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Survival Strategies of Host, Parasite, and Vector in Human Malaria

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Abstract

Malaria, the best example of infectious protozoan diseases, has been tremendously impacted the human genome. The global spread of malaria reflects the successful adaptations of *Plasmodium* in human host and its *Anopheles* vector. The potential defenses of *Plasmodium* deal with diverse mechanisms of host immunity and persist in human with headstrong success. In an evolutionary arms race, human has developed malaria protective polymorphisms to survive. These polymorphisms safeguard human against the malaria. *Anopheles* has developed pesticide resistance for their survival. This paper briefs the interactions among *Plasmodium, Anopheles*, and human to provide evolutionary insight on malaria related genetic polymorphisms and to determine the evolutionary fitness of human, *Plasmodium* and *Anopheles*.

Keywords: *Human malaria; Genetic polymorphisms, Insecticide resistance, Drug resistance*

1. Introduction

Still now, malaria related human mortality remains high in many countries. In 2018 alone, more than 0.4 million people died due to malaria worldwide, of which more than 90% in only sub-Saharan Africa (WHO, 2008). Despite our efforts, *Plasmodium* causes a global health burden of about 250-600 million episodes of malaria per year in Africa, Asia, Latin America, and Oceania (Snow *et al.*, 2005). About 40% of these episodes are due to *P. falciparum*, another 40% is due to *P. vivax*.

The female *Anopheles* sucks blood from the host for maturation of their eggs. In the process of sucking blood, they also ingest the male and female gametocytes of *Plasmodium*, from the infected host. Mature gametocytes of the opposite sexes unite in the mosquito gut to produce the male and female gamete and both the gametes unite to form the rounded zygote. In sporogony, the zygote transforms into the ookinete, which subsequently produces the oocyst that bursts to liberate the sporozoites, the infective stage of *Plasmodioum*, inhabiting the salivary gland of mosquito. When the infected female *Anopheles* mosquito sucks blood, the sporozoite takes entry into the blood stream of the human host. *Plasmodium* undergoes pre-erythrocytic schizogony, erythrocytic schizogony, and gametogony in the human. Asexual life cycle involves RBC and liver cells with ultimate end product of male and female gametocytes in the

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peripheral blood of human from the schizont. In the liver cell, the sporozoite transforms into the schizont, which upon bursting liberates the merozoites, and this cycle in the liver continues and known as the exo-erythrocytic schizogony. Some merozoites enter the RBS and transform into the schizont, which again releases the merozoites. This process of merozoite production in the RBC is called the erythrocytic schizogony. Some of the merozoites transform into gametocytes in the RBC through the process called the gametogony. When the mature gametocytes enter the *Anopheles* during their biting and blood sucking, they develop into the sporozoites in the mosquito. The complexity of malaria is due to factors like presence of confusing sequence of various antigens, which are highly polymorphic in human immune system.

Spread of malaria reflects the successful adaptations of *Plasmodium* in the human host and its *Anopheles* vector. The biological success of *Plasmodium* depends mostly on their capability to invade, grow, and thrive in the human RBCs and liver cells of human. *Plasmodium* induced behavior in *Anopheles* also helps the parasite to achieve significant success. Lifecycle stages of *Plasmodium* impact the host genetic variations, importantly the RBC. Through an evolutionary arms race involving the parasites, hosts and vectors, *Plasmodium* species have developed survival strategies to effectively deal with the complex immune mechanism of human host and therefore successfully persist in humans.

Historically, the *Plasmodium* driven selective pressure on the human genome has resulted in the selection of human genetic variants to provide protection against the malaria. Most human diseases of the modern human societies at least partly to be due to malaria driven evolutionary pressure on our ancestors (Kwiatkowski, 2005). Hypoglycemia, glomerulonephritis, and pulmonary edema complicate the malaria (Playfair and Bancroft, 2008). A wealth of published literature deals with malaria protective genetic polymorphism in human (Malaguarnera *et al*., 2003; López *et al*., 2010; Lithanatudom *et al*., 2016; Ravenhall *et al*., 2018; and Malaria Genomic Epidemiology Network, 2019).

2. Malaria Protective Human Genetic Polymorphism

Since some RBC polymorphisms associate with susceptibility, or resistance to malaria, their effects, and distribution would have significant bearing in the epidemiological studies. Environmental condition and ethnicity influence the distribution of polymorphism showing the role played by the environmental natural selection in shaping the human genetic diversity. In the distribution of erythrocytes phenotypes, the ethnic group difference is also important. Interaction between the malaria parasites and human-receptor–ligand mediate the invasion mechanism of the parasite. Interplay between the human host and malaria parasite is balanced to ensure the survival of both, which is evident in the genetics of both the parasite and host (Faik *et al*., 2009). Human haemoglobinopathies, the first example of balanced polymorphisms protects against malaria and is also associated with the death burden (Roberts and Williams, 2003). There is an association between the host gene mutations and malaria protection. After Haldane's study, Beet (1946) recorded low malaria rates among the sickle-cell carriers than among the non-sicklers. However, presently consensus on how haemoglobinopathies bestow malaria protection appears to be lacking. Different haemoglobinopathies cause decreased growth and virulence of *Plasmodium*, mild haemolytic condition, auto-oxidation of haemoglobin, and ineffective erythropoiesis (Genton *et al*., 1995; and Roberts and Williams, 2003). However, perhaps the same mechanism does not operate in such cases. *Plasmodium spp*. have co-evolved together with human for thousands of years (Jongwutiwes *et al*., 2005).

3. *Plasmodium Vivax* Offers Protection to Human

Zimmerman *et al.* (2013) stated that for the *P. vivax* the human Duffy antigen on RBCs is the receptor of parasites. Absence of such receptor due to fy gene mutations prevents the entry of *Plasmodium* into the RBCs and protects the human against *vivax* malaria (Zimmerman *et al*., 1999). Combined missense mutation and lack of glycoprotein receptors on RBCs enhances the *P. vivax* resistance (Pogo and Chaudhuri, 2000). Two chief polymorphisms are found in fy gene. The Asp → Gly peptides replacement associates with the Fyb and Fya blood group antigens, corresponding with the first polymorphism. The second polymorphism leads to negative Duffy expression by silent RBCs (Murphy *et al*., 2000). Individuals with the Fya are more resistant to *P. vivax* infections. In Haiti, 99% of patients having silent erythrocytes with no Duffy antigen expression was *P. vivax* negative (Weppelmann *et al*., 2013). G6PD deficiency protects against the *P. vivax* infections and protects both the hemizygous males and heterozygous females from severe malaria (Clark *et al*, 2009); also protective against severe malaria and limits the severe anemia imposed increased risk (Shah *et al*., 2016).

Glycophorins (GYPA, GYPB, and GYPC) attach with the surface membrane proteins of *Plasmodium* (Wassmer and Carlton, 2016) and play role in bringing out the clinical malaria. Consequently, in absence of glycophorin, the entry of parasite in RBCs reduces and thus provides protection against the malaria (Maier *et al*., 2003). Dantu mutation in glycophorin molecules draws special attention. Through a specific impact on receptor-ligand interaction Dantu reduces

invasion but rather through a more non-specific way whereby Dantu increases red cell tension (Kariukki *et al.*, 2018). Glucose-6-phosphate dehydrogenase (G6PD) is linked to protection against the *P. vivax*, but not against the *P. falciparum* malaria (Louicharoen *et al.*, 2009). In the western Africa, *P. vivax* is not very common because most of the population is Duffy negative (Chitnis and Miller, 1994).

4. Resistance against *Plasmodium falciparum* in Human

In people with erythropoietic protoporphyria, the RBCs become unsuitable for *P. falciparum* due to low level of ferrochelatase in such patient with resistance to *P. falciparum* (Smith *et al.*, 2015). CD36 receptor binds with the vascular endothelial cells, activated immune cell surfaces, and play role in lipid metabolism as well as in phagocytosis. CD36 deficiency derived reduced cytoadherence of the infected RBCs protects the children against the anemia (Chingola *et al.*, 2009; and Ochola *et al.*, 2011). The host gene APOBEC3B mediates the innate response in *P. falciparum* infection. Enhanced frequency of deleted allele shows correlation with the higher susceptibility to *P. falciparum* (Jha *et al.*, 2012). Malaria thus serves as a positive selection force for APOBEC3B insertion. The mutants--MBL2 and MASP2 affect the congenital malaria as well as the placental transmission (Holmberg *et al.*, 2012). In Africa, double mutations in MBL gene in children with severe malignant malaria occur naturally (Luty *et al.*, 1998).

The severity of infection, and cerebral complications in falciparum malaria (Fernandez-Reyes *et al.*, 1997) increases mutation in gene encoding adhesion molecule 1 (ICAM-1, CD54). Malignant malaria has linkage with polymorphisms, MBL gene, promoter regions of the tumor necrosis factor-α (TNF-α) and nitric oxide synthesis 2 (NOS2). Point mutation in NOS2 produces the higher NO and protect against the *P. falciparum* malaria (Coia *et al.*, 2005). The MBL gene mutation and severe manifestations of *P. falciparum* is correlated in children from the Ghana (Holmberg *et al.*, 2008). A mutation in gene coding TNF-α was identified as a risk factor for *P. falciparum* re-infections (Meyer *et al.*, 2002). The anion-exchange protein prevents the binding of infected RBCs with endothelial cells (von Kalckreeuth *et al.*, 2006). Children with mutation in gene encoding anion-exchange protein 1 face severe malignant malaria.

Plasmodium has significant impact on human evolution (Cavalli-Sfroza *et al.*, 1994). To escape, the host immunity *Plasmodium* sequesters in the deep capillaries (Rowe *et al.*, 1995; Williams *et al.*, 2002; and Rowe *et al.*, 2009). Haldane (1948) first proposed the "malaria hypothesis." Allison *et al.* (1954) thought that selection through malaria might explain the high frequency of HbS in malaria endemic areas which confers the strongest protection against the severe malaria with more than 80% in heterozygous carriers (HbAS ; sickle cell trait). In the Alpha thalassaemia patient, about 40% homozygotes remains malaria protected (MGEN, 2014; and Ndila *et al.*, 2018). In malaria endemic region, other protective RBC polymorphisms including the glucose-6-phosphatase (G6PD) deficiency, O blood group, and gene variants for complement receptor 1 (CR1) occur at varied frequencies (Kwiatkowski, 2005). Duffy Antigen Receptor for Chemokines (DARC), which is expressed on RBC membranes exert strong selective pressure on the human genome and serve both as a chemokine receptor (Pogo and Chaudhuri, 1995) and a receptor for merozoites of *Plasmodium vivax* (Chitnis and Miller, 1994).

5. Malaria Protective Genes

The heparan sulfate proteoglycans of the human attaches with the circumsporozoite protein (a protein of parasite) of *Plasmodium*. The host genes viz. HS3ST3A1 and HS3ST3B1 encode for the enzymes, required for synthesis of heparan sulfate proteoglycans that probably influence malaria (Atkinnson *et al.*, 2012). Mutation of FcγRIIa (CD32 gene) affects the affinity of receptor for human IgG. Malaria resistance is associated with the gene that encodes for chitotriosidase (Chit). Chit gene mutation in higher frequency in Mediterranean population relates with high malaria resistance (Kanneegati *et al.*, 2012). Mutant hemoglobin variants like sickle-cell anemia (Ayi *et al.*, 2004) or thalassemia (Mokenhaupt *et al.*, 2004) provide significant protection against the human malaria. More than 180 mutations are associated with the PK deficiency (Min-Oo *et al.*, 2003).

The liver/erythrocyte specific enzyme (PKLR) contributes for energy generation for mature RBCs. Deficiency of PKLR causes the nonspherocytic hemolytic anemia, which inherits as an autosomal recessive. RBCs of PKLR-deficient patients reduce parasite's entry in RBCs and enhance the early phagocytosis of infected RBCs (Durand and Coetzer, 2008). The partial or complete loss of PKLR function results in malaria protection (van Buuggen *et al.*, 2015).

The ANK-1 gene encodes the Ankyrin-1, a cytoskeletal protein on the RBC membrane and its mutation mediates the human-inherited hemolytic anemic disorders. t ank-1 mutation enhances the malaria resistance (Greth *et al.*, 2012). Mild

malaria is found in boys with hemoglobin AA and O blood group. Similarly, the girls without mutation in gene encoding G6PD exhibits the mild malaria (Migot-Nabias *et al.*, 2000). Mutation related only to TNF-α has an association with the serious manifestations. However, nor the promoter regions of neither NOS2 nor the MBL gene are involved with the malaria manifestations (Migot Nabias *et al.*, 2000). Protection in Indian patients from clinical malaria was also found (Dhangadamajhi *et al.*, 2009).

6. Insecticide Resistance

Extensive use of DDT and pyrethroids increase the KDR mutation rate resulting in emergence of new mutation to ACE-1R (organophosphates) in *An. gambiae* (Cooling, 2015; and Tizifa *et al.*, 2018). Both the mutations influence (KDR and ACE-1R) the outcome of malaria transmission (Leucet *et al.*, 2012). The KDR resistant strain reduces the parasite burden, compared with the susceptible strain (Reimer *et al.*, 2016). Such reduction has not been observed in ACE-1R mutation. This gives us warning against the extensive use of DDT and pyrethroid (Alout *et al.*, 2013). Deletion of gene mutation at KDR locus increases the susceptibility of *An. gambiae* to *P. falciparum* infection. Development of new strategy for malaria control should consider all these evolution driven results (Ndiath *et al.*, 2014). KDR mutations are found in 13 *Anopheles* species. Insecticide resistance programs in malaria endemic regions should carry out, and monitored routinely (Silva *et al.*, 2014). The increased frequency of KDR mutations in *An. funestus* in Mali (Riveron *et al.*, 2015) and *An. arabiensis* in Senegal (Ndiath *et al.*, 2015) are also documented.

7. Drug Resistance

Chloroquine was effective, cheap, and easy to use in Africa and it was supplied in massive quantities. As a result, children death due to malaria in Africa was dropped in 1970s related in approaching half the level of pre-chloroquine years (Carter and Mendis, 2002). In the late 1970s, chloroquine-resistant *falciparum* took entry into the Africa and began to spread rapidly. Consequently, the malaria related morbidity and mortality resurged (Trape *et al.*, 1998). Mortality due to the malaria across large areas again approached the levels of pre-chloroquine years in the late 1990s. The former efficacy of chloroquine against the *falciparum* malaria produced major global health impacts of any ever-discovered antimicrobial drug. Spread of resistant parasites caused treatment failures and showed clearly how easily a drug can become ineffective in the therapy-based combinations in many African countries. Cytochrome P450 is involved in the artemisinin metabolism. Based on the frequency distribution (ranges between 10% and 78%) of cytochrome P450 mutation variants in Tanzanian *falciparum* patients, further evaluation of drug for the treatment of malignant malaria was suggested in Tanzania (Marwa *et al.*, 2014).

Frequency distribution of 62 mutations, the main cause of evolution locates on 17 human chromosomes (candidate immune genes). Study assessed the genes encoding immune response factors involved in the clearance of drug resistant mutant parasites in Cameroonian children. CD36, *TNF-α*, IL-22, IL-4, IL-10, and IL-17 are vital for clearance of resistant parasites (Ali *et al.*, 2011; Vincent and N"Guessan, 2013; Menze *et al.*, 2016; and Ondento *et al.*, 2017).

8. Fitness of *Plasmodium*

Now, it is clear that the human-*Plasmodium* interactions have resulted in malaria protective genetic polymorphisms through mediation of various genes in human and drug resistance in *Plasmodium*, which leads to the greater longevity of *Plasmodium* in human, and consequently extends the period of infectiveness. Gene mutation and selection of resistant mutants produce drug and insecticide resistance (Beagle, 1980). Chloroquine-resistant *P. falciparum* are prevalent throughout the world except Haiti, North Africa, Mexico, the Dominican Republic, and Central America. Mefloquine resistance is found in South-east Asia, especially in parts of the Africa and South America, Thailand, the Middle East, and Oceania. Quinine resistance is also common in the South Asia, Brazil and parts of Africa. Sulfadoxine/pyrimethamine resistance has recorded in the Indian subcontinent, South-east Asia, the Amazon basin, Oceania (Reviewed in Kristian *et al.*, 2003).

In the history of life, the lifestyle of parasite was incredibly successful. A fitness consequence of human malaria parasite rhythm is advantageous for parasites to have a definite phase relative to rhythm of the host. Hawking hypothesis has been reviewed for success of human malaria parasites (reviewed in Reece *et al.*, 2017). This hypothesis states that parasites change or match their behaviors to maximize opportunities to transmit the parasites to a vector. While discussing the parasite offense and host defense (Reece *et al.*, 2017) noted the induction of a strong inflammatory response due to synchronized bursting of *Plasmodium* in blood stream causing immunopathology of the host. Such

bursting benefits the parasite for its multiplication facility but harm the human health. Recently researchers have shown that people with transmittable malaria attracts mosquito. Sweat and breath odor in addition to high body temperature, enhances mosquito's lust for human blood (Lacroix *et al*., 2005). Hamilton realized that in case of increasingly less random mating, the natural selection favors skewed sex ratios strongly towards the females, to reduce wastage of resources on males that compete with each other for the same fertilization. Life cycles that favor this type of sex allocation behavior are widespread. Life cycle of *Plasmodium* selects for the evolution of 'Hamiltonian' sex ratio behavior. Key assumptions and predictions of sex allocation theory are upheld in malaria parasites, which help us to better understand the biology and within-host behavior of the malaria parasites (reviewed in Knowles and Sheldon, 2008).

Now the contribution of various fitness components to the overall fitness of sensitive and resistant *Plasmodium* are (i) growth and decay rates of the merozoites under drug pressure; (ii) starting of the gametocytogenesis; (iii) duration of gametocytes in blood stream; (iv) threshold gametocytaemia for transmissibility; (v) isolation periods of clinical malaria episodes. The gametocytes occur earlier in *P. vivax* but persist longer in *P. falciparum*. Late gametocytogenesis in infection and longer lifespan of the gametocytes will promote the spread of drug resistance. Thus, when comparing these two malarial parasites, resistance will spread easier in *P. falciparum* than in *P. vivax*. Transmission is the ultimate measure of the parasites' fitness (Reviewed in Schneider and Escalante, 2013). Although malaria protective genetic polymorphisms provide protection against the malaria, it definitely reduces fitness of human host because of vast burden of haemoglobinopathies.

Lastly, it is safe to conclude that history of malaria for at least last six thousand years is on record although definitely not systematically, which shows that *Plasmodium* offers cost in the form of mutation, manipulating the host and vector behavior for its successful spread and to ensure its survival. Human hosts have also helped *Plasmodium* in extending their cellular niche through human population expansion, drastic changes in the environment, and by promoting the unscientific use of insecticides. *Plasmodium falciparum* is virulent and life threatening. Other malaria parasite is benign, less virulent and all these factors increases their fitness or the evolutionary success.

Conclusion

Ultimate aim of survival is the production of copies of genes through reproduction (Mandal, 2015). Transmission efficiency, manipulation with the host and parasite behaviors, less virulence, not to threaten the survival of hosts and vectors are undoubtedly the fitness component of *Plasmodium*. Now, it appears that *P. falciparum* is less fit than the *P. vivax*. It would be of great interest to predict the success of new Anopheles-*Plasmodium* interactions in the context of drastic environmental changes such as global warming. The outcome of infection is the parasite genotype-vector genotype dependent; no parasite has optimal transmission in all the hosts and no host resists all the parasites. An. gambiae can be highly susceptible to some parasite genotypes, and, at the same time, highly resistant to other (Lambrechts *et al*., 2005). That mutations provide the protection to human against the malaria are highly prevalent in malaria endemic regions (Yuthavong and Wilairat,1993). As per Haldane's malaria hypothesis (Haldane, 1949), this might result in a "balanced polymorphism". In such conditions, the homozygote's hematological disadvantage balances the malaria resistance, which heterozygote exhibits (Yuthavong and Wilairat,1993). Malaria protective polymorphisms exhibit varied geographical distribution, parasite growth inhibition ability, and increased ability for host phagocytosis (Roberts and Williams, 2003). Genetically based resistance mechanism perhaps determine the geographic distribution of the parasites in both severe and non-severe cases of malaria and in homozygotic, or heterozygotic individuals (Hill *et al*., 1991; Lelliott *et al*., 2015; and Howes *et al*., 2016). *Plasmodium*-human co evolution confers protection against the malaria to the host and, it also limits the virulence of parasite allowing it to remain within the host for a longer period of time (Leung *et al*., 2017). Insecticide resistances of the *Anopheles* vector certainly shape the parasite-vector dynamics.

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