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Review

Mechanisms of genetically-based resistance to malaria

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ABSTRACT

Malaria remains one of the most prevalent parasitoses worldwide. About 350 to 500 million febrile episodes are observed yearly in African children alone and more than 1 million people die because of malaria each year. Multiple factors have hampered the effective control of this disease, some of which include the complex biology of the *Plasmodium* parasites, their high polymorphism and their increasingly high resistance to antimalarial drugs, mainly in endemic regions. The ancient interaction between malarial parasites and humans has led to the fixation in the population of several inherited alterations conferring protection against malaria. Some of the mechanisms underlying protection against this disease are described in this review for hemoglobin-inherited disorders (thalassemia, sickle-cell trait, HbC and HbE), erythrocyte polymorphisms (ovalocytosis and Duffy blood group), enzymopathies (G6PD deficiency and PK deficiency) and immunogenetic variants (HLA alleles, complement receptor 1, NOS2, tumor necrosis factor-α promoter and chromosome 5q31–q33 polymorphisms).

1. Introduction

Malaria is a parasitic disease transmitted by Anopheline mosquitoes and is highly widespread throughout tropical and subtropical regions. The exact magnitude of the problem still remains unknown (Carvalho et al., 2002) since this disease is most commonly found in poor countries (Olumese, 2005) having less developed health systems and control strategies (Phillips, 2001). In these areas, the high rates of morbidity and mortality can be mainly attributable to the lack of access to effective treatment (Suh et al., 2004) and to the growing parasite resistance to antimalarial drugs such as chloroquine and pyrimethamine (Smith et al., 2002). According to the World Malaria Report 2008, published by the World Health Organization and UNICEF, 3.3 billion people living in 109 countries or territories were at risk of acquiring malaria by the end of 2006. It has been calculated that 250 million clinical episodes of malaria occur each year (mainly due to *Plasmodium falciparum* and *Plasmodium vivax* infections), of which more than 1 million people die (WHO and UNICEF, 2008).

The immune response induced in humans by infection caused by malarial parasites is complex and varies depending on the level of endemicity, epidemiological factors, genetic makeup, host age, parasite stage and parasite species. Repeated infection and continuous exposure are required to achieve clinical immunity (which reduces the risk of death from malaria and reduces the intensity of the clinical symptoms) and later anti-parasitic immunity (which directly reduces the numbers of parasites in an infected individual or inhibits parasite replication) (Mohan and Stevenson, 1998). Both innate and acquired immunity processes are invoked during the infection. Resistance involves genetically-based resistance mechanisms and cell-mediated immunological mechanisms, but also specific antibodies, which are able to reduce the severity of the symptoms and mortality are found among the main actors in the acquired immune response (Smith et al., 2002).

Innate immunity can be defined as being the host cells' ability to resist infection by the parasite, irrespective of their previous exposure to it (the review by Stevenson and Riley, 2004 gives detailed information about innate immunity against malaria). Resistance mechanisms have been described in both sporozoite entry to liver cells and erythrocyte invasion by merozoites (Yuthavong and Wilairat, 1993) (Fig. 1). Genetically-based resistance is involved in either altering erythrocyte invasion by merozoites, in lowering parasite

Abbreviations: 6PGL, 6-phosphogluconolactonase; CR1, Complement receptor-1; CSF, Granulocyte-macrophage colony-stimulating factor; DARC, Duffy antigen receptor for chemokines; DBL, Duffy binding like; DBP, Duffy binding protein; G6PD, Glucose-6-phosphate dehydrogenase; HBB, Hemoglobin beta gene; HbC, Hemoglobin C; HbE, Hemoglobin E; HbF, Fetal hemoglobin; HbH, Hemoglobin H; HbS, Hemoglobin S; HE, Hereditary elliptocytosis; HLA, Human leukocyte antigen; ICs, Immune complexes; MHC, Major histocompatibility complex; NADP, Nicotinamide adenine dinucleotide phosphate; NADPH, Reduced form of NADP; NO, Nitric oxide; NOS, NO synthase; NOS2, NO synthase 2; PBMCs, Peripheral blood mononuclear cells; PEP, Phosphoenolpyruvate; Pfbi, *P. falciparum* blood infection; PfEMP-1, *P. falciparum* erythrocyte membrane protein-1; Pfil1, *P. falciparum* infection level 1; PK, Pyruvate kinase; PMM, Prior mild malaria; PSM, Prior severe malaria; SAO, Southeast Asian ovalocytosis; SCD, Sickle-cell disease; SNP, Single nucleotide polymorphism; TNF, Tumor necrosis factor.

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growth or in impairing merozoite viability after being released from schizonts (Smith et al., 2002).

Some genetic mutations resulting in protection against parasitic infection are highly prevalent in regions where malaria is endemic. According to Haldane's malaria hypothesis (Haldane, 1949; Yuthavong and Wilairat, 1993; Smith et al., 2002; Duffy and Fried, 2006; Pasvol, 2006), this could result in a "balanced polymorphism" where the homozygote's hematological disadvantage is balanced by the resistance to malaria displayed by the heterozygote (Yuthavong and Wilairat, 1993; Agarwal et al., 2000; Smith et al., 2002; Akide-Ndunge et al., 2003).

Among the main alterations conferring resistance against malaria, various blood group polymorphisms such as hemoglobinopathies (including thalassemias, HbS, HbC and HbE), erythrocyte polymorphisms and immunogenetic variants, have been observed in different populations where malaria is prevalent (Yuthavong and Wilairat, 1993; Michon et al., 2001).

This review focused on mechanisms leading to genetically-based resistance against *Plasmodium* parasites.

2. Genetically-based resistance mechanisms

2.1. Hemoglobinopathies

Although hemoglobinopathies (hemoglobin structure and production disorders) confer resistance to malaria through immune mechanisms (Luzzi et al., 1991; Roberts and Williams, 2003; Williams et al., 2005c), they are also a major worldwide health problem. These disorders have a high carrier frequency, particularly in certain regions where malaria is endemic, and are characterized by having broad clinical and hematological phenotypic heterogeneity (Patrinos et al., 2005). Thalassemias and abnormal hemoglobins (which can be grouped together as hemoglobinopathies) (Weatherall, 2008), constitute the most common single-gene disorders (Yuthavong and Wilairat, 1993).

Although it is not always clear how erythrocyte abnormalities might confer protection against malaria, the overlapping geographical distribution displayed by malaria and hemoglobinopathies (such as thalassemias) led Haldane to propose his "malaria hypothesis" (Haldane, 1949; Duffy and Fried, 2006). The relatively high prevalence of heterozygous individuals for inherited erythrocyte diseases in areas where malaria is endemic seems to have been maintained by a balanced polymorphism in the human population (Haldane, 1949; Cooke et al., 2004; Richer and Chudley, 2005).

Distinct mechanisms conferring protection against severe and complicated malaria have been proposed for the different hemoglobinopathies (such as sickle-cell trait, beta thalassemia trait, homozygous HbH, HbAS), as will be detailed below (Weatherall, 1997; Ayi et al., 2004; Williams et al., 2005b). Among the most relevant mechanisms, reduced erythrocyte invasion by the parasite, decreased intra-erythrocytic parasite growth (Pasvol et al., 1978), enhanced phagocytosis of parasite-infected erythrocytes (Cappadoro et al., 1998; Ayi et al., 2004) and increased immune response against parasite-infected erythrocytes (Duffy and Fried, 2006) have all been described.

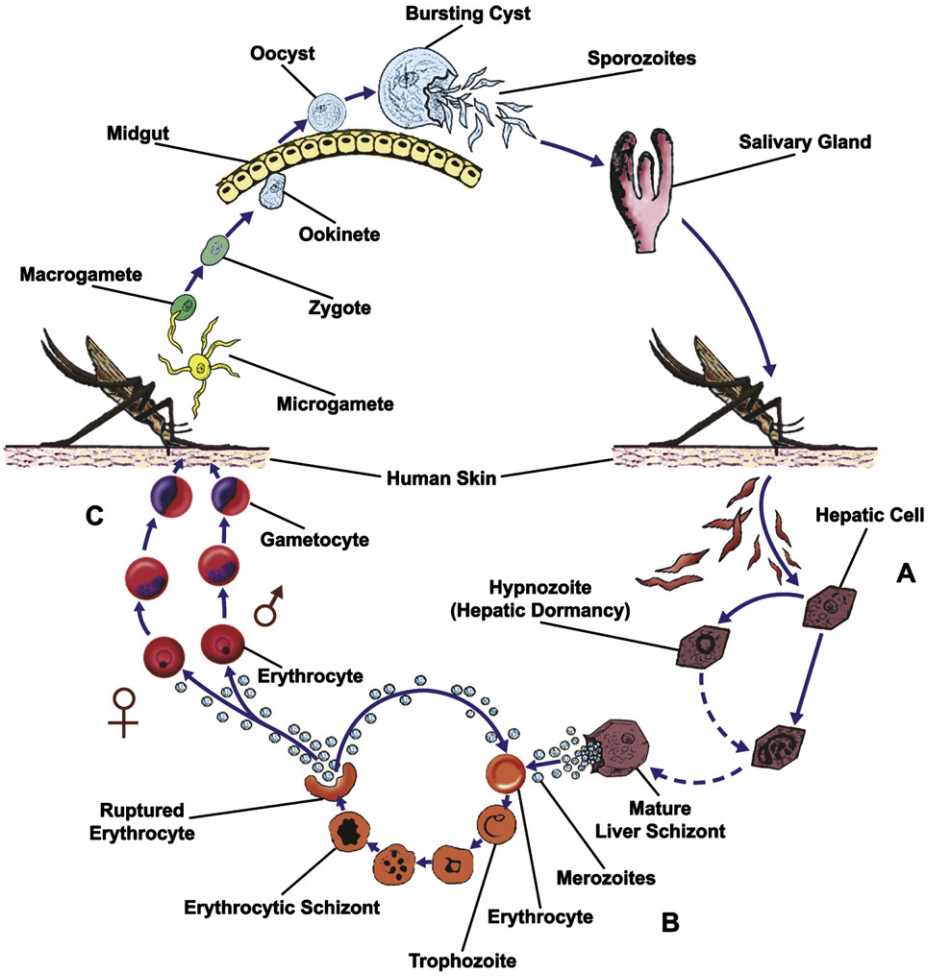

Fig. 1. Life cycle of the malaria parasite. The asexual stage pre-erythrocyte or hepatic (A) and erythrocyte (B) cycles as well as the sexual stage sporogonic (C) cycle are represented. (The hypnozoite form occurs only in *Plasmodium vivax* and *Plasmodium ovale*.)
Adapted from Oaks et al. (1991).