MALARIA AND INNATE HUMAN RESISTANCE: A REVIEW OF SOME GENETIC VARIANTS THAT AFFECT RED BLOOD CELLS

TJ Lisinski PhD

University of the Sciences in Philadelphia,
600 South 43rd Street, Philadelphia, Pennsylvania, 19104-2744, USA.

Abstract

Malaria is a major threat to human lives in tropical regions throughout the world. The long-term persistence of the Plasmodium species, the causative agent of malaria, has had an impact on the human race as an evolutionary force. Several genetic adaptations have arisen to offer survival advantages against this protozoan parasite. The most-studied malaria-protective genetic variants affect the red blood cell. The red blood cell is crucial in the life cycle of the Plasmodium species. These adaptations include changes in receptors, enzyme function, and hemoglobin protein. Identification of these host defenses involved in protection from malaria may help reveal new therapeutic options.

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Introduction

Malaria is the leading cause of mortality (20%) of African children under 5 years old.(1) According to the Centers for Disease Control and Prevention, 41% of the world's population lives in an area where malaria can be transmitted.(2) Therefore, malaria is a serious global problem.

Malaria is caused by protozoan parasites of the genus Plasmodium and is transmitted to humans via the bite of an infected female Anopheles mosquito. Four species of Plasmodium (P) cause malaria in humans: P falciparum, P vivax, P ovale, and P malariae. All 4 species can infect human red blood cells. The red blood cell has nutrients on which the Plasmodium parasite thrives, an environment for multiple rounds of replication, and shelter from attack by the human immune system.

Evolutionary pressure has selected several genes within the red blood cell as sites that may change the disease progress. These adaptations include changes in receptors, enzyme function, and hemoglobin protein. The best known genetic variant is the change in hemoglobin that causes sickle cell anemia.

Of the many genetic variants, only a few are described here; the Duffy antigen (Fy), complement receptor 1 (CR1), glucose-6-phosphate dehydrogenase (G6PD), hemoglobin C (HbC), and thalassemia.

DUFFY ANTIGEN

The Duffy antigen, encoded by the FY gene, is also known as the Duffy antigen receptor for chemokines (DARC) because of its role in chemokine regulation.(3) In addition, it modulates human susceptibility to infection by P vivax.

Duffy antigen expression on red blood cells has been demonstrated to be a receptor for P vivax entry into the red blood cell. The results from several studies suggest that the Duffy antigen is necessary for invasion of red blood cells by P vivax.(4,5) Therefore, people who are lacking the Duffy antigen (Fy-negative) are naturally protected from P vivax-induced infection (6) Most West Africans and 68% of African Americans do not express Duffy antigen subtypes, Fya or Fyb, on their red blood cells.(7)

The discovery of the importance of the Duffy antigen in P vivax infection led to the identification of the parasite protein, P vivax Duffy-binding protein, which is involved in the interaction with Duffy antigen on the red blood cells.(8) In addition, these proteins represent potential vaccine candidates and targets for receptor-blockade therapy.(8,9)

COMPLEMENT RECEPTOR 1

Complement receptor 1 is a protein found on red blood cells and functions with other complement regulatory proteins to attenuate the complement cascade. Also, CR1 is involved in the binding of opsonized immune complexes and their removal. These functions protect red blood cells and other cells from complement-mediated damage. In addition, there is evidence to support that CR1 is a receptor for the P falciparum erythrocyte membrane protein 1 (PfEMP-1).(10,11)

The binding of PfEMP-1 to CR1 may cause rosetting, which is an occurrence of red blood cells clumping together due to malarial parasitized red blood cells binding to nonparasitized ones. In in vitro experiments, red blood cells that are infected with P falciparum bind to uninfected red blood cells.(10,11) Rosetting is thought to contribute to malaria pathology by causing obstruction in the microvascular system and impairing tissue perfusion.(12,13) Rosetting has been associated with severe malaria in studies in Africa.(14-16) In addition, rosetting has

been associated with cerebral malaria.(14,15)

Red blood cell CR1 deficiency confers protection against severe malaria; those humans who are heterozygous for the CR-1 low-expression allele are protected from severe malaria.(17)

The CR1 gene encodes polymorphic proteins including the Knops blood group antigens, the Swain-Langley (Sl) and McCoy (McC) alleles.(18-20) These alleles may affect disease progression of severe malaria. Red blood cells with a CR1 polymorphism (Sl(a-)) have a reduced adhesion to the portion of PfEMP1 that is involved in binding normal red blood cells.(12) There are conflicting reports about the Sl2 and McC alleles.(21,22) Zimmerman and colleagues suggest that Sl2 and McC(b) have arisen to confer a selective advantage against infectious disease, but not solely to P falciparum malaria.(21) There was no association between Sl2 or McCb and resistance to severe malaria in The Gambia, West Africa. In contrast, Thathy and others reported that the Sl2 allele evolved in the context of malaria transmission and confers an advantage to the host in malaria infections.(22) Future studies may delineate the role of these alleles of CR1 in malaria disease state progression.

Glucose-6-phosphate dehydrogenase, G6DH

G6DH is an enzyme in the hexose monophosphate pathway, which is in all cells. G6DH facilitates NADPH production, which coenzyme protects the sulfhydryl groups of hemoglobin and the red cell membrane from oxidation by highly reactive oxygen radicals. Defects in the hexose monophosphate pathway decrease protection from oxidation, with oxidation of sulfhydryl groups, precipitation of hemoglobin, and lysis of red blood cells.(23)

G6PD enzyme deficiency is one of the most common enzyme deficiencies in humans, affecting approximately 400 million. A resulting clinical effect could involve various degrees of severity of anemia due to red blood cell rupture by oxidative stress. These clinical manifestations of G6PD deficiency could be triggered by certain foods (for example, fava beans), drugs (for example, primaquine), or infection.(23-25) At least 130 different mutations in the G6PD gene are known to cause G6PD enzyme deficiency.(24,25) Some genetic variants are area-specific. For example, G6PD B, G6PD A, and G6PD A- are found in Africa. Variants G6PD B and G6PD A have a normal enzymatic activity (that is, 90 to 100% enzyme activity). Variant G6PD B is the most common with a frequency of 60 to 80%, and G6PD A is the second most common with 15 to 40% frequency. However, G6PD A- has an enzymatic activity of only 10 to 20%, and has a frequency of 0 to 20%.(26) In 2 large case-control studies with over 2,000 African children, the G6PD A- phenotype was associated with a 46 to 58% reduction in risk of severe malaria.(27) In addition, pregnant women who were heterozygous for G6PD deficiency had a reduced risk of P falciparum infection and consequent anemia.(28)

Proposed mechanisms of protection against malaria due to the G6PD enzyme deficiency phenotype have been suggested by researchers. Since NADPH is essential for protection against oxidative damage, red blood cells with deficient G6PD enzyme activity are more sensitive to hydrogen peroxide generated by the malaria parasite.(29) The internal environment of the red blood cell with G6PD enzyme deficiency may inhibit the growth of the malarial parasites, however, in vitro experiments are conflicting with respect to growth.(30-32)

Another mechanism could involve accelerated phagocytosis of infected G6PD deficient red blood cells as demonstrated by in vitro experiments.(32) Phagocytic marker levels were significantly higher on parasitized red blood cells with G6PD deficiency compared with non-deficient parasitized red blood cells. In addition, the level of glutathione was lower in parasitized red blood cells with G6PD deficiency. Therefore, Cappadoro and colleagues hypothesized that impaired oxygen radical removal in the deficient red blood cells may cause membrane damage and increased phagocytosis by the immune system.(32)

With respect to G6PD deficiency, a better understanding of the pathways involved in offering protection against malaria are needed.

Hemoglobin C

The difference between normal HbA and hemoglobin C (HbC) is a change in a single amino acid. In normal adult hemoglobin, the sixth amino acid in the B-globin chain is glutamate.

In HbC, glutamate is changed to lysine. This same position 6 is the cause of sickle cell anemia, where glutamate is changed to valine and the mutated hemoglobin known as HbS. In both HbC and HbS the mutated amino acid changes the shape of the hemoglobin, the valine substitution is bulkier and has a greater effect on hemoglobin folding.

HbC homozygotes (HbCC) have a relatively mild hemolytic anemia, and HbC heterozygotes (HbAC) do not have significantly reduced hemoglobin.(33)

HbC occurs mostly in West Africa, where its prevalence in some regions is estimated around 10-20%.(34)

Epidemiological studies in the Dogon and Mossi ethnic populations of Mali and Burkina Fasso have found that the HbC phenotype protects against severe malaria.(35-37) In addition HbC has been reported to result in less frequent malaria attacks than HbA in humans of the same age group.(37) Furthermore, a 29% reduction has been reported in the risk of clinical malaria in HbC heterozygotes and 93% reduction in HbC homozygotes.(36) Thus, the HbC phenotype appears to offer more protection in

the homozygote state rather than the heterozygote state.

Although reduced parasite proliferation in HbC red blood cells has been proposed as a mechanism of protection in vitro and in vivo evidence suggest this is not a true occurrence.(38,39) P falciparum grows normally in HbAC red blood cells in vitro.(38) In addition, P falciparum parasites are able to replicate with HbCC red blood cells in vivo.(35) Therefore, the presence of parasite densities in HbAC and HbCC people indicates that a process of protection other than reduced proliferation must operate in vivo.

Other theories proposed to explain how HbC protects against malaria include reduced parasite cytoadherence, abnormal PfEMP1 expression, clustering of erythrocyte band 3 proteins, and altered surface topography of the erythrocyte membrane in the presence of hemoglobin C.(40-42) Fairhurst and colleagues reported that HbC might protect against malaria by reducing PfEMP-1-mediated adherence of parasitized red blood cells.(41) An abnormal display of PfEMP-1 on HbC red blood cells was observed. In addition, parasitized HbAC and HBCC red blood cells showed reduced adhesion to endothelial monolayers in comparison with parasitized normal HbAA red blood cells. Arie and colleagues reported that knobs on HbAC and HbCC red blood cells were more aggregated.(40) Knobs are protuberances on the red blood cell surface that are induced by infection with Plasmodium and they play a role in the pathogenesis of severe malaria by serving as points of adherence for parasitized red blood cells. Arie and colleagues hypothesize that larger knobs are promoted by HbC, and reduce the adherence of parasitized red blood cells, thereby causing an amelioration in severity of infection.(40) Tokumasu and colleagues reported that erythrocyte band 3 molecule clusters were larger and more abundant in HbCC red blood cells with HbCC than with HbAA.(42) Increased band 3 clustering may enhance recognition for autoantibodies, which may contribute HbC protection against malaria.

THALASSEMIAS

The thalassemias are a group of disorders caused by reduced or absent synthesis of 1 of the 4 globin chains of hemoglobin. Normal adult hemoglobin comprises 4 units, each with an amino acid chain wrapped around a heme group. The amino acid chains are of 2 types, α- and β–, each encoded by 2 copies of genes. When a single α-gene is deleted, in α-thalassemia, the resulting clinical effects are modest and reduce α-globin chain synthesis. Even if both chains are deleted, the sufferer will only have mild anemia.(43)

The geographic distribution of α+-thalassemia includes areas where malaria is endemic. In sub-Saharan Africa, almost 50% of the population has α+-thalassemia.(44) α+-thalassemia may protect against severe malaria.(43-46) Mockenhaupt and colleagues reported that heterozygous α+ thalassemia protected African children from severe malaria.(44) Williams and colleagues reported that heterozygous and homozygous forms of α+ thalassemias protect against severe and fatal P falciparum malaria from a study with 655 patients in Kenya.(45) Similar data are reported by Wambua and colleagues in their study of children in Kenya.(46) Another way that α+- thalassemia may help protect against malaria is suggested from a report of Mochenhaupt and colleagues that homozygous α+-thalassemia may protect from a P falciparum-induced decrease of hemoglobin.(47)

Although the α+ thalassemia trait offers protection from severe or fatal P falciparum, it likely does not prevent the infection or affect parasite densities.(46,47) Wambua and colleagues reported α-+ thalassemia was not associated with the prevalence of symptomless P falciparum parasitemia, the incidence of uncomplicated P falciparum disease, or parasite densities during mild or severe malaria episodes.(46) In addition, Mockenhaupt and colleagues reported that parasite densities were independent of α+-globin genotypes.(47)

Conclusions

Malaria has had an impact on the human genome as an evolutionary force. Studies designed to gain knowledge of the host-parasite relationship will help elucidate this complex disease process and may even offer new therapies to combat this disease.

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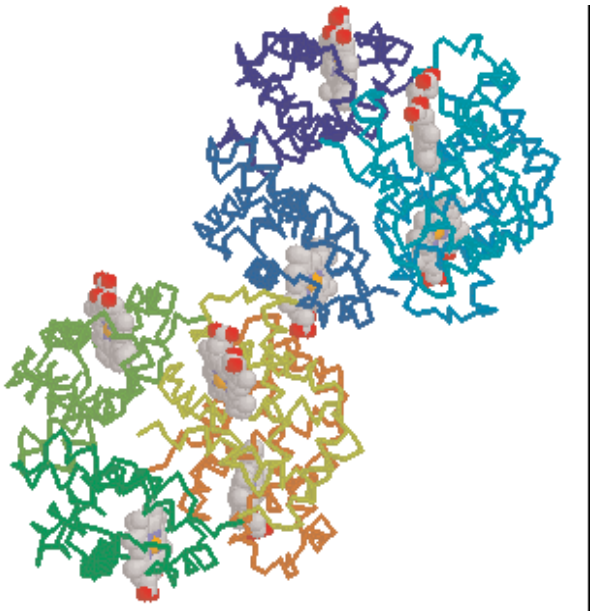

Figure 1. A model of 2 Hb S hemoglobin molecules clumping together. Model downloaded from ornl.gov

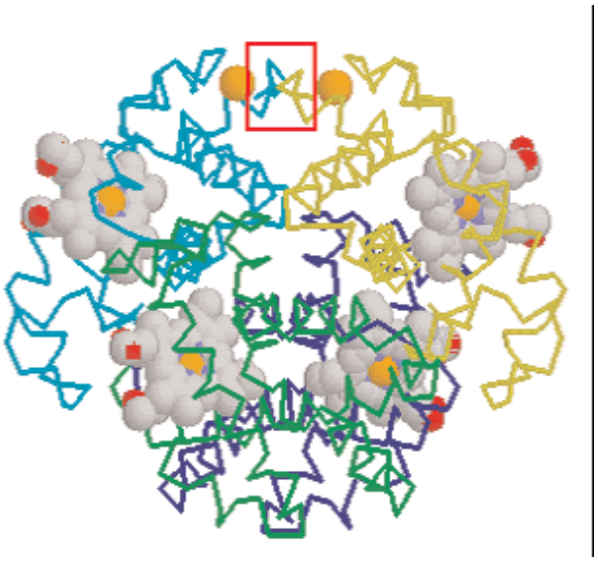

Figure 2. The Crystal Structure of Human Deoxy- haemoglobin at 1.74 A Resolution, Model downloaded from ornl.gov