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Chapter

Duffy Antigens and Malaria: The African Experience

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Abstract

The Duffy blood group antigen is also known as Duffy Antigen Receptor for Chemokines (DARC) serves more functions than just a blood group antigen for serological reactions. It is a receptor for pro-inflammatory chemokines and \textit{Plasmodium vivax} invasion of the red blood cells. A point mutation in the promoter region of the Duffy gene disrupts the binding of a transcription factor, leading to a lack of expression of the antigen on the erythrocytes. This Duffy negative phenotype is found predominantly in the African population. This mutation is advantageous as individuals with the Fy(a-b-) phenotype are less susceptible to \textit{P. vivax} malaria. Malaria is caused by plasmodium parasites and it is endemic in Africa, where it is one of the leading causes of morbidity and mortality. It is believed that the absence of Duffy antigen in most Africans contributed to the resistance to \textit{P. vivax} and by extension, reduced the burden of malaria in these endemic areas.

Keywords: Duffy antigen, DARC, Duffy-negative, \textit{P. vivax}, malaria, Africa

1. Introduction

The red blood cell membranes have numerous antigenic determinants—carbohydrates, proteins, or the combination of the two, the knowledge of which has been employed in immunohematology in the provision of safe blood. These inherited however, may subserve other physiological functions or be involved in many pathological conditions or disease susceptibility [1, 2].

Duffy blood group system is important in clinical medicine where it may be involved in transfusion reaction, hemolytic disease of the fetus and newborn (HDFN), and as chemokine receptors. More importantly, it determines susceptibility to \textit{Plasmodium vivax} infection. The absence of the antigens in red blood cells of Africans provides an apparent explanation for the protection against the parasite [3].

Malaria is endemic in the tropics, but the susceptibilities to infection are not the same. The African populations are largely resistant to \textit{P. vivax} and \textit{P. knowlesi} infections due to the absence of the Duffy antigen, a critical receptor in the invasion of human host red cells by these species of malaria parasite [4, 5].

This chapter serves as a synopsis of the Duffy antigen and malaria infection. It presented the history of the discovery of Duffy antigens, their gene, protein, antibodies, and functions. The selective pressure of malaria on the Duffy gene and mutation that led to a protective phenotype against the \textit{P. vivax} malaria infection in Africa were discussed.
2. Duffy blood group system

Duffy blood group was first described in 1950 by Cutbush in a multiply transfused hemophilic patient [6, 7]. The alloantibody against the antigen was designated as Fy\(^a\). The antibody was named after the patient. A year later, another antibody was described in the serum of a multiparous woman and was designated anti-Fyb. Duffy antigen maps to the long arm of chromosome 1 at position 1q22 \(\rightarrow\) q23 while the RH gene is the short arm of the same chromosome [8]. The significance of the co-location of these genes on the same chromosome is that their interaction produced the Fy\(^5\) antigen as red cell from individuals with Fy(a-b-) and the Rh\(_{null}\) phenotype lack this antigen [9].

2.1 Duffy antigen

Duffy antigen is a glycoprotein. It is also known as the Duffy antigen receptor for chemokines (DARC). It is a seven-transmembrane helix receptor with the N-terminus in the extracellular domain while the C-terminus forms the intracellular domain (Figure 1) [10]. It has a structural similarity with G-protein-coupled receptor but is not a member of this family [11, 12]. There are six known Duffy antigens—Fy\(^a\), Fy\(^b\), Fy\(^3\), Fy\(^4\), Fy\(^5\), Fy\(^6\) and four phenotypic expressions—Fy(a+b+), Fy(a+b-), Fy(a+b-), and Fy(a-b-) as shown in Tables 1 and 2 respectively. The most common antigens are Fy\(^a\) and Fy\(^b\). The Fy\(^3\) antigen results from the weak expression of Fy\(^b\), is found in whites and is due to a single mutation in the FYB gene. The Duffy null phenotype Fy(a-b-) occurs in about two-thirds of the black population, while it is rare in Caucasians. The genetic basis of this null phenotype is distinct in these populations (see genetic basis below).

Duffy antigen is a receptor for chemokines in the C-X-C class (e.g., interleukin-8 (IL-8) and C-C class (e.g., MCP-T). The physiological function of this receptor is

![Duffy glycoprotein seven-transmembrane domain structure. Amino acid changes responsible for the Fya/Fyb polymorphism, the Fy3 mutation, and Fy4 and Fy6 regions [10].](image)
to modulate the blood–tissue gradient of these cytokines during immune responses [13]. The red blood cells through the DARC receptors act as adsorption surfaces or as chemokine scavengers for inflammatory cytokines such as IL-8, thereby eliminating excess chemokines during immune responses. Duffy antigens are expressed on epithelial cells of capillary and post-capillary venules, epithelial cells of the kidney collecting ducts, lung alveoli, and Purkinje cells of the cerebellum.

### 2.2 Duffy antibodies

The Duffy antibodies are rarely naturally occurring. Anti-Fy\(^a\) and anti-Fy\(^b\) are IgG antibodies in the IgG1 subclass [14]. They result from sensitization after transfusion or pregnancy. Anti-Fy\(^a\) is more frequently encountered than Anti-Fy\(^b\). In the black population with Fy(a-b-) phenotype anti-Fy\(^a\) is produced but not anti-Fy\(^b\). Contrastingly, white individuals with rare Fy(a-b-) produce anti-Fy\(^a\). Anti-Fy\(^3\), -Fy\(^4\), -Fy\(^5\), have been described but no human anti-Fy\(^6\) has been identified but a mouse monoclonal antibody has been raised against Fy\(^6\) epitope.

### 3. Genetic basis and biochemistry of Duffy antigen

The gene, ACKR1 also known as DARC or FY, that encodes the Duffy blood group antigens is located at chromosome 1q23.2. The two allelic forms FYA and FYB differ by a single nucleotide at position c.125G\(\rightarrow\)A and define the Fy(a-b-), Fy(a-b+), and Fy(a+b+). The gene products differ by a single amino acid at residue...
42—glycine and aspartic acid respectively [3]. The Fy(a-b-) phenotypes (Duffy negative) seen in many Africans, African Americans, and some European and Asians result from two genetic mechanisms. The most common mutation occurs in the promoter region of the FYB allele, where a point mutation c.1-67T>C prevents expression of the antigen on the red blood cells but allows expression on other tissues. This is an erythroid-specific mutation and it is commoner in Africans. A similar mutation has been found FYA allele but, it is rarer [8].

In Europeans and Asians, Fy(a-b-) phenotype arises from a mutation in the coding region (a point mutation introduces a premature stop codon) of the FYA or FYB allele preventing the antigen expression in all tissues. These are true Duffy null phenotypes.

4. Malaria

Malaria remains a major public health problem in tropical and subtropical areas of the world. It is one of the major causes of childhood mortality and an indirect cause of maternal mortality [15].

It is a mosquito-borne disease. The parasite responsible for malaria belongs to the genus *Plasmodium*. The most common species causing human infections include *P. falciparum* which causes malignant tertian malaria, *P. vivax*, benign tertian malaria, *P. ovale* benign tertian, *P. malariae* benign quartan and *P. knowlesi* quotidian malaria. The lifecycle of the *Plasmodium* spp. is complex with the sexual phase occurring in the mosquito vector (*Anopheles* genus) and the asexual phase in the human host [16]. Infected female *Anopheles* mosquitoes inject sporozoites into the human host during a blood meal. The sporozoites gain access to the hepatocytes within 30–60 min where they form merozoites through asexual reproduction. These merozoites are released into the bloodstream where they parasitize and replicate with the red blood cells (erythrocytic schizogony). Some merozoites differentiate into male and female gametocytes that are ingested by the mosquitoes in the next blood meal. The gametocytes produce sporozoites to continue the cycle [17].

The severity of *Plasmodium* infection depends on the species and the host immunity which is the function of previous exposures [17]. *P. vivax* infection usually causes uncomplicated malaria, although severe forms have been reported while *P. falciparum* causes severe malaria. Malaria infection usually presents with fever, abdominal discomfort, headache, joint aches, muscle aches, abdominal discomfort, vomiting, lethargy, anorexia [18]. One of the defining characteristics of *P. vivax* infection is the dormant liver stage (hypnozoites) it forms which reactivates weeks to months after initial infection [19]. Malaria infection is associated with complications such as splenomegaly, thrombocytopenia, derangements in liver enzymes such as raised alanine aminotransferase (ALT), jaundice, renal failure, ARDS, and cerebral malaria [20]. Although *P. vivax* infection is generally benign, it could have these complications similar to *P. falciparum* malaria.

4.1 Epidemiology

*Plasmodium falciparum* and *P. vivax* are the most common causes of malaria accounting for an estimated 229 million cases in 2019 in 87 endemic countries. Of these cases, 97% are found in Africa especially in sub-Saharan (SSA), and estimated malaria-related deaths of 409,000. Most of these deaths are in Africa, with children aged under 5 being disproportionately affected [15]. The most prevalent *Plasmodium* parasite outside Africa is *P. vivax* responsible for about 6 million cases [21, 22]. *P. vivax* is the most widely distributed plasmodium species putting over
4 billion people at risk of infection. Transmission has been reported in the Horn of Africa, Central and South American, Asia, and Pacific Islands [19]. The largest burden of *P. vivax* malaria occurs in the Indian subcontinent and the horn of Africa. The sub-Saharan Africa has a very low prevalence (Figure 2) [23].

Due to the high prevalence of Duffy negative phenotype in the sub-Saharan African, (SSA) there is a relative absence of *P. vivax* malaria infection. However, evidence is accumulating that there are *P. vivax* malaria infections in SSA occurring at lower prevalence [21, 24]. A prevalence of 2.9% was found in a nationwide survey in the Democratic Republic of Congo [21], a seroprevalence of 15.2% was found in Beninese blood donors [25].

### 4.2 Malaria adaptation and selective pressure

Malaria is known to be a major driving force in evolutionary selection in the human genome [26, 27]. The ethnic differences in susceptibility to malaria infection, the protective effects of G6PD deficiency, thalassemia, and hemoglobin C on severe malaria infection have been linked to this selective pressure. Malaria may also modulate genes involved in immunity inflammation, cell adhesion [26]. There is a strong correlation between the prevalence of negative FY A and FYB alleles, consequently the absence of the Duffy antigens on the endemicity for *P. vivax*. The Duffy negative phenotype was found to be due to a single nucleotide polymorphism in the promoter region leading to disruption of the binding site for GATA-1 erythroid transcription factor and resistance to *P. vivax* invasion of erythrocytes [28]. GATA-1 is one of the nuclear transcription factors in the GATA hemopoietic subfamily. It contributes to erythroid commitment and differentiation [29]. GATA-1 recognizes and binds to GATA consensus binding motif on the Duffy gene. As demonstrated by Tournamille et al., a point mutation on the DARC promoter (CTTATCT → CTTACCT) affects the interaction with the transcription factor [28]. This single nucleotide change from T to C found only in the Duffy-negative genome abolishes or disrupts the binding of GATA-1 to the DARC promoter leading to the absence of Duffy antigen on their red cell membranes [30].

### 4.3 Mechanism of *P. vivax* invasion of red blood cells

Malaria parasites exhibit different red cell tropisms. *P. vivax* merozoites preferentially bind to reticulocytes than normocytes. The invasion of red blood cells by *P. vivax* depends on the membrane glycoprotein of the Duffy blood group system.
The *P. vivax* merozoites express a protein on their surface, *P. vivax* binding protein (PvDBP) through which they interact with the Duffy antigen [31]. The PvDBP is a 140KD protein with a 330-amino acid cysteine-rich region responsible for this interaction. The merozoite of *P. vivax* is able to re-orient its apical surface in apposition to both Duffy-positive and Duffy-negative red cell membranes [32, 33].

Figure 3.
Overview of *P. vivax* merozoite interaction with the human red blood cell. Red blood cells without the Duffy antigen are resistant to invasion by *P. vivax* [31].

Figure 4.
Duffy glycoprotein showing different interaction sites for the *P. vivax* and the chemokines [11].
However, the tight junction is not formed between the merozoite and the Duffy-negative red blood cells, suggesting that the Duffy antigen is necessary for the invasion of the red blood cells by the parasite (Figure 3) [31]. Consequently, Duffy-negative erythrocytes do not bind to \( P. vivax \) merozoites [34]. Unlike \( P. falciparum \) which uses a series of receptors to invade the red cells, \( P. vivax \) requires the antigens of the Duffy blood system to invade the red blood cells (Figure 4) [11]. Thus, in African populations where most have the Fy(a-b-) phenotype, invasion is uncommon. Recently, however, invasion of red cells has been reported in Duffy negative individuals, this suggests that there may be other targets used by the parasite [35]. Susceptibility to \( P. vivax \) infection has also been shown to exhibit a dosage effect. This means that there are twice as many Fy\(^a\) antigens on RBCs from an individual who is homozygous for the Fya allele than on RBCs from an individual who is heterozygous. Consequently, in some populations, carriers of the Fy(a-b+) or Fy(a+b-) have half of the Duffy antigen and reduced ability for their red blood cells to be infected by \( P. vivax \) [36]. The implication of \( P. vivax \) preference of parasitizing reticulocytes is that in African populations, where sickle cell anemia and glucose-6-phosphate dehydrogenase deficiency are endemic, and reticulocytosis is a common finding in these disorders due to recurrent hemolytic anemia, a \( P. vivax \) infection would have been added burden to the mortality and morbidity already caused by \( P. falciparum \).

5. Conclusion

Earlier discoveries of the red cell antigens and their antibodies helped provide safe blood for transfusion. In addition to its roles in transfusion medicine, Duffy antigen acts as a receptor for the \( P. vivax \) malaria parasite and as a receptor for chemokines. The fortuitous mutation that resulted in less susceptibility to the parasite in the African population led to relieving the burdens that would have resulted in synergistic infection with \( P. falciparum \) infection which already cause significant mortality and morbidity.

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Conflict of interest

The author declares no conflict of interest.
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