Multi-level Characterization of Host and Pathogen in *Helicobacter pylori*- associated Gastric Carcinogenesis.

Akademisk avhandling

som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin
vid Göteborgs universitet kommer att offentligen försvaras
i hörsal Ivan Östholm, Medicinaregatan 13, Göteborg

Fredagen den 28 november 2014, kl 9.00

av
Kaisa Thorell

Fakultetsopponent: Professor Thomas F Meyer,
Director of the Department of Molecular Biology,
Max Planck Institute for Infection Biology, Berlin

Avhandlingen baseras på följande arbeten:

I. Nookaew I, **Thorell K**, Worah K, Wang S, Hibberd ML, Sjövall H, Pettersson S, Nielsen J, and Lundin SB.
Transcriptome signatures in *Helicobacter pylori*-infected mucosa identifies acidic mammalian chitinase loss as a corpus atrophy marker. *BMC Med Genomics. 2013 Oct 11;6:41.*

II. **Thorell K,** Hosseini S, Palacios Gonzáles RV, Chaotham C, Graham DY, Paszat L, Rabeneck L, Lundin SB, Nookaew I, and Sjöling Å.
Identification of a Latin American specific babA variant through whole genome sequencing of *Helicobacter pylori* patient isolates from Nicaragua. *Submitted for publication*.

III. **Thorell K,** Karlsson R, Hosseini S, Kenny D, Sihlbom C, Karlsson A, Sjöling Å, and Nookaew I.
Comparative proteomes of two *Helicobacter pylori* strains using genomics and mass spectrometry-based proteomics. *Manuscript.*

IV. **Thorell K**, Bengtson-Palme J, Liu O, Nookaew I, Paszat L, Nielsen J, Lundin SB, and Sjöling Å.
In vivo analysis of the viable microbiota and *Helicobacter pylori* transcriptome in gastric infection and early stages of carcinogenesis. *Manuscript.*

V. **Thorell K**, Andersson Y, Gatto F, Fassan M, El-Zimaity H, Paszat L, Nookaew I, Sjöling Å, Nielsen J, and Lundin SB.
Transcriptome analysis reveals differential expression of kynurenine pathway enzymes in *Helicobacter pylori*-induced gastric inflammation. *Manuscript.*

UNIVERSITY OF GOTHENBURG

Göteborg 2014

Multi-level Characterization of Host and Pathogen in *Helicobacter pylori*- associated Gastric Carcinogenesis

Kaisa Thorell

Department of Microbiology and Immunology, Institute of Biomedicine, the Sahlgrenska Academy, University of Gothenburg

Abstract:
Today, more than half of the world's population is infected with *Helicobacter pylori*, and two to three per cent of these will develop gastric cancer associated with this infection. Gastric cancer is today the third largest cause of cancer mortality worldwide, with more than 700 000 deaths annually, a number that is expected to increase. *H. pylori* is usually acquired in childhood, and establish a lifelong infection in the absence of treatment. However, most infected individuals remain asymptomatic; the causal relationship between *H. pylori* and gastric cancer is complex, affected both by bacterial and host factors, as well as environmental factors.

To study this relationship we took a multi-level approach looking both at the host and bacteria in patients during the early stages of gastric cancer development. We studied patients from a low-risk, and a high-risk population for gastric cancer, Sweden and Nicaragua respectively. Altogether, we investigated the human gene expression, *H. pylori* genomic and transcriptomic, features, as well as microbiota composition, all in material from the same individuals. We also made a smaller study of the surface proteome of two *H. pylori* isolates.

We found the Nicaraguan *H. pylori* isolates to carry and express *in vivo*, several of the established virulence factors associated with increased gastric cancer risk, such as CagA and the s1/m1 VacA genotype. We also identified the adhesin BabA to have a South American variant with a specific selection pressure on the BabA protein in this region. This could have effects on the adhesion properties and consequently, strain virulence in these strains. On the host level, we identified the kynurenine pathway of tryptophan degradation to be differentially expressed during the early stages of gastric carcinogenesis, a pathway that has been described to be involved both in immune modulation and in cancer development. We also identified the loss of acidic chitinase (CHIA) expression as a potential biomarker for pre-cancerous gastric lesions.
This is the first study that in a large scale explores both the human and bacterial gene expression in the same tissue, an approach that presents new possibilities for the understanding of gastric cancer development.

ISBN: 978-91-628-9168-8