RECRUITMENT, DIFFERENTIATION, AND FUNCTION OF MONOCYTES DURING *SALMONELLA* INFECTION

AKADEMISK AVHANDLING

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av

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Avhandlingen baseras på följande delarbeten:

I. Anna Rydström and Mary Jo Wick. Monocyte recruitment, activation, and function in the gut-associated lymphoid tissue during oral *Salmonella* infection. J. Immunol. 2007 May 1;178(9):5789-801.

II. Anna Rydström and Mary Jo Wick. MyD88 is required to recruit neutrophils and monocytes to intestinal lymphoid tissues during oral *Salmonella* infection. *Manuscript*

III. Anna Rydström and Mary Jo Wick. Toll-like receptor signalling blocks the differentiation of immature monocytes to dendritic cells. *Manuscript*

RECRUITMENT, DIFFERENTIATION, AND FUNCTION OF MONOCYTES DURING *SALMONELLA* INFECTION

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Monocytes are a heterogeneous population in the blood with an enormous plasticity whose fate and functions are dictated by the microenvironment. They are phenotypically and functionally related to neutrophils and dendritic cells (DCs) and share an overlapping expression pattern of surface molecules with these cells. The presence of phagocytic cells including neutrophils, monocytes/macrophages and DCs in infected tissues is critical to host survival. However, how these cells respond to bacterial infections regarding differentiation and effector functions is not fully understood. The overall aim of this thesis was to examine the recruitment, function and differentiation of monocytes and neutrophils in the blood, Peyer's patches and mesenteric lymph nodes during oral *Salmonella* infection.

Ly6C^{hi} monocytes and neutrophils rapidly accumulated in the blood, Peyer's patches and mesenteric lymph nodes of mice orally infected with *Salmonella*. The recruitment of neutrophils and monocytes was not diminished in infected TLR4$^{-/-}$ mice, but was reduced in MyD88$^{-/-}$ mice and almost absent in MyD88$^{-/-}$TLR4$^{-/-}$ mice. The chemokine receptors CCR2 and CXCR2 were expressed by monocytes and neutrophils, respectively, in the blood and their cognate ligands CCL2 and CXCL2 were produced early during infection in infected organs. Furthermore, the production of these chemokines was dependent on MyD88/TLR4 indicating a critical role of these signaling pathways in myeloid cell recruitment. Upon migration into the organs, neutrophils and monocytes formed inflammatory foci and one to two percent of the cells phagocytosed *Salmonella*. In addition, monocytes were the major producers of TNFα and iNOS, which are important to controlling *Salmonella* infection.

The upregulation of MHC-II and costimulatory molecules on monocytes initiated the investigation of whether they differentiated into DCs and became antigen-presenting cells. However, activated monocytes were unable to present antigens to T cells ex vivo although they differentiated into DCs after in vitro culture. Furthermore, *Salmonella* added to in vitro cultures inhibited monocyte differentiation to DCs through inducing cytokines via a MyD88-dependent pathway. This suggests a mechanism for the incapacity of monocytes to present antigens in vivo.

Collectively, these studies reveal MyD88/TLR4-dependent recruitment of phagocytes to infected intestinal tissues. They also suggest a major role for monocytes in eliminating bacteria and producing pro-inflammatory cytokines but not for inducing adaptive immunity during *Salmonella* infection. Increased knowledge of monocytes improves the chances to find therapies against a broad spectrum of diseases ranging from atherosclerosis to infectious diseases where monocytes have opposing roles of either being beneficial or detrimental to the host.

Keywords: *Salmonella*, monocyte, neutrophil, chemokine, Toll-like receptor, differentiation

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