsson, Medicinaregatan 3, måndagen den 12 november, klockan 13:00.

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### Avhandlingen baseras på följande delarbeten

- I. Jabbar KS, Verbeke C, Hyltander AG, Sjövall H, Hansson GC, Sadik R. **Proteomic mucin profiling for the identification of cystic precursors of pancreatic cancer.** J Natl Cancer Inst. 2014; 106(2): djt439.
- II. Jabbar KS, Arike L, Verbeke CS, Sadik R, Hansson GC. **Highly accurate identification of cystic precursor lesions of pancreatic cancer through targeted mass spectrometry: a phase IIc diagnostic study.** J Clin Oncol. 2018; 36(4): 367–375.
- III. van der Post S\*, Jabbar KS\*, Birchenough GMH, Arike L, Akhtar N, Sjövall H, Johansson MEV, Hansson GC. **Structural weakening of the colonic mucus barrier is an early event in ulcerative colitis pathogenesis.** *Submitted.*
- IV. Jabbar KS, van der Post S, Johansson MEV, Hansson GC. **The protein composition of the colonic mucus barrier predicts disease course in ulcerative colitis patients.** *Manuscript.*
- V. Jabbar KS, Dolan B, Eklund L, Wising C, Ermund A, Johansson Å, Törnblom H, Simrén M\*, Hansson GC\*. **The presence of *Brachyspira* species in the colonic epithelium and inner mucus layer may be linked to disease development in up to a third of IBS patients.** *Manuscript.*

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**SAHLGRENSKA AKADEMIN  
INSTITUTIONEN FÖR BIOMEDICIN**



# Early Stage Inflammation and Cancer as Reflected in the Gastrointestinal Mucus Composition

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## Abstract

Mucus covers our inner interfaces towards the environment, providing protection while enabling vital interaction with the outside world. The mucus is built around mucin proteins, which are important for our defenses against infection and inflammation, but may also contribute to carcinogenesis and tumor progression. These divergent aspects of mucin biology are exemplified in the different studies in this thesis, which are all based on mass spectrometry. The topics covered range from mucin biomarkers for the early diagnosis of pancreatic cancer, to the discovery of a link between a mucus-associated bacterial genus and irritable bowel syndrome.

Pancreatic cancer is a relatively rare tumour form, but is postulated to become the second leading cause of cancer deaths in the United States by 2030. The poor prognosis is largely explained by late detection. With advances in imaging, cystic precursors of pancreatic cancer are detected with increasing frequency, offering an unprecedented opportunity for prevention and cure. Unfortunately, available diagnostic tools are not sufficiently robust to enable targeted intervention against high-risk cystic lesions. Here, we describe the development and evaluation of a mass spectrometry based method for quantification of mucins and other biomarkers in pancreatic cyst fluid samples. In a prospective validation cohort, the analysis identified cystic precursors of pancreatic cancer with 97% accuracy. This result represented a significant improvement upon state-of-the-art diagnostic methods. Thus, clinical implementation of the analysis may facilitate early detection of pancreatic cancer, which is a prerequisite for increasing survival rates.

Ulcerative colitis is an inflammatory bowel disease with a chronic and relapsing course. According to the current view, ulcerative colitis results from inappropriate interactions between colonic microbiota and host immunity, against a background of genetic susceptibility. Normally, the abundant luminal microbes are segregated from the colonic epithelium, through an impervious mucus barrier. Here, abnormalities in mucus protein composition were detected in ulcerative colitis patients, also in samples from non-inflamed areas. This implies that structural weakening of the colonic mucus barrier could be important for the development of the disease.

The natural history of ulcerative colitis varies considerably between patients. Prognostic markers for the disease course could reduce relapses and colectomies, as well as the unnecessary use of medication. Herein, we identified a ratio of two proteins in colonic mucus as a powerful predictor of the requirement for intensified medication or surgery during a five year period. Interestingly, these two proteins differentially regulate the sensing of specific microbial ligands. An altered equilibrium of these proteins was tentatively associated with infiltration of bacterial endospores in the colonic lamina propria. Thus, intermittent activation of endospores may conceivably contribute to relapses in patients with severe ulcerative colitis.

*Brachyspira* is a bacterial genus that includes several pathogenic species. In this thesis, *Brachyspira* colonization of the colonic epithelial surface and inner mucus layer was detected in one third of IBS patients, but rarely observed in healthy individuals. Furthermore, *Brachyspira* colonization was associated with a distinctive symptom profile and mucosal immune response. This suggests that targeted antibiotic therapy of this patient group may reduce the morbidity burden of IBS. However, in our investigation antibiotic treatment paradoxically resulted in *Brachyspira* invasion of goblet cell mucus granules. This observation may represent a novel bacterial strategy to evade and survive antibiotic treatment, with potential, broad implications for our understanding of therapy resistant infections and pathogen persistence in the intestinal reservoir.

**Keywords:** Mucus, mass spectrometry, MUC2, MUC5AC, IPMN, pancreatic cysts, ulcerative colitis, IBS, *Brachyspira*