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Evolution and selection of human leukocyte antigen alleles by *Plasmodium falciparum* infection

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ABSTRACT

Infection by *Plasmodium falciparum* malaria was one of the major driving forces for the selection of various genes, some of which might be involved in protection against this infection. The human leukocyte antigen (HLA) system is a highly polymorphic supergene complex with extensive diversity across different populations. In areas traditionally endemic for malaria for centuries, there seems to be some selection of certain HLA alleles that may somehow be involved in protection against the infection. One of the major conundrums is the lack of homogeneity in the HLA alleles selected by *P. falciparum* across different populations. Various factors like microheterogeneity in parasite species, genetic drift in parasitic antigens, varying intensities of transmission, different polymorphisms of red cell antigens, and diversity in the HLA system have exerted selection pressure, which probably determined the emergence of different dominant HLA antigens in different endemic populations. The complex life cycle of *P. falciparum*, with different antigens becoming important at different phases of the cycle and invasion of different tissues causing different clinical manifestations of the same disease, is also another significant factor contributing to a selection pattern. Evolutionary selection pressure probably selected different HLA antigens for modulations of different components of the disease as well as the severity of the disease. A coevolution, where the parasite polymorphisms meet the host heterogeneity, is likely to have occurred, resulting in the selection of a few HLA antigens associated with *P. falciparum* infection. Data might have been overwhelmed by the noise of additional selection pressure exerted by other infectious agents prevalent in endemic areas of *P. falciparum* malaria.

1. Introduction

Plasmodium falciparum parasite is a mosaic of several antigens that undergo conformational and compositional changes during different stages of development in the host [1]. Immune response may be mounted by the host against both stage-specific antigens and antigens common to all stages. However, the specific immune response elicited by the host that is responsible for the protection or modulation of the clinical course of disease is unknown.

The identification of peptide sequences presented by human leukocyte antigens (HLA) made it possible to align these peptide structures with various *P. falciparum*-specific antigens to study the amino acid sequence homology with a particular peptide or a particular epitope of the *P. falciparum* antigen mosaic. Prima facie, this provides the information that a given peptide may be a protective immunogen against *P. falciparum* malaria infection. In other words, a specific HLA antigen selected in a given population endemic for *P. falciparum* malaria will provide strong statistical evidence that the antigen presented by the selected HLA antigen in the population is involved in the protection against severe malaria. The knowledge of peptide sequences presented by the HLA may help not only in the development of a malaria vaccine, but also in studying whether humoral or cell-mediated immunity to that peptide is globally protective or protects only against some complications of severe falciparum malaria. Malaria is becoming resistant to various drugs and the drug cost is becoming exorbitant and unaffordable. New drug discovery for malaria is not a priority for pharmaceutical industries; hence, developing a vaccine against malaria is gaining overwhelming importance. To date, our experience with a malaria vaccine remains far from satisfactory [2].

This paper provides a brief overview of different HLAs associated with severe malaria that provide some degree of protection against certain complications or reduce the severity of disease.

2. Subjects and methods

Individual studies were selected from Pubmed and Ovid databases without any time restrictions. The following search words were used: HLA antigen and malaria, HLA antigen and malaria vaccine, falciparum malaria and HLA antigen, and resistance to

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Table 1
HLA polymorphism linked to susceptibility or resistant to *P. falciparum* malaria (positive associations)

Country	HLA for susceptibility ($p < 0.05$)	Reference	HLA for resistance ($p < 0.05$)
Gambia (Africa)	—	Hill *et al.* [4]	B*53; DRB1*1302
Maharashtra (India)	—	Shankarkumar *et al.* [9]	B*53; A*2
Mumbai (India)	DRB1*0809, 04, A*3, B*27, B*49	Shankarkumar *et al.* [3]	DQB1, 0203, B*35, B*27
Thailand	B*46	Hanantachai, Stephens [5, 25]	B*56, DRB1*1001 DPB1*0501
Sardinia	—	Contu [13]	B*35
Senegal	DR*3, DR*10; DR*13 (cerebral malaria)	Ndiaye [6]	—
Papua New Guinea	DR*2 (hyperreactive spleen)	Bhatia [7]	—
New Delhi (India)	—	Mehera [14]	A*0211
New Caledonia and Melanesia	No pattern	Maitland [11]	No pattern
Vietnam	—	Busson [16]	HLA-DQ1 *0502
Malayasia	—	Hirayama [12]	B*1513

*Positive association only.

malaria and HLA antigen. The major papers were carefully studied, as well as papers available from cross-references when applicable. A total of 278 papers were evaluated for the current review. Papers published in nonindexed journals were also included in the review process if the paper included HLA data from a malaria-resistant population.

2.1. HLA polymorphisms and severe malaria

A study from Mumbai Hospital involving 171 severe *P. falciparum* cases demonstrated HLA B49 and DRb1 *0809 to be strongly associated with severe disease, whereas A19 and DQB1*0203 were significantly underrepresented compared with the control population [3]. Several other HLA antigens such as A1 and B27 were increased in these patients. HLA B53, which provided significant protection against *P. falciparum* malaria in Gambia [4], was not highly prevalent either in the control or in the affected population.

In Thai patients with severe cerebral malaria, HLA B46 was significantly increased, whereas HLA B56 and HLADR1*1001 were underrepresented [5]. In Senegal, HLADR3 and DR10 were strongly associated with cerebral malaria [6]. An association between hyperreactive malarial splenomegaly and HLA DR-2 was demonstrated in the Papua New Guinea islands [7].

Hill and colleagues [8] completed the most exhaustive study in the area of HLA gene polymorphism and resistance to *P. falciparum* malaria. In a large case–control study from Gambia, it was demonstrated that HLAB53 is strongly linked to protection against severe malaria. Detailed analysis also indicated that the protection offered is directly linked to the HLA-B53 antigen rather than any indirect effect through linkage with any other gene as a result of linkage disequilibrium [3]. A study involving tribals in Maharashtra, where malaria transmission is very common yet clinically mild, demonstrated a high prevalence of HLA B53 [9] (*i.e.*, 26.4–28.9% in two different tribes), whereas in the general population in Maharashtra HLAB53 is less prevalent (*i.e.*, 1% [$p < 0.05$]). If every population in the world in which *P. falciparum* malaria is endemic demonstrated a prevalence of HLA-B53, things would be simpler, but that is not the case, as in some of the ethnic groups in Burkina Faso (West Africa). None of the traditional factors, including HLA-B53, was associated with reduced susceptibility to malaria infection [10]. The Muong population in Vietnam is chronically exposed to malaria and demonstrates a striking presence of the HLADQ1*0502 allele (48%) [11]. HLA polymorphisms in various populations associated with significant resistance (reduced susceptibility) or susceptibility to severe infection are presented in Table 1.

2.2. HLA polymorphisms in a healthy population where falciparum malaria is endemic

Several studies exist of healthy populations from countries where falciparum malaria is endemic [12–14]. These population studies demonstrate that different HLA alleles have been selected in these populations. During the course of evolution, as a strategy of protection against severe malaria, a complex interplay of various selection processes that involves virulence of the parasite strains, parasitic antigen polymorphisms, variations of HLA polymorphisms in the population on which the selection process works, different intensities of transmission resulting from differences in vector species (for instance, *Anopheles gambiae* as one of the most efficient vectors for *P. falciparum* transmission), associated selection of major red cell protein polymorphisms providing varied levels of protection (sickle cell gene, β thalassemia gene, South Eastern ovalocytosis gene), other important blood groups, and red cell enzyme polymorphisms giving protection against severe malaria and selection as a result of other infections (see Table 3) occurs.

The following groups of population studies may provide slightly different information regarding the involvement of the HLA antigen in malaria.

i. HLA studies in the population group infected with *P. falciparum* and admitted with severe malaria (*i.e.*, hospitalized populations) may identify susceptibility alleles if a large fraction of patients demonstrates a particular allele that is otherwise rare in the population. A striking absence of an otherwise common allele in that population may also suggest that particular allele's involvement in resistance to malaria.
ii. HLA studies in communities where falciparum malaria is endemic but mortality is low will allow us to identify alleles that might have been selected for resistance to infection.
iii. Studies that correlate the titer of certain antimalarial antibodies with the presence of certain HLA alleles will shed light on the involvement of that particular HLA antigen with the humoral immune response and *in vitro* studies involving presumed resistance by conferring HLA antigen for their ability to present malaria antigen leading to a humoral or cellular response.

Table 2
HLA antigen influencing antibody titer to malaria antigen GLURP (glutamate-rich protein) [23]

Antigen	HLA class II genotype	Association of antibody response ($p < 0.05$)
GLURP-RO		
P3	HLA-DR4, -DQ8	Positive
P4	HLA-DR13	Positive
P8	HLA-DR13	Positive
P9	HLA-DR13	Positive
P10	HLA-DR8	Positive
P11	HLA-DR8, -DQ4	Positive
GLURP-R2		
S4	HLA-DR7	Negative