Short Review

Cytokines and their role in modulating the severity of Plasmodium falciparum malaria

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Abstract

Malaria is the major cause of death in the tropical areas. Efficient clearance of Plasmodium falciparum parasites by the immune system depends on the type of immune response mounted by the host. Cytokines, as immune mediators, play a major role in the interplay between the parasite and the host immune response. It is believed that the balance between anti and proinflammatory cytokines is crucial in determining the outcome of malaria infection. Measuring the ratios of the opposing groups of cytokines can hence, provide clues to predict the prognosis of the disease.

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Background

Malaria caused by Plasmodium falciparum imposes great socio-economic burden on humanity afflicting approximately ninety countries and territories in the tropical and subtropical regions and almost one-half of them are in Sub Saharan Africa. Being a predominantly tropical disease, malaria is one of the top three killers among communicable diseases in Africa [1]. Non-immune individuals, pregnant women and children bear most of the morbidity and mortality due to the disease, which manifests as severe malaria anaemia and cerebral malaria complications. The generation and maintenance of clinically protective immune responses requires repeated infections over the lifetime of the individual. Both antibody dependent and cell-mediated mechanisms contribute to immune protection against the asexual blood stages of the parasite. The rupture of erythrocytic schizonts is typically accompanied by bouts of fever, nausea, headaches and other symptoms of a systemic pro-inflammatory cytokine response, much of which is now believed to be derived from cells of the innate immune system [2].

Observations in populations exposed to repeated malaria infections have revealed that innate immune mechanisms are triggered when parasite density crosses a predefined threshold and functions to limit maximum parasite density. However, gradually acquired adaptive immunity is required to eliminate the parasite [3]. The kinetics of malaria infections indicate that innate immune responses are essential to limit the initial phase of parasite replication, controlling the first wave of parasitaemia and allow time to develop specific adaptive responses that will enable clearance of the infection, Importantly, these density-dependent mechanisms seem to limit the growth of all blood-stage parasites, irrespective of species or strain, indicating that innate immunity is triggered by molecules that are conserved between different species and strains of Plasmodium [4,5]. The need for better understanding of immunological basis of protective immunity to malaria is evident with the growing number of anti-malarial multi-drug resistance coupled with the vector's resistance to available insecticides.

Recently, the implication of cytokines as mediators of the immune response in falciparum malaria has given rise to an acceptable view that malaria is, at least in part, an immune mediated disease. In this view, the impact of cytokines released during the course of malaria infection on the presentation of the disease and the pathways of cytokines that lead to either severe or uncomplicated phenotype of the disease will be discussed.

Triggering of the immune system

In Plasmodium falciparum infection, the rapid production of proinflammatory and phagocyte activating cytokines by NK cells is a key factor of early host response against intracellular infection [6,7]. Immunological cytokines are divided into those which promote the proliferation and functioning of either helper T-cells type 1(Th1) or type 2 (Th2) cytokines [8,9]. Th1 immune responses activate macrophages as part of cell-mediated immunity required for clearance of intracellular pathogens, whereas Th2 immune responses regulate humoral immune responses, stimulate growth of mast cells and act to suppress cell-mediated immunity [10,11]. As a result, Th1 and Th2 cytokines work antagonistically to regulate each other's activities [10].

Blood-stage immunity in experimental malaria models and in humans is dependent on CD4+ T cells subset, B cells and antibodies while the CD8+ T-cell subset

has been associated with cytolytic activity against the parasite in liver stages [12].

The host immune response against falciparum malaria is affected by many factors such as the rate of transmission, age, rate of exposure and presence of haemoglobinopathies. In areas with high transmission rates, malaria-related mortality is highest during the first few years of life after which, most children develop a considerable degree of immunity. By the age of five, most children develop a considerable degree of immunity, which reduces the risk of death from P. falciparum malaria, provides protection against severe disease, and reduces the frequency of clinical malaria episodes [13-15]. In areas with lower transmission intensity, on the other hand, the age at which clinical immunity develops shifts upwards. In such areas, all age groups are affected, but the risk of getting a clinical attack is about twice as high in the age group from five to 20 years as in adults aged above 30 years [16]. Naturally, acquired immunity builds up with repeated exposure to malaria, which is manifested by lower parasite densities and fewer clinical malaria episodes in older children and adults [16].

Cytokines pathways and pathogenicity of malaria:

The interplay between the parasite and the immune response likely determines the outcome of the infection. Early and effective immune response is indicated by increased production of Th1 cytokines during the acute phase of the disease [17]. IL-12, being a critical linker between innate and adaptive immunity, is released from monocytes/macrophages, B cells, NK and CD8+ T cells in response to various malaria antigens. It is important in initiating the inflammatory cascade by its ability to enhance the differentiation of $CD4^+$ T cells into Th1 cells for the secretion of interferon-γ (IFN- γ) [18]. Production of IL-12 from activated macrophages is also crucial to early activation of γδ-T cells, resulting in additional production of IFN-γ [19,20]. γδ -T cells represent the interface between innate and adaptive immune response [21] and these cells, together with NK cells, contribute to a rapid resolution of clinical malaria. Similarly, IL-18 was also reported to stimulate production of IFN-γ by activation of NK and $CD8^+$ T cells and with IL12 are considered key factors that determine the overall magnitude of IFN-γ [22].

Early production of IFN-γ is critical since it directly mediates antiparasitic effects [23] and hence helps to limit progression from mild malaria to severe and life-threatening complications. Augmented release of IFN-γ stimulates monocytes/macrophage and γδ-T cells to secrete TNF-α which can further promote antiplasmodial properties through formation of toxic free radicals, such as nitric oxide [18]. Although this action is essential for the clearance of parasite, nevertheless, excessive release of proinflammatory cytokines has immunopathogenic effects and contributes to the development of severe symptoms. IL6 and IL1-β, like TNF-α, are other inflammatory cytokines that also play a role in limiting parasite replication but are involved in induction of fever and acute phase response [24,25].

The ability to balance effectively the antiparasitic and immunopathogenic effects of these cytokines is a hallmark of clinical immunity to malaria. In order to inhibit their pathologic action, proinflammatory cytokines are balanced by the release of the anti-inflammatory cytokines (Fig 1) such as, IL10 [26,27], Tumor growth factor (TGF)-β [28] as well as IL13 which works synergistically with IL4 to suppress cellular immunity and provoke humoral immune response [29].

Timing and relative concentration of the opposing groups of cytokines are the critical factors in this scenario. IL10 produced by Th2, T-cytotoxic (Tc2), T-regulatory (Tr1) subsets, as well as macrophages, monocytes and B cells have a pivotal role in controlling the deleterious action of the inflammatory cascade. Nevertheless, early production of high concentration of IL10 paralleled by marked and persistent production of TNF-α will shift the situation to the severe (Fig 2A) form of infection leading to complications such as cerebral malaria [30]. This is attributed to the fact that early production of IL10 inhibits the release of IL12 and consequently that of IFN-γ required for clearance of malaria parasite. A recent study among Sudanese children infected with severe malaria showed elevated levels of both TNF-α and IL10 [31]. Persistent release of TNF-α accompanied by decreased production of IL10 and TGF-β during the transition from the innate to the adaptive phase of the immune response (fig 2B) will facilitate the progress into severe malaria [28]. TGF-β seems to be an important cytokine, which maintains the balance between protection and progression toward P. falciparum malaria and hence contributes to protection from malarial pathology. However, some reports pointed to the importance of the concentration of TGF-β induced. Omer et al postulated that TGF-β, at low concentrations, stimulates the early pro-inflammatory cytokine response to lead to a prompt and complete resolution of malaria infection. By contrast, high levels of TGF-β in the early phase of immune response up-regulate the anti-inflammatory cytokine response, which provokes reduced production of IL12, IL18, and IFN-γ with increased and persistent production of TNF-α, leading to severe manifestation of the disease such as cerebral malaria [32].

The ratio between the pro- and anti- inflammatory cytokine responses should be also considered to evaluate the outcome of the disease. High ratios of TNF-α, IFN-γ and IL12 to TGF-β were found to be associated with increased risk of fever and complications [28]. On the other hand, increased

levels of TNF-α and IFN-γ relative to that of IL6 were associated with reduced incidence of P. falciparum clinical episodes, while an increased P. falciparum-induced IL6 level relative to TNF-α and IFN-γ levels was associated with increased incidence of P. falciparum febrile episodes. This has lead to the suggestion that IL6 is an important febrile mediator [33] and increased levels of IL6 are associated with fatal outcomes [34,35].

In conclusion, malaria infection is on a delicate balance of pro- and anti-inflammatory cytokines and measuring levels and ratios of these cytokines can give clues to the prediction of the outcome of the diseases. Moreover, understanding how the balance of the opposing groups of cytokines is regulated during a malarial infection may lead to novel approaches to immunotherapy and immunoprophylaxis.

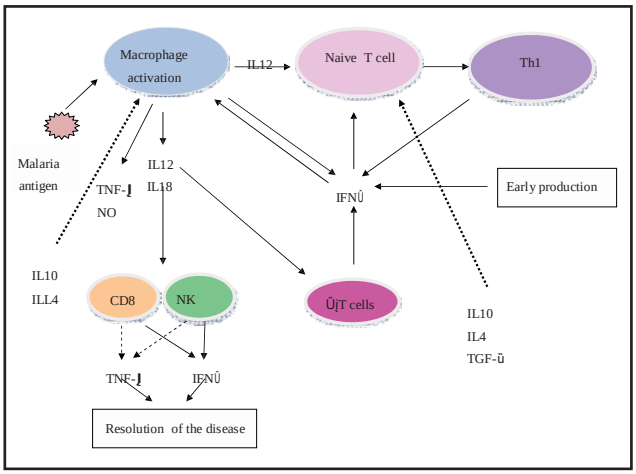

Figure 1: Proposed pathway of mild malaria episode, NK: natural killer cells, Th1: T helper 1 cells, NO: nitric oxide, solid lines indicates increased production, dashed lines indicate decreased production, and dotted lines indicate inhibited production of cytokines. Early production of IFN-γ ensures elimination of parasites and later production of anti-inflammatory (IL10,IL4,TGF-α) cytokines is needed to control production of pro-inflammatory cytokines.
A. Early high production of IL10 B. Reduced production of IL10 in the transition phase

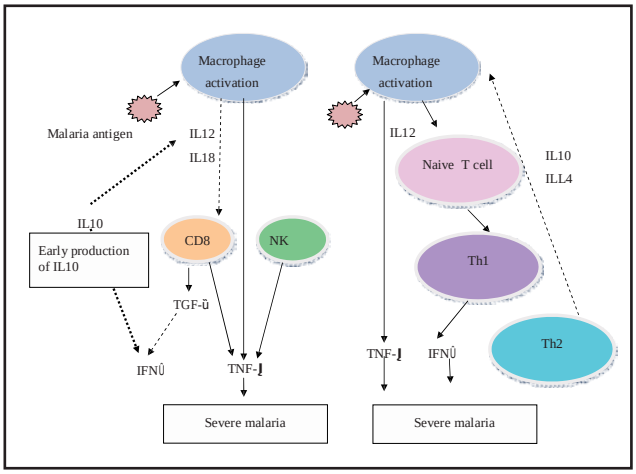

Figure 2: Proposed pathways of severe malaria episode. Solid lines indicate increased production, dashed lines indicate decreased production, and dotted lines indicate inhibited production of cytokines.

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