A CO-EVOLUTIONARY LOOK AT A HOST-PARASITE INTERACTION: SICKLE CELL ANEMIA AND MALARIA

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Despite major attempts over the last century to control malaria, this disease still claims the lives of over one million African children each year. The malaria parasites are becoming increasingly drug resistant and there is still no vaccine to effectively work against them. However, about half a century ago genetic resistance factors were discovered by Haldane who believed that this was likely to be the evolutionary driving force behind common erythrocyte variants in tropical populations (Kwiatkowski, 2000). The high gene frequency of hemoglobin S in Africa, the protective agent against severe malaria in heterozygotes but causing fatal sickle cell disease in homozygotes, illustrates the powerful selective pressure exerted by malaria on the human genome (Kwiatkowski, 2000). When looking at this interaction from an evolutionary perspective, one could say that due to selective pressures the sickle cell trait became advantageous as a response to disease. Because of this, the sickle cell trait is found in regions where malarial pressures are high or in the descendants of people who came from these types of areas. This paper will discuss sickle cell anemia, malaria, and how the malaria parasites played a role in human evolution by providing protective qualities that insured reproductive success in individuals who carried the sickle cell trait.

Sickle cell anemia is a result of a point mutation caused by the production of abnormal hemoglobin. It is characterized by the abnormally shaped (sickled) red blood cells, which are removed from the blood stream and destroyed at high rates, leading to anemia (Lonergan et al., 2001). The underlying abnormality in the red blood cells of sickle cell anemia is the presence of abnormal sickle cell hemoglobin (Hb S), which when deoxygenated becomes relatively insoluble and forms rod-like polymers that impair the flow through blood vessels (Jones, 1997). More notably than the anemia, the sickling causes vascular occlusion, which leads to tissue ischemia and infraction that are much more clinically troublesome than the anemia (Lonergan et al., 2001).

Sickle cell anemia is the most common single gene disorder in African Americans and affects one in 375 African Americans in the United States.

Approximately 0.15% of this population is afflicted with the homozygous disorder (Hb SS), and just under one in 12 African Americans has the heterozygous sickle cell trait (Hb SA) (Lonergan et al., 2001). However, sickle cell anemia is prevalent in other ethnic groups as well, including Mediterranean area countries, Turkey, the Arabian peninsula, the Indian subcontinent, and a few in the Caribbean (Aluoch, 1996). Within sickle cell anemia populations the estimated survivorship of Hb SS individuals is 20% and the average age at death is 14.3 years. However, in areas with higher medical availability such as the United States significant numbers of individuals with Hb SS are surviving to adulthood. Individuals with the heterozygous form of the trait (Hb SA) are not physically affected by the disorder and live normal lives, most of which do not know they are carriers of the trait (Jones, 1997).

"The malaria parasite is a prevalent human pathogen with at least 300 million acute cases of malaria each year globally and more than a million deaths" (Pouriotis et al., 2004). In many parts of Africa, the average child is infected with malaria several times each year and continuously has parasites in their blood (Kwiatkowski, 2000). The malaria parasite (*Plasmodium falciparum*) has a very complex life cycle that involves the human host and the *Anopheles gambiae* mosquito as the carrier. The human stages develop after an infected female mosquito injects sporozoites (which can be between 10 and 100 during the blood meal) into the human. These migrate to the liver within a half an hour, where they then penetrate the liver and begin dividing within hepatocytes. This replication lasts from 2 to 10 days, and merozoites develop within hepatocytes. These cells then rupture, and merozoites enter the blood and invade erythrocytes. These events comprise the pre-erythrocytic (liver) stage of malaria (Pouriotis, 2004). After merozoites have invaded host erythrocytes, they mature and continue to divide to become schizots that are released upon lysis of the red blood cell. This entire cycle takes 48 hours to complete and the later two-thirds happen throughout the vascular network of the tissues (Friedman, 1978). The fever that periodically accompanies malaria is then a result of "the synchronous lysis of infected cells upon maturation of the parasite" (Friedman, 1978).

After understanding what is happening within the human body when affected by these two diseases we can then explain how they interact with each other and how an evolutionary advantage has come about through the heterozygous sickle cell trait (Hb SA) to avoid the damaging effects of malaria. Because malaria multiplies and infects the red blood cells it makes it a perfect candidate to be blocked by the effects of the sickle cell trait. Malaria parasites have highly specific needs in order to survive and this is shown in its narrow range of hosts. The only cells known to support the growth of ma-

laria are erythrocytes of humans and a few other primates (Friedman, 1978). In the Hb S containing red blood cells, the parasites cannot adapt due to the deoxygenation which forms the paracrystalline needles and distorts their shape and alters the intracellular viscosity. Therefore, any deviation from the normal red blood cells of humans would result in an inhibition of the parasite to infect or grow and would not make it the perfect host that it needs (Friedman 1978).

"The high frequency of the gene for sickle cell hemoglobin (Hb S) in malarial endemic regions, despite the high mortality rate among homozygotes, is thought to be due to the selective advantage conferred by Hb SA against malarial mortality" (Aidoo et al., 2002). In a survival analysis using the sickle cell trait as a risk factor for mortality, Aidoo et al. (2002) found that when compared to Hb AA, the Hb SA was significantly associated with a reduction in all-case mortality. Aidoo et al. (2002) also found that Hb SA but not Hb SS was associated with a reduced risk of severe anemia episodes and both alleles were significantly associated with reduced risk of high density parasitaemia when compared to Hb AA. When looking at the distribution of the Hb AA, Hb SA, and Hb SS traits across populations and regions, Jones (1997), reported that where the distribution of the sickle cell trait, characterized by a mixture of sickling and non-sickling hemoglobin's, areas with hyperendemic malaria showed prevalence at 10% or more. However, in areas with low epidemic or no malaria the prevalence of the sickle cell trait was less than 10%. In other studies done by Friedman (1978), it was found that 90% of young parasites are killed in a population of Hb SA cells where only 60% are sickled or distorted. This suggests that the parasite contributes to conditions that induce sickling in the host cell. Jones (1997) came up with similar results when he did a study on 30 individuals with the sickle cell trait and when exposed to the malaria parasite only two out of 15 people with the Hb SA trait developed malaria compared to 14 out of 15 people with the Hb AA trait that developed malaria. Jones (1997) suggested that due to the low oxygen levels that the parasite produces when invading the red blood cells this causes the collapse of the cells and shows a physiological basis for the protection in Hb SA and Hb SS people.

Since we are looking at the sickle cell gene in relation to malaria we also need to know what happens to the gene when malarial pressures are alleviated in order to fully understand the evolutionary effect that these two diseases have on one another. When taking an evolutionary perspective, one would argue that if the two evolved together, when malarial pressures are gone the frequency in the Hb S gene would drop unless other factors are keeping it in the populations. In recent studies of this there have been conflicting outcomes in

this debate. First, Hoff et al. (2001) has hypothesized that in African-derived populations in nonmalarial environments the Hb SA individual would lose any malarial fitness advantage and would become equal to that of Hb AA individuals. This lose in fitness would reduce the Hb S gene frequencies over time through directional selection pressures. After performing a study of African American's in the United States, Hoff et al. (2001) found that Hb SA women maintained higher fertility than Hb AA women therefore continuing to pass the Hb S gene down at high rates and maintaining it in nonmalarial environments. However, Hoff et al. (2001) does explain that there might also be other directional selection agents at work and more studies need to be done in order to know if this is correct. In contrast to this, Jones (1997) hypothesized that in the absence of malaria transmission the Hb S gene advantage would also be absent. He reports that when studying the frequency of the Hb S gene over generations the frequency drops with each generation and Hb AA is increasingly selected for. To support Jones (1997), Feng et al. (2004) found in their studies to show that the frequency of the Hb S gene drops as the selective pressure for the Hb S gene drops and malarial environments disappear.

From these findings we can conclude that the high mortality associated with malaria has led to strong selection for resistance, and hence for single major genes that give resistance in heterozygotes (Hb SA), despite the associated burden of possible death borne by both homozygotes (Hb AA and Hb SS) (Feng et al., 2004). Due to this protection individuals who are carriers of the Hb S gene have a reproductive advantage over the rest because they are able to survive the malarial effects and are able to reproduce which allows them to pass on the protective trait. However, due to the conflicting findings on whether or not the Hb S gene stays in a nonmalarial population, it is very important that more studies are done to understand what happens to the Hb S gene in such environments. This will help us to understand the evolution of these two diseases and if they are significantly related to one another in an evolutionary perspective. Due to the huge prevalence of malaria in Africa and other tropical regions where the co-evolution of the two diseases is thought to have originated, it is possible to collect a large number of families that would be needed when looking at the Hb S gene heritability. By looking at these families, one could perform longitudinal studies on the family members and their descendants to look at the Hb S gene frequency in the family members who stay in the malarial environment, compared to the Hb S gene frequency in the family members who leave the malarial environment. This would give us a better understanding of how this particular gene is passed and its relative affect from environmental pressures.

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