Colonic mucus structure and processing

Avhandling

som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet, kommer att offentligen försvaras i hörsal Arvid Carlsson, Medicinaregatan 3, fredagen den 26e oktober, klockan 13.00

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Avhandlingen baseras på följande delarbeten


II. Nyström EEL, Birchenough GMH, van der Post S, Arike L, Gruber AD, Hansson GC, Johansson MEV Calcium-activated Chloride Channel Regulator 1 (CLCA1) Controls Mucus Expansion in Colon by Proteolytic Activity. EBioMedicine, 2018, 33:134-143

III. Nyström EEL, Arike L, Recktenwald CV, Hansson GC, Johansson MEV CLCA1 forms non-covalent oligomers in colonic mucus and has MUC2-processing properties Manuscript

IV. Nyström EEL, Martinez Abad B, Eklund L, Birchenough GMH, Johansson MEV Mucus secreted from intercrypt goblet cells is required for proper mucus layer formation in the distal colon and protection against colitis Manuscript

SAHLGRENSKA AKADEMIN
INSTITUTIONEN FÖR BIOMEDICINE
Colonic mucus structure and processing

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Abstract
The mucus layer covering the colonic epithelium creates a crucial first line of defense against the gut residing bacteria. Several lines of evidence suggest that a functional mucus layer is essential for health. For example, it is suggested that ulcerative colitis is correlated with mucus layer defects. The barrier properties of colonic mucus are partly achieved by creating a dense gel with the MUC2 gel-forming mucin as scaffold. Available MUC2 biochemical and histological data suggest that the mucus is highly structured and organized. Mucus homeostasis is dependent on production, secretion and processing of mucus components. Thus, factors such as goblet cell differentiation, secretory capacity of different cells, and the presence of mucus degrading proteases can affect mucus properties. However, a detailed understanding of mucus structure and processing in vivo is lacking.

We have now further developed an existing ex vivo system to study the mucus structure at the microscopic level, as well as investigate the involvement of subpopulations of goblet cells in mucus secretion. This ex vivo method was also used for studies of mucus proteolytic processing by CLCA1, an abundant protease within the mucus. The results suggest that the colonic mucus gel is heterogeneous due to the presence of different goblet cell populations that secrete mucus with different properties. Furthermore, proteolytic processing of MUC2 by CLCA1 is involved in baseline mucus dynamics.

Increased understanding of mucus structure and processing is important for future development of pharmacological interventions to improve barrier function in ulcerative colitis and prevent mucus stagnation in diseases such as asthma, chronic obstructive lung disease and cystic fibrosis.

Keywords: lectin, CLCA1, SPDEF, MUC2, colitis, mucus structure, mucus dynamics, mucus homeostasis