Upregulation of interleukin-4 induced Arginase1 leads to a more sufficient infection control in Salmonella Typhimurium infected macrophages

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Introduction:
The intracellular pathogen Salmonella Typhi can cause a life-threatening disease. The disease is controlled through the production of pro-inflammatory cytokines. Interferon gamma (IFNγ) and tumor necrosis factor alpha (TNFα) are potent inducers of inducible nitric oxide (NO) synthase (iNOS) by macrophages. High expression of Arginase1 (Arg1), which cleaves L-arginine, the substrate of iNOS, impairs host control of infection with intracellular microbes. Herein, we investigated the protective effects of iNos and Arg1 expression in macrophages and how this affects the immune control of Salmonella infection in vitro.

Materials and Methods:
Bone marrow derived macrophages (BMDMs) differentiated with M-CSF were infected with S. Typhimurium (mouse correlate of S. Typhi) for one hour. Cells were stimulated with either interleukin-4 (IL-4), IFNγ, or TNFα and combinations. mRNA expression of Arg1 and iNos was analyzed. Furthermore, bacterial load of infected BMDMs was determined by plating lysates on LB-agar plates for determining colony forming units.

Results:
We observed that IL-4 is a potent inducer of Arg1 expression. Accordingly, inducible Arg1 expression was significantly suppressed by IFNγ. IFNγ was the most potent inducer of iNos expression, and IL-4 blocked the latter effect. Surprisingly, high iNos expression did not translate into improved control of intracellular Salmonella proliferation and IL-4 stimulation resulted in reduction of bacterial numbers.

Conclusions:
Our data underline the inhibitory effects of IFNγ on Arg1 expression, leading to an enhanced generation of NO by iNOS in vitro. However, IL-4 stimulation even resulted in better infection control. A knock-out of ARG1 lead to the reversal of this effect. Ongoing experiments aim to investigate the mechanism in which IL-4 leads to improved infection control in vitro and in vivo and how these cytokines influence the transcriptional and epigenetic regulation of iNOS and ARG1.

Keywords : Salmonella, Macrophages, ARG1, iNOS
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