Colonic barrier function in ulcerative colitis
Interactions between ion and mucus secretion

Akademisk avhandling

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Av

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The thesis is based on the following papers:

I. Gustafsson JK, Ermund A, Johansson MEV, Schütte A, Hansson GC, and Sjovall H. **An ex vivo method for studying mucus formation, properties and thickness in human colonic biopsies and mouse small and large intestinal explants**
Am J Physiol Gastrointest Liver Physiol. 2012 Feb;302(4):G430-8

II. Gustafsson JK, Alwan A, Scholte BJ, Hansson GC, Lindén SK and Sjövall H
Relation between carbachol induced ion and mucus secretion in the murine colon
Manuscript

III. Gustafsson JK, Ermund A, Ambort D, Johansson MEV, Nilsson H, Thorell K, Hebert H, Sjövall H and Hansson GC
Bicarbonate and functional CFTR channel are required for proper mucin secretion and link cystic fibrosis with its mucus phenotype
Submitted to Journal of Experimental Medicine

IV. Gustafsson JK, Hansson GC and Sjövall H
Ulcerative colitis patients in remission have an altered secretory capacity in the proximal colon despite macroscopically normal mucosa
Submitted to Neurogastroenterology and Motility

V. Johansson MEV, Gustafsson JK, Holmén-Larsson J, Jabbar KS, Xia L, Xu H, Ghishan FK, Carvalho FA, Gewirtz AT, Sjövall H and Hansson GC
Bacteria penetrate the inner colon mucus layer in both murine colitis models and in patients with ulcerative colitis
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ABSTRACT

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Anion and mucus secretions have traditionally been looked upon as two separate parts of the epithelial defense system. The importance of anion secretion has been attributed to its role in creating the driving force for fluid secretion that flushes the epithelium from bacteria, while mucus secretion ensures protection via the mucus layer that forms a physical barrier between the bacteria and the epithelium. In addition to its role in fluid secretion it is becoming increasingly clear that anion secretion contributes to the regulation of mucus properties. This opens up for the possibility that alterations in epithelial transport can regulate the colonic barrier also via its effects on the mucus layer. The aim of the present thesis was to clarify how epithelial anion secretion regulates the intestinal mucus layer, and to delineate how these two systems are affected in Ulcerative colitis, the most common chronic inflammatory bowel disease.

By using an in house developed *ex vivo* method for the study of mucus properties, it was shown that CFTR mediated bicarbonate secretion regulates many aspects of mucus properties in the mouse small intestine, including mucus growth, adherence and penetrability. In the colon, baseline mucus growth was CFTR independent whereas secretagogue (carbachol) induced mucus growth required a functioning CFTR channel. The impaired mucus growth seen in mice lacking a functional CFTR channel was probably not due to reduced mucus secretion since the exocytosis response to carbachol was unaffected. In WT colon, carbachol induced mucus exocytosis required functioning basolateral transport via NKCC1 and K^+ channels.

To test how epithelial transport and mucus properties were affect by inflammation, the barrier properties of the colonic mucus were studied in various murine colitis models ($IL10^{-/-}$, $TLR5^{-/-}$, $NHE3^{-/-}$, $C1GalT^{-/-}$ and DSS induced colitis) and in UC patients. The results showed that all tested colitis models had signs of a defective mucus barrier, defined as abnormal amounts of bacteria in contact with the epithelium. Alterations in the mucus layer were also found in the human colon. Colonic biopsies from control patients secreted mucus that separated beads the size of bacteria from the epithelium, whereas biopsies from UC patients with acute disease secreted mucus that was penetrable to the beads. The majority of UC patients in remission secreted mucus with normal penetrability, while a subset of patients secreted mucus that was permeable to the beads. Also epithelial anion secretion was normal in the distal colon of UC patients in remission, but in the proximal colon the reactivity to secretagogues was shifted towards an increased forskolin response and a decreased carbachol response.

In summary, the results from this thesis show that acute colitis makes the colonic mucus layer unable to physically separate bacteria from the epithelium. In the small intestine, CFTR mediated secretion regulates most aspect of mucus properties while in the colon only secretagogue-induced mucus growth seems to be CFTR dependent. In ulcerative colitis in remission, the epithelium of the proximal colon becomes more reactive to stimulation of the CFTR system, which may be a defense mechanism to reduce the degree of contact between bacteria and epithelium.

Key words: intestine, mucus, ion transport, colitis, CFTR
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