Mucus and mucins during gastrointestinal infections

Akademisk avhandling

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Avhandlingen baseras på följande arbeten:

I. **Helicobacter pylori infection impairs the mucin production rate and turnover in the murine gastric mucosa.**

Navabi N, Johansson ME, Raghavan S, Linden SK (2013).
Infect Immun, 2013. 81: 829-837.

II. **Gastrointestinal cell lines form polarized epithelia with an adherent mucus layer when cultured in semi-wet interfaces with mechanical stimulation.**

Navabi N, McGuckin MA, Linden SK (2013).
PLoS One, 2013. 8: e68761.

III. **Dynamic Changes in Mucus Thickness and Ion Secretion during Citrobacter rodentium Infection and Clearance.**

Gustafsson JK*, Navabi N*, Rodriguez-Pineiro AM, Alomran AH, Premaratne P, Fernandez HR, Banerjee D, Sjövall H, Hansson GC, Lindén SK.
PLoS One, 2013. 8: e84430. **These authors contributed equally to this work.*

IV. **Impact of cytokine environment on mucins during infection wih intestinal pathogens.**

Navabi N, Gustavsson J, Sjöling Å, Lindén SK (2014).
Manuscript

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Mucus and mucins during gastrointestinal infections

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The gastrointestinal tract is protected by a continuously secreted mucus layer formed by mucin glycoproteins. The mucus layer and mucins change dynamically during infection. The main focus of this thesis was to investigate the changes in mucin and the mucus layer in the gastrointestinal tract during infection with the gastrointestinal pathogens *C. rodentium* (a mouse model for intestinal A/E pathogens), ETEC and *H.pylori*. To be able to compare the results from murine studies to the effect of infection in humans, we needed an *in vitro* mucosal surface to most resemble the *in vivo* environment. Therefore, we developed a method of culture to create an *in vitro* model suitable for studies of host-pathogen interactions at the mucosal surface that caused the cells to polarize, form functional tight junctions, a three-dimensional architecture resembling colonic crypts, and produce an adherent mucus layer.

We investigated the effect of infection with *H. pylori* on mucin synthesis *in vivo*. The results of our non-radioactive "pulse" experiments showed *H. pylori* colonization in the mucus niche of the murine stomach leads to decreased mucin production and secretion rate. *H. pylori* infection also decreased levels of MUC1 in the mucosa.

The effect of *C. rodentium* infection on the distinct aspects of the mucus layer and mucins was also investigated during this work. Our results in the WT mice demonstrated mucus transcription and secretion are dynamically altered in response to the infection. Furthermore, the clearance of the infection coincides with the reformation of the organized inner mucus layer and an increased mucus thickness, which corresponded with altered ion channel activities.

To examine the effect of the cytokine environment on the changes of mucin and mucus layer, we infected WT and IFN-$\gamma^{-/-}$ mice with *C. rodentium* that resulted in a vast enhancement of mucus thickness in the IFN-$\gamma^{-/-}$ mice compared to the WT animals. The effect of individual cytokines was further studied using our *in vitro* model with and without infection with *C. rodentium*/ETEC. The outcome demonstrated that changes in the goblet cells, mucin and mucus layer during infection is dependent on the combined impact of the pathogen and cytokines, and that the presence of the Th2 cytokines accelerated the process of mucin synthesis.

Keywords: Mucin, gastrointestinal cell lines, mucus layer, secreted mucin, cell surface mucin, *H. pylori*, *C.rodentium*, ETEC, mucin secretion, goblet cells

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