Trafficking of Human Dendritic Cells and B cells in *Helicobacter pylori*-induced Gastritis

Akademisk avhandling

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av

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Avhandlingen baseras på följande delarbeten:

I. **Hansson M., Lundgren A., Elgbratt K., Quiding-Järbrink M., Svennerholm A-M., Johansson E-L.**
Dendritic cells express CCR7 and migrate in response to CCL19 (MIP-3β) after exposure to *Helicobacter pylori*.
Microbes and Infection. 8 (2006) 841-850

II. **Hansson M., Sundquist M., Hering S., Hermansson M., Quiding-Järbrink M.**
Retention of mature dendritic cells in the gastric mucosa of patients with *Helicobacter pylori*-induced gastritis.
In manuscript.

III. **Hansson M., Hermansson M., Svensson H., Elfvin A., Hansson L-E., Johnsson E., Sjöling Å., Quiding-Järbrink M.**
CCL28 is increased in human *Helicobacter pylori*-induced gastritis and mediates recruitment of gastric immunoglobulin A-secreting cells.
Infection and Immunity, July 2008, p 3304-3311

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Abstract

Infection with the bacterium *Helicobacter pylori* is widespread throughout the world, and is associated with development of gastric and duodenal ulcer disease as well as gastric adenocarcinoma and mucosa associated lymphoid tissue lymphoma. The infection generally leads to a large infiltration of immune cells, among them dendrite cells (DC) and IgA-secreting cells. Even though there is a strong innate and adaptive immune response, the bacteria are not eliminated from the stomach and the infection usually remains throughout life.

The inductive site for the adaptive immune responses to *H. pylori* has not yet been identified and very little is known about the role of DC in the immune defense of the human stomach. The migration of DC from sites of antigen capture in peripheral tissues to the secondary lymphoid organs and the simultaneous maturation are crucial for initiation and amplification of primary immune responses. In this thesis we hypothesized that gastric DC fails to migrate to the lymph node and instead remains in the tissue and contribute to the chronic inflammation.

Tissue-specific lymphocyte homing to the intestinal mucosa tissue is dependent on interactions between specific adhesion molecules. These are, however, not changed during *H. pylori* infection. Instead, we hypothesized that mucosal chemokines contribute to recruitment of B cells to the *H. pylori* infected gastric mucosa. Therefore, the overall aims of this thesis were to evaluate how *H. pylori* infection affect the recruitment, functions and migration of DC and to investigate the role of chemokines for B cell homing to the gastric mucosa.

We have shown that DC stimulated with live *H. pylori in vitro* up-regulate the expression of the chemokine receptor CCR7, important for migration to the secondary lymphoid tissue, and that *H. pylori* stimulated DC migrate toward the CCR7 ligand CCL19. *H. pylori* stimulated DC were also capable of presenting antigen to T cells and secreted Th1 inducing cytokines. Using human gastric tissue we could also show that there is an accumulation of mature DC associated with lymphoid follicles and $CD4^+$ T cells, in the infected gastric mucosa, and also increased levels of CCL19.

Further, we have shown that production of the mucosal chemokine CCL28 is increased in *H. pylori* infections and that there is a correlation between CCL28 and IgA concentration in the gastric tissue of *H. pylori* infected individuals. Moreover, gastric IgA-secreting cells from *H. pylori* infected, but not uninfrcted, tissue had a robust migration toward CCL28.

Based on our results in this thesis we suggest that mature DC are retained in the gastric mucosa due to *H. pylori* infection, and that they contribute to sustaining the chronic inflammation. We have also shown that the expression of CCL28 is increased in human *H. pylori*-induced gastritis and that CCL28 may contribute to effector B-cell recruitment to the gastric mucosa in *H. pylori*-induced gastritis.

Keywords: *Helicobacter pylori*, migration, homing, dendritic cells, B cells, gastric mucosa.