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Several Molecular Factors/Genes That are Involved in Making Development of Resistance against *Plasmodium Falciparum* Induced Disease Progression in Human Species

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ABSTRACT

Malaria is an acute parasite-induced disorder caused because of infection induced by a species of plasmodium parasites. The life cycle of Plasmodium parasites occurs through 3 stages: Gametocytes, Sporozoites, and Merozoites. The onset of clinical symptoms happens within 7 days to 10 days of the initial mosquito bite have dormant forms called the hypnozoite stage. Malaria caused by Plasmodium falciparum can be of 4 types: - asymptomatic, symptomatic, severe, or placental. Some factors like hemoglobinopathy (sickle cell anemia, thalassemia, etc.), low oxygen saturation, Glucose-6-phosphate dehydrogenase deficiency, and dantu mutation in glycophorin molecules provide natural resistance against malaria. Generally, most of antimalarial drugs (chloroquine, primaquine, etc.) work based on these molecular factors, responsible for providing resistance against malaria.

Keywords: *Plasmodium falciparum,* Sickle cell disease, Resistance against malaria, Hbc Low oxygen tension; G-6-PD deficiency, Dantu blood group, Thalassaemia

INTRODUCTION

Malignant malaria is a lethal disease caused because of infection induced by *Plasmodium falciparum*. Scientists have examined some molecular factors that are involved in the development of resistance against malaria. In heterozygous sickle cell anemia patients (HbAHbS), HbS polypeptide shows normal resistance against *Plasmodium falciparum* induced disease progression. In the case of sickle cell anemia patients, at low oxygen concentrations, reduction in parasite growth occurs [1]. In sickle cell anemia, patients' heterozygote advantage and balanced polymorphism is seen. In sickle cell anemia heterozygotes, HbS polypeptide prevents symptomatic malaria infection progression. Erythrocytes of individuals suffering from sickle cell anemia show reduced adherence to endothelial cells which could reduce the risks of malaria progression [2]. Scientists have discovered some advantages of Sickle cell heterozygotes in areas with heavy malaria endemicity showing a natural immunity for inducing protection against malaria [1].

Factors that are Involved in the Development of Malarial Resistance

There are several factors that help to develop resistance against malaria. These are described below:

Low oxygen concentration causes stalled parasite growth: In low oxygen concentrations, the growth of *P. falciparum* is likely to get impaired, albeit that's become tangled by the RBC hybridity of sickle cell anemia sufferer. Parasites remain stalled at low oxygen concentrations in HbAs heterozygotes remain halted at the late ring/early trophozoite stage [2]. We have found that termination in the DNA replication process occurred in parasites developing in low oxygen concentration. *P. falciparum* parasites were stalled at the lathering early trophozoite stage, in an isoleucine-deprived culture media, at low oxygen concentration [3]. At low oxygen concentrations or hypoxic conditions, the production of reactive oxygen radicals (like Superoxide radicals dioxidanidyl (O^{2-}), Dihydrogen dioxide (H_2O_2), Hydroxide ion (-OH), Dioxygen ($1O_2$), Peroxy radicals (RO_2) occurs. Nicotinamide Adenine Dinucleotide Phosphate Hydrogen (NADPH) oxidase activity plays a defensive roles in phagocytic cells [3]. We can use free radicals in the treatment of malaria and in reducing the growth of parasite growth. Long-term free radical production can cause oxidative damage to cells. Damage induced by oxidative stress causes loss of plasmodium membrane integrity [3]. It also causes a reduction in parasitic growth. Generally various antimalarial drugs like chloroquine and other quinolone act via the production of Reactive Oxygen Species (ROS) (Figure 1) [4].

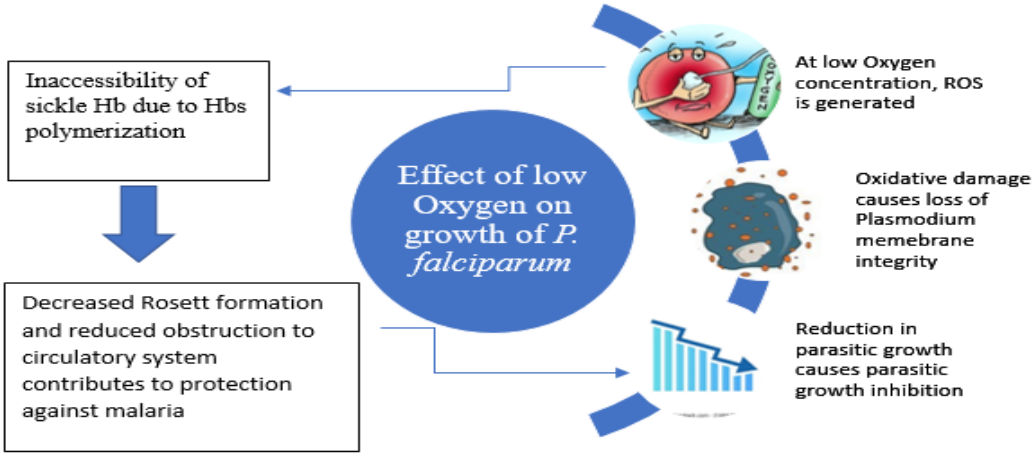

Figure 1 Effect of low oxygen concentration on *Plasmodium falciparum* growth [4]

Parasitic growth inhibition due to hypoxic condition: Polymerization of sickle hemoglobin at low oxygen concentration has a crucial effect in the progression of non-acceptance against malaria. At low oxygen concentrations, HbS polymerization plays an important role in malaria resistance. Impaired growth occurs due to the inaccessibility of sickle hemoglobin due to digestion by protease enzyme [5]. Sickle hemoglobin suppresses the pathogenesis of malaria by expressing Hemeoxygenase^{-1} (HO^{-1}), which prevents the accumulation of cytotoxic free haem. Polymerization of sickle hemoglobin causes growth impairment in intraerythrocytic stages of *P. falciparum* parasites [6]. Hemoglobin-S polymerization-influenced development hindrance is envisaged to decrease parasitemia more than diminished cytoadherence. Polymerization of sickle hemoglobin causes weakened growth that helps to negatively influence parasitic proliferation to collate with diminished cytoadherence. In low oxygen concentrations, ROS and RNS are generated which play a crucial role in systemic complication development caused by malaria [7]. Decreased rosette formation and reduced obstruction to the circulatory system might contribute to the safety against infectious malaria in individuals with sickle cell hemoglobin. Ring-stage parasites of *P. falciparum* did not grow in HbAS red blood cells under O^{2-} deprived conditions [8]. Parasites have a tendency to sequester in hypoxic microcirculation, was at a point when they show sensitivity to growth inhibition induced by hypoxia (Figure 2) [9].

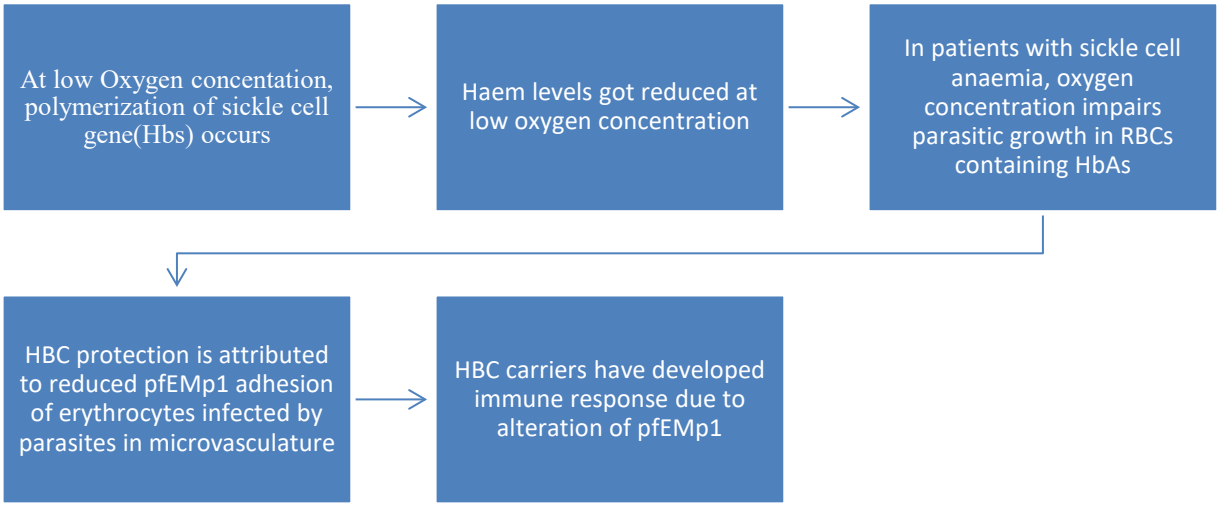

Figure 2 Mechanism of resistance in HbS and Hbc patients against malaria [9]

Heterozygote Advantage or Balanced Polymorphism Helps in Development of Resistance against *Plasmodium Falciparum* Induced Malaria

Balanced polymorphism in sickle cell anaemia patients: After millions of studies aimed for studying deleterious effect of sickle cell anaemia could cause any benefit. Because of genetic incomplete dominancy heterozygous sickle cell anaemia produces a phenotype intermediate between those with the disease and those without [10]. This incomplete phenotypic condition is termed as "heterozygous advantage" or "balanced polymorphism", results in enough cellular alteration for preventing plasmodium from surviving within cell [10].

Plasmodium falciparum parasites provides a lot of evidence of counter mechanisms in the fight between human and malaria [11]. In sickle cell anaemic individuals, malarial reproduction is induced by a protein. In sickle cell anaemic individuals, G-6-PD is often deficient. *Plasmodium falciparum* parasites begin to synthesize their own G-6PD enzymes to act as a proxy in their host [12].

When a single nucleotide mutation in the beta-globin gene occurs, it causes the production of abnormal Hb, resulting in sickle RBCs.Sickle red blood cells, which are fragile, crog the vessels and cause damage to organs [13].

Heterozygous carriers (HbA/HbS) of sickle cell anemia have greater proportions of sickle red blood cells in their blood. Sickle cell heterozygotes have the advantage of being resistant to malaria. Sickle cell heterozygotes have a tendency to survive more and they will tend to increase sickle cell gene frequency over homozygotes (HbA/HbA) [14].

Role of Hbc and HbS in the development of resistance: In sickle cell anemia, sickle cell hemoglobin (HbS) is seen. An abnormal condition in which an individual has one allele of beta globin gene, that is abnormal in nature. A person with β- the globin gene has two copies of the abnormal beta-globin gene. Sickle cell anemia occurs due to the substitution of one amino acid glutamine into valine (G→V) [15]. Factors helping HbS to be resistant against *Plasmodium falciparum*-induced malaria are as follows:

- Parasite genotype determines malaria protection in HbS patients [15].
- Polymerization of sickle cell hemoglobin (HbS) at low oxygen concentration plays a role in safety against malaria in patients with sickle cell hemoglobin (Hbs).
- Parasitic growth inhibition occurs at low oxygen concentrations in HbS patients [16].
- Reduced haem levels in red blood cells with sickle cell anemia may induce, Hemeoxygenase-1 [HO^{-1}].

- Reduced cytoadherence is a resistance mechanism in HbAS individuals [16].
- Higher levels of antibodies directed against pfEmp1, potentially manifested by biochemically provided protection against high densities of parasites, might diminish an effective response [16].
- In patients with sickle cell anemia oxygen concentration impairs parasite growth in RBCs containing HHbAS [16].
- Second ring stage infected RBCs with HbAS undergo increased phagocytosis in comparison to Red blood cells from HbAA individuals [17].
- The alleles associated with HbS include non-synonymous variants in members of bifunctional Ni-Fe-S containing enzyme acyl coA synthetase family PfACS8 located on chromosome no. 2 [18].
- In case of sickle cell anemia patients, loci associated HbS such as pfsa1, pfsa2 and pfsa3 for *Plasmodium falciparum*, study of sickle associated genes and positive or negative alleles associated with HbS, can be used in detection of disease [19].
- HBC is a rare unusual condition in which glutamic acid residue at the 6th no. position of β-globin chain is substituted by a lysine amino acid residue, caused because of a point mutation in HBB gene [20]. It might be possible for a person to have both haemoglobin-S and haemoglobin-C disease causing gene and this disorder is called Haemoglobin SC disease and is generally more drastic than Haemoglobin-C disease [20].
- HbAc tended to be more recurrent in parasitemia than in a healthy control subject. In vitro, HbAC erythrocytes, have a mechanism of supporting the growth of *Plasmodium falciparum*, whereas rate of replication is substantially reduced in HbCC red blood cells [21].
- Frequency complexity for Hbc is very high than HbS. The people with HBC were resistant against malaria, and carried at least 1 βC allele. The reduced risk of malaria associated with CC homozygosity (93%) is stronger than AC heterozygotes (29%) [14].
- HBC protection is attributed to reduced PfEMP-1-induced adhesion of erythrocytes infected by parasites in microvasculature [22].
- HBC carriers can develop an immune response that is caused due to alteration in PfEmp-1 [22].

In malaria-infected RBCs, HBC inhibits polymerization of actin and Maurer's cleft is produced, which helps in directing RBCs infected with parasites. HBC containing erythrocyte sequestration would be diminished compared with HbAA-infected RBCs, it represents a protective potent mechanism (Figure 3) [23].

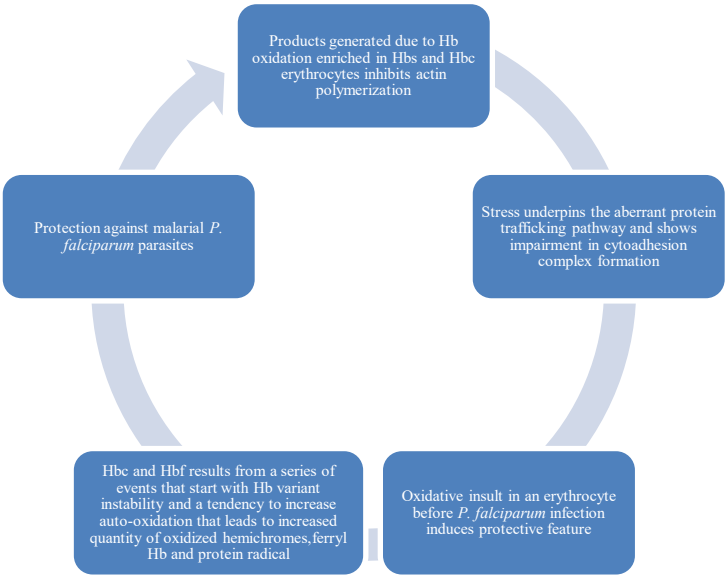

Figure 3 Mechanism of protection against malarial parasites in HbS and Hbc patients [23]

Factors that Play an Important Role in Development of Resistance Against *Plasmodium Falciparum* in Hbs and Hbc Patients

- Actin cytoskeleton and Maurer's cleft were found abundant in HbS and Hbc erythrocytes [24].
- Products generated due to Hb oxidation enriched in HbS and Hbc erythrocytes, inhibits actin polymerization in vitro and account for a protective role in malaria [24].
- Stress underpins the aberrant protein trafficking organization pathway and impairment in cytoadhesion complex formation, hemoglobinopathic, HbS, and Hbc protects individuals from severe malaria [24].
- Oxidative insult in an erythrocyte before infection with *P. falciparum*, induces protective features in hemoglobinopathic and fetal erythrocytes [25].
- HbC and HbF result from a series of events that start with Hb variants instability and a tendency to increase autoxidation, which leads to an increased quantity of oxidized hemochromes, ferry Hb, and protein radical. This pro-oxidative environment is likely to interfere with malarial parasite pathophysiological functions [25].

Role of Thalassemia in the Development of Resistance against *P. Falciparum* Induced Malaria

- Thalassemia is a hemoglobinopathy that is characterized by the following features.
- Thalassemia results due to defects in the Synthesis of polypeptide chains α and β of HbA [26].
- Depending upon whether alpha or beta chains are not synthesized, α or β-thalassemia syndrome may represent the following forms depending on deletion on α-globin loci- α-thalassemia carrier may be asymptomatic or carrier (silent) or may resemble β-thalassaemia minor [26].

Features of α-Thalassemia

- In this state there is an excess of γ-globin form, i.e. Hb Bart's which has very high oxygen affinity. Hence there is no delivery of oxygen to fetal tissues [27].
- Heterozygous alpha^{+} thalassemia can protect an individual leading to asphyxia, edema, congestive heart failure, and death in vitro [27].
- It protects from the severe effects of malaria. Most of the alpha globin gene is missing from each chromosome in a condition and this condition is known as alpha^{+} thalassemia [27].
- Alpha-thalassaemia red blood cells infected by *P. falciparum*, have a tendency to show decreased capacity in forming Rosett which was a pathogenic marker of severe malaria [23].

Protection against Malaria in Thalassemia Patients

- Entry of merozoite stage into red blood cell is inhibited.
- Intracellular growth of the parasite is impaired [27].
- Erythrocyte lysis prevention occurs at the end of parasite maturation, that leads to merozoite release into bloodstream [27].
- Parasite infected RBCs show enhanced phagocytosis [28].
- Cytoadherence is reduced in infected erythrocytes to endothelial cell APCs [29].

Alpha^{+} thalassemia shows reduced rate of infection to malaria.Both homozygote and heterozygote individuals had much lower rates of severe malaria than normal children [30].

Increased binding of antibody to thalassemic parasitized red cells suggests increased neoantigen expression and it results in enhanced immune recognition and increased clearance of parasites [29].

Children with α-thalassemia makes small RBCs. α-thalassemic children have acclimitized to the deprivation of erythrocytes associated with malarial disease by making more of these cells with less Hb [29].

Scientists have proved that individual with mild α-thalassemia, inherit mutations in the 'alpha' part of Hb genes from each parent that were protected against malaria [31]. These children were 60% less likely to get

malaria than others with normal 'alpha' Hb gene [31].

Some scientists have proposed that thalassemic cells will not be able to form rosettes, which causes damage by cherishing and nourishing the hindrance of capillary blood flow and guiding the separation of the infected red blood cells that remain in the schizont phase in some major organs [31]. Red blood cells of the thalassaemic individuals bind to immunoglobulin, which favors the removal of parasites that contain RBCs [32].

Thalassemia only provides resistance to cerebral malaria accompanied by anemia. Malarial parasites also cause cytoadherence equally well to endothelial cells as do normal RBCs infected with parasites [33].

Average Hb concentrations remain diminished in α^+ thalassemia patients, both in a state of steady condition and during mild malarial attacks. The absence of malaria parasites in the blood of severe anaemic individuals, may not be sufficient to include the diagnosis of malaria [34]. Thalassemia appears to be protected against severe complications associated with or without malaria and that causes the mechanism of protection against infection to occur in the lower respiratory tract [34].

The increased occurrence of microcytosis in thalassemia homozygous individuals plays a protective role against anemia due to malaria.α-thalassemia has an impaired effect in the attachment of parasite-infected erythrocytes to microvascular endothelial cells and monocytes [34]. α-thalassemia acts as a safeguard against clinical forms of severe malarial anemia associated with fatal outcomes. *P. falciparum* parasites can invade alpha-thalassaemic RBCs and develop into pfEmp1 expressing trophozoites that are not viable [34].

α-Thalassemia reduces the edacity of parasite-infected RBCs for microvascular endothelial cells and monocytes. Scientists have also proved that α-thalassemic heterozygous and homozygous individuals act as a safeguard against cerebral malaria along with severe malarial anemia [34]. α-thalassemia associated lower mean corpuscular Hb, have a tendency to contribute in a protective mechanism, exempts upon the rupture of each schizont-infected RBC [30].

Parasitized RBCs display abnormal pfEmp1 abnormalities that are evocative on the periphery of parasitized HbS and Hbc. HbS, Hbc, and unpaired beta-globin genes undergo induced degradation occurs due to hemichromes.These hemichromes like to RBC inner leaflet membrane where they foster heme iron(Fe^{2+}) mediated oxidation of membrane proteins and lipids [21]. Excessive damage to parasitized RBC membrane induced by excessive hemochrome interferes with parasite trafficking and knob pfEMp1-induced knob incorporation (Figure 4) [30].

Figure 4 Role of α-thalassemia in providing resistance against malaria [30]

G-6-Pd Deprivation as an Element in the Development of Resistance Against *Plasmodium Falciparum* Induced Disease

Glucose-6-phosphate dehydrogenase is an enzyme present in cytosol that helps in the body's defense against oxidant damage.G-6-PD is the only source of NADPH cofactor, that will be needed for generating reduced glutathione, a major antioxidant defense system [35]. G-6-PD maintains RBC redox potential and reduces oxidative stress [35]. Cellular G-6-PD activity helps in the production of inflammatory cytokines. G-6-PD can regulate the differentiation of T-cells. G-6-PD catalyzes the reaction in the HMP pathway to generate a reduced form of NADPH, which helps in the regulation of GSH homeostasis [36].

Reasons Behind the Development of Resistance against *P. Falciparum* Induced Disease Progression for G-6-Pd Deprived Individuals

Glucose-6-phosphate dehydrogenase deficiency has a role in providing protection against cerebral malaria. Scientists have investigated a process in mice with normal Glucose-6-phosphate dehydrogenase activity that died between 5 days-9 days post-infection exhibiting typical malarial symptoms [36]. Cerebral malaria has an effect on the integrity of Blood- the brain barrier. In Glucose-6-phosphate dehydrogenase-deprived mice, the blood-brain barrier leakage was less extensive [37].

G-6-PD deficiency suppresses malarial immune response and thus suppresses malaria complications. Scientists have done a little experiment, to determine the role of G-6-PD deprivation on malaria [37]. Scientists have extracted transcriptome of malarial parasite from dual RNA seq raw reads, examined that most of ribosomal genes of malarial parasites became downregulated for mice having inadequate amount of G-6-PD [38].

Scientists have drew-out lymphocytes from liver and spleen of mice in each category for discovering differentiation of Th1 cells expressing CD45+, CD3+, CD4+, IFN-γ and Treg cells showing expression of CD45+,CD4+,CD25+, with the help of a technique called flow cytometry. Having an inadequate amount of G-6-PD, tends to inhibit the differentiation of Th1 in mice suffering from malaria [39].

In G-6-PD-deprived individuals suffering from malaria show lower levels of microvascular obstruction than wild-type individuals. G-6-PD deficiency can alleviate complications caused by cerebral malaria and liver injury via supressing immune response. For G-6-PD-deprived individuals. G-6-PD deficient RBCs are unable to generate ribose for purine nucleotide metabolism [40]. Scientists have discovered some mutations are responsible for Glucose-6-phosphate dehydrogenase deficiency. According to their study, the 202A/376G G-6A variant shows combined protection against asymptomatic malaria. Erythrocytes with G-6-PD deficiency are more vulnerable to destruction by oxidative stress due to lower NADPH levels. An increase in G-6-PD has been associated with the natural selection of G-6-PD deficients [41].

Individuals Having Deprived G-6-Pd can be Grouped into the Following Classes

- Class 1 individuals:- Class -1 G-6-PD individuals show deficiency correlated with chronic non-spherocytic anemia.
- Class 2 individuals:-Individuals showing severe deficiency with less than 10% enzyme activity [41].
- Class 3 individuals:- Individuals showing moderate deficiency with 10%-60% of enzyme activity [41].
- Class 4 individuals:- Individuals are generally normal with an activity of 60%-150% [42].
- Class 5 individuals:- Individuals showing enzyme activity greater than 150% [42].

These G-6-PD variants provide resistance in female heterozygotes and male hemizygotes against both *P. falciparum* and *P. vivax*. In vitro studies have shown that an impairment in the growth of parasites occurs in the case of G-6-PD-deprived erythrocytes [42].

Parasitized G-6-PD-deprived erythrocytes were susceptible to phagocytosis by monocytes that provide protection against malaria [42]. Our study highlights the importance of testing Glucose-6-phosphate dehydrogenase testing before primaquine treatment to prevent hemolysis [43].

In G-6-PD A(-) patients coexistence of an oxidative stimulus can increase the resistance of a cell against parasite infection [43]. In Glucose-6-phosphate dehydrogenase deficient patients, such a condition provides protection against malaria infestation. Protection against *P. falciparum* parasites concerns more in female heterozygotes than males who are hemizygous to this trait [43].

Chemokines play key roles in generating inflammatory responses. Quantitative Real time PCR shows that G-6-PD deficiency shows reduced mRNA expression of chemokines and adhesion molecules in brain [43]. In individuals having inadequate amount of G-6-PD, shows decreased expression of proinflammatory cytokines TNF-α,IL-6,IL-12, occurs significantly [44].

Maturation of dendritic cells (CD45+, CD80+, CD86+, CD11C+) have an important role in development of cerebral malaria [44]. When scientists have selected CD80, CD86 and MHC-2 markers for the observation of maturation of dendritic cells. Scientists have found that individuals having inadequate amount of G-6-PD deficient, have significantly lower rate of maturation of dendritic cells occur [45].

G-6-PD deprived erythrocytes are vulnerable to destruction because of oxidative stress due to reduced levels of NADPH. It is confirmed that when G-6-PD deficiency increases,it confers protection of resistance against *P. Sp*. induced malaria (Figure 5)[45].

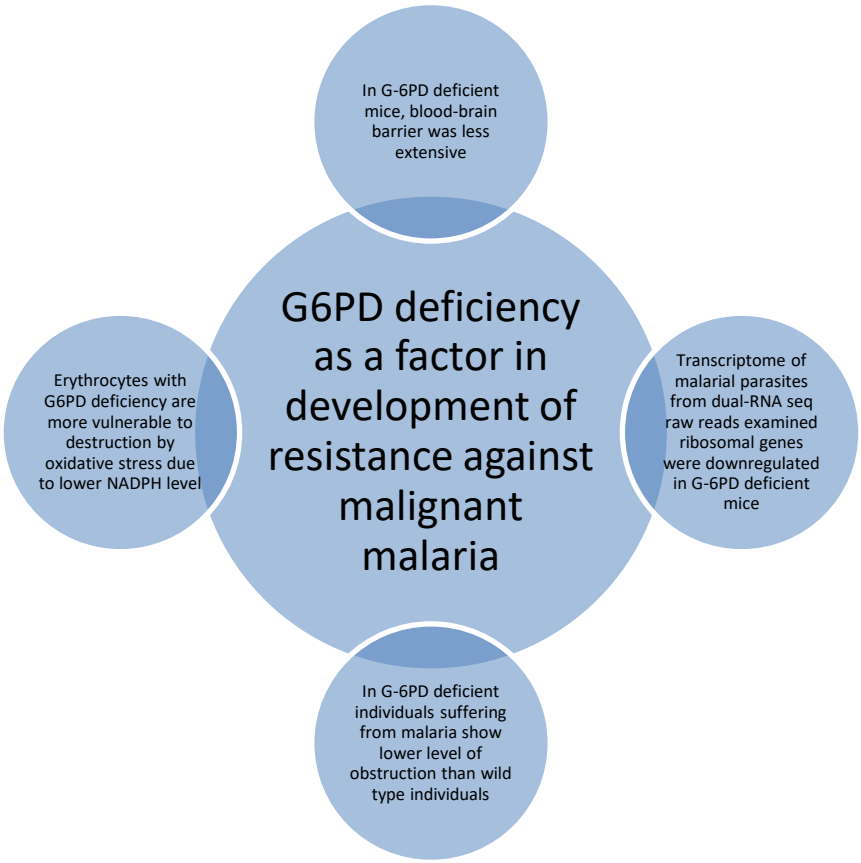

Figure 5 G-6-PD deficiency as a factor in the development of resistance against malignant malaria [45]

Role of Dantu Mutation as a Factor in the Development of Resistance Against *P. Falciparum*-Induced Malaria

- Dantu is a blood group is seen in the MNS blood group individuals. The Red Blood Cells (RBCs) have specific glycophorins in them. Glycophorin A (GYPA) and Glycophorin B (GypB) are two types of receptors found in *Plasmodium*, the causative agent of malaria, used for entering into healthy cells [45].
- Antigenic determinants of MN and SS blood groups are coded by both of these glycophorins,i.e., GYPA and GYPB [45].
- Two genes named GYPA and GYPB remain adjacent on the same chromosome and they become regrouped in various ways for producing specific antigens in the case of the MNS blood group. Dantu antigen is one such hybrid of GYPA and GYPB gene [46].
- Scientists have found that the GYPB-A gene has less ability to develop severe complications of malaria [46].

To examine the effects of dantu blood group, scientists have collected red blood cell samples from some healthy children in Kenya, who had one, two or zero copies of the dantu gene. These red blood cells were then exposed to the malaria parasite in the laboratory. The samples were examined using multiple tools along with time-lapse video microscopy, that identified the point of parasite invasion impairment [46].

Reason behind Development of Resistance Against Severe Malaria in Individuals with Dantu Blood Group

Dantu blood group has a novel "chimeric" protein that remain expressed on the periphery of Red blood cell and it can alter the balance between other surface proteins [47].

Dantu mutation can create cells with a higher surface tension like a drum with a tighter skin. Due to mutation, malaria parasites were no longer able to enter the cell and it can also halt their life cycle and can prevent the multiplication ability of the parasites within blood [47].

Dantu mutation can create cells with a higher surface tension like a drum with a tighter skin. Due to mutation, malaria parasites are no longer able to enter the cell and it can also halt their life cycle and can prevent the multiplication ability of the parasites within blood [48].

Scientists have done a test and there he tested dantu RBCs, non-dantu RBCs, dantu heterozygous, and homozygous, where the lower invasion of parasites was seen within dantu RBC for 3 parasitic strains (3d7, Dd2, SA075). It has been observed a greater shift of resistance against attack by dantu homozygous RBcs, in comparison to, heterozygous RBCs [16]. In dantu RBCs infected with 3d7 parasites, a decreased level of attack can be seen. Dantu creates a whole copy of GYPA inside the genome. GYPA expression in dantu RBCs was notably diminished. A strain eclipsed the inhibition of *P. falciparum* seizure inside dantu RBCs, dantu on the RBC membrane mediates this tension [16].

The Dantu blood group Â variant provides the carriers with protection from severe malaria. It is a result of a mutation in GYPA and GYPB genes, which codes for dantu antigen. The Dantu variant has a role in protecting an individual against contracting severe malaria [46].

Scientists have Discovered Two types of Dantu Mutation

- **Dantuâɛ:** Exhibits resistance greater to infection. It generally shows higher tension is thought to be due to increased expression of ion channels located on the surface of RBC. RBC tension negatively impacts the parasite's ability to enter the RBC of individuals with the Dantu blood group [49].
- **Non-Dantuâɛ**: It provides less tension and resistance to the shape of RBC [49]. Dantu impacts the surface of RBC, by altering RBC surface composition. Dantu blood group can generate a 'tension threshold' above which,it becomes too difficult for the growth of parasites [50].

DUP4 is a complex structural genomic variant that conveys extra copies of a glycophorin A-glycophorin B fusion gene. It has a role on the reduction of malaria by up to 40%. Dup4 has a role in protecting individuals against malaria [11].

Dantu alters the component of the RBC surface. So based on this property, some treatments are developed that prevent Dantu RBCs from entering into RBCSs. RBCs that express the rare dantu group are resistant to attack by *P. falciparum* merozoites as they are tenser than normal cells (Figure 6) [16].

Figure 6 Role of Dantu mutation in providing a mechanism of resistance against malaria [16]

CONCLUSION

As we have already discussed, we can use these factors in the treatment of malaria. We can prevent malarial infection using these factors. Scientists have also discovered an effective treatment against malaria utilizing these factors in the treatment of malaria. Normally some antimalarial drugs like chloroquine, and primaquine work on the basis of the mechanism of free radical generation. At low oxygen concentration. We can use antimalarial agent artemether for the treatment of acute uncomplicated malaria. This combination therapy exerts its effect against erythrocytic stages of P. sp. We can also use artemether and lumefantrine for the treatment of *P. falciparum* induced malaria. The generally accepted mechanism of action of peroxide antimalarial involves peroxide-containing drug interaction with heme. In the case of antimalarial drug Artisuanate,it can cause double stranded breaks in plasmodial DNA, which causes the generation of free radicals. Artemisin and other endoperoxides tend to generate free radicals at the mitochondrial level by changing transfer of electrons from complex-3 to molecular oxygen. In the end, some Hb oxidation products enriched in HbS and Hbc erythrocytes, reduced actin polymerization outside the body, have a protective role against malarial parasites.

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