LEUKOCYTE RECRUITMENT TO HUMAN GASTROINTESTINAL TISSUES

- STUDIES IN *H. PYLORI*-INDUCED GASTRITIS AND COLON ADENOCARCINOMAS

AKADEMISK AVHANDLING

som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin vid Göteborgs Universitet kommer att offentligen försvaras i hörsal Arvid Carlsson, Medicinaregatan 3, Göteborg.

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av

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Avhandlingen baseras på följande delarbeten:

I. Helena Svensson[*#], Malin Hansson[#], Jan Kilhamn[#], Steffen Backert[¤] and Marianne Quiding-Järbrink[#]
Selective upregulation of endothelial E-selectin in response to *Helicobacter pylori*-induced gastritis. *Infect. Immun 77, 3109-3116. (2009).*

II. Helena Svensson[#*€], Veronica Olofsson[*€], Lars Börjesson[¤], Bengt Gustavsson[¤], Åsa Sjöling[*], Marianne Quiding-Järbrink[*] . [€]Authors contributed equally
Decoy receptor D6 is decreased in colon adenocarcinomas. *In manuscript.*

III. Helena Svensson[*#], Veronica Olofsson[*], Hanna Stenstad[*], Chakradhar Yakkala[*], Stellan Björck[¤], Lars Börjesson[¤], Bengt Gustavsson[¤] and Marianne Quiding-Järbrink[*]
Accumulation of $CCR4^{+}$ $CTLA4^{hi}$ $FOXP3^{+}CD25^{hi}$ regulatory T cells in colon adenocarcinomas correlate to reduced activation of conventional T cells. *Submitted.*

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ABSTRACT

Chronic inflammation is a major pathological basis for tumor development and two examples are *H. pylori* infection of the stomach mucosa and inflammatory bowel disease, which are strongly associated with gastric and colon adenocarcinoma, respectively. In this thesis we investigated *H. pylori*-induced chronic gastritis and colon adenocarcinoma in patients with no history of IBD. The overall aim was to determine how inflammation and endothelial cell function influence the composition of infiltrating cell populations in inflamed tissue as well as tumors in the gastrointestinal tract.

In the first paper we characterized the effect of *H. pylori*-induced gastritis on the expression of endothelial adhesion molecules. By *ex vivo* analyses of human stomach biopsies as well as *in vitro* stimulation of endothelial cells we concluded that endothelial E-selectin expression was induced by *H. pylori* strains expressing the Cag Pathogenicity Island, which encode major virulence factors in *H. pylori.* The increased E-selectin expression in infected patients probably contributes to the characteristic *H. pylori* induced chronic inflammation with a large influx of neutrophils and tissue damage.

Increased expression of chemokines is known to contribute to the progression of tumors, and we next studied the decoy chemokine receptors D6, DARC and CCX-CKR, mediating degradation of chemokines. Using real time RT-PCR on clinical samples we detected significantly decreased D6 expression in the colon tumor tissue compared to unaffected tissue accompanied by increased chemokine levels, but similar levels of DARC and CCX-CKR. Our results also indicate that D6 is expressed mainly on infiltrating B cells. Hence the tumor environment is directed towards a more pro-inflammatory response due to the inability to inactivate chemokines and our results indicate that D6 contribute significantly to promote tumor progression.

Since we could show that the chemokine composition is altered in colon tumors we also wanted to characterize the infiltration of immune cells in tumor and unaffected colon mucosa. Lymphocyte composition and activation stage was determined by flow cytometry. We demonstrated that $CTLA4^{+}CCR4^{+}$ regulatory T cells, which may suppress tumor-specific T cell responses at the tumor site, accumulate in colon tumors. Additionally, the frequencies of activated conventional Th1 type T cells, one of the most important effector mechanisms in immunity against tumors, are decreased in the tumors. This altered lymphocyte composition in the colon tumor will probably diminish the ability of the immune system to effectively attack tumor cells.

In conclusion we have shown that chronic mucosal inflammation and tumor development change the expression of several endothelial receptors and chemokines leading to an altered immune cell composition in inflamed tissue and tumors. Our studies also indicate that the decoy chemokine receptor D6 may play an important role in tumor development.

Keywords: *Helicobacter pylori*, E-selectin, Lymphocyte homing, T lymphocytes, colon adenocarcinoma, regulatory T cells.

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