Malaria is still a serious mosquito-borne disease in many tropical and sub-tropical countries. Human malaria is caused by five different species of the phylum Apicomplexa, genus *Plasmodium* including *P. falciparum*, *P. malariae*, *P. ovale*, *P. vivax* and *P. knowlesi*. Malaria is spread through the bite of infected female *Anopheles* mosquitoes. The life cycle of the malaria is complicated and involved with two hosts including human and mosquitoes. In human, two cell types are infected that are hepatocytes and red blood cells (RBCs). The sporozoites enter the liver and infect hepatocytes and then release the merozoites into the blood vessels. Inside the infected red blood cells, the parasites develop into several stages (ring, trophozoite, schizont and gametocyte). The crucial process of red blood cell infection is the receptor-ligand binding between the molecules on merozoites and red blood cells. The merozoites of the individual species employ the unique receptor-ligand interactions to invade RBCs, i.e. Band 3MSP1 complex, DARCs-DBP. Some of the receptors for merozoite protein being blood group antigens. Nowadays, we have more evidence and reports on three major blood group systems are known to be associated with malaria, i.e. Duffy, Knops and ABO blood group systems. However, the evidence at the molecular level is still limited. Duffy blood group antigens show the strongest association with the malarial infection through their ability to bind with *P. vivax* merozoite protein. Knops and ABO blood groups are thought to be involved with the formation of rosetting in severe *P. falciparum* infection. In this article we describe the basic structures of the three blood group systems (Duffy, Knops and ABO) and the interaction between malarial proteins (ligand) and proteins on RBCs (receptors). Moreover, we summarize the related studies on the correlation between the blood group antigens and malarial infection in the last decade to support our understanding about the association between human blood groups and malaria.

**Duffy blood group system**

The Duffy blood group system consists of five antigens: two major antigens; Fy^a^ and Fy^b^, and three minor antigens; Fy^3^, Fy^5^ and Fy^6^. Four phenotypes include: Fy(a+b+), Fy(a+b−), Fy(a−b+) and Fy(a−b−), encoded by several sets of FY alleles. The polymorphism of Fy^a^ and Fy^b^ is caused by an amino acid substitution at position 42 (Gly→Asp), while Fy− is caused by a single base change (T→C) at position -33 in the promoter region, resulting in Duffy gene suppression on RBCs, but not affecting other cell types. The Duffy antigens are transmembrane proteins consisting with seven hydrophobic segments with glycosylation in the extracellular loop, extracellular N- and intracellular C-terminal ends (Figure 1). This antigen provides the receptor on RBCs for the malarial infection, especially *P. vivax* infection. The interaction between Duffy blood group and *P. vivax* infection is the most well-known example of a blood group affecting malarial infection. Nowadays, research on Duffy blood group antigens and *P. vivax* influence our understanding of how malaria interacts with human RBCs at the molecular level. There are two important molecules involved in the invasion of human RBCs by *P. vivax*: 1) Duffy blood group antigen as a receptor on RBCs and 2) *P. vivax* Duffy binding protein (PvDBP) as a ligand on the surface of merozoites.

The distribution of the Duffy blood group phenotypes has shown that the Fy^a^ antigen is common among...
Asians, including the Thai population, while the Fy\textsuperscript{b} antigen is more frequent in Caucasians, and the Duffy-negative phenotype is more common in the Black population\textsuperscript{4-5} (Table 1). In Africa, a low prevalence of \textit{P. vivax} infection was observed due to the high prevalence of Duffy-negative phenotype. Tropical and subtropical areas, including in Thailand, are endemic for \textit{P. vivax} infection due to the high prevalence of Duffy positive people.\textsuperscript{6} These different frequencies could be explained by the fact that the Duffy blood group antigens serve as receptors for \textit{P. vivax} merozoite protein and chemokines (known as Duffy Antigen Receptor for Chemokines, DARCs). DARCs are transmembrane glycoproteins of 236 amino acids consisting of seven transmembrane regions a with large extracellular N-terminal domain, which contains the binding site for \textit{P. vivax} protein named “\textit{P. vivax} Duffy binding protein (PvDBP)”, between amino acids 8 and 42.\textsuperscript{4,7}

### Table 1  Duffy phenotypes and population frequency\textsuperscript{4-6}

<table>
<thead>
<tr>
<th>Phenotypes</th>
<th>USA Whites</th>
<th>USA Blacks</th>
<th>Africa</th>
<th>Brazil</th>
<th>China</th>
<th>India</th>
<th>Thailand</th>
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</thead>
<tbody>
<tr>
<td>Fy(a+b+)</td>
<td>49</td>
<td>1</td>
<td>&lt; 1</td>
<td>27</td>
<td>7</td>
<td>4.5</td>
<td>20.5</td>
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<tr>
<td>Fy(a+b-)</td>
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<td>3</td>
<td>33</td>
<td>93</td>
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<tr>
<td>Fy(a-b+)</td>
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<td>22</td>
<td>8</td>
<td>35</td>
<td>&lt; 1</td>
<td>12.3</td>
<td>1</td>
</tr>
<tr>
<td>Fy(a-b-)</td>
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<td>68</td>
<td>89</td>
<td>5</td>
<td>0</td>
<td>0.3</td>
<td>0.5</td>
</tr>
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</table>

*Figure 1  Schematic structures of ABO, Knops, and Duffy blood group antigens*

\textbf{P. vivax Duffy binding protein (PvDBP)}

PvDBP is a merozoite surface protein of 140 kDa located in the micronemes of \textit{P. vivax}, and is used to invade RBCs. PvDBP belongs to the Duffy binding-like erythrocyte-binding protein (DBL-EBP) family. The PvDBP ligand domain (DBPII) is a conserved cysteine-rich domain of 330 amino acids containing 12 conserved cysteine residues. Cysteines at positions 4-7 are critical for binding to DARCs on human RBCs.\textsuperscript{8,9}

**Receptor–ligand interaction between DARCs and PvDBP**

The initiation of receptor-ligand interaction starts when the N-terminal end of DARCs binds to the cysteine residues of DBPII. The binding of DARCs and DBPII induces dimerization of DBPII which promotes heterotramer (1 DARCs: 2 DBPII) formation that subsequently induces the formation of a heterotetramer (2 DARCs: 2 DBPII) by addition of a second DARCs molecule.\textsuperscript{10}
The binding affinity of DARCs is different for each Duffy antigen. Fy\(^b\) antigen binds more efficiently than Fy\(^a\) as a result of the charge of the antigens; Fy\(^b\) is negatively charged while Fy\(^a\) is neutral and more susceptible to arylsulfatase action causing the loss of sulfate groups which are required for PvDBP binding. Furthermore, Fy\(^a\) has a higher affinity for anti-PvDBP which inhibits the binding of PVDB. Duffy-negative Fy(a-b-) persons are resistant to \(P. \text{vivax}\) invasion because they lack DARCs on RBCs.\(^{11}\)

**P. vivax Duffy-independent red cell invasion**

In the past, it was thought that \(P. \text{vivax}\) can only invade Duffy positive erythrocytes, but some studies have shown that \(P. \text{vivax}\) can also infect Duffy negative people. The case numbers of \(P. \text{vivax}\)-Duffy independent red cell invasion are increased in sub-Saharan Africa and South America where both Duffy negative and Duffy positive people live together.\(^{12-15}\)

Another ligand for \(P. \text{vivax}\) invasion, erythrocyte binding protein 2 (EBP2), was also studied. EBP2 is a \(P. \text{vivax}\) merozoite protein which binds to reticulocytes of Duffy positive RBCs and can also weakly bind to Duffy negative reticulocytes. It was proposed that EBP2 may represent a novel ligand for an alternate invasion pathway of Duffy positive reticulocytes but not for Duffy negative blood cells.\(^{16}\)

In conclusion, the alternative pathway for erythrocyte invasion of \(P. \text{vivax}\) remains unclear. Studies of receptor-ligand interaction between parasite and host molecules for Duffy-independent \(P. \text{vivax}\) invasion are still needed.

**Knops blood group system**

The Knops blood group system consists of 9 antigens, KN1-KN9. All antigens are located on the complement receptor one (CR1) protein. CR1 is a single pass transmembrane glycoprotein with extracellular N- and intracellular C-terminal ends (Figure 1). The CR1 gene encodes short consensus repeats (SCRs) of 60 amino acids and further arrangements as long homologous repeats (LHRs) which consist of 7 SCRs. There are 4 proteins with different molecular weights encoded by CR1 genes: CR1-1 (220 kDa), CR1-2 (250 kDa), CR1-3 (190kDa) and CR1-4 (280 kDa). The most common protein is CR1-1 which consists of four LHRs (A, B, C and D), and one transmembrane region with a cytoplasmic tail.\(^{17}\)

CR1s are involved with rosetting of the malarial infection by interaction between CR1 ligand on uninfected RBCs and \(P. \text{falciparum}\) erythrocyte membrane protein 1 (PfEMP1) receptor on infected RBCs. The formation of rosettes causes the obstruction of blood flow in small blood vessels associated with severe \(P. \text{falciparum}\) malaria. The null Knops phenotype RBCs (known as Helgeson RBCs) can decrease the rosetting. Furthermore, soluble recombinant CR1 protein can also inhibit rosetting.\(^{18}\)

A study in Papua New Guinea where most people express low levels of CR1 showed that the low levels of CR1 expression are associated with polymorphisms in the CR1 gene and can protect against severe \(P. \text{falciparum}\) malaria.\(^{19}\) A study in Thailand suggests that homozygotes of CR1 low density allele are at an increased risk of severe malaria.\(^{20}\) The discrepancy between these two studies may came from the level of CR1 expression, which is dependent on malaria endemicity. In low endemic areas, the correlation between low CR1 expression and severe malaria is significant while in high endemic area, high CR1 expression was associated with severe malaria.\(^{21}\)

**ABO blood group system**

The ABO blood group system consists of four common antigens: O, A, B, and AB. The ABO antigens are oligosaccharide chains attached to peripheral proteins and lipids on RBC membranes (Figure 1). The antigen A contains N-acetylgalactosamine, while antigen B contains D-galactose.

In the past, there have been several studies on statistical and survey studies on ABO blood group
antigens and \textit{P. falciparum} infection. However, no molecular evidence demonstrates a correlation between ABO blood groups and \textit{P. falciparum} infection.\textsuperscript{4} A correlation of ABO blood group antigens and severe malaria was observed. Recent studies showed that blood group O can protect against severe malaria by reducing rosette formation, whereas the others cannot.\textsuperscript{22-24} Blood groups A and B can bind to PfEMP1 on the infected RBCs via the DBL\textsubscript{a} domain and then form large rosettes. Rosetting also occurs in blood group O, but at a smaller scale compared to blood groups A and B.\textsuperscript{25} Furthermore, people with blood group A are more susceptible to severe malaria because the binding of anti-PfEMP1 antibodies is reduced due to PfEMP1 being masked by rosetting.\textsuperscript{26}

\textbf{Conclusion}

Recent studies of the correlation between the blood group systems (Duffy, ABO and Knops) and malarial infection have been summarized. Further evidence at the molecular level needs to be gathered, including: the pathway for \textit{P. vivax} Duffy-independent red cell invasion, the correlation between ABO blood group and \textit{P. falciparum} infection, and the receptor-ligand interaction in the formation of rosettes. To provide additional information, further studies between other blood group antigens and malaria should be performed.

\textbf{References}


