The role of intestinal dendritic cells and the microbiota during oral *Salmonella* infection

AKADEMISK AVHANDLING

som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin
vid Göteborgs universitet kommer att offentligen försvaras i hörsal
Ivan Östholm, Medicinaregatan 13, Göteborg

Fredagen den 18 december 2015, kl 9.00

av
María Fernández

Fakultetsopponent
Associate Professor **Siegfried Hapfelmeier**, PhD
Institute for Infectious Diseases, University of Bern, Bern, Switzerland

Avhandlingen baseras på följande arbeten:

I. Wenzel UA, Fernández-Santoscoy M, Tam MA, Tegtmeyer P and Wick MJ.
Synergy between CD40 and MyD88 does not influence host survival to *Salmonella* infection
Front Immunol (2015) **6**:460.

II. Fernández-Santoscoy M, Wenzel UA, Yrlid U, Cardell S, Bäckhed F and Wick MJ.
The normal gut microbiota reduces colonization of the mesenteric lymph nodes and IL-12-independent IFN-γ production during *Salmonella* infection
Submitted

III. Fernández-Santoscoy M, Wenzel UA, Yrlid U, Persson EK, Agace WW and Wick MJ.
The influence of intestinal CD103^{+}CD11b^{+} dendritic cells on oral *Salmonella* infection
Manuscript

GÖTEBORGS UNIVERSITET
Göteborg 2015

The role of intestinal dendritic cells and the microbiota during oral *Salmonella* infection

María Fernández
Department of Microbiology and Immunology, Institute of Biomedicine
Sahlgrenska Academy at University of Gothenburg
Gothenburg, Sweden

ABSTRACT

The intestinal pathogen *Salmonella* causes millions of infections per year worldwide. The immune response to these bacteria involves interactions between several cell types via specific molecules and is under the influence of the intestinal microbiota.

Dendritic cells (DC) initiate immune responses including those to *Salmonella*. Toll-like receptors and CD40 can act synergistically on DC activation but their cooperativity during bacterial infection had not been addressed. *Salmonella*-infected mice lacking MyD88, CD40 or both (DKO) showed that synergistic effects of CD40 and MyD88 do not influence host survival, bacterial burden in intestinal tissues or serum levels of IFN-γ and IL-10 during infection. However, cooperativity between CD40 and MyD88 influenced IL-10 production in DC-T cell co-cultures using killed *Salmonella* as the antigen. Moreover, cooperative effects of CD40 and MyD88 on T cell effector functions such as proliferation and IFN-γ production were influenced by the complexity of the antigen.

Although some studies had addressed the role of DC subsets in infection, the influence of the $CD103^+CD11b^+$ DC in *Salmonella* infection was unknown. Studies using mice with a reduced $CD103^+CD11b^+$ DC population in mesenteric lymph nodes (MLN) and small intestine lamina propria showed no alterations in *Salmonella* colonization of intestinal tissues or spleen. Moreover, mechanisms important in host survival to *Salmonella* infection such as IFN-γ production analyzed by flow cytometry and antibody production analyzed by ELISA were not altered. This suggests that the absence of $CD103^+CD11b^+$ DC has a limited effect on the host response to *Salmonella* infection.

Interactions between *Salmonella* and the microbiota at an early phase of colonization have been reported, but the role of the microbiota later during infection was poorly understood. *Salmonella*-infected germ-free (GF) and antibiotic treated mice (ABX) revealed a higher bacterial burden in the MLN, which seems to be due to increased intestinal bacterial translocation to MLN caused by the lack of the microbiota. Furthermore, higher IFN-γ in MLN of GF and ABX relative to controls was detected by flow cytometry despite similar IL-12 levels six days post infection. While the higher IFN-γ in MLN of ABX mice correlated to the severity of infection, a lack of immune signals provided by the microbiota from birth may influence IFN-γ production in GF mice.

These studies provide further information about the role of DC and the microbiota during *Salmonella* infection, which could be used for the generation of vaccines or treatments for this infection.

Keywords: *Salmonella*, dendritic cells, NF-κB, MyD88, CD40, CD103, IRF4, microbiota

ISBN 978-91-628-9569-3 **ISBN** 978-91-628-9570-9 (e-pub)