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Current Opinion in Immunology

Regulatory issues in immunity to liver and blood-stage malaria

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T cells play a major role in control of both blood and liver stage of plasmodium infection. While immunization with certain attenuated whole-parasite vaccines that are attenuated at the liver stage of the infection induces protective T cell responses, even multiple exposures to natural infection in endemic areas do not lead to stable T cell memory or humoral immunity and sterilizing protection. One of the key differences between vaccination and natural exposure is the absence of blood stage during vaccination. Here we will discuss possible immunoregulatory strategies employed by blood stage of malaria leading to generation of severely compromised T cell and humoral immune responses and subsequent lack of sterilizing immunity.

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Current Opinion in Immunology 2016, **42**:91–97

This review comes from a themed issue on **Host pathogens**

Edited by **Paul Zhou** and **Zheng W Chen**

http://dx.doi.org/10.1016/j.coi.2016.06.008

Introduction

Malaria continues as a major global health problem, with ~200 million annual cases associated with ~500,000 deaths, primarily in young children in sub-Saharan Africa. Plasmodium species are transmitted by mosquito vectors carrying infectious sporozoites. Once injected into a human host, low numbers of sporozoites establish an asymptomatic infection of liver hepatocytes, during which they undergo extensive replication and a dramatic increase in numbers. Unless eradicated at the liver stage, the infection progresses through release of the erythrocyte-tropic merozoites into the blood, resulting in the symptomatic blood stage of infection [1].

Although immune mechanisms of protection against malaria have been extensively studied in both rodent models and humans, they are still not completely defined. A substantial amount of work points to a crucial role of T lymphocytes (both CD4 and CD8) in protection against both liver and blood stage malaria, either as direct mediators of protection or as an important regulatory arm to amplify humoral immunity. In this review, we discuss clues and knowledge gaps relating to the potential for malaria-specific regulatory mechanisms to limit development of sterilizing liver-stage immunity in endemic regions and to modulate the severity of blood stage infections.

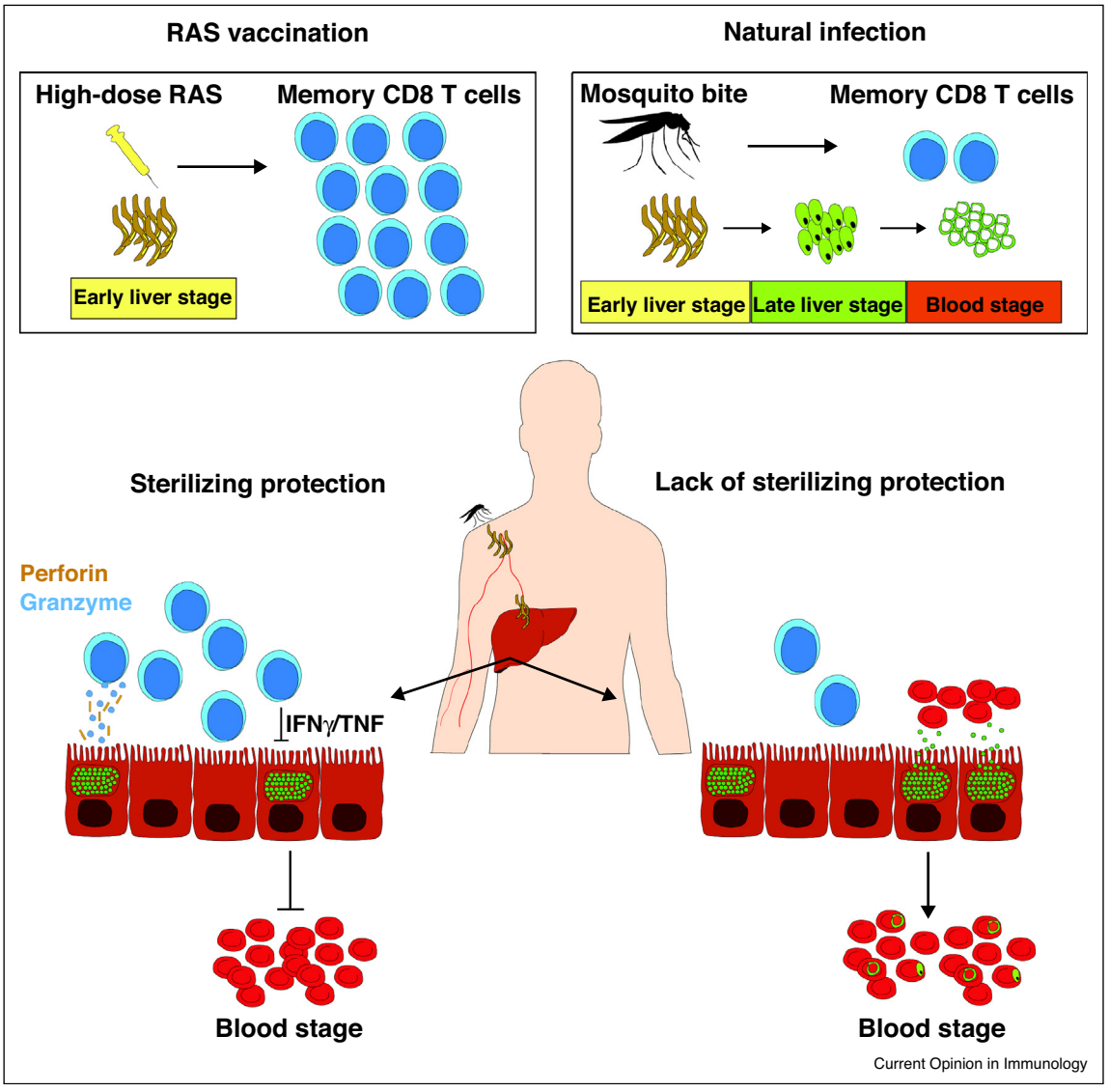
Immunity to liver-stage malaria

Sterilizing protection against malaria is described as the prevention of the symptomatic, blood stage of the disease after sporozoite infection [2]. Most of our current understanding of sterilizing protection is derived from mouse immunization studies using radiation attenuated sporozoites (RAS), which are developmentally arrested at an early liver stage of infection [3]. Importantly, RAS immunization is also effective in inducing sterile protection in human subjects, and is considered the 'gold standard' in malaria immunization [4,5]. Mouse models of RAS vaccination have been extensively used to gain knowledge about mediators of vaccination-induced sterilizing protection [2]. Initial antibody-mediated depletion studies, together with more recent studies utilizing different combinations of mouse strains and plasmodium species have identified CD8 T cells as critical mediators of protection [6–9]. *In vivo* imaging enabled for the fist time visualization of the killing of the plasmodium liver stage by transferred plasmodium-specific effector CD8 T cells [10•] and revealed that CD8 T cells in RAS-immune mice form large clusters around infected hepatocytes in a process dependent on signaling by G-protein coupled receptors [10•]. The clustering of CD8 T cells around infected hepatocytes is consistent with the general notion that the extremely large numbers of liver-stage specific CD8 T cells are required for sterilizing protection [8]. Thus, vaccination-induced sterilizing protection relies on the recognition of infected hepatocytes by CD8 T cells specific for liver stage-expressed epitopes and consequent elimination of the parasite or parasite infected cells (Figure 1).

Lack of sterilizing protection after natural plasmodium infections: more than antigen dose?

Humans living in malaria endemic areas never develop sterilizing protection, despite repeated infections [11••]. The prevailing notion in the field is that the small number

Figure 1



Induction of CD8 T cell responses by RAS vaccination or natural *Plasmodium* infection. (Left) Immunization with high doses of radiation attenuated sporozoites (RAS), induces protective CD8 T cells. During subsequent natural infection, small numbers of sporozoites are deposited in the dermis of vaccinated individual. Upon arrival at the liver, sporozoites infect small numbers of hepatocytes and establish the liver stage of infection. RAS-induced memory CD8 T cells survey the liver and eliminate infected cells upon recognition of cognate antigen, through IFNγ/TNF or Perforin/GzB pathways. Thus, the symptomatic blood stage infection is prevented. (Right) In contrast, exposure of an individual in the field to natural infection, which starts with early liver stage, and progresses to late liver stage and finally to infection of red blood cells, induces unstable, low-magnitude CD8 T cell responses. In addition to low numbers, these CD8 T cell responses express exhausted phenotype and seem to be 'heavily' regulated to prevent excessive tissue damage. Upon subsequent exposure they do not provide sterile protection and infection progresses to the blood stage.

of sporozoites delivered by mosquito bite is insufficient to induce the robust memory CD8 T cell responses required for protection [12]. Consistent with this notion, liver-stage-specific CD8 T cell responses in peripheral blood of malaria-experienced subjects are unstable and of low magnitude, compared to responses induced by RAS immunization (Figure 1) [13–15]. However, it has been suggested that immunity in mice can be generated by repeated immunizations with low numbers of RAS [16]. Thus, the question remains: what is the basis for failure to develop sterilizing protection after repeated natural infection in the field?

One clue may implicate regulatory events brought on by the blood stage of malaria itself. Numerous studies in mouse malaria models show that memory CD8 T cells