INFECTIOUS DISEASE

Opposing effects of IL-10

Children with acute or recent malarial infection are particularly vulnerable to bacteraemia caused by non-typhoidal *Salmonella* species. Now, Lokken *et al.* show that interleukin-10 (IL-10) — which is produced in response to malaria infection — increases susceptibility to non-typhoidal *Salmonella* infection by suppressing the ability of macrophages and neutrophils to control the bacterial infection.

To investigate the immunological mechanisms by which malaria contributes to this increased risk of infection, the authors co-infected mice with the malarial parasite *Plasmodium yoelii* and *Salmonella enterica* subsp. *enterica* serovar Typhimurium. Co-infection had no effect on the levels of parasite infection. However, co-infected mice showed increased bacterial loads in the liver at day 2, and at day 4 these mice had a high bacterial burden in the blood compared with mice that were infected with *S. Typhimurium* alone.

“co-infected mice and mice that were infected with *P. yoelii* alone had higher levels of circulating IL-10”

Next, the authors carried out histopathological analyses to investigate whether underlying malaria infection affected inflammatory responses in the livers of mice that were infected with *S. Typhimurium*. Interestingly, co-infected mice had fewer microabscesses and smaller-sized lesions than mice that were infected with *S. Typhimurium* alone. This indicates that a reduced inflammatory response to invasive *S. Typhimurium* in the liver during co-infection with malaria could contribute to the increased bacterial burden in this tissue.

IL-10 production by CD4⁺ T cells has previously been shown to have a protective role during malaria infection by preventing excessive pathology both in mouse models and in patients with malaria. The authors found that co-infected mice and mice that were infected with *P. yoelii* alone had higher levels of circulating IL-10 than mice infected with only *S. Typhimurium*. Neutralizing antibodies against IL-10 reduced bacterial burdens in both the liver and blood of co-infected mice but not in mice that were infected with *S. Typhimurium* alone. Furthermore, co-infected mice that lacked *Il10* did not show reduced expression of genes that encode pro-inflammatory cytokines compared with control mice.

Thus, the IL-10 production that is induced by malaria infection led to reduced inflammatory responses to *S. Typhimurium* in the liver.

In a mouse model of chronic typhoid, *S. Typhimurium* persists within alternatively activated macrophages. Hence, the authors investigated whether IL-10 production by macrophages could have a role in the malaria-mediated susceptibility to *S. Typhimurium* infection. Indeed, they found that macrophages are both the major producers of and the targets of the IL-10 that exacerbates systemic bacterial infection in co-infected mice.

Taken together, the results of this study indicate that IL-10 has opposing effects during co-infection with malaria parasites and *S. Typhimurium* — it protects against the excessive inflammation caused by malaria infection but it also leads to increased susceptibility to *S. Typhimurium*. It will be interesting to see whether this holds true in humans with malaria.

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ORIGINAL RESEARCH PAPER Lokken, K. L. *et al.* Malaria parasite infection compromises control of concurrent systemic non-typhoidal *Salmonella* infection via IL-10-mediated alteration of myeloid cell function. *PLoS Pathog.* **10**, e1004049 (2014)