Dipl.-Biol. Tanja Hundertmark: *"Helicobacter pylori-dependent regulation of MMP-1 expression in human gastric epithelial cells"*

Summary

Helicobacter pylori infects human gastric mucosa of the antrum and corpus and is considered the main cause of chronic gastritis and peptic ulcerus disease. It induces an inflammatory response in its host cells and contributes to the development of gastric carcinomas. Under conditions of chronic inflammation, the extracellular secretion of matrix metalloproteinases (MMPs) considerably contributes to the destruction of tissue structures. Therefore, MMPs play an important role in the pathogenesis of gastric diseases.

To investigate the pathogenesis of *H. pylori* infection in the stomach under *in vivo*-like conditions, we established a method to isolate primary epithelial cells of the stomach. *H. pylori* changed the gene expression pattern of epithelial cells of the stomach: of 96 genes of the cDNA microarrays involved in processes, such as cellular growth, extracellular matrix remodeling and signal transduction, 17 genes were significantly upregulated, and 19 genes were significantly downregulated. As this study reveals that MMP-1 is the most strongly upregulated gene under the influence of *H. pylori*, all the following investigations concentrated on this protease.

The *H. pylori*-induced increase in MMP-1 expression was confirmed at the mRNA (quantitative PCR) and protein levels (western blot, MMP-1, activity ELISA, immunohistochemistry), as well as by *in vitro* (AGS and primary epithelial cells of the stomach) and *in vivo* (biopsies) investigations. The increase in MMP-1 expression is an additive effect of epithelial cells and fibroblasts of stromal tissue. Increased MMP-1 expression in AGS and primary epithelial cells of the stomach is dependent on the presence of the functional type IV-secretion system, but not on cagA.

Although the cytokines IL-1ß and TNF-α triggered a significant increase of MMP-1 at the mRNA and protein levels *in vitro*, the neutralization of these factors during *H. pylori* infection did not lead to a significant reduction of the MMP-1 level. To increase the expression of MMP-1, other factors and signals must play a role. In this study, we demonstrate that ERK 1/2 and JNK have a major role in the upregulation of MMP-1 in response to *H. pylori*.

To gain a better understanding of the molecular connections and to establish new therapeutic concepts, it is necessary to conduct further studies that concentrate on the functional participation of MMP-1 in tissue reconstruction during the development of gastric ulcers and carcinomas, and in investigations that decode factors, their functions and the involved regulation cascades of *H. pylori*-induced increase in MMP-1 expression.