Journal of Basic and Applied Pharmacology
Vol. 3 No. 2 July - December 2023

Page: [R8-25]

Review article

Host and malaria parasite factors associated with disease susceptibility and severity

Wanna Chaijaroenkul*

Chulabhorn International College of Medicine, Thammasat University, Paholyothin Road, Klongluang, Pathumthani 12120, Thailand

Received 12 March 2023; Received in revised form 8 April 2023
Accepted 15 August 2023; Available online 3 October 2023

ABSTRACT

Malaria remains one of the major global public health problems despite a decline in its incidence in recent years. Both parasite and human host-related factors play significant roles in malaria susceptibility, pathogenesis, and disease severity. Among the six malaria species that infect humans, *Plasmodium falciparum* has a unique capacity to infect host erythrocytes and develop a variety of surface antigens during this intra-erythrocyte stage to evade host immunity. Polymorphisms of the gene encoding *Plasmodium falciparum* erythrocyte membrane protein 1 (PfEMP1) results in severe pathogenesis and clinical manifestations. Among the host-related factors, the polymorphisms of the genes encoding proteins involved in immune functions (immunomodulatory proteins, toll-like receptors) and the binding of malaria parasites to host cells (cytoadhesion proteins) are the key proteins involved in malaria pathogenesis and severity. Results of various reports for the relationship between the polymorphisms of both parasite and host genes and malaria susceptibility, pathogenesis and disease severity are, inconclusive, depending on endemic areas and observation periods under investigation.

Keywords: malaria, host factors, immunomodulation, cytoadhesion

*Corresponding author: wn_ap39@yahoo.com
https://li01.tci-thaijo.org/index.php/JBAP

Introduction

Malaria remains one of the major global public health problems despite a decline in its incidence in recent years. In 2018, 3. 2 billion people were at risk of malaria infection, with an estimated 219 million cases and 435,000 malaria- related deaths.[1] Over 90% of death cases were reported from sub- Saharan Africa, most of which are children under five years of age. Malaria is caused by the infection of Plasmodium protozoa, a blood- borne disease transmitted by the female Anopheles mosquito. Six species of the malaria parasite can infect humans, *i.e.*, *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale curtisi*, *Plasmodium ovale wallikeri*, *Plasmodium malariae*, and *Plasmodium knowlesi*. Acute flu- like symptoms are due to the rupture of infected parasites from hepatocytes into blood stream. Severe complications with vascular compromise and organ involvement can be found in some cases, particularly with *P. falciparum* infection.[2] The infections with *P. vivax*, *P. ovale*, and *P. malariae* cause milder disease manifestations that are generally not fatal. *P. vivax* malaria is the most geographically widespread, and the second prevalent cause of global malaria. *P. vivax* and *P. ovale* have the potential to cause relapse after several years due to persistent liver stages.[3,4] The key components of malaria control programs are currently based on early diagnosis and the use of effective antimalarial drugs. Other control measures include disease surveillance, landscaping measures, and innovative vector control.[5] Through various elimination efforts, particularly by the World Health Organization (WHO) Global Malaria Eradication Program, malaria has been eliminated in some areas with low levels of transmission.[6] Nevertheless, the main problem that limits the effective malaria control or elimination is the emergence and spread of *P. falciparum* to most of the available antimalarial drugs.

Factors associated with malaria susceptibility and severity

Both parasite and human host- related factors play significant roles in malaria susceptibility, pathogenesis, and disease severity. *P. falciparum* has a unique capacity to infect host erythrocytes and develop a variety of surface antigens during this intra- erythrocyte stage to evade host immunity. Among the host- related factors, the polymorphisms of the genes encoding proteins involved in immune functions and the binding of malaria parasites to host cells have been the research focus in recent years to understand malaria pathogenesis and severity and exploited the knowledge for malaria control. Results of various reports for the relationship between the polymorphisms of these genes and malaria susceptibility, pathogenesis and disease severity are, however, conflicting, depending on endemic areas and observation periods under investigation.

Parasite factors

Malaria virulence is the ability of *Plasmodium* parasite, particularly *P. falciparum*, to express variant antigens on infected red blood cell' s surface, which enables the elusion of antibodies developed by the human host. PfEMP1 (*Plasmodium falciparum* erythrocyte membrane protein 1), is the most critical protein that is responsible for cytoadherence of infected erythrocytes to the vascular endothelium of the host and lead to lethal cerebral malarial. *PfEMP1* gene (200–400 kDa) is encoded by a family of the polymorphic *var* genes.[7,8] Two- exons of *var* genes encode a semi- conserved C- terminus (contains a predicted transmembrane region), and a highly polymorphic extracellular N- terminus. This part has a modular structure containing various numbers of Duffy- binding- like and cysteine- rich domains which are involved in sequestration of the infected erythrocytes.[9,10] The activation and silencing of *var* gene expression are epigenetically regulated, but the molecular

basis of this expression remains unclear.[8] Several host receptors have been shown to interact with PfEMP1 and subsequently lead to severe manifestation through resetting and sequestration.[11,12]

Approximately 60 *var* genes are distributed as clusters on fourteen chromosomes. The genes are classified into three groups based on the conserved sequence upstream of the coding region (Fig. 1). Group A *var* genes are located in the subtelomeric areas and are involved in the pathogenesis of severe malaria.[13] Group B *var* genes are found both within chromosomes and at the subtelomere region. Group C *var* genes are confined only in internal chromosomal areas of chromosomes 4, 7, 8, and 12.[14] In addition, two intermediate groups (B/A and B/C) are defined based on the presence of one of the 5′ upstream sequences and the position and orientation of the genes within a genomic context.[15,16] Although PfEMP1 is highly polymorphic, all forms share similar structures consisting of N-terminal segment (NTS), Duffy-Binding like (DBL), and cysteine-rich interdomain regions (CIDR) that are encoded from the first exon. The second exon is semi-conserved and encodes the intracellular component of PfEMP1. The DBL domains are subdivided into six major classes (DBL-α, β, γ, δ, ε, and ζ). The CIDR domains are subdivided into four classes (CIDR-α, β, γ, and δ); each class consists of subclasses.[17]

Among the 60 *var* genes family, only one is expressed during the time when the parasites give rise to an antigenically distinct PfEMP1 variants.[18] The switching of *var* gene expression in each new asexual blood-stage cycle results in antigenic variation of the malaria parasite that helps in evading the immune response and may result in new adhesion phenotype.[19] The expression of PfEMP1 on the surface of infected erythrocytes is known as membrane protrusions called knobs.[20] The knobs are complex molecules involved with multiple host and parasite molecules, including KAHRP (knob-associated histidine-rich protein).[21] The role and function of knob formation remain unclear. However, the expression of PfEMP1 is likely to be modulated by host immunity.

The sequence analysis of DBLα diversity suggests 40-70% and 46-50% conservation of amino acid sequences in *P. falciparum* laboratory strains and Asia Pacific field isolates, respectively.[22-24] Association between parasite rosetting phenotype and the expression of Group 2 PfEMP1-DBLα sequences was reported in *P. falciparum* isolates in Kenya.[25] The association between *var* genes expression and severity of malaria infection was reported from the isolates from French Guiana, Papua New Guinea, Brazil, Tanzania, and India.[26-34] For the isolates in Thailand, PfEMP1-DBL α domains are highly diverse, but no difference was found between clinical isolates collected from patients with severe and uncomplicated malaria.[35] A high rate of *var* gene exon mutations has been shown to mainly occur during the asexual stage of the parasite life cycle.[14]

Host factors

Cytoadhesion molecules

Parasite cytoadherence is an important process associated with cerebral malaria and malaria severity. Several hypotheses have been proposed to explain the mechanisms of cytoadherence. Host receptors play an important role in the adhesion of infected red blood cells to vascular endothelial cells. Several surface proteins and carbohydrates on the endothelial cells can serve as cytoadherence receptors such as CD36,[36] intercellular adhesion molecule 1 (ICAM-1),[37] endothelial protein C receptor (EPCR),[38] oncofetal chondroitin sulfate (CSA),[39,40] and ABO blood group antigen.[41,42]

CD36: Group B and C PfEMP-1 contain CIDRα2-6 domain that binds to CD36.[43] CD36 is the class B scavenger

receptor[44] which plays a role in immunity (phagocytosis), fatty acid metabolism, and angiogenesis.[45] This protein is found in many tissues, allowing adhesion of infected red blood cells in different sites within the vascular endothelium.[36] Current knowledge on the role of CD36 in malaria pathogenesis remains controversial. It is believed that CD36 is a central receptor mediating severe malaria. It is shown to assist in creating a microenvironment that enhances the replication of *P. berghei* in mice.[46] In addition, it is also reported to play a role in host and parasite interaction on the immune system cells.[47,48] This interaction leads to avoidance of parasite splenic clearance[47,49] by reducing dendritic cell-mediated T-cell activation. On the other hand, the binding of infected red blood cells to CD36 is shown to facilitate parasites clearance by macrophages and thus, reducing the risk of development of high parasitemia.[48] The binding of infected red blood cells with CD36 on platelets is required for the formation of platelet-mediated clumps, which are associated with severe manifestation of malaria infection.[50]

Reports of the association between *CD36* gene polymorphism and clinical consequences of malaria pathogenesis and severity from various studies are controversial.[51,52] The study from Kenya showed the association between *CD36* 1264G (T1264G; *rs3211938*) and a 1.5-fold increase in the risk of malaria severity (odds ratio=1.5, 95%CI 1.03-2.18).[53] This finding was supported by the study showing a 1.49-fold increase in the risk of malaria severity (odds ratio= 1.49, 95% CI 1.09-2.15).[54] Mutation at the position 188G (T188G) resulted in a 8-fold increase in the risk of cerebral malaria in Sudan patients.[55] The study in Thailand suggested the link between 539delAC allele mutation and cytoadherence in severe malaria.[56] In contrast to these studies, heterozygosity of *CD36* T188G mutation was associated with protection from severe malaria in African ethnic (odds ratio=0.74, 95%CI 0.55-0.99).[57] Similarly, heterozygote mutant allele of *CD36* T188G was also reported to protect from severe malaria in Indian patients (odds ratio=3.51, 95%CI 1.67-7.36).[58] No significant association between malaria severity and *CD36* polymorphism (*CD36* T1264G and other 70 SNPs) was found in 3,420 patients with severe and uncomplicated malaria from 66 ethnic groups.[58,59]

Intercellular adhesion molecule-1 (ICAM-1): ICAM-1 or CD54, is a member of the immunoglobulin superfamily which is expressed on the surfaces of several host cells, particularly the brain endothelial cells. The pro-inflammatory cytokines upregulated ICAM-1 expression.[60] ICAM-1 functions as a binding receptor to PfEMP1, specifically to subclasses of DBLβ domains in Group A, B, and C.[61,62] It is proposed to play an essential role in parasite sequestration in vascular endothelial cells, leading to severe and cerebral malaria.[63-66] Besides, ICAM-1 also binds to lymphocyte function-associated antigen (LFA)-1 on the leukocyte cell surface,[67] resulting in increased permeability of leukocytes through blood-brain-barrier and thus, enhanced activation of natural killer cells during *P. falciparum* infection.[68]

The relationship between ICAM-1 polymorphism and the clinical consequences of malaria pathogenesis and severity is unclear. The investigation in rodent malaria revealed the association between malaria severity and ICAM-1-mediated cytoadherence in *P. berghei*- and *P. chabaudi*- infected mice.[46, 69] In addition, a study in ICAM-1 mutant mice also demonstrated the association between vascular occlusion in cerebral malaria and the expression of ICAM-1 on leukocytes, but not endothelial cells.[70] *In vitro* study showed the prevalence of binding of *P. falciparum* isolates from African children with cerebral malaria to ICAM-1,[71] but not the isolates from Asia.[72,73] Recently, infected red blood cells have been shown to bind to ICAM-1 as well as other receptors at a similar level, without association with malaria severity.[74]

The association between ICAM- 1 expression and severity of *P. falciparum* infection was observed in the organs of fatal cases in one study,[63] while no association was found in other studies. [71,75] Increased susceptibility to cerebral malaria was reported in Kenyan patients with K56M mutation of *ICAM-1* (*ICAM-1*^{Kilifi} or *rs5491*) (odds ratio 1.55, 95%CI 1.17-2.01).[76] On the other hand, the study in Gabon showed a protective effect from this mutation (odds ratio= 0. 54, 95% CI 0. 34- 0. 84) . [77] The mutation of *ICAM-1* at *rs5498* (exon 6) G allele was associated with increased risk of severe malaria in Indian population (odds ratio 1.91, 95%CI 1.05-3.49).[51] In contrast to these studies, subsequent studies of *ICAM-1*^{Kilifi} in Gambia,[78] Thailand,[79] Senegal,[80] Nigeria[81] and Kenya[53,82] reported no significant association with malaria severity. Genetic surveillance study of *ICAM- 1*^{Kilifi}, *rs5498* and other SNPs in Gambia, Malawi and Kenya also showed no significant association between ICAM- 1 and malaria susceptibility.[59]

Endothelial protein C receptor (EPCR): EPCR is an essential receptor for PfEMP1 proteins contain DBLα2-CIDRα1.1-DBLβ12-DBLγ4/6, DBLα1.7 and CIDRα1.4, which are known as domain cassette 8 and 13, respectively.[38] These two variants of PfEMP1 are commonly bound to endothelial cells of the lung, heart, and bone marrow[83] and are expressed at high levels in *P. falciparum* isolates from patients with severe and cerebral malaria from African children and Indian adults.[84-88] The association with cerebral malaria is explained by selective binding of infected red blood cells to brain endothelial cells which highly express these domain cassettes.[89] However, the linkage between the receptor binding and cerebral malaria is not well understood.

In contrast to the endothelial cell-bound EPCR which activates protein C, the soluble form of EPCR (sEPCR) inhibits the activation of protein C by competing for protein C with endothelial cell- bound EPCR. sEPCR can bind to infected red blood cells and inhibit their adhesion to human brain microvasculature endothelial cells.[90] Mutation of *EPCR* at r*s867186*-GG, and protection from malaria was reported from Thailand. [91] This *EPCR rs867186*- G allele markedly increased plasma sEPCR levels.[92-94] The r*s867186*-GG genotype was associated with increased plasma sEPCR level and, although the reduced level was associated with severe malaria in Ugandan children.[95] No association between *rs867186*-G variant and malaria severity was found in African children.[96, 97]

Complement receptor 1 (CR1): CR1 is a complement receptor found on the surface of erythrocytes and most leucocytes. This receptor has been proposed to play an important role in the pathogenesis of severe anemia and cerebral malaria, and acts as an alternate receptor for *P. falciparum* to invade red cells. [98] The CR1 contains 30 short consensus repeats which are divided into four long homologous regions (LHR A, B, C, and D). The *CR1* polymorphism involves size, quantitative, and sequence polymorphisms. The deletion or duplication of LHRs during unequal cross results in size polymorphisms[99,100] known as size variants CR1* 1- 4. [101, 102] Quantity of the receptor presented on the red cells varies and is regulated by putative co-dominant alleles L (low expression) and H (high expression), which give rise to low (LL), intermediate (HL), and high (HH) expression phenotype. [103] CR1 carries the antigens for the Knops blood group system, *i. e.* , Knops (*Knp*$^{a/b}$) , McCoy (*McC*$^{a/b}$) , Swain-Langley (*Sl*1/2), and York (*Yk*^{a}), with several single nucleotide substitutions. [98,104] The *rs11118133* T allele was found to correlate with the decrease in rosetting of malaria parasite with erythrocytes. [11,12] This mutation and association with protection against cerebral malaria and the decrease in disease severity were reported from Papua New Guinea. [105,106] The *rs2274567* G allele was associated with a decrease in sialic-acid-independent malarial invasion of red cells.[107]

The relationship between *CR1* polymorphism and CR1 level is unclear.[108-111]

Immunomodulatory molecules

Tumor necrosis factor-alpha (TNFα): TNFα is a pro-inflammatory cytokine released from activated endothelial cells through the interaction of infected red cells binding to EPCR. The process then triggers the pathogenesis of severe malaria, including cerebral malaria. High levels of cytokines, particularly TNFα, are observed in blood and brains of patients and animals with cerebral malaria.[112] In the *in vitro* study, exposure to TNFα induced the activation of endothelial cells and pro-adhesion factors that led to the increase in the binding of infected red blood cells to human and mouse brain microvascular cells.[113,114] TNFα was shown to be responsible for parasite killing and thereby, reduction of parasitemia.[115] High serum TNFα level was associated with parasite clearance and low parasitemia.[116]

Several single nucleotide polymorphisms (SNPs) of TNFα promoter regions have been reported. These SNPs are associated with TNFα gene expression/production[117-120] and control of parasitemia and IgG level.[120-124] The polymorphisms at -238 (*TNFα*- 238), -244 (*TNFα* -244), -308 (*TNFα* -308), -857 (*TNFα* -857), -863 (*TNFα* -863), -1031 (*TNFα* -1031) and -376 (*TNFα* -376) resulted in high TNFα level in plasma and serum of malaria patients.[125] Besides, the *TNFα* -308 allele mutation was found to be associated with high serum TNFα level in severe malaria.[126] The *TNFα* -238 polymorphism was associated with severe malaria in Gambia[127].

Lymphotoxin α (LTα): LTα, formerly known as TNFβ, is produced by T and B lymphocytes.[128,129] Its structure is similar to TNFα with 30% homology.[130] LTα is a soluble homotrimer which binds to TNF receptor 1 and 2 (TNFR1 and TNFR2) similarly to TNFα. However, both have some distinct molecular and biological differences.[131,132] LTα is expressed by CD4+ T helper type 1 (Th1) cells, CD8+ cells, natural killer (NK) cells, B cells, and macrophages, and has crucial roles in the development and functioning of the immune system mainly in lymphoid organ development, organization and maintenance of lymphoid microenvironments, host defense, and inflammation.[132] LTα was shown to be involved in host defense against malaria infection in mice.[133]

Transforming growth factor β1 (TGFβ1): TGFβ isoforms are involved in immune responses to various pathogens, including *Plasmodium*.[134] TGFβ1 is a pro-inflammatory cytokine which is produced by leukocytes. It plays an important role in balancing parasite load and the host immune response.[134] In the animal model, low TGFβ1 level was observed at early infection, which promoted parasite clearance. At the later phase, the increase in TGFβ1 level was found, which played a role in host anti-inflammation or immuno-compromization.[135] Injection of recombinant TGF-β1 or antibody neutralization to mice resulted in high and low TGF-β1 levels at the early or late phase, which was associated with uncontrolled parasitemia and increased pathology.[136] Subsequent studies in infected patients showed that severe late-stage infection was associated with a significant reduction of serum TGFβ1 levels.[137,138] Altogether, these data suggest that severe malaria is resulted from uncontrolled immunopathology which exacerbates clinical responses.

Interleukin family (ILs): During malaria parasite infection, the interaction of infected red cells and endothelial cells stimulates inflammatory cytokine response, including the release of interleukins. In the early stage of malaria infection, IL6 plays a role in malaria protection, but the increased level is associated with severe malaria.[139] Several interleukins have been reported to be associated with severe or uncomplicated malaria. IL1β, IL6 and IL18 are up-regulated in severe malaria, whereas the anti-inflammatory cytokines IL10 and IL12 are down-regulated in severe malaria.[140,141]

IL1 is an endogenous pyrogen and an inducer of the acute phase immune response. It is an important part of host immune response to malaria infection. [142] The *IL1* gene consists of two parts: interleukin- 1 alpha (IL1α) and interleukin- 1 beta (IL1β) . [143] The two polymorphisms, *IL1α* +4845 G/T and *IL1β* +3953 C/T, were found to be associated with a mild degree of malaria in Gambian patients.[144]

IL4 is a key cytokine that regulates the expression of immunoglobulins in B cells.[145, 146] It induces the differentiation of naive helper T cells (Th0 cells) to Th2 cells. Upon activation by IL4, Th2 cells subsequently produce additional IL4 in a positive feedback loop.[147] The polymorphism of *IL4* promoter region (*IL4* -590 C/T) affected the production of IL4.[148, 149] IL4-524T and association with malaria protection was reported from West Africa.[150] Moreover, the *IL4* -589T mutation was associated with increased IgE levels in children with severe malaria in Burkina Faso.[151] The IgE levels were markedly increased in cerebral malaria children in Ghanian patients who carried *IL4* -590T allele.[152] The *IL4* -590T allele was associated with high IgG levels in patients with severe malaria in Thailand.[153] Additionally, *IL4* -590 C/T polymorphism has been proposed to play a role in balancing IL4 and IFN-γ activities and thus, alteration of malaria severity.[154]

IL6 is a pro- inflammatory cytokine produced by endothelial cells and antigen-presenting cells (APC) which plays a role in malaria clearance. Genetic variation of *IL6* is poorly investigated in malaria. The -174 C/G SNP of *IL6* gene was associated with the increased risk of uncomplicated *P. vivax* infection in Brazil.[155] IL6 level was found to be higher in patients who died from *P. falciparum* than those who survived. It was also associated with hyperparasitemia, jaundice, and shock.[156] Increased IL6 levels were found both in malaria patients with cerebral complication or renal failure.[157]

IL10 is produced by several cells such as B cells, Th1, Th2, Th17, and innate immune cells.[158] The IL10 secreted by CD4+ T cells inhibits T cells function and antigen-presenting cells (APCs) activities that lead to the suppression of the inflammation process.[159] On the other hand, IL10 produced by Th1 cells promotes infections to persist by suppressing Th1 cell- mediated immunity. Both functions of IL10 are essential to protect tissue damages by preventing excessive inflammation. [160] The evidence form animal studies suggested that IL10 is a molecule in controlling inflammatory responses and preventing tissue damage. [158, 161- 163] The *IL10* - 1082A/ G polymorphisms resulted in low IL10 production and was associated with a decreased risk for clinical malaria. [164,165] High level of *IL10* was found in mild and severe malaria patients. [166,167] In Kenya children, the *IL10* haplotype (GCC: -1082G/-819C/-592C) resulted in high serum IL10 level which was associated with protection against severe malaria- related anemia.[168]

IL12 is a pro-inflammatory cytokine that plays an essential role in immune-regulation in malaria infection. [169] The *IL12* gene consisted of two subunits: *IL12A* and *IL12B*. The *IL12B* was found to be associated with high parasite density and severe malaria. [170- 172] The polymorphism in the *IL12B* promoter region was associated with increased mortality in Tanzanian children with cerebral malaria, but not in Kenya children with severe malaria. [173] Moreover, the study in Kenya children revealed the association between the polymorphisms of *IL12A* (*rs2243140*) and its receptor *IL12 RB1* (*rs429774*) and the reduced risk of anemia associated with severe malaria.[174]

Toll-like receptors (TRLs)

Toll- like receptors (TLRs) are molecules of the immune system that recognize pathogen- associated molecular patterns (PAMPs). The binding to infected red blood cells and recognition of *Plasmodium* molecules such as glycosylphosphatidylinositol

(GPI) or hemozoin-DNA complexes can be triggered by several TLRs.[175,176] TLR2, TLR4 and TLR9 have recently been implicated in human malaria pathogenesis.[177,178]

TLR2 is expressed on the cell surface and is activated by a glycosylphosphatidylinositol (GPI) of the malaria parasite.[176] This *TLR2* gene is highly polymorphic, *e.g.*, TLR2 Δ22 (insertion/deletion polymorphism) or several GT repeats (GTn).[179,180] Deletion of *TLR2 (TLR2 Δ22)* was associated with host protection from cerebral malaria but had no effect on serum cytokine levels. The insertion of TLR2 polymorphism in the uncomplicated malaria was linked to elevated inflammatory cytokines.[181]

TLR4 is also expressed on the cell surface and is activated by bacterial lipopolysaccharides.[161,182] Thus, GPI may weakly activate *TLR4*.[176] Two non-synonymous mutations at *TLR4* D299G and T399I have been associated with various infectious and inflammatory diseases. Cohort studies in children in Ghana and in Kenya showed that these two polymorphisms were associated with severe and symptomatic malaria.[183] The mutations confer a hyporesponsive phenotype *in vitro*[184] but not in others.[185]

TLR9 is expressed in endosomal compartments, where it binds to and is activated by malarial hemozoin and/or DNA.[186,187] Two polymorphisms in the promoter regions (*TLR9* -1486T/C and -1237T/C) were associated with severe malaria.[188] Moreover, *TLR9* +1174A/G was associated with an increased risk of symptomatic malaria and high parasitemia, whereas *TLR9* +2848A/G was associated with a reduced risk of malaria symptoms.[189]

Heme oxygenase-1 (HO-1)

Heme oxygenase-1 (HO-1) is a human enzyme that degrades heme to generate biliverdin, carbon monoxide, and ferrous iron. It is a rate-limiting, inducible enzyme. It possesses anti-inflammatory effects and protects against severe malaria in mice.[190,191] *Hmox1* is the gene that encodes HO-1. Possible association between HO-1 and malaria was investigated in several studies. Increase in enzyme expression during malaria infection was reported.[192-194] The association between the short (GT)n repeat alleles and risk of severe malaria was reported in clinical studies in Gambia, Myanmar, and Angola.[195-197] Lack of association between malaria severity and length of GT repeats was reported from the study in Thailand.[198]

Hemoglobinopathies

Red blood cells are the target cells for malaria infection and propagation. The variants of red blood cells occur due to are polymorphisms of human genetics, which is believed to confer selective suppression of malaria evolution.[199] Hemoglobin is the oxygen-carrying protein of the red blood cells and is normally formed as a tetramer of two α-globins and two β-globins, which constitute adult hemoglobin A (HbA). Red cell hemoglobinopathies such as HbS, HbC and HbE are caused by either the decrease of α-/β-globins production or the abnormality of amino acid changes. Red cell hemoglobinopathies have been shown to be associated with the protection human host from malaria infection and severity. Individuals with homozygous HbS, HbC, HbE, α-thalassemia and β-thalassemia genotypes were shown to be at low risk of developing severe and cerebral malaria, whereas those with heterozygous genotypes were at risk of mild to uncomplicated malaria.[200] It has been proposed that these red blood cell variants might occur due to unsuitable conditions for the malaria parasite to invade or proliferate. High oxidative stress together with low hemoglobin levels also impact the parasite growth. In addition, the inflexibility of the red cell membrane is favorable for phagocyte to engulf.[201]

The *in vitro* studies demonstrated a reduction in the invasion of the malaria parasite to red blood cells with α-thalassemia trait, HbH, HbEE, HbAE, and heterozygous β-thalassemia/HbE disorders.[202-205] A reduction

in parasite growth and development in red blood cells was also observed with HbH, β-thalassemia minor, HbSS, HbAS, HbCC, HbEE, HbAE, and HbF. [205- 209] However, these findings were not supported by results of other studies.[207, 210-213]

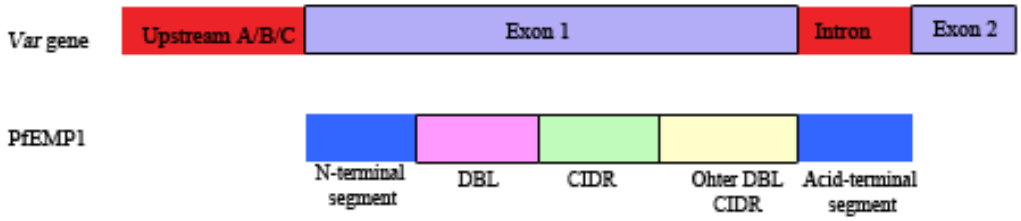

Fig. 1. The structure of *var* genes.

Conclusion

Both parasite and human host-related factors play significant roles in malaria susceptibility, pathogenesis, and disease severity. Among the six malaria species that infect humans, *Plasmodium falciparum* has a unique capacity to infect host erythrocytes and develop a variety of surface antigens during this intra-erythrocyte stage to evade host immunity. Polymorphisms of the gene encoding *Plasmodium falciparum* erythrocyte membrane protein 1 (PfEMP1) results in severe pathogenesis and clinical manifestations. Among the host-related factors, the polymorphisms of the genes encoding proteins involved in immune functions (immunomodulatory proteins, toll-like receptors) and the binding of malaria parasites to host cells (cytoadhesion proteins) are the key proteins involved in malaria pathogenesis and severity. Results of various reports for the relationship between the polymorphisms of both parasite and host genes and malaria susceptibility, pathogenesis and disease severity are, inconclusive, depending on endemic areas and observation periods under investigation. Further studies are required to confirm these findings in various malaria-endemic areas.

Acknowledgements

We thank Chulabhorn International College of Medicine (CICM) of Thammasat University, Center of Excellence in Pharmacology and Molecular Biology of Malaria and Cholangiocarcinoma of Thammasat University, the National Research Council of Thailand under the Research Team Promotion grant (grant number NRCT 820/2563) and the Thailand Science Research and Innovation Fundamental Fund fiscal year 2023 for the support of this research.

Conflicts of Interest

The author declared no conflict of interest.

References

[1] WHO. World malaria report 2018. Geneva, Switzerland: World Health Organization; 2018.

[2] Renia L, Howland SW, Claser C, Charlotte Gruner A, Suwanarusk R, Hui Teo T, et al. Cerebral malaria: mysteries at the blood-brain barrier. Virulence. 2012; 3(2):193-201.

[3] Howes RE, Battle KE, Mendis KN, Smith DL, Cibulskis RE, Baird JK, et al. Global Epidemiology of *Plasmodium vivax*. Am J Trop Med Hyg. 2016; 95(6):15-34.

[4] Groger M, Fischer HS, Veletzky L, Lalremruata A, Ramharter M. A systematic review of the clinical presentation, treatment and relapse characteristics of human Plasmodium ovale malaria. Malar J. 2017; 16(1):112.

[5] Gari T, Lindtjorn B. Reshaping the vector control strategy for malaria elimination in Ethiopia in the

context of current evidence and new tools: opportunities and challenges. Malar J. 2018;17(1): 454.

[6] Bridges DJ, Winters AM, Hamer DH. Malaria elimination: surveillance and response. Pathog Glob Health. 2012;106(4):224-231.

[7] Baruch DI, Pasloske BL, Singh HB, Bi X, Ma XC, Feldman M, et al. Cloning the *P. falciparum* gene encoding PfEMP1, a malarial variant antigen and adherence receptor on the surface of parasitized human erythrocytes. Cell. 1995;82(1):77-87.

[8] Kim K. Malaria var gene expression: keeping up with the neighbors. Cell Host Microbe. 2012;11(1):1-2.

[9] Chen Q, Barragan A, Fernandez V, Sundstrom A, Schlichtherle M, Sahlen A, et al. Identification of *Plasmodium falciparum* erythrocyte membrane protein 1 (PfEMP1) as the rosetting ligand of the malaria parasite *P. falciparum*. J Exp Med. 1998; 187(1):15-23.

[10] Smith JD, Chitnis CE, Craig AG, Roberts DJ, Hudson-Taylor DE, Peterson DS, et al. Switches in expression of *Plasmodium falciparum* var genes correlate with changes in antigenic and cytoadherent phenotypes of infected erythrocytes. Cell. 1995; 82(1):101-110.

[11] Rowe JA, Moulds JM, Newbold CI, Miller LH. *P. falciparum* rosetting mediated by a parasite-variant erythrocyte membrane protein and complement-receptor 1. Nature. 1997;388(6639):292-295.

[12] Rowe JA, Rogerson SJ, Raza A, Moulds JM, Kazatchkine MD, Marsh K, et al. Mapping of the region of complement receptor (CR) 1 required for *Plasmodium falciparum* rosetting and demonstration of the importance of CR1 in rosetting in field isolates. J Immunol. 2000;165(11):6341-6346.

[13] Smith JD, Rowe JA, Higgins MK, Lavstsen T. Malaria's deadly grip: cytoadhesion of *Plasmodium falciparum*-infected erythrocytes. Cell Microbiol. 2013;15(12):1976-1983.

[14] Claessens A, Hamilton WL, Kekre M, Otto TD, Faizullabhoy A, Rayner JC, et al. Generation of antigenic diversity in *Plasmodium falciparum* by structured rearrangement of Var genes during mitosis. PLoS Genet. 2014;10(12):e1004812.

[15] Bull PC, Kortok M, Kai O, Ndungu F, Ross A, Lowe BS, et al. *Plasmodium falciparum*-infected erythrocytes: agglutination by diverse Kenyan plasma is associated with severe disease and young host age. J Infect Dis. 2000;182(1):252-259.

[16] Lavstsen T, Salanti A, Jensen AT, Arnot DE, Theander TG. Sub-grouping of *Plasmodium falciparum* 3D7 var genes based on sequence analysis of coding and non-coding regions. Malar J. 2003;2: 27.

[17] Rask TS, Hansen DA, Theander TG, Gorm Pedersen A, Lavstsen T. *Plasmodium falciparum* erythrocyte membrane protein 1 diversity in seven genomes--divide and conquer. PLoS Comput Biol. 2010;6(9).

[18] Kraemer SM, Smith JD. A family affair: var genes, PfEMP1 binding, and malaria disease. Curr Opin Microbiol. 2006;9(4):374-380.

[19] Ralph SA, Scheidig-Benatar C, Scherf A. Antigenic variation in *Plasmodium falciparum* is associated with movement of var loci between subnuclear locations. Proc Natl Acad Sci U S A. 2005;102(15): 5414-5419.

[20] Luse SA, Miller LH. *Plasmodium falciparum* malaria. Ultrastructure of parasitized erythrocytes in cardiac vessels. Am J Trop Med Hyg. 1971;20(5): 655-660.

[21] Cutts EE, Laasch N, Reiter DM, Trenker R, Slater LM, Stansfeld PJ, et al. Structural analysis of *P. falciparum* KAHRP and PfEMP1 complexes with host erythrocyte spectrin suggests a model for cytoadherent knob protrusions. PLoS Pathog. 2017; 13(8):e1006552.

[22] Ward CP, Clottey GT, Dorris M, Ji DD, Arnot DE. Analysis of *Plasmodium falciparum* PfEMP-1/var genes suggests that recombination rearranges constrained sequences. Mol Biochem Parasitol. 1999; 102(1):167-177.

[23] Kyes S, Taylor H, Craig A, Marsh K, Newbold C. Genomic representation of var gene sequences in *Plasmodium falciparum* field isolates from different geographic regions. Mol Biochem Parasitol. 1997; 87(2):235-238.

[24] Fowler EV, Peters JM, Gatton ML, Chen N, Cheng Q. Genetic diversity of the DBLalpha region in *Plasmodium falciparum* var genes among Asia-Pacific isolates. Mol Biochem Parasitol. 2002; 120(1):117-126.

[25] Bull PC, Berriman M, Kyes S, Quail MA, Hall N, Kortok MM, et al. *Plasmodium falciparum* variant surface antigen expression patterns during malaria. PLoS Pathog. 2005;1(3):e26.

[26] Ariey F, Hommel D, Le Scanf C, Duchemin JB, Peneau C, Hulin A, et al. Association of severe malaria with a specific *Plasmodium falciparum* genotype in French Guiana. J Infect Dis. 2001; 184(2):237-241.

[27] Falk N, Kaestli M, Qi W, Ott M, Baea K, Cortes A, et al. Analysis of *Plasmodium falciparum* var genes expressed in children from Papua New Guinea. J Infect Dis. 2009;200(3):347-356.

[28] Kaestli M, Cortes A, Lagog M, Ott M, Beck HP. Longitudinal assessment of *Plasmodium falciparum* var gene transcription in naturally infected asymptomatic children in Papua New Guinea. J Infect Dis. 2004;189(10):1942-1951.

[29] Kirchgatter K, Portillo Hdel A. Association of severe noncerebral *Plasmodium falciparum* malaria in Brazil with expressed PfEMP1 DBL1 alpha sequences lacking cysteine residues. Mol Med. 2002; 8(1):16-23.

[30] Kyriacou HM, Stone GN, Challis RJ, Raza A, Lyke KE, Thera MA, et al. Differential var gene

transcription in *Plasmodium falciparum* isolates from patients with cerebral malaria compared to hyperparasitaemia. Mol Biochem Parasitol. 2006; 150(2):211-218.

[31] Montgomery J, Mphande FA, Berriman M, Pain A, Rogerson SJ, Taylor TE, et al. Differential var gene expression in the organs of patients dying of falciparum malaria. Mol Microbiol. 2007;65(4):959-967.

[32] Mugasa J, Qi W, Rusch S, Rottmann M, Beck HP. Genetic diversity of expressed *Plasmodium falciparum* var genes from Tanzanian children with severe malaria. Malar J. 2012;11:230.

[33] Rottmann M, Lavstsen T, Mugasa JP, Kaestli M, Jensen AT, Muller D, et al. Differential expression of var gene groups is associated with morbidity caused by *Plasmodium falciparum* infection in Tanzanian children. Infect Immun. 2006;74(7):3904-3911.

[34] Rout R, Dhangadamajhi G, Mohapatra BN, Kar SK, Ranjit M. Genetic diversity of PfEMP1-DBL 1-α and its association with severe malaria in a hyperendemic state of India. Asian Pacific Journal of Tropical Medicine. 2010;3(7):505-509.

[35] Horata N, Kalambaheti T, Craig A, Khusmith S. Sequence variation of PfEMP1- DBLalpha in association with rosette formation in *Plasmodium falciparum* isolates causing severe and uncomplicated malaria. Malar J. 2009;8:184.

[36] Ockenhouse CF, Tandon NN, Magowan C, Jamieson GA, Chulay JD. Identification of a platelet membrane glycoprotein as a falciparum malaria sequestration receptor. Science. 1989;243(4897):1469-1471.

[37] Berendt AR, Simmons DL, Tansey J, Newbold CI, Marsh K. Intercellular adhesion molecule-1 is an endothelial cell adhesion receptor for *Plasmodium falciparum*. Nature. 1989;341(6237):57-59.

[38] Turner L, Lavstsen T, Berger SS, Wang CW, Petersen JE, Avril M, et al. Severe malaria is associated with parasite binding to endothelial protein C receptor. Nature. 2013;498(7455):502-505.

[39] Rogerson SJ, Chaiyaroj SC, Ng K, Reeder JC, Brown GV. Chondroitin sulfate A is a cell surface receptor for *Plasmodium falciparum*-infected erythrocytes. J Exp Med. 1995;182(1):15-20.

[40] Fried M, Duffy PE. Adherence of *Plasmodium falciparum* to chondroitin sulfate A in the human placenta. Science. 1996;272(5267):1502-1504.

[41] Carlson J, Wahlgren M. *Plasmodium falciparum* erythrocyte rosetting is mediated by promiscuous lectin-like interactions. J Exp Med. 1992;176(5): 1311-1317.

[42] Hsieh FL, Turner L, Bolla JR, Robinson CV, Lavstsen T, Higgins MK. The structural basis for CD36 binding by the malaria parasite. Nat Commun. 2016;7:12837.

[43] Robinson BA, Welch TL, Smith JD. Widespread functional specialization of *Plasmodium falciparum* erythrocyte membrane protein 1 family members to bind CD36 analysed across a parasite genome. Mol Microbiol. 2003;47(5):1265-1278.

[44] Canton J, Neculai D, Grinstein S. Scavenger receptors in homeostasis and immunity. Nat Rev Immunol. 2013;13(9):621-634.

[45] Silverstein RL, Febbraio M. CD36, a scavenger receptor involved in immunity, metabolism, angiogenesis, and behavior. Sci Signal. 2009;2(72): re3.

[46] Fonager J, Pasini EM, Braks JA, Klop O, Ramesar J, Remarque EJ, et al. Reduced CD36-dependent tissue sequestration of Plasmodium-infected erythrocytes is detrimental to malaria parasite growth in vivo. J Exp Med. 2012;209(1):93-107.

[47] Urban BC, Ferguson DJ, Pain A, Willcox N, Plebanski M, Austyn JM, et al. *Plasmodium falciparum*-infected erythrocytes modulate the maturation of dendritic cells. Nature. 1999; 400(6739):73-77.

[48] McGilvray ID, Serghides L, Kapus A, Rotstein OD, Kain KC. Nonopsonic monocyte/ macrophage phagocytosis of *Plasmodium falciparum*-parasitized erythrocytes: a role for CD36 in malarial clearance. Blood. 2000;96(9):3231-3240.

[49] Elliott SR, Spurck TP, Dodin JM, Maier AG, Voss TS, Yosaatmadja F, et al. Inhibition of dendritic cell maturation by malaria is dose dependent and does not require *Plasmodium falciparum* erythrocyte membrane protein 1. Infect Immun. 2007;75(7): 3621-3632.

[50] Pain A, Ferguson DJ, Kai O, Urban BC, Lowe B, Marsh K, et al. Platelet-mediated clumping of *Plasmodium falciparum*-infected erythrocytes is a common adhesive phenotype and is associated with severe malaria. Proc Natl Acad Sci U S A. 2001; 98(4):1805-1810.

[51] Sinha S, Qidwai T, Kanchan K, Anand P, Jha GN, Pati SS, et al. Variations in host genes encoding adhesion molecules and susceptibility to falciparum malaria in India. Malar J. 2008;7:250.

[52] Omi K, Ohashi J, Patarapotikul J, Hananantachai H, Naka I, Looareesuwan S, et al. CD36 polymorphism is associated with protection from cerebral malaria. Am J Hum Genet. 2003;72(2):364-374.

[53] Ayodo G, Price AL, Keinan A, Ajwang A, Otieno MF, Orago AS, et al. Combining evidence of natural selection with association analysis increases power to detect malaria-resistance variants. Am J Hum Genet. 2007;81(2):234-242.

[54] Aitman TJ, Cooper LD, Norsworthy PJ, Wahid FN, Gray JK, Curtis BR, et al. Malaria susceptibility and CD36 mutation. Nature. 2000;405(6790):1015-1016.

[55] Babiker M, Mergani A, Elwali N. A Cd36 polymorphism associated with eight-times increased susceptibility to cerebral malaria in Central Sudan. Global Science Research Journals. 2018;6:321-325.

[56] Omi K, Ohashi J, Naka I, Patarapotikul J, Hananantachai H, Looareesuwan S, et al.

Polymorphisms of CD36 in Thai malaria patients. Southeast Asian J Trop Med Public Health. 2002;33 (3):1-4.

[57] Pain A, Urban BC, Kai O, Casals-Pascual C, Shafi J, Marsh K, et al. A non-sense mutation in Cd36 gene is associated with protection from severe malaria. Lancet. 2001;357(9267):1502-1503.

[58] Das A, Das TK, Sahu U, Das BP, Kar SK, Ranjit MR. CD36 T188G gene polymorphism and severe falciparum malaria in India. Trans R Soc Trop Med Hyg. 2009;103(7):687-690.

[59] Fry AE, Ghansa A, Small KS, Palma A, Auburn S, Diakite M, et al. Positive selection of a CD36 nonsense variant in sub- Saharan Africa, but no association with severe malaria phenotypes. Hum Mol Genet. 2009;18(14):2683-2692.

[60] Dietrich JB. The adhesion molecule ICAM-1 and its regulation in relation with the blood-brain barrier. J Neuroimmunol. 2002;128(1-2):58-68.

[61] Lennartz F, Adams Y, Bengtsson A, Olsen RW, Turner L, Ndam NT, et al. Structure- Guided Identification of a Family of Dual Receptor-Binding PfEMP1 that Is Associated with Cerebral Malaria. Cell Host Microbe. 2017;21(3):403-414.

[62] Janes JH, Wang CP, Levin-Edens E, Vigan-Womas I, Guillotte M, Melcher M, et al. Investigating the host binding signature on the *Plasmodium falciparum* PfEMP1 protein family. PLoS Pathog. 2011;7(5): e1002032.

[63] Turner GD, Morrison H, Jones M, Davis TM, Looareesuwan S, Buley ID, et al. An immunohistochemical study of the pathology of fatal malaria. Evidence for widespread endothelial activation and a potential role for intercellular adhesion molecule-1 in cerebral sequestration. Am J Pathol. 1994;145(5):1057-1069.

[64] Silamut K, Phu NH, Whitty C, Turner GD, Louwrier K, Mai NT, et al. A quantitative analysis of the microvascular sequestration of malaria parasites in the human brain. Am J Pathol. 1999;155(2):395-410.

[65] Armah H, Dodoo AK, Wiredu EK, Stiles JK, Adjei AA, Gyasi RK, et al. High-level cerebellar expression of cytokines and adhesion molecules in fatal, paediatric, cerebral malaria. Ann Trop Med Parasitol. 2005;99(7):629-647.

[66] Cojean S, Jafari-Guemouri S, Le Bras J, Durand R. Cytoadherence characteristics to endothelial receptors ICAM- 1 and CD36 of *Plasmodium falciparum* populations from severe and uncomplicated malaria cases. Parasite. 2008;15(2): 163-169.

[67] Marlin SD, Springer TA. Purified intercellular adhesion molecule- 1 (ICAM- 1) is a ligand for lymphocyte function-associated antigen 1 (LFA-1). Cell. 1987;51(5):813-819.

[68] Baratin M, Roetynck S, Pouvelle B, Lemmers C, Viebig NK, Johansson S, et al. Dissection of the role of PfEMP1 and ICAM- 1 in the sensing of *Plasmodium falciparum*- infected erythrocytes by natural killer cells. PLoS One. 2007;2(2):e228.

[69] Cunningham DA, Lin JW, Brugat T, Jarra W, Tumwine I, Kushinga G, et al. ICAM- 1 is a key receptor mediating cytoadherence and pathology in the Plasmodium chabaudi malaria model. Malar J. 2017;16(1):185.

[70] Ramos TN, Bullard DC, Darley MM, McDonald K, Crawford DF, Barnum SR. Experimental cerebral malaria develops independently of endothelial expression of intercellular adhesion molecule- 1 (icam-1). J Biol Chem. 2013;288(16):10962-10966.

[71] Newbold C, Warn P, Black G, Berendt A, Craig A, Snow B, et al. Receptor-specific adhesion and clinical disease in *Plasmodium falciparum*. Am J Trop Med Hyg. 1997;57(4):389-398.

[72] Ockenhouse CF, Ho M, Tandon NN, Van Seventer GA, Shaw S, White NJ, et al. Molecular basis of sequestration in severe and uncomplicated *Plasmodium falciparum* malaria: differential adhesion of infected erythrocytes to CD36 and ICAM-1. J Infect Dis. 1991;164(1):163-169.

[73] Udomsangpetch R, Taylor BJ, Looareesuwan S, White NJ, Elliott JF, Ho M. Receptor specificity of clinical *Plasmodium falciparum* isolates: nonadherence to cell-bound E-selectin and vascular cell adhesion molecule-1. Blood. 1996;88(7):2754-2760.

[74] Mahamar A, Attaher O, Swihart B, Barry A, Diarra BS, Kanoute MB, et al. Host factors that modify *Plasmodium falciparum* adhesion to endothelial receptors. Sci Rep. 2017;7(1):13872.

[75] Rogerson SJ, Tembenu R, Dobano C, Plitt S, Taylor TE, Molyneux ME. Cytoadherence characteristics of *Plasmodium falciparum*-infected erythrocytes from Malawian children with severe and uncomplicated malaria. Am J Trop Med Hyg. 1999;61(3):467-472.

[76] Fernandez-Reyes D, Craig AG, Kyes SA, Peshu N, Snow RW, Berendt AR, et al. A high frequency African coding polymorphism in the N- terminal domain of ICAM-1 predisposing to cerebral malaria in Kenya. Hum Mol Genet. 1997;6(8):1357-1360.

[77] Kun JF, Klabunde J, Lell B, Luckner D, Alpers M, May J, et al. Association of the ICAM- 1Kilifi mutation with protection against severe malaria in Lambarene, Gabon. Am J Trop Med Hyg. 1999; 61(5):776-779.

[78] Bellamy R, Kwiatkowski D, Hill AV. Absence of an association between intercellular adhesion molecule 1, complement receptor 1 and interleukin 1 receptor antagonist gene polymorphisms and severe malaria in a West African population. Trans R Soc Trop Med Hyg. 1998;92(3):312-316.

[79] Ohashi J, Naka I, Patarapotikul J, Hananantachai H, Looareesuwan S, Tokunaga K. Absence of association between the allele coding methionine at position 29 in the N- terminal domain of ICAM-1

(ICAM-1(Kilifi)) and severe malaria in the northwest of Thailand. Jpn J Infect Dis. 2001;54(3):114-116.

[80] Ndiaye R, Sakuntabhai A, Casademont I, Rogier C, Tall A, Trape JF, et al. Genetic study of ICAM1 in clinical malaria in Senegal. Tissue Antigens. 2005; 65(5):474-480.

[81] Amodu OK, Gbadegesin RA, Ralph SA, Adeyemo AA, Brenchley PE, Ayoola OO, et al. *Plasmodium falciparum* malaria in south-west Nigerian children: is the polymorphism of ICAM-1 and E-selectin genes contributing to the clinical severity of malaria? Acta Trop. 2005;95(3):248-255.

[82] Jenkins NE, Mwangi TW, Kortok M, Marsh K, Craig AG, Williams TN. A polymorphism of intercellular adhesion molecule-1 is associated with a reduced incidence of nonmalarial febrile illness in Kenyan children. Clin Infect Dis. 2005;41(12):1817-1819.

[83] Avril M, Brazier AJ, Melcher M, Sampath S, Smith JD. DC8 and DC13 var genes associated with severe malaria bind avidly to diverse endothelial cells. PLoS Pathog. 2013;9(6):e1003430.

[84] Bernabeu M, Danziger SA, Avril M, Vaz M, Babar PH, Brazier AJ, et al. Severe adult malaria is associated with specific PfEMP1 adhesion types and high parasite biomass. Proc Natl Acad Sci U S A. 2016;113(23):E3270-3279.

[85] Bertin GI, Lavstsen T, Guillonneau F, Doritchamou J, Wang CW, Jespersen JS, et al. Expression of the domain cassette 8 *Plasmodium falciparum* erythrocyte membrane protein 1 is associated with cerebral malaria in Benin. PLoS One. 2013;8(7): e68368.

[86] Jespersen JS, Wang CW, Mkumbaye SI, Minja DT, Petersen B, Turner L, et al. *Plasmodium falciparum* var genes expressed in children with severe malaria encode CIDRalpha1 domains. EMBO Mol Med. 2016;8(8):839-850.

[87] Lavstsen T, Turner L, Saguti F, Magistrado P, Rask TS, Jespersen JS, et al. *Plasmodium falciparum* erythrocyte membrane protein 1 domain cassettes 8 and 13 are associated with severe malaria in children. Proc Natl Acad Sci U S A. 2012;109(26): E1791-1800.

[88] Storm J, Jespersen JS, Seydel KB, Szestak T, Mbewe M, Chisala NV, et al. Cerebral malaria is associated with differential cytoadherence to brain endothelial cells. EMBO Mol Med. 2019;11(2):e9164.

[89] Avril M, Tripathi AK, Brazier AJ, Andisi C, Janes JH, Soma VL, et al. A restricted subset of var genes mediates adherence of *Plasmodium falciparum*-infected erythrocytes to brain endothelial cells. Proc Natl Acad Sci U S A. 2012;109(26):E1782-1790.

[90] Petersen JE, Bouwens EA, Tamayo I, Turner L, Wang CW, Stins M, et al. Protein C system defects inflicted by the malaria parasite protein PfEMP1 can be overcome by a soluble EPCR variant. Thromb Haemost. 2015;114(5):1038-1048.

[91] Naka I, Patarapotikul J, Hananantachai H, Imai H, Ohashi J. Association of the endothelial protein C receptor (PROCR) rs867186-G allele with protection from severe malaria. Malar J. 2014;13:105.

[92] Uitte de Willige S, Van Marion V, Rosendaal FR, Vos HL, de Visser MC, Bertina RM. Haplotypes of the EPCR gene, plasma sEPCR levels and the risk of deep venous thrombosis. J Thromb Haemost. 2004; 2(8):1305-1310.

[93] Medina P, Navarro S, Estelles A, Vaya A, Woodhams B, Mira Y, et al. Contribution of polymorphisms in the endothelial protein C receptor gene to soluble endothelial protein C receptor and circulating activated protein C levels, and thrombotic risk. Thromb Haemost. 2004;91(5):905-911.

[94] Kallel C, Cohen W, Saut N, Blankenberg S, Schnabel R, Rupprecht HJ, et al. Association of soluble endothelial protein C receptor plasma levels and PROCR rs867186 with cardiovascular risk factors and cardiovascular events in coronary artery disease patients: the Athero Gene study. BMC Med Genet. 2012;13:103.

[95] Shabani E, Opoka RO, Bangirana P, Park GS, Vercellotti GM, Guan W, et al. The endothelial protein C receptor rs867186-GG genotype is associated with increased soluble EPCR and could mediate protection against severe malaria. Sci Rep. 2016;6:27084.

[96] Schuldt K, Ehmen C, Evans J, May J, Ansong D, Sievertsen J, et al. Endothelial protein C receptor gene variants not associated with severe malaria in ghanaian children. PLoS One. 2014;9(12):e115770.

[97] Hansson HH, Turner L, Moller L, Wang CW, Minja DT, Gesase S, et al. Haplotypes of the endothelial protein C receptor (EPCR) gene are not associated with severe malaria in Tanzania. Malar J. 2015;14: 474.

[98] Stoute JA. Complement receptor 1 and malaria. Cell Microbiol. 2011;13(10):1441-1450.

[99] Holers VM, Chaplin DD, Leykam JF, Gruner BA, Kumar V, Atkinson JP. Human complement C3b/C4b receptor (CR1) mRNA polymorphism that correlates with the CR1 allelic molecular weight polymorphism. Proc Natl Acad Sci U S A. 1987; 84(8):2459-2463.

[100] Vik DP, Wong WW. Structure of the gene for the F allele of complement receptor type 1 and sequence of the coding region unique to the S allele. J Immunol. 1993;151(11):6214-6224.

[101] Nickells MW, Seya T, Holers VM, Atkinson JP. Analysis of C3b/C4b receptor (CR1) polymorphic variants by tryptic peptide mapping. Mol Immunol. 1986;23(6):661-668.

[102] Moulds JM, Brai M, Cohen J, Cortelazzo A, Cuccia M, Lin M, et al. Reference typing report for complement receptor 1 (CR1). Exp Clin Immunogenet. 1998;15(4):291-294.

[103] Wilson JG, Wong WW, Schur PH, Fearon DT. Mode of inheritance of decreased C3b receptors on erythrocytes of patients with systemic lupus erythematosus. N Engl J Med. 1982;307(16):981-986.

[104] Moulds JM, Thomas BJ, Doumbo O, Diallo DA, Lyke KE, Plowe CV, et al. Identification of the Kna/Knb polymorphism and a method for Knops genotyping. Transfusion. 2004;44(2):164-169.

[105] Thomas BN, Donvito B, Cockburn I, Fandeur T, Rowe JA, Cohen JH, et al. A complement receptor-1 polymorphism with high frequency in malaria endemic regions of Asia but not Africa. Genes Immun. 2005;6(1):31-36.

[106] Cockburn IA, Mackinnon MJ, O'Donnell A, Allen SJ, Moulds JM, Baisor M, et al. A human complement receptor 1 polymorphism that reduces *Plasmodium falciparum* rosetting confers protection against severe malaria. Proc Natl Acad Sci U S A. 2004;101(1):272-277.

[107] Tham WH, Wilson DW, Lopaticki S, Schmidt CQ, Tetteh-Quarcoo PB, Barlow PN, et al. Complement receptor 1 is the host erythrocyte receptor for *Plasmodium falciparum* PfRh4 invasion ligand. Proc Natl Acad Sci U S A. 2010;107(40):17327-17332.

[108] Cockburn IA, Rowe JA. Erythrocyte complement receptor 1 (CR1) expression level is not associated with polymorphisms in the promoter or 3' untranslated regions of the CR1 gene. Int J Immunogenet. 2006;33(1):17-20.

[109] Herrera AH, Xiang L, Martin SG, Lewis J, Wilson JG. Analysis of complement receptor type 1 (CR1) expression on erythrocytes and of CR1 allelic markers in Caucasian and African American populations. Clin Immunol Immunopathol. 1998; 87(2):176-183.

[110] Rowe JA, Raza A, Diallo DA, Baby M, Poudiougo B, Coulibaly D, et al. Erythrocyte CR1 expression level does not correlate with a HindIII restriction fragment length polymorphism in Africans; implications for studies on malaria susceptibility. Genes Immun. 2002;3(8):497-500.

[111] Zimmerman PA, Fitness J, Moulds JM, McNamara DT, Kasehagen LJ, Rowe JA, et al. CR1 Knops blood group alleles are not associated with severe malaria in the Gambia. Genes Immun. 2003;4(5):368-373.

[112] Grau GE, Fajardo LF, Piguet PF, Allet B, Lambert PH, Vassalli P. Tumor necrosis factor (cachectin) as an essential mediator in murine cerebral malaria. Science. 1987;237(4819):1210-1212.

[113] Jambou R, Combes V, Jambou MJ, Weksler BB, Couraud PO, Grau GE. *Plasmodium falciparum* adhesion on human brain microvascular endothelial cells involves transmigration-like cup formation and induces opening of intercellular junctions. PLoS Pathog. 2010;6(7):e1001021.

[114] El-Assaad F, Wheway J, Mitchell AJ, Lou J, Hunt NH, Combes V, et al. Cytoadherence of Plasmodium berghei-infected red blood cells to murine brain and lung microvascular endothelial cells in vitro. Infect Immun. 2013;81(11):3984-3991.

[115] Clark IA, Virelizier JL, Carswell EA, Wood PR. Possible importance of macrophage- derived mediators in acute malaria. Infect Immun. 1981; 32(3):1058-1066.

[116] Mordmuller BG, Metzger WG, Juillard P, Brinkman BM, Verweij CL, Grau GE, et al. Tumor necrosis factor in *Plasmodium falciparum* malaria: high plasma level is associated with fever, but high production capacity is associated with rapid fever clearance. Eur Cytokine Netw. 1997;8(1):29-35.

[117] Higuchi T, Seki N, Kamizono S, Yamada A, Kimura A, Kato H, et al. Polymorphism of the 5'-flanking region of the human tumor necrosis factor (TNF)-alpha gene in Japanese. Tissue Antigens. 1998;51(6): 605-612.

[118] Huizinga TW, Westendorp RG, Bollen EL, Keijsers V, Brinkman BM, Langermans JA, et al. TNF-alpha promoter polymorphisms, production and susceptibility to multiple sclerosis in different groups of patients. J Neuroimmunol. 1997;72(2):149-153.

[119] Kaluza W, Reuss E, Grossmann S, Hug R, Schopf RE, Galle PR, et al. Different transcriptional activity and in vitro TNF- alpha production in psoriasis patients carrying the TNF- alpha 238A promoter polymorphism. J Invest Dermatol. 2000;114(6): 1180-1183.

[120] Wilson AG, Symons JA, McDowell TL, McDevitt HO, Duff GW. Effects of a polymorphism in the human tumor necrosis factor alpha promoter on transcriptional activation. Proc Natl Acad Sci U S A. 1997;94(7):3195-3199.

[121] Flori L, Delahaye NF, Iraqi FA, Hernandez-Valladares M, Fumoux F, Rihet P. TNF as a malaria candidate gene: polymorphism-screening and family-based association analysis of mild malaria attack and parasitemia in Burkina Faso. Genes Immun. 2005; 6(6):472-480.

[122] Basu M, Maji AK, Chakraborty A, Banerjee R, Mullick S, Saha P, et al. Genetic association of Toll-like- receptor 4 and tumor necrosis factor- alpha polymorphisms with *Plasmodium falciparum* blood infection levels. Infect Genet Evol. 2010;10(5):686-696.

[123] Afridi S, Atkinson A, Garnier S, Fumoux F, Rihet P. Malaria resistance genes are associated with the levels of IgG subclasses directed against *Plasmodium falciparum* blood- stage antigens in Burkina Faso. Malar J. 2012;11:308.

[124] Nguyen TN, Baaklini S, Koukouikila-Koussounda F, Ndounga M, Torres M, Pradel L, et al. Association of a functional TNF variant with *Plasmodium falciparum* parasitaemia in a congolese population. Genes Immun. 2017;18(3):152-157.

[125] Penha- Goncalves C. Genetics of Malaria Inflammatory Responses: A Pathogenesis Perspective. Front Immunol. 2019;10:1771.

[126] Perera MK, Herath NP, Pathirana SL, Phone-Kyaw M, Alles HK, Mendis KN, et al. Association of high plasma TNF-alpha levels and TNF-alpha/IL-10 ratios with TNF2 allele in severe *P. falciparum* malaria patients in Sri Lanka. Pathog Glob Health. 2013; 107(1):21-29.

[127] Clark TG, Diakite M, Auburn S, Campino S, Fry AE, Green A, et al. Tumor necrosis factor and lymphotoxin- alpha polymorphisms and severe malaria in African populations. J Infect Dis. 2009; 199(4):569-575.

[128] Williams TW, Granger GA. Lymphocyte in vitro cytotoxicity: lymphotoxins of several mammalian species. Nature. 1968;219(5158):1076-1077.

[129] Aggarwal BB, Moffat B, Harkins RN. Human lymphotoxin. Production by a lymphoblastoid cell line, purification, and initial characterization. J Biol Chem. 1984;259(1):686-691.

[130] Pennica D, Nedwin GE, Hayflick JS, Seeburg PH, Derynck R, Palladino MA, et al. Human tumour necrosis factor: precursor structure, expression and homology to lymphotoxin. Nature. 1984;312(5996): 724-729.

[131] Gommerman JL, Browning JL. Lymphotoxin/light, lymphoid microenvironments and autoimmune disease. Nat Rev Immunol. 2003;3(8):642-655.

[132] Ware CF. Network communications: lymphotoxins, LIGHT, and TNF. Annu Rev Immunol. 2005; 23:787-819.

[133] Engwerda CR, Mynott TL, Sawhney S, De Souza JB, Bickle QD, Kaye PM. Locally up- regulated lymphotoxin alpha, not systemic tumor necrosis factor alpha, is the principle mediator of murine cerebral malaria. J Exp Med. 2002;195(10):1371-1377.

[134] Omer FM, Kurtzhals JA, Riley EM. Maintaining the immunological balance in parasitic infections: a role for TGF-beta? Parasitol Today. 2000;16(1):18-23.

[135] Omer FM, Riley EM. Transforming growth factor beta production is inversely correlated with severity of murine malaria infection. J Exp Med. 1998; 188(1):39-48.

[136] Tsutsui N, Kamiyama T. Transforming growth factor beta- induced failure of resistance to infection with blood- stage Plasmodium chabaudi in mice. Infect Immun. 1999;67(5):2306-2311.

[137] Perkins DJ, Weinberg JB, Kremsner PG. Reduced interleukin-12 and transforming growth factor-beta1 in severe childhood malaria: relationship of cytokine balance with disease severity. J Infect Dis. 2000; 182(3):988-992.

[138] Wenisch C, Parschalk B, Burgmann H, Looareesuwan S, Graninger W. Decreased serum levels of TGF-beta in patients with acute *Plasmodium falciparum* malaria. J Clin Immunol. 1995;15(2):69-73.

[139] Perkins DJ, Were T, Davenport GC, Kempaiah P, Hittner JB, Ong'echa JM. Severe malarial anemia: innate immunity and pathogenesis. Int J Biol Sci. 2011;7(9):1427-1442.

[140] Mahanta A, Kar SK, Kakati S, Baruah S. Heightened inflammation in severe malaria is associated with decreased IL-10 expression levels and neutrophils. Innate Immun. 2015;21(5):546-552.

[141] Luty AJ, Perkins DJ, Lell B, Schmidt-Ott R, Lehman LG, Luckner D, et al. Low interleukin-12 activity in severe *Plasmodium falciparum* malaria. Infect Immun. 2000;68(7):3909-3915.

[142] Merriman CR, Pulliam LA, Kampschmidt RF. Comparison of leukocytic pyrogen and leukocytic endogenous mediator. Proc Soc Exp Biol Med. 1977; 154(2):224-227.

[143] Dunn E, Sims JE, Nicklin MJ, O'Neill LA. Annotating genes with potential roles in the immune system: six new members of the IL-1 family. Trends Immunol. 2001;22(10):533-536.

[144] Walley AJ, Aucan C, Kwiatkowski D, Hill AV. Interleukin- 1 gene cluster polymorphisms and susceptibility to clinical malaria in a Gambian case-control study. Eur J Hum Genet. 2004;12(2):132-138.

[145] Cerutti A, Zan H, Schaffer A, Bergsagel L, Harindranath N, Max EE, et al. CD40 ligand and appropriate cytokines induce switching to IgG, IgA, and IgE and coordinated germinal center and plasmacytoid phenotypic differentiation in a human monoclonal IgM+IgD+ B cell line. J Immunol. 1998; 160(5):2145-2157.

[146] Fear DJ, McCloskey N, O'Connor B, Felsenfeld G, Gould HJ. Transcription of Ig germline genes in single human B cells and the role of cytokines in isotype determination. J Immunol. 2004;173(7): 4529-4538.

[147] Sokol CL, Barton GM, Farr AG, Medzhitov R. A mechanism for the initiation of allergen-induced T helper type 2 responses. Nat Immunol 2008; 9(3): 310-318.

[148] Rosenwasser LJ, Klemm DJ, Dresback JK, Inamura H, Mascali JJ, Klinnert M, et al. Promoter polymorphisms in the chromosome 5 gene cluster in asthma and atopy. Clin Exp Allergy. 1995;25(2):74-78.

[149] Nakashima H, Miyake K, Inoue Y, Shimizu S, Akahoshi M, Tanaka Y, et al. Association between IL-4 genotype and IL-4 production in the Japanese population. Genes Immun. 2002;3(2):107-109.

[150] Luoni G, Verra F, Arca B, Sirima BS, Troye-Blomberg M, Coluzzi M, et al. Antimalarial antibody levels and IL4 polymorphism in the Fulani of West Africa. Genes Immun. 2001;2(7):411-414.

[151] Verra F, Luoni G, Calissano C, Troye-Blomberg M, Perlmann P, Perlmann H, et al. IL4- 589C/ T

polymorphism and IgE levels in severe malaria. Acta Trop. 2004;90(2):205-209.

[152] Gyan BA, Goka B, Cvetkovic JT, Kurtzhals JL, Adabayeri V, Perlmann H, et al. Allelic polymorphisms in the repeat and promoter regions of the interleukin-4 gene and malaria severity in Ghanaian children. Clin Exp Immunol. 2004;138(1): 145-150.

[153] Tangteerawatana P, Perlmann H, Hayano M, Kalambaheti T, Troye-Blomberg M, Khusmith S. IL4 gene polymorphism and previous malaria experiences manipulate anti-*Plasmodium falciparum* antibody isotype profiles in complicated and uncomplicated malaria. Malar J. 2009;8:286.

[154] Tangteerawatana P, Pichyangkul S, Hayano M, Kalambaheti T, Looareesuwan S, Troye-Blomberg M, et al. Relative levels of IL4 and IFN-gamma in complicated malaria: association with IL4 polymorphism and peripheral parasitemia. Acta Trop. 2007;101(3):258-265.

[155] Sortica VA, Cunha MG, Ohnishi MD, Souza JM, Ribeiro-dos-Santos AK, Santos SE, et al. Role of IL6, IL12B and VDR gene polymorphisms in Plasmodium vivax malaria severity, parasitemia and gametocytemia levels in an Amazonian Brazilian population. Cytokine. 2014;65(1):42-47.

[156] Day NP, Hien TT, Schollaardt T, Loc PP, Chuong LV, Chau TT, et al. The prognostic and pathophysiologic role of pro- and antiinflammatory cytokines in severe malaria. J Infect Dis. 1999; 180(4):1288-1297.

[157] Wenisch C, Linnau KF, Looaresuwan S, Rumpold H. Plasma levels of the interleukin-6 cytokine family in persons with severe *Plasmodium falciparum* malaria. J Infect Dis. 1999;179(3):747-750.

[158] Freitas do Rosario AP, Langhorne J. T cell-derived IL-10 and its impact on the regulation of host responses during malaria. Int J Parasitol. 2012;42(6): 549-555.

[159] Kumar R, Ng S, Engwerda C. The Role of IL-10 in Malaria: A Double Edged Sword. Front Immunol. 2019;10:229.

[160] Couper KN, Blount DG, Riley EM. IL-10: the master regulator of immunity to infection. J Immunol. 2008; 180(9):5771-5777.

[161] Chow JC, Young DW, Golenbock DT, Christ WJ, Gusovsky F. Toll-like receptor-4 mediates lipopolysaccharide-induced signal transduction. J Biol Chem. 1999;274(16):10689-10692.

[162] Sanni LA, Jarra W, Li C, Langhorne J. Cerebral edema and cerebral hemorrhages in interleukin-10-deficient mice infected with Plasmodium chabaudi. Infect Immun. 2004;72(5):3054-3058.

[163] Kossodo S, Monso C, Juillard P, Velu T, Goldman M, Grau GE. Interleukin-10 modulates susceptibility in experimental cerebral malaria. Immunology. 1997; 91(4):536-540.

[164] Zhang G, Manaca MN, McNamara-Smith M, Mayor A, Nhabomba A, Berthoud TK, et al. Interleukin-10 (IL-10) polymorphisms are associated with IL-10 production and clinical malaria in young children. Infect Immun. 2012;80(7):2316-2322.

[165] Apinjoh TO, Anchang-Kimbi JK, Njua-Yafi C, Mugri RN, Ngwai AN, Rockett KA, et al. Association of cytokine and Toll-like receptor gene polymorphisms with severe malaria in three regions of Cameroon. PLoS One. 2013;8(11):e81071.

[166] Peyron F, Burdin N, Ringwald P, Vuillez JP, Rousset F, Banchereau J. High levels of circulating IL-10 in human malaria. Clin Exp Immunol. 1994;95(2):300-303.

[167] Lyke KE, Burges R, Cissoko Y, Sangare L, Dao M, Diarra I, et al. Serum levels of the proinflammatory cytokines interleukin-1 beta (IL-1beta), IL-6, IL-8, IL-10, tumor necrosis factor alpha, and IL-12(p70) in Malian children with severe *Plasmodium falciparum* malaria and matched uncomplicated malaria or healthy controls. Infect Immun. 2004;72(10):5630-5637.

[168] Ouma C, Davenport GC, Were T, Otieno MF, Hittner JB, Vulule JM, et al. Haplotypes of IL-10 promoter variants are associated with susceptibility to severe malarial anemia and functional changes in IL-10 production. Hum Genet. 2008;124(5):515-524.

[169] Stevenson MM, Su Z, Sam H, Mohan K. Modulation of host responses to blood-stage malaria by interleukin-12: from therapy to adjuvant activity. Microbes Infect. 2001;3(1):49-59.

[170] Flori L, Kumulungui B, Aucan C, Esnault C, Traore AS, Fumoux F, et al. Linkage and association between *Plasmodium falciparum* blood infection levels and chromosome 5q31-q33. Genes Immun. 2003;4(4):265-268.

[171] Rihet P, Traore Y, Abel L, Aucan C, Traore-Leroux T, Fumoux F. Malaria in humans: *Plasmodium falciparum* blood infection levels are linked to chromosome 5q31-q33. Am J Hum Genet. 1998; 63(2):498-505.

[172] Marquet S, Doumbo O, Cabantous S, Poudiougou B, Argiro L, Safeukui I, et al. A functional promoter variant in IL12B predisposes to cerebral malaria. Hum Mol Genet. 2008;17(14):2190-2195.

[173] Morahan G, Boutlis CS, Huang D, Pain A, Saunders JR, Hobbs MR, et al. A promoter polymorphism in the gene encoding interleukin-12 p40 (IL12B) is associated with mortality from cerebral malaria and with reduced nitric oxide production. Genes Immun. 2002;3(7):414-418.

[174] Zhang L, Prather D, Vanden Eng J, Crawford S, Kariuki S, ter Kuile F, et al. Polymorphisms in genes of interleukin 12 and its receptors and their association with protection against severe malarial anaemia in children in western Kenya. Malar J. 2010; 9:87.

[175] Gowda DC. TLR-mediated cell signaling by malaria GPIs. Trends Parasitol. 2007;23(12):596-604.

[176] Krishnegowda G, Hajjar AM, Zhu J, Douglass EJ, Uematsu S, Akira S, et al. Induction of proinflammatory responses in macrophages by the glycosylphosphatidylinositols of *Plasmodium falciparum*: cell signaling receptors, glycosyl-phosphatidylinositol (GPI) structural requirement, and regulation of GPI activity. J Biol Chem. 2005;280(9):8606-8616.

[177] Bali P, Pradhan S, Sharma D, Adak T. Toll like receptor 2 and 4 polymorphisms in malaria endemic populations of India. Hum Immunol. 2013;74(2):223-229.

[178] Greene JA, Moormann AM, Vulule J, Bockarie MJ, Zimmerman PA, Kazura JW. Toll-like receptor polymorphisms in malaria-endemic populations. Malar J. 2009;8:50.

[179] Noguchi E, Nishimura F, Fukai H, Kim J, Ichikawa K, Shibasaki M, et al. An association study of asthma and total serum immunoglobin E levels for Toll-like receptor polymorphisms in a Japanese population. Clin Exp Allergy. 2004;34(2):177-183.

[180] Bochud PY, Hawn TR, Siddiqui MR, Saunderson P, Britton S, Abraham I, et al. Toll-like receptor 2 (TLR2) polymorphisms are associated with reversal reaction in leprosy. J Infect Dis. 2008;197(2):253-261.

[181] Greene JA, Sam-Agudu N, John CC, Opoka RO, Zimmerman PA, Kazura JW. Toll-like receptor polymorphisms and cerebral malaria: TLR2 Delta22 polymorphism is associated with protection from cerebral malaria in a case control study. Malar J. 2012;11:47.

[182] Hoshino K, Takeuchi O, Kawai T, Sanjo H, Ogawa T, Takeda Y, et al. Cutting edge: Toll-like receptor 4 (TLR4) - deficient mice are hyporesponsive to lipopolysaccharide: evidence for TLR4 as the Lps gene product. J Immunol. 1999;162(7):3749-3752.

[183] Mockenhaupt FP, Cramer JP, Hamann L, Stegemann MS, Eckert J, Oh NR, et al. Toll-like receptor (TLR) polymorphisms in African children: Common TLR-4 variants predispose to severe malaria. Proc Natl Acad Sci U S A. 2006;103(1):177-182.

[184] Arbour NC, Lorenz E, Schutte BC, Zabner J, Kline JN, Jones M, et al. TLR4 mutations are associated with endotoxin hyporesponsiveness in humans. Nat Genet. 2000;25(2):187-191.

[185] Erridge C, Stewart J, Poxton IR. Monocytes heterozygous for the Asp299Gly and Thr399Ile mutations in the Toll-like receptor 4 gene show no deficit in lipopolysaccharide signalling. J Exp Med. 2003;197(12):1787-1791.

[186] Parroche P, Lauw FN, Goutagny N, Latz E, Monks BG, Visintin A, et al. Malaria hemozoin is immunologically inert but radically enhances innate responses by presenting malaria DNA to Toll-like receptor 9. Proc Natl Acad Sci U S A. 2007;104(6):1919-1924.

[187] Coban C, Ishii KJ, Kawai T, Hemmi H, Sato S, Uematsu S, et al. Toll-like receptor 9 mediates innate immune activation by the malaria pigment hemozoin. J Exp Med. 2005;201(1):19-25.

[188] Munde EO, Okeyo WA, Anyona SB, Raballah E, Konah S, Okumu W, et al. Polymorphisms in the Fc gamma receptor IIIA and Toll-like receptor 9 are associated with protection against severe malarial anemia and changes in circulating gamma interferon levels. Infect Immun. 2012;80(12):4435-4443.

[189] Omar AH, Yasunami M, Yamazaki A, Shibata H, Ofori MF, Akanmori BD, et al. Toll-like receptor 9 (TLR9) polymorphism associated with symptomatic malaria: a cohort study. Malar J. 2012;11:168.

[190] Pamplona A, Ferreira A, Balla J, Jeney V, Balla G, Epiphanio S, et al. Heme oxygenase-1 and carbon monoxide suppress the pathogenesis of experimental cerebral malaria. Nat Med. 2007;13(6):703-710.

[191] Seixas E, Gozzelino R, Chora A, Ferreira A, Silva G, Larsen R, et al. Heme oxygenase-1 affords protection against noncerebral forms of severe malaria. Proc Natl Acad Sci U S A. 2009;106(37):15837-15842.

[192] Medana IM, Mai NT, Day NP, Hien TT, Bethell D, Phu NH, et al. Cellular stress and injury responses in the brains of adult Vietnamese patients with fatal *Plasmodium falciparum* malaria. Neuropathol Appl Neurobiol. 2001;27(6):421-433.

[193] Schluesener HJ, Kremsner PG, Meyermann R. Heme oxygenase-1 in lesions of human cerebral malaria. Acta Neuropathol. 2001;101(1):65-68.

[194] Clark IA, Awburn MM, Harper CG, Liomba NG, Molyneux ME. Induction of HO-1 in tissue macrophages and monocytes in fatal falciparum malaria and sepsis. Malar J. 2003;2:41.

[195] Sambo MR, Trovoada MJ, Benchimol C, Quinhentos V, Goncalves L, Velosa R, et al. Transforming growth factor beta 2 and heme oxygenase 1 genes are risk factors for the cerebral malaria syndrome in Angolan children. PLoS One. 2010;5(6):e11141.

[196] Takeda M, Kikuchi M, Ubalee R, Na-Bangchang K, Ruangweerayut R, Shibahara S, et al. Microsatellite polymorphism in the heme oxygenase-1 gene promoter is associated with susceptibility to cerebral malaria in Myanmar. Jpn J Infect Dis. 2005;58(5):268-271.

[197] Walther M, De Caul A, Aka P, Njie M, Amambua-Ngwa A, Walther B, et al. HMOX1 gene promoter alleles and high HO-1 levels are associated with severe malaria in Gambian children. PLoS Pathog. 2012;8(3):e1002579.

[198] Kuesap J, Hirayama K, Kikuchi M, Ruangweerayut R, Na-Bangchang K. Study on association between genetic polymorphisms of haem oxygenase-1, tumour necrosis factor, cadmium exposure and malaria pathogenicity and severity. Malar J. 2010;9:260.

[199] Taylor SM, Cerami C, Fairhurst RM. Hemoglobinopathies: slicing the Gordian knot of *Plasmodium falciparum* malaria pathogenesis. PLoS Pathog. 2013;9(5):e1003327.

[200] de Mendonca VR, Goncalves MS, Barral-Netto M. The host genetic diversity in malaria infection. J Trop Med. 2012;2012:940616.

[201] Evans AG, Wellems TE. Coevolutionary genetics of Plasmodium malaria parasites and their human hosts. Integr Comp Biol. 2002;42(2):401-407.

[202] Bunyaratvej A, Butthep P, Sae-Ung N, Fucharoen S, Yuthavong Y. Reduced deformability of thalassemic erythrocytes and erythrocytes with abnormal hemoglobins and relation with susceptibility to *Plasmodium falciparum* invasion. Blood. 1992; 79(9):2460-2463.

[203] Ifediba TC, Stern A, Ibrahim A, Rieder RF. *Plasmodium falciparum* in vitro: diminished growth in hemoglobin H disease erythrocytes. Blood. 1985; 65(2):452-455.

[204] Chotivanich K, Udomsangpetch R, Pattanapanyasat K, Chierakul W, Simpson J, Looareesuwan S, et al. Hemoglobin E: a balanced polymorphism protective against high parasitemias and thus severe P falciparum malaria. Blood. 2002;100(4):1172-1176.

[205] Brockelman CR, Wongsattayanont B, Tan-ariya P, Fucharoen S. Thalassemic erythrocytes inhibit in vitro growth of *Plasmodium falciparum*. J Clin Microbiol. 1987;25(1):56-60.

[206] Pasvol G, Weatherall DJ, Wilson RJ. Cellular mechanism for the protective effect of haemoglobin S against *P. falciparum* malaria. Nature. 1978; 274(5672):701-703.

[207] Pasvol G. The interaction between sickle haemoglobin and the malarial parasite *Plasmodium falciparum*. Trans R Soc Trop Med Hyg. 1980;74(6): 701-705.

[208] Friedman MJ, Roth EF, Nagel RL, Trager W. The role of hemoglobins C, S, and Nbalt in the inhibition of malaria parasite development in vitro. Am J Trop Med Hyg. 1979;28(5):777-780.

[209] Nagel RL, Raventos-Suarez C, Fabry ME, Tanowitz H, Sicard D, Labie D. Impairment of the growth of *Plasmodium falciparum* in HbEE erythrocytes. J Clin Invest. 1981;68(1):303-305.

[210] Luzzi GA, Merry AH, Newbold CI, Marsh K, Pasvol G, Weatherall DJ. Surface antigen expression on *Plasmodium falciparum*- infected erythrocytes is modified in alpha- and beta-thalassemia. J Exp Med. 1991;173(4):785-791.

[211] Williams TN, Weatherall DJ, Newbold CI. The membrane characteristics of *Plasmodium falciparum*-infected and -uninfected heterozygous alpha(0)thalassaemic erythrocytes. Br J Haematol. 2002;118(2):663-670.

[212] Olson JA, Nagel RL. Synchronized cultures of P falciparum in abnormal red cells: the mechanism of the inhibition of growth in HbCC cells. Blood. 1986; 67(4):997-1001.

[213] Amaratunga C, Lopera-Mesa TM, Brittain NJ, Cholera R, Arie T, Fujioka H, et al. A role for fetal hemoglobin and maternal immune IgG in infant resistance to *Plasmodium falciparum* malaria. PLoS One. 2011;6(4):e14798.