Sickle Cell Trait and Resistance to Malaria: A Review

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Abstract

This paper explores the intricate relationship between sickle cell trait (SCT) and malaria, analyzing the dimensions of genetics, evolution, and molecular biology. Sickle cell trait is an inherited blood disorder that is prevalent amongst individuals of African descent. A point mutation in the *HBB* gene, results in the synthesis of both sickle hemoglobin (HbS) and normal hemoglobin (HbA). Despite the anomalous protein structure of the *HBB* gene, individuals generally lead a normal life. Malaria, a widespread endemic in tropical regions, is transmitted by *Anopheles* mosquitoes and poses a global health threat. The disease is caused by the *Plasmodium* parasite and presents a range of symptoms, making young children, the elderly, and pregnant women more vulnerable (Malaria: Causes, Symptoms, Diagnosis, Treatment & Prevention, 2017). The interaction between sickle cell trait and malaria reveals a compelling connection between evolution and adaptation. Individuals with SCT display at least 90% resistance to malaria due to the altered physiology of the red blood cells, which hinders parasite growth (Carter & Mendis, 2002). The resistance is ascribed to the enhanced immune system responses, which are heightened when sickle hemoglobin is present, creating an unfavorable environment for the parasite. These genetics and immunological processes elucidate the evolutionary forces shaping human populations. This paper synthesizes the current research on SCT and malaria to underscore the intricate interplay between genetics, epidemiology, and evolution. Further research in genetics will allow for a more complex understanding of disease susceptibility and the human species as a whole.

Background Information

Important context to know before diving further into this paper are: DNA, mutations, and genes.

DNA

Starting off with DNA, which stands for deoxyribonucleic acid; it is the hereditary material in humans and most other organisms. Most of a cell's DNA is located in its nucleus and some in its mitochondria. Human DNA is 3 billion base pairs long, and its code contains the chemical bases adenine (A), thymine (T), cytosine (C), and guanine (G). The order of the chemical bases determine the genetic sequence for each individual organism (What Is DNA?: MedlinePlus Genetics, 2021).

Mutations

Mutations are a change in the sequence of the DNA in an organism. Mutations can be advantageous (it helps the organism survive more efficiently compared to others) or disadvantageous (it holds back and may cause harm to the organism), or silent (it doesn't affect the organism's growth in either way) (Mutation, 2024).

Genes

Finally, genes are the basic unit of heredity and are made up of DNA. Humans inherit two copies of each gene; one from each parent. Studies show that there are 19,900 genes in our bodies which make proteins (What Is a Gene?: MedlinePlus Genetics, 2022).

Sickle Cell Trait

Sickle cell trait is a widespread, inherited blood disorder; and is common in people of African descent. Approximately 1 in 13 African Americans carry the trait (Sickle Cell Trait, 2024). The trait has to be inherited, meaning it is passed down to offspring, and people with sickle cell trait consist of one normal hemoglobin gene and one abnormal gene (one gene from each parent). Individuals with sickle cell trait contain both sickle shaped red blood cells and normal shaped red blood cells in their circulation (Figure 1). Individuals usually do not have any severe symptoms with the trait and are expected to live a normal life. However, they can face some difficulties when they get too dehydrated or get exposed to places with low amounts of oxygen (ex: high altitudes; intense physical activity) (Sickle Cell Trait, 2021).

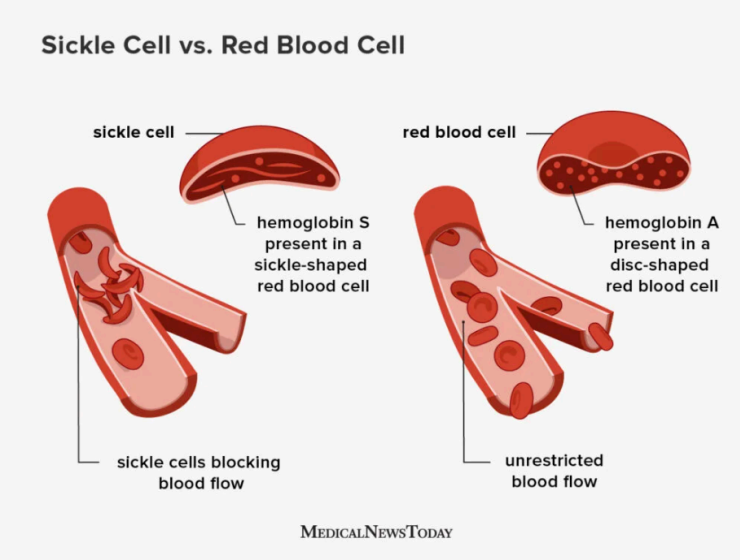

Figure 1
Sickle Cell vs. Normal Red Blood Cell. The distinction between sickle cells and normal red blood cells is exemplified through their shapes. Normal red blood cells with hemoglobin A have the shape of a round disk, and they flow smoothly through blood vessels. Sickle cells take the shape of a crescent moon due to the hemoglobin S that is present within their cells. The sickle cells can clump together and block the blood vessels, which cause blockages within the body not allowing oxygen to go through. They can cause severe pain by restricting blood flow (Williams, 2022).
Note: This figure is from Bailey Mariner Illustration by Brittany England
https://www.medicalnewstoday.com/articles/sickle-cell-vs-normal-cell

Genetic Makeup

Sickle cell trait is caused by an abnormal hemoglobin gene, which is the protein in red blood cells that is responsible for carrying oxygen to the rest of the body. Now focusing on the molecular level of the condition, specifically the *HBB* gene. Hemoglobin subunit beta also known as *HBB* gene is on human chromosome 11 and contains instructions for making the protein beta-globin (a subunit of hemoglobin) (HBB Gene: MedlinePlus Genetics, 2021). Hemoglobin is a complex protein that consists of four subunits: two beta-globin and two alpha-globin (produced by another gene called HBA). Additionally, each of these components is bound to an

iron-containing molecule called “heme.”The iron at the heme binds to one oxygen molecule. Sickle cell trait, also known as HbS or HbAS, is formed due to a mutation in one beta-globin chain resulting in hemoglobin S (sickle hemoglobin).

There are 146 amino acids that code for each beta-globin chain, and in order for hemoglobin S to be created, there must be a point mutation on the sixth position on any one chain. In a normal hemoglobin (HbA), the beta-globin chains code for glutamic acid at the sixth position; however, individuals who have sickle cell trait code for valine on the sixth position—on one of their beta-globin chains (Bridges, 2024). This means that individuals with SCT have two beta-globin chains that code for two different proteins. Yet, this change in protein structure doesn’t harm the individual too much because the normal hemoglobin allele (the A allele) is dominant over the S allele (sickle cell hemoglobin). This allows individuals who have SCT to lead normal lives.

Background for Malaria

Some basic terms that will be used throughout the next few sections are: vectors and hosts. Vectors are living organisms that can transmit infectious pathogens (things that can cause diseases) from animal to human, or from human to human. Majority of these vectors are blood sucking insects and can induce microorganisms during blood meals. A host is anything/anyone that acts as an environment for the microorganism. Specific microorganisms can affect the host in different ways: positively, negatively, mutually, or no effect (Table 1).

Table 1
Host and Microorganism Relationships

Mutualism	Both the organisms benefit from each other
Commensalism	One organism benefits but the other one is not harmed or benefited
Amensalism	Neither organism benefits but neither one is harmed
Parasitism (ex: *Plasmodium*)	The parasitic organism benefits at the expense of the host

Note: All information in this table can be accredited to (Symbiotic Relationship | Definition, Types & Examples Video, 2023)

Malaria

Malaria is a chronic disease which is transmitted to humans through mosquitoes. Today malaria is commonly found in Sub-Saharan Africa and in some regions across Asia and South America. Young children, the elderly, and pregnant women are more prone to this disease. Malaria is an infection in the bloodstream (or a blood infection) by parasites called 'protozoan' in the genus *Plasmodium*. These are transmitted from mosquito to human by the female *Anopheles* mosquitoes.

Although, historically scientists believed only four species had the capabilities to infect humans, scientists today have found five known species that can infect humans. These include the following, which are listed in order from causing the most severe cases of malaria to the least: *(1) Plasmodium falciparum, (2) Plasmodium knowlesi, (3) Plasmodium vivax(4) Plasmodium ovale, and (5) Plasmodium malariae* (Stanford Health Care, 2019).

Malaria symptoms are similar to those of a bad fever or cold; they include: fever, chills, headache, fatigue, chest pain, anemia, etc. The symptoms usually appear 10 days to one month after infection day. Depending on the specific species of parasite, the symptoms can vary in severity.

More about the mosquito

The *Anopheles* mosquitoes are considered highly zoophilic: they prefer animals to humans for their blood meals rather than anthropophilic: the preference of humans to animals for blood meals. However, it has been discovered that in Sub-Saharan Africa, these mosquitoes are highly anthropophilic (Hedrick, 2011). This difference between the *Anopheles* mosquitoes in Sub-Saharan Africa versus the other parts of the world can be traced back to their environment. In other parts of the world like the Middle East or Asia, there were many domesticated animals (Hedrick, 2011). On the contrary, Sub-Saharan Africa had only a few domesticated animals. In places that had an abundance of animals, the mosquitoes could turn to for blood meals, the people did not have to worry about malaria (because the *Anopheles* mosquitoes are zoophilic). In Sub-Saharan Africa, due to the lack of animals, the mosquitoes turned towards humans for their blood meals. This change in environment and climate introduced malaria to humans.

Plasmodium Cycle

When a mosquito bites a person and injects the *Plasmodium* parasite into the bloodstream it begins the initial stage of the *Plasmodium* cycle. A form of the parasite reaches the liver and multiples for 7-10 days until it ruptures the cells—after it matures—it moves into the lungs. After this, they leave the lung capillaries and move into red blood cells; they multiply within the cell

until it ruptures—which causes waves of fever. After some parasites mature further they can be taken up by a mosquito when it bites the individual again. The parasite proceeds to develop within the mosquito and prepares itself to repeat the same cycle when the mosquito bites another individual (Malaria Parasite Life Cycle, 2015).

Evolution

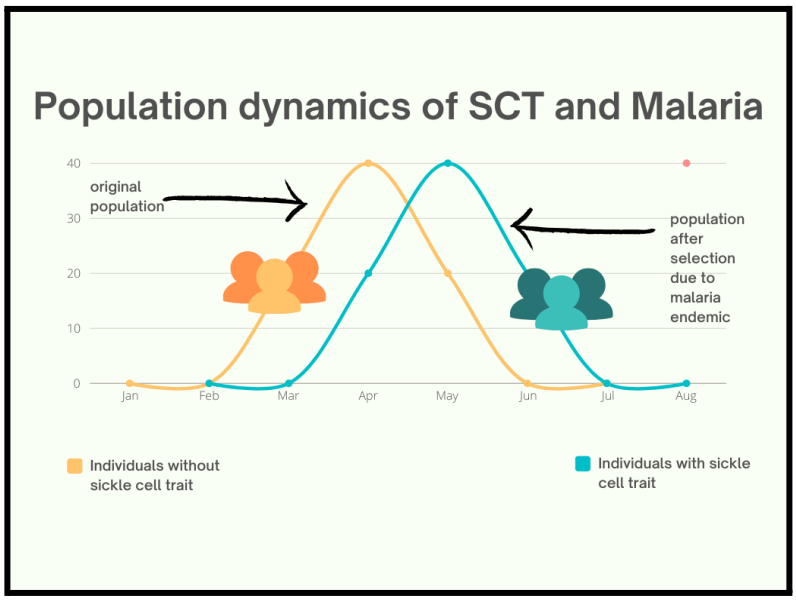

Figure 2
Population dynamics of SCT and Malaria. The sickle cell trait has been known to evolve in humans originally in tropical regions, which suffer from malaria endemic (e.g. Sub-Saharan Africa). Due to the *Plasmodium* parasite's inability to grow within sickle red blood cells, the hemoglobin S allele is believed to have originated as a protective agent against malaria (History and Evolution of Sickle Cell Disease, 2014). Overtime, individuals with hemoglobin S paired with hemoglobin A have shown special resistance towards malaria. People with hemoglobin HbAS have survived through the evolutionary forces long enough to reproduce and pass the trait down. This is due to natural selection, which is a theory of evolution, proposed by Charles Darwin and Alfred Wallace. The theory states that individuals who are better adapted to their environment are more likely to survive and pass their traits down to their offspring. So, the sickle cell trait has been naturally selected overtime to aid in malaria obstruction; and individuals with the trait have been more successful surviving in their environment (What Is Natural Selection?, 2019).

Correlation and Connections

In this section, I will explain how the immune responses of an individual with SCT can provide protection against malaria. Due to the presence of normal hemoglobin and sickle cell hemoglobin in the body. The HbS (sickle hemoglobin) in RBCs (red blood cells) can lead to sickling (the process of hemoglobin in RBCs sticking or clumping together) under extreme conditions, which makes it difficult for the parasite to grow (What Is Sickling? | Meaning, Causes, & Consequences, 2024). People with SCT often have an enhanced immune system, meaning that their body can identify and eliminate infected red blood cells easily. When the parasite enters the red blood cells, the infected cells can undergo changes that cause them to sickle. This alerts the immune system to start eliminating the infected blood cells because it comes across as a threat inside the body. This means there are fewer infected RBCs that can survive long enough for the parasite to reproduce because the immune system is eradicating

them early on. The response of the immune system can reduce the severity of the parasite and likelihood of obtaining malaria for the individual overall.

Conclusion

This research paper illustrates the association between sickle cell trait (SCT) and malaria, covering the dimensions of genetics, molecular composition, and evolution. Sickle cell trait is an inherited blood disorder that is more prevalent amongst individuals of African descent; and it also demonstrates a fascinating resistance to malaria. The genetic mutation in the *HBB* gene creates the presence of hemoglobin S (sickle hemoglobin) alongside hemoglobin A (normal hemoglobin), which results in resistance to malaria through various workings: altered red blood cell physiology (RBC) and heightened immune responses.

From the lens of evolution, the workings of natural selection have influenced the populations of individuals in malaria-endemic regions like Sub-Saharan Africa. The presence of hemoglobin S alongside hemoglobin A has given individuals a survival advantage against malaria. Hence, the increased number of individuals carrying this trait in tropical regions. This displays how genetic mutations that emerge due to environmental pressures can be beneficial for populations (Natural Selection: Uncovering Mechanisms of Evolutionary Adaptation to Infectious Disease | Learn Science at Scitable, 2014).

Further exploration in genetics and disease resistance will not only enhance our comprehension of these fields but will also aid in our progression towards a more developed healthcare system. The applications of precision medicine will create novel innovations and treatments that can apply the basis of genetics to navigate through genetic disorders and infectious diseases. By analyzing the connections between complex mechanisms, such as genetics and evolution, we can contribute effective treatments on a global scale.

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