

# THE FUNCTION OF NATURAL KILLER CELLS IN *HELICOBACTER PYLORI* INFECTION AND GASTRIC CANCER

AKADEMISK AVHANDLING

som för avläggande av medicine doktorsexamen vid Sahlgrenska akademien vid Göteborgs  
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CD8<sup>+</sup> natural killer cells are greatly enriched in the human gastrointestinal tract and have the capacity to respond to bacteria. *J Innate Immun.* 2010 In press

**II. Åsa Lindgren, Voja Pavlovic, Carl-Fredrik Flach, Åsa Sjöling & Samuel Lundin**  
Interferon-gamma secretion is induced in IL-12 stimulated human NK cells by recognition of *Helicobacter pylori* or TLR2 ligands. *Innate Immun.* 2010 In press

**III. Åsa Lindgren<sup>\*</sup>, Cheol-Heui Yun<sup>\*</sup>, Åsa Sjöling, Camilla Berggren, Jia-Bin Sun, Erik Jonsson, Jan Holmgren, Ann-Mari Svennerholm & Samuel B. Lundin.** \* These authors contributed equally.

Impaired IFN- $\gamma$  production after stimulation with bacterial components by natural killer cells from gastric cancer patients. *Submitted*



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## ABSTRACT

*Helicobacter pylori* infection is one of the most wide-spread infections in the world and causes a chronic inflammation in the gastrointestinal mucosa characterised by increased production of IFN- $\gamma$ , and associated with an increased risk of developing gastric cancer. The mechanisms behind the development of gastric cancer in *H. pylori* infected individuals are unclear but probably constitute a combination of bacterial factors and host susceptibility. Since the persistent *H. pylori*-induced inflammation may promote tumour development, and tumour cells must acquire the ability to evade the immune system, it is important to study the immune response to *H. pylori* to understand how gastric cancer develops.

The presence of Natural Killer (NK) cells in the gastric mucosa and the ability of NK cells to produce IFN- $\gamma$  suggest an important role of NK cells in the immune response towards *H. pylori*. NK cells in the gastrointestinal mucosa are likely to encounter *H. pylori* as well as other bacteria and may play an important role in the mucosal innate immune defence.

The focus of this project has been the ability of human NK cells to respond to bacterial components with IFN- $\gamma$  production. We have investigated the mechanisms for recognition of *H. pylori* as well as the NK-cell subsets involved in the recognition. Furthermore, we have examined the ability of NK cells derived from gastric cancer patients to respond to bacterial stimuli.

We have demonstrated that in contrast to peripheral blood, most NK cells in the human gastrointestinal mucosa lack CD8 expression. Importantly, we show that CD8<sup>-</sup> and CD8<sup>+</sup> NK cells have different functional properties; only CD8<sup>-</sup> NK cells were capable of responding with IFN- $\gamma$  production to stimulation with lysate from *H. pylori* and other bacteria.

Our studies also indicate an involvement of Toll-like receptors (TLRs), and in particular TLR2 in the recognition of *H. pylori*. Furthermore, we have shown that the *H. pylori* specific membrane bound lipoprotein HpaA induce IFN- $\gamma$  production from NK cells through TLR2.

In addition, we have examined the IFN- $\gamma$  producing ability of NK cells from gastric cancer patients. Our results show that NK cells from gastric cancer patients have a severely suppressed ability to produce IFN- $\gamma$  after stimulation with *H. pylori* lysate and the synthetic bacterial lipoprotein FSL-1. We propose that the suppression is due to tumour-derived TGF- $\beta$ , since TGF- $\beta$  treatment of NK cells from healthy individuals leads to a similar suppression of NK-cell activity.

In conclusion, we have shown that (i) CD8<sup>-</sup> NK cells are the predominant NK-cell subset in the gastric mucosa, (ii) CD8<sup>-</sup> NK cells are especially adapted to respond to bacterial stimuli, (iii) NK cells recognise *H. pylori* via TLR2, (iv) NK cells from gastric cancer patients have an impaired ability to produce IFN- $\gamma$  and (v) that the impaired IFN- $\gamma$  production may be due to tumour-derived TGF- $\beta$ . These findings may have important implications for the understanding of NK-cell subsets and the innate defence against gastrointestinal bacterial infections, and of the development and progression of gastric cancer caused by chronic *H. pylori* infection.

**Keywords:** Natural killer cells, *Helicobacter pylori*, gastric cancer, TLR, IFN- $\gamma$

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