Helicobacter spp. interactions with mucins

-Adhesion and mucin regulation of pathogen proliferation and gene expression

Akademisk avhandling

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Avhandlingen baseras på följande arbeten:

I. **Strain-dependent proliferation in response to human gastric mucin and adhesion properties of *Helicobacter pylori* are not affected by co-isolated *Lactobacillus* sp.**
Skoog EC, Lindberg M, Lindén SK
Helicobacter. 2011;16(1):9-19.

II. **Human gastric mucins differently regulate *Helicobacter pylori* proliferation, gene expression and interactions with host cells.**
Skoog EC, Sjöling Å, Navabi N, Holgersson J, Lundin SB, Lindén SK
PLoS One. 2012;7(5):e36378.

III. ***Helicobacter pylori* responses to mucins are dependent on adhesion and gene regulation via ArsS and Fur.**
Skoog EC, Gauntlett J, Nilsson H-O, Benghezal M, Lindén SK
Manuscript

IV. ***Helicobacter suis* and *Helicobacter heilmannii* adhesion to gastric mucins during health and infection.**
Skoog EC, Padra M, Flahou B, Smet A, Haesebrouck F, Lindén SK
Manuscript

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Helicobacter spp. interactions with mucins

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Helicobacter pylori colonizes the gastric mucosa of approximately half of the world's population and is a risk factor for gastritis, peptic ulcers and gastric cancer. *H. pylori* is surrounded by, and adheres to, the heavily glycosylated mucins that build up the mucus layer. The carbohydrate structures on the mucins that act as ligands for *H. pylori* vary between individuals and change during disease. In this thesis, we investigated how *H. pylori* interacts with differently glycosylated mucins by analyzing adhesion, proliferation, gene expression and the resulting effect on virulence to host cells. We found that mucins can interfere with *H. pylori* proliferation, partly dependent on binding to the mucins and the presence of known antimicrobial structures, but also observed an inhibition of *H. pylori* proliferation independent of these two factors. The gene expression of *H. pylori* varied greatly in the response to differently glycosylated mucins. Expression of the virulence factor CagA increased in response to some mucins, presumably by Fur-dependent regulation as a result of binding via the SabA adhesin. The varying interaction of *H. pylori* and mucins resulted in alterations in the response of infected gastric epithelial cells *in vitro*.

There are several *Helicobacter* species that commonly infects other animals, but can also infect and cause disease in humans. Their modes of interaction with mucins are unclear. We examined the adhesion of two non-*H. pylori Helicobacter* species to differently glycosylated gastric mucins and mucosal tissue from a range of animals. Our results demonstrated that they can adhere to mucins and gastric tissue via specific glycan structures that change during infection, although the binding ability to human mucins are lower than that of *H. pylori*. In addition, there are other bacteria in the stomach that may interfere with mucin interactions of *Helicobacter* spp. We showed that *Lactobacillus* species isolated from the same stomachs as *H. pylori* did not compete for the same mucin ligands and did not markedly change how co-isolated *H. pylori* interact with the mucins.

In summary, *H. pylori* adhesion to human mucins differs from that of other *Helicobacter* spp. and is not affected by co-colonizing *Lactobacillus* spp. The interactions of *H. pylori* to mucins affect proliferation and expression of virulence factors that may influence the colonization ability, virulence and host response and ultimately play a role in the development of symptoms displayed in the host.

Keywords: *Helicobacter*, *Lactobacillus*, mucin, glycosylation, adhesion, proliferation, gene expression, CagA, SabA, BabA, Fur, ArsS
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