Green Medical Journal Vol.7 Issue: 1 (April, 2025): 10-16
E-ISSN: 2686-6668
DOI: 10.33096/gmj.v7i1.134

Green Medical Journal
Volume 7 Issue 1

Literature Review Open Access

Sickle Cell Trait and Protection Against Malaria: Review Literature

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ABSTRACT

Introduction: Malaria is an infectious illness caused by various Plasmodium parasites transmitted by Anopheles mosquitoes. Currently, malaria is still a health problem with a significant incidence globally and has high morbidity and mortality. This makes researchers continue to seek solutions for malaria eradication. One of the things that is known to be protective against severe malaria infection is the sickle cell trait or HbAS.
Content: Sickle cell trait is a condition in which an individual is a carrier or has a single gene that causes sickle cell disease. The way sickle cell trait protects against malaria has been suggested for a long time. Along with the development of science and technology, various mechanisms of how the sickle cell trait protects against severe malaria are becoming known. Several mechanisms include sickling, miRNA, decreased cytoadherence, and immunological mechanisms.
Conclusion: Malaria is most often caused by Plasmodium falciparum. Indonesia is still an endemic country with the most frequent cases of malaria in children. One thing that is known to be protective against severe malaria, both symptomatic and asymptomatic malaria is the sickle cell trait with various underlying mechanisms.

Keywords: Malaria; sickle cell trait (HbAS); protection

GREEN MEDICAL JOURNAL
E-ISSN 2686-6668

Published by:
Faculty of Medicine
Universitas Muslim Indonesia

Address:
Jl. Urip Sumoharjo Km. 5, Makassar
South Sulawesi, Indonesia

Email: greenmedicaljournal@umi.ac.id

Article history:
Received: 22 December 2022
Accepted: 20 April 2025
Published: 4 May 2025

Introduction

Malaria is an infection caused by plasmodium transmitted by female Anopheles mosquitoes. Malaria is a life-threatening disease and a global health threat, especially in malaria-endemic areas and tourists visiting the endemic areas.[1] Based on Malaria World Report data, the number of people suffering from malaria in 2021 increased by 2 million cases from 2020 to 2021 and the most cases are in Africa. The occurrence of malaria also increased to 59 cases per 1000 at-risk populations in 2021. Cases of death due to malaria increased from 2019 to 2020 by 10%, but in 2021 the cases of death decreased to 610,000. [2]

One of the things known to protect against malaria is the sickle cell trait [3]. Sickle hemoglobin trait is a disorder of hemoglobin with the HbAS phenotype. It is a condition when an individual is heterozygous for the sickle cell gene.[4] Sickle cell trait occurs when there is a genetic variation in the beta chain of hemoglobin when glutamate is replaced by valine at the sixth codon [5 6 7]. It is estimated that around 300 million people worldwide have sickle cell trait and one-third of these are from Sub-Saharan Africa [4]. HbAS provides 91% protection from serious malaria cases and malaria morbidity.[8,9] Based on a study by Tambunan 2022, it was found that HbAS mutase provides a protective effect against mild malaria that varies from 20% to 60% in the first 10 years of life and decreases to 30% at a later age.[10] Another study conducted in West Africa found that HbAS protects about 90% of severe malaria cases.[11]

Sickle cell trait and sickle cell disease, are two different conditions. In sickle cell trait, individuals have only one sickle hemoglobin gene (HbAS) while in sickle cell disease, there are monozygous sickle hemoglobin genes (HbSS). The presence of 2 sickle genes causes abnormal hemoglobin production resulting in sickle-shaped erythrocytes.[12,13] Individuals with sickle cell trait usually live normally and without any symptoms.[4,12]

This review aims to provide an overview related to the role of sickle cell trait in protecting against severe malaria, by summarizing current knowledge on the molecular and immunological mechanisms involved. Sickle cell trait leads to a decreased frequency of non-symptomatic malaria and delays the emergence of malaria [12]. Several mechanisms are known by which sickle cell trait protects against severe malaria, including decreased cytoadherence, decreased oxygen concentration in infected red blood cells[3], immunological mechanisms, miRNA changes, and hemolysis.[3,12] Through this review, we want to clarify how sickle cell trait influences susceptibility to malaria, providing insights for future research and clinical strategies.

This article reviews literature from the PubMed, Google Scholar, and ProQuest database from 2014 to 2025, related to the role of sickle cell trait in protecting against severe malaria. The literature was conducted using the keywords “sickle cell trait”, “malaria”, and “protection”.

Plasmodium falciparum's relationship with red blood cells

Plasmodium infects its host by colonizing erythrocytes. Plasmodium falciparum is the most lethal of all species of plasmodium that can cause malaria [1]. P. falciparum has two stages of reproduction, asexual and sexual, involving humans and female Anopheles mosquitoes. The sexual reproduction process occurs when the parasite is in the mosquito's gut. After several stages of development, the parasite will move to the mosquito's salivary glands before finally being transmitted to humans through mosquito bites. When the mosquito bites, the saliva, and P. falciparum sporozoites enter the blood vessels.[14]

After entering the body, P. falciparum will go to the liver and infect hepatocytes. In the liver, the parasite will reproduce asexually and copy its DNA repeatedly so that one infected liver cell can produce thousands of merozoites in approximately 10 days. The merozoites will go into the blood vessels and infect red blood cells. P. falciparum will change the shape of the erythrocytes. This change in shape is caused by the release of protein molecules from the parasite into the erythrocytes, which then changes the membrane, allowing the parasite to enter the erythrocyte and avoid the immune system. In addition, the surface of erythrocytes lacks MHC1 molecules, making it difficult for immune cells to recognize infected erythrocytes. Upon successfully entering the red blood cells, the parasite will develop into trophozoites, will later turn into schizonts. Each schizonts will produce up to 32 merozoites. The infected red blood cells will become sticky and adhere to the blood vessel wall (cytoadherence), and when mature, the red blood cells (RBCs) will explode and release thousands of merozoites that will also infiltrate erythrocytes.[8,15]

When the plasmodium falciparum matures in RBCs, it expresses proteins on the outer layer of the RBCs, one of them is P. falciparum erythrocyte membrane protein 1 (PfEMP-1) encoded by the parasite var gene. The expression of proteins leads to the formation of knobs. The knob allows infected erythrocytes to attach to blood vessels (cytoadherence).[15] Knobs are essential to ensure strong attachment of erythrocytes in the vascular wall. The knob causes the infected red blood cell membrane to stiffen by joining the membrane to the host cell's actin network.[16] Cytoadherence is possible due to the attachment of PfEMP-1 to receptors on endothelial cells. The attachment of erythrocytes to blood vessels prevents clearance by the spleen, obstructs blood flow, and damages tissue, potentially leading to more severe malaria and complications.[15]

Protective mechanism of sickle cell trait against malaria

Haemolysis

Free haem is known to cause worsening oxidative stress, leading to severe proinflammatory reactions. When red blood cells infected with p. falciparum burst, haem is released. Haem accumulation in malaria

infection is correlated with severe complications of malaria. Free haem is also reported to be engaged in the disease progression of malaria complications such as cerebral malaria and other non-cerebral complications.[17]

Based on a study by Ademolue, Amodu, and Awandare, 2017, it is found that HbAS has better control of haem. Plasma haem levels were reduced in HbAS patients compared to HbAA during malaria infection. In addition, there was also a positive relationship between haem concentration and parasite density in HbAA, still in HbAS, there was no significant change in haem concentration in acute infection, HbAS likely has a good and efficient mechanism for breaking down haem. When the erythrocytes burst, cells are exposed to haem, increasing HO-1 expression to break down the haem and prohibit its cytotoxic effects. From the study results, it was found that HO-1 was more in HbAA than HbAS during malaria infection, indicating a higher concentration of free haem in HbAA than HbAS. Free haem can trigger immune cells, causing extreme release of proinflammatory cytokines.[17]

In the same study, it was found that the concentration of proinflammatory cytokines such as Interleukin-12, IFN-alpha, Interleukin-1beta, Interleukin-6, and Interleukin-2 surge in HbAA, while in HbAS no significant increase in proinflammatory cytokines was found. High proinflammatory cytokines are associated with dyserythropoiesis, which can end in severe anemia due to malaria. Adhesion molecules in vascular endothelial cells are also elevated and increase the sequestration of infected RBCs, and if sequestration occurs in the brain microvasculature, cerebral malaria can occur. [17]

Sickling

Plasmodium falciparum infection promotes red blood cell shape change to sickle shape. One study found that infected HbAS changed into sickle shape more than uninfected ones. In addition, increased hemoglobin polymerization in infected red blood cells or increased intracellular acidity causes sickling. This increase in sickling accelerates the process of phagocytosis of infected blood cells, thus reducing parasitemia compared to individuals with normal hemoglobin (HbAA)[18,10] and also accelerates clearance by the spleen.[18] Several studies have found that Plasmodium falciparum parasite growth deteriorates in HbAS erythrocytes in oxygen deficiency conditions. When oxygen levels are low, infected HbAS red blood cells become sickling[3,18] and do not appear to undergo DNA scanning, which indicates inhibition of parasite growth.[3]

Role of microRNAs

Recently, the possibility of human micro RNAs (miRNAs) translocating to parasite mRNAs has also been raised, leading to inhibition of parasite growth in erythrocytes. MiRNAs are a class of non-coding

single-stranded RNA molecules with a length of 21-25 nucleotides. In one study, two human miRNAs, namely miR-451 and let-7i, were found in HbAS and HbSS erythrocytes [15,19], both of the miRNAs can be integrated into parasite mRNAs, and by interfering with ribosome loading, the process inhibits the translocation of parasite-specific mRNA transcription in vitro. In the same study to further investigate whether miR-451 and let-7i have a significant effect, the two miRNAs were restrained with antisense 2'O-methyl-oligonucleotides and parasite development in HbSS and HbAS RBCs was increased by 50%, while their inhibition in HbAA had a small effect on parasite development. This suggests that miRNAs contribute significantly to providing protection against malaria in the erythrocytes of individuals with HbAS and HbSS.[19] Other studies have found miR-451a and let-7i-5p to be associated with parasite density. The higher the levels of miR-451a and let-7i-5p, the lower the levels of trophozoites, so it is likely that these miRNAs participate in parasite duplication and reduce trophozoite formation. In addition, an increase in miR-451a causes a decrease in parasite counts.[9]

Decrease in cytoadherence

In HbAS, one of the protective mechanisms is by inhibiting cytoadherence to the blood vessel wall.[6,12,8] The molecule PfEMP-1 is expressed on the outer layer of the infected erythrocyte. Through the protein, the parasite will attach to endothelial cells in the microvasculature. The process, called cytoadherence, allows the parasite to be concealed within the blood vessels and evade clearance by the spleen. Cytoadherence promotes endothelial activation, resulting in inflammation in the brain and other organs, making it crucial in the development of severe malaria. Changes in PfEMP-1 expression were seen in HbAS RBCs in vitro. In addition, there was also a decrease in attachment to endothelial cells that expressed the adhesion ligands CD36 and ICAM-1. In HbAS, PfEMP-1 surface signal was decreased compared to HbAA in cytometric essays indicating a decrease in PfEMP-1 expression on the erythrocyte surface[5,7,8,15,20] accompanied by abnormal morphology and distribution of knob.[6,8] In HbAS erythrocytes infected with P. falciparum, knobs are enlarged and more distant from each other.[6] In addition, the attachment between infected and uninfected erythrocytes (rosette) is decreased.[5,7,8,6,13,8]

In these erythrocytes, oxygenated hemoglobin with sickle hemoglobin is also found, which may interfere with actin reorganization, disrupting vesicle-mediated transport of PfEMP-1 to the erythrocyte outer membrane, thus decreasing cytoadherence. Decreased cytoadherence of HbAS and HbSS erythrocytes induced faster clearance by the spleen, thus contributing to lower parasitemia and decreased severe malaria cases in the HbAS population [5 20].

Immunology

Memory CD8 T cell compartment is developed more in children with HbAS than in HbAA. This contributes to controlling the onset of disease and decreasing parasitemia. In a study by Loiseau et al., 2021 which examined the role of CD8 in protection against malaria by analyzing memory T cell subsets and NK cells using flow cytometry, it was reported that memory CD8 T cells were elevated in individuals with HbAS compared to HbAA before the P. falciparum transmission period. Elevated memory CD8 T cells correlated with protection against malaria mediated by HbAS through the role of CD8. Between the onset and first episode of infection in children with HbAS, blood levels of effector memory CD8 T cells decreased significantly, suggesting that early on, CD8 T cells rapidly migrated to infected tissues or the hepatic system to help control parasite replication [21]. In addition, in HbAS-infected erythrocytes, oxygen damage occurs at the membrane, causing aggregation of band three proteins and binding of autologous and complement IgG. This allows for faster antibody action due to changes in antigen expression.[10]

Conclusion

Sickle cell trait plays a significant role in providing protection against severe malaria through various mechanism such as hemolysis, sickling, miRNA changes, decreased cytoadherence, and immunology, contribute to lower malaria severity. Understanding this protective effect is essential for treatment and prevention strategies. Future research should continue to explore the complex relationship between sickle cell trait and malaria.

Conflicts of Interest

There is no conflict of interest.

Funding sources

There is no funding source

Acknowledgments

There is no acknowledgment

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