Malaria parasite infection dampens the immune response to Salmonella Typhimurium: a role for macrophage polarization

Annica Stull-Lane, Kristen L. Lokken, and Renée M. Tsolis

Department of Microbiology & Immunology, School of Medicine, University of California at Davis, One Shields Avenue, Davis, CA 95616 USA

Introduction

Malaria is an important risk factor of disseminated non-typhoidal Salmonella (NTS), which has a case fatality of 20-25% in children in sub-Saharan Africa.1 Multiple co-infection mouse studies have begun to elucidate molecular mechanisms behind this impaired immune response to NTS during malaria parasite infection. For instance, Lokken et al. (2014) found that IL-10 produced during malaria infection likely suppresses the ability of macrophages to control bacterial infection.2 Macrophage activation can be seen on a spectrum, from more pro-inflammatory macrophages (M1) that have enhanced killing of intracellular microorganisms to more anti-inflammatory macrophages (M2) that dampen the immune response.3 We hypothesize that malaria infection polarizes the macrophage playing field from M1 to M2, weakening the immunological response to subsequent NTS infection. Elucidating molecular mechanisms during co-infection can reveal important targets for therapeutic intervention.

Animal Model in C57BL/6 mice

A. % Parasitized RBCs

B. Malaria Parasitemia

C. CSF2 (GM-CSF) and IL-10

Malaria parasite infection shifts macrophages to an anti-inflammatory phenotype

A. Control

B. Pro-inflammatory

C. Anti-inflammatory

Malaria parasite infection alters the inflammatory cytokine environment to promote Salmonella outgrowth

A. CFU per Liver

B. Circulating IL-10 (pg/mL)

C. CSF1 (M-CSF) (pg/mL)

Malaria parasite infection depletes CSF1 to lead to altered pro-inflammatory cytokine and mixed infection control of Salmonella outgrowth

A. Pynfect

B. % Parasitized RBCs

C. CSF1 (M-CSF) levels

Conclusions

- Malaria parasite infection leads to outgrowth of STm at systemic sites, suggesting that malaria dampens the immune response to STm.
- Malaria parasite infection leads to increased circulating IL-10 and CSF1, anti-inflammatory cytokines.
- Malaria parasite infection shifts macrophages to an anti-inflammatory phenotype.

Future directions

- Assess protein levels of CSF1, CSF1R, CSF2, CSF2Ra and see if they correlate with transcript findings.
- Add back CSF2 during co-infection and see if it restores control of the STm infection.
- Deplete CSF1 earlier during malaria infection and see if there is a time-dependent shift in pro-inflammatory and anti-inflammatory cytokines that leads to better control of STm infection.

References


Acknowledgements

Thank You: We appreciate guidance from the laboratories of Dr. Renée Tsolis and Dr. Andreas Bämmer.

Funding:
This work was supported by NIH/NIAID grant AI098678.