

Elevated Immune Responses an Evidence of Protection against Malaria Infection in Sickle Hemoglobin Individuals

Keywords: Immune responses; Malaria endemic region; Sickle cell individuals

Abstract

The development of malaria is partially inhibited in sickle hemoglobin (HbS) individuals especially those with heterozygote trait (HbAS) living in malaria endemic region. Factors such as immune responses are associated with this protection. Therefore, this review was conducted to describe the immunological mechanisms involved in protecting HbS individuals against malaria infection. In summary, immune factors contribute significantly in malaria protection; naturally, HbS individuals are prevented from the parasites density through an enhanced phagocytosis of the infected red blood cells in the spleen as a result of an improved antigen presentation. Moreover, humoral responses such as increased levels of Immunoglobulin G (IgG) and cellular mediated responses i.e. cytokines (interleukin 6,8,10,12 and tumor necrotic factors) protect HbS individuals from clinical malaria. This review recommends that, sickle hemoglobin should be considered when designing malaria vaccine trial.

Introduction

In the past two decades malaria especially caused by *Plasmodium falciparum* continued to be a disease of public health consequences in sub-Saharan Africa [1]. Furthermore, malaria is the evolutionary driving force behind erythrocyte defects that comprise the most common Mendelian diseases of humankind [2]. This evolutionary mutations on the human genome has selected multiple genetic polymorphisms such as sickle hemoglobin (HbS) to confers protection against malaria [3,4].

On the other hand, HbS occurs as a single point mutation (Glutamate→Valine) on the sixth codon of the beta globin gene responsible for the production of hemoglobin [2,4]. Individuals with either HbAS (heterozygous with normal hemoglobin A and sickle hemoglobin S) or HbSS (homozygous with sickle hemoglobin S) are considered to have sickle cell trait or sickle cell anemia respectively while those with HbAA (homozygous hemoglobin A) are considered to be normal [5-7]. Therefore, this review discusses the immunological mechanisms associated with the protection against malaria in HbS individuals.

Malaria immunity

Plasmodium infection involves two hosts where some of developmental stages occur in humans and other stages occurring in Anopheles female mosquitos as the vector for the parasite [8]. Immune responses to malaria parasites in human stage begins when the infected female Anopheles mosquito bites human skin for sucking blood [9]. The saliva of infected mosquitos contains sporozoites which



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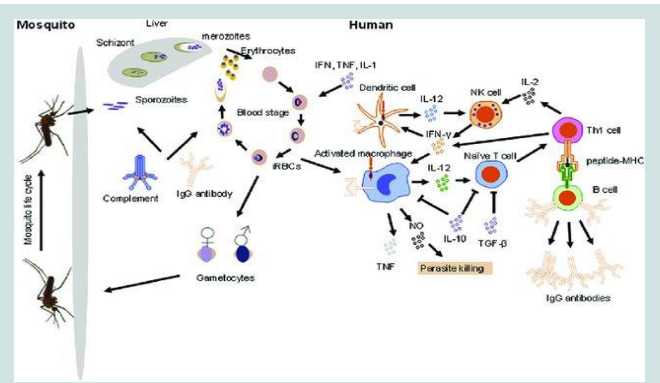
when injected into the patients' skin they may remain for hours or days [10]. This prompts the eliciting of innate immune system against the invading parasites where factors such as complement system and dendritic cells are involved. If uncontrolled the sporozoites then cross the endothelium of the capillaries of the skin and moves to infect hepatocytes in the liver. Sporozoites within liver cell replicate and differentiate into blood stage parasites called merozoites [8]. Merozoites are then released into the blood stream where they begin 48 h cycles of invasion of Red Blood Cells (RBCs) [8,10]. During the blood stage different components are released when the infected RBCs lyse. The release of these parasites' components triggers the humoral and cellular mediated responses as indicated in figure 1 below.

Innate immunity

Natural (innate) immunity refers to non-specific or first line of defense, which come into play within hours of an antigen's presentation in the body. Different mechanisms i.e. Phagocytosis and complement activation involving factors such as skin, chemicals in saliva and blood, mucosal, dendritic and epithelial cells are involved in natural defense. Innate immune responses contribute to the control of malaria infection and influence the nature and magnitude of the adaptive immune response to malaria [9].

Moreover, dendritic cells (DCs) and Natural Killer T (NKT) cells play a role in immunity to liver stage malaria parasites and contribute to parasite clearance [11]. In addition to that NKT cells are frequently the earliest source of interferon- γ during a blood-stage malaria infection and have an essential role in controlling acute parasitaemia [9,10].

DCs and NKT in individuals with sickle cell trait reduce the number of parasites density by preventing the establishing of blood stage infection through enhanced phagocytic mechanisms [14]. Furthermore, membrane-bound hemichromes, aggregated band 3, autologous and complement (C3c) fragments are reported to be highly expressed in all mutants Red Blood Cells (RBCs) [12-14]. This results to an enhanced phagocytosis of ring-parasitized mutant



Source: <https://www.researchgate.net/publication/321831431>
Figure 1: The *Plasmodium falciparum* life cycle and human host immunity.

RBCs by complement mediated and removal of senescent through phagocytic recognition [14].

Adaptive immunity

Adaptive (acquired) immunity refers to antigen specific immune response. This is more complex than innate but both innate and adaptive immune significantly protect an individual from an infection. Unlike innate, in adaptive immunity and antigen should first be processed and recognized, the recognized antigen is attached by the body immunity while keeping memory cells for future responses against the antigen more efficient [4].

Children with HbAS have lower parasite densities, which result to a decreased risk of progression of symptomatic malaria [9]. Findings from research revealed that HbAS associated protection against high-density parasitemia is mediated by an innate mechanism, whereas HbAS-associated protection against acquisition of infection and development of symptomatic malaria is mediated by acquired mechanisms [4].

The hypothesis that HbAS accelerates the development of acquired immunity to *P falciparum*, was proved from a cross-sectional study of children 9 months to 6 years of age which found that HbAS were most protective in children between 2 and 6 years of

age in addition to that another recent study also found a trend toward increased protection with advancing age, from 20% at 2 years of age to 56% at 10 years of age [4,15]. Enhanced acquisitions of acquired immunity in HbAS individuals are suggested to be a result of innate mechanisms of protection, with increased phagocytosis of infected RBCs in the spleen resulting in improved antigen presentation [4]. Find the specific discussions on two types of adaptive responses i) the cell-mediated immune response, which is carried out by T cells, and ii) the humoral immune response, which is controlled by activated B cells and antibodies.

Humoral immunity

Recently, investigators found that humoral responses are involved in malaria protection of HbS individuals [4]. Higher levels of *Plasmodium falciparum* Immunoglobulin G (IgG) responses directed against specific antigens have been shown to correlate with clinical protection in children with HbS [16]. More recently, IgG responses against *Plasmodium falciparum* (Pf) erythrocytes binding antigens (PEBA-175), gametocyte Protein (Pfg27) and zygote and ookinete protein (yPfs28C) were elevated in HbSS as compared to HbAA children [17]. Another study, which tried to establish how genetic factors including hemoglobinopathies, influence progression from the initial infection with *Plasmodium* spp. to the development of the infection through liver and blood-stage to clinical malaria attack, and finally to severe malaria found sickle haemoglobin play a protective effect [18].

Moreover, enhanced levels of cross-reactive anti-variant surface antigens (VSA) responses in children with HbAS were intimately associated with the protection they have against malaria [16].

Another evidence from children living in area with low malaria transmission revealed an increased levels of antibodies toward malaria parasites antigens apical membrane antigen (AMA1), Erythrocytes Binding Antigen (EBA175), Merozoites Surface Protein (MSP1, MSP2, MSP3), Circumsporozoite Protein (CSP), and Parasite Schizont Extract (PSE) in HbAS when compared to Has children [19]. In contrast to that, a study which was conducted in the endemic area with high malaria transmission found a significant high total IgG, directed against malaria parasites [20].

Table 1: Summery of immunological mechanisms associated with malaria protection.

Mechanism of protection		Evidence	
Immunological mechanisms	Enhanced innate immune response	Sickle cell trait protect against the establishment of blood-stage infection, development of high densities of parasites and the progression of infection to symptomatic malaria	Gong et al., 2012
		Phagocytosis is enhanced in ring parasitized RBCs in sickle cell trait	Ayi et al., 2004; Lang et al., 2009; Field et al., 2013
	Improved adaptive immune response	HbS is associated with protection against acquisition of infection and development of malaria	Williams et al., 2004; Gong et al., 2012
	Elevated humoral immune response	High levels of IgG in HbS individuals	Bwire et al., 2019; Grant et al., 2015; Verra et al., 2007; Cabrera et al., 2005; Nafady et al., 2014
	Increased cell mediated immune response	Elevated cytokines in HbS individuals	Ferreira et al., 2015; Nafady et al., 2014; Hassan et al., 2009; Mussa et al., 2010

Cell mediated immunity

The human cellular immune response to malaria parasites antigens involves the release of cytokines that may contribute to the control of the parasites' replication. These cytokines are also involved in the pathogenesis of the malaria that lead to the manifestation of clinical symptoms [21].

Study on cytokines among malaria patients [Interleukin (IL); IL 6,12,18] and uncomplicated clinical malaria were found to be higher in children with HbS than those with normal hemoglobin [20]. Research by Ferreira et al found sickle-conferring protection against *Plasmodium* infection, HbS inhibits activation and/or expansion of pathogenic CD8+ T cells recognizing antigens expressed by *Plasmodium*, an immunoregulatory effect that does not involve transcription factor NF-E2-related factor 2 (Nrf2) and/or heme oxygenase-1 (HO-1 [22]. Furthermore, study by Hassan et al on cellular immune responses on children with either non-HbS, with severe malaria, mild malaria or no symptoms of malaria, or asymptomatic HbS found that IL-12 was weakly expressed by all the groups of children. When compared with the other groups, the asymptomatic non-HbS had lower expression of all the cytokines studied. In addition, the asymptomatic HbS had significantly lower expression of tumour necrosis factor (TNF) than the non-HbS with severe malaria, but these two groups showed similar expression of interferon- γ , IL-4 and IL-6. Gene expression of the regulatory cytokine, IL-10, by the asymptomatic HbS was significantly lower than that by the non-HbS with severe malaria but higher than that in the non-HbS with mild malaria [21].

Another study found a coexistence of both high and low levels of helper T cells (TH), TH1- and TH2-type cytokines, as well as diminished levels of T-cell subsets in sickle cell disease children [23]. To summarize, these regulations of cytokine release appear to protect HbS from clinical malaria.

Conclusion

This review concludes that, immune systems play roles in protection against malaria in HbS individuals. HbS individuals are prevented from increased number of parasites (parasites density) through an enhanced phagocytosis of infected RBCs in the spleen as a result of the improved antigen presentation. This finally enhance the acquisitions of acquired immunity in HbS particularly HbAS individuals. Humoral responses such as increased levels of IgG and cellular mediated responses such as cytokines (IL-6,8,10,12 and TNF) expression are the specific immune factors that protect HbS individuals from clinical malaria.

In summary, this review recommends more studies to be conducted to establish the effect of sickle hemoglobin and its implication on malaria vaccine development. Moreover, investigators should consider sickle hemoglobin when designing malaria vaccine trial.

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