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Helicobacter spp.-host interaction in the mucus niche

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i hörsal Arvid Carlsson, Medicinaregatan 3, den 21 december, klockan 9:00

av Médea Padra

Fakultetsopponent:

Professor Julia Davies, PhD

Department of Oral Biology, Faculty of Odontology, Malmö University, Malmö, Sweden

I. **BabA dependent binding of *Helicobacter pylori* to human gastric mucins cause aggregation that inhibits proliferation and is regulated via ArsS.**
Skoog EC*, Padra M*, Åberg A, Gideonsson P, Obi I, Quintana-Hayashi MP, Arnqvist A, Lindén SK. *Sci Rep. 2017. 20;7:40656.** Equal contribution

II. ***Helicobacter suis* binding to carbohydrates on human and porcine gastric mucins and glycolipids occurs via two modes**. Padra M, Adamczyk B, Benktander J, Flahou B, Skoog EC, Padra JT, Smet A, Jin C, Ducatelle R, Samuelsson T, Haesebrouck F, Karlsson NG, Teneberg S, Lindén SK. *Virulence. 2018. 31;9(1):898-918.*

III. ***Helicobacter suis* infection alters glycosylation and decreases the pathogen growth inhibiting effect and binding avidity of gastric mucins**. Padra M, Adamczyk B, Flahou B, Erhardsson M, Chahal G, Smet A, Jin C, Thorell A, Ducatelle R, Haesebrouck F, Karlsson NG, Lindén SK. *Manuscript*

IV. **Carbohydrate-dependent and antimicrobial peptide defense mechanisms against *Helicobacter pylori* infections**. Médea Padra, John Benktander, Karen Robinson and Sara K. Lindén. *Book chapter in "Current Topics in Microbiology and Immunology (CTMI)" by Springer. Accepted*

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INSTITUTIONEN FÖR BIOMEDICINE

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Helicobacter spp.-host interaction in the mucus niche

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Abstract

Helicobacter pylori is the most common human gastric pathogen, colonizing half of the world's population. *Helicobacter suis* colonizes the stomach of 60-95% of pigs at slaughter age and it is the most prevalent non-*Helicobacter pylori Helicobacter* species found in the human stomach causing severe gastric disorders. The first barrier that gastric pathogens encounter is the mucus layer, of which the main components are highly glycosylated mucin glycoproteins. Mucins carry a high diversity of mucosal glycan chains terminating with glycan structures that vary between species, individuals and tissue locations and provides an extensive repertoire of interaction surfaces for bacteria.

In this thesis, we describe a constant dynamic interplay between *Helicobacter* spp. and host gastric mucins. *Helicobacter* infection induces changes in host gastric mucin composition and glycosylation, and these alterations affect the binding avidity, growth and gene expression of the bacteria. The mucin interaction with pathogens is mediated by its glycan composition and shows high inter-individual difference. We show that *H. pylori* and *H. suis* bind to human and pig gastric mucin glycans and glycolipids via different binding modes and with different specificity. *H. suis* binding to gastric mucins and glycolipids occurs via two modes of adhesion: to structures with terminal galactose at both neutral and acidic pH, and to negatively charged structures at acidic pH. These binding modes enable *H. suis* adhesion to mucins at lower pH close to the gastric lumen and in parietal cells and a more intimate adhesion to mucin glycans and glycolipids closer to the host epithelial cells.

We demonstrated that mucins play important role in host defense mechanism against gastric pathogens. Mucins are able to limit bacterial growth by adhesion and aggregation of *H. pylori* and they affect the adhesin gene expression of the bacteria. *Helicobacter* spp. infection changes host mucin glycosylation in a way that decreases the amount of mucin glycan structures targeted in binding and impairs the growth regulating effects of the mucins maintaining a more inhabitable niche in the stomach.

Understanding the dynamic interplay between Helicobacters and host gastric mucins and alleviating the impairments of the host defense by these pathogens can contribute to the development of preventive strategies against *Helicobacter* infection.

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Keywords: *Helicobacter*, adhesion, mucin, glycosylation

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