Immune responses to *Helicobacter pylori*, with focus on the relation to gastric cancer development

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Gastric cancer is the second most common cause of cancer death in the world and is an increasing problem in many low- and middle-income areas. A major risk factor of gastric cancer is chronic infection with the bacterium *Helicobacter pylori*, which is highly prevalent in countries with high incidence of gastric cancer.

In this project we study the gastric immune responses to *H. pylori* infection, as well as the details of local immune networks in gastric cancer patients, in order to understand the process of gastric cancer development. The overall aim of the project is to find ways that will lower the mortality of stomach cancer, by determining useful immunological biomarkers for early stomach cancer and/or prognostic markers that reveal which *H. pylori*-infected individuals suffer the greatest risk of developing stomach cancer.

Our studies have shown that chronic *H. pylori* infection is associated with high numbers of suppressive T cells (regulatory T cells, Treg) in the stomach mucosa, which suppress the T-cell response to *H. pylori*. Furthermore, even higher numbers of Treg are found in the tumour areas of gastric cancer patients, possibly contributing to tumour-induced immunosuppression in these patients.

We have also demonstrated that NK cells are responding to *H. pylori* infection, but that both gastric and systemic NK cells from gastric cancer patients are totally refractory to stimulation with bacterial components, possibly mediated by tumour-derived TGF-β and subsequent increased expression of GATA-3 in the NK cells.

In parallel with the suppression of potentially tumour-clearing immune responses, we and others have shown that there is a strong ongoing local innate inflammation. We are now analyzing the details of the proinflammatory and immune regulatory gastric cytokine networks in gastric cancer patients and in patients with precancerous conditions. This is done by systems biology approaches using microarray data.

An important aspect of the project is the collection of patient samples, and we have recently initiated a large collaborative study in Nicaragua (coordinated by L Paszat, Toronto), where gastric cancer is a major problem. This study is expected to run for several years, which will allow the collection of follow-up data and enable the detailed analysis of early gastric cancers.

Main collaborations:

Associate Professor, MD Lawrence Paszat, University of Toronto.
Prof. Jens Nielsen, Systems biology, Chalmers Technical University, Gothenburg.
Prof. Sven Pettersson, Karolinska Institute.
Docent Christer Wingren, Lund University.
Prof. Henrik Sjövall, Inst. of Medicine, University of Gothenburg.
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Prof. Ann-Mari Svennerholm and Docent Åsa Sjöling, Inst. of Biomedicine, University of Gothenburg.

Key publications:

1. Lundgren, A., Suri-Payer, E., Enarsson, K., Svennerholm, A. & Lundin, B.S. *Helicobacter*


9. Lindgren, Å., Pavlovic, V., Flach, C., Sjöling, Å. & Lundin, B.S. IFN-γ secretion is induced in IL-12 stimulated human NK cells by recognition of *Helicobacter pylori* or TLR2 ligands. *Inn Immunity In press*, (2010).