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Ethnic differences in susceptibility to malaria: What have we learned from immuno-epidemiological studies in West Africa?

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ABSTRACT

There are many fundamental aspects of the immunobiology of *Plasmodium falciparum* infections that are not fully understood, therefore limiting our comprehension of how people become immune to malaria and why some ethnic groups living in malaria endemic areas are less susceptible than others. The complexity of parasite–host interactions and the genetic diversity of the parasites as well as the human host complicate our strategy to address this issue.

In this mini-review we discuss and summarize what we have learned about African ethnic differences in susceptibility to malaria from immuno-epidemiological studies. Additionally, we suggest research topics that might be of great value for dissecting the mechanisms of protection by providing new insights into molecular interactions between the parasite and the host.

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1. Introduction

The outcome of an infection and its progression to pathology depends on many factors involving the specific and dynamic combination of host and parasite properties. Concerning the host, it seems likely that the ability to mount an effective immune response to *P. falciparum* infection might involve host genetic factors. It is well accepted that *P. falciparum* is an evolutionary driving force that has shaped the human genome and may select for genes that contribute to resistance (Kwiatkowski, 2005). Strikingly, this selective pressure led to the emergence of a particular population in Africa that is relatively protected against malaria.

The Fulani from Sudan and West Africa constitute a particularly interesting ethnic group because of their lower susceptibility to malaria as compared to other sympatric populations such as the Dogon in Mali (Dolo et al., 2005a), the Mossi and Rimaibé in Burkina Faso (Modiano et al., 1995a, 1996a) and the other ethnic

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groups of Darawesh village in Sudan (Creasey et al., 2004). These sympatric ethnic groups live under the same conditions of meso-endemic (Mali) or hyperendemic (Burkina Faso) transmission in the Sudanese-savannah area. Numerous studies have clearly demonstrated interethnic differences in susceptibility and in immune responses to malaria. The Fulani have lower infection rates, fewer clinical episodes and stronger humoral responses to various *P. falciparum* antigens compared to sympatric ethnic groups (Modiano et al., 1998; Farouk et al., 2005a). The higher immune reactivity to malarial antigens in the Fulani supports the notion that immunogenetic factors involved in the regulation of humoral and/or other immune responses contribute to decreased malaria susceptibility. These differences should be considered in the in the evaluation of malaria vaccines trials and the application of malaria control strategies such as drug treatment. Also, the possibility of combining inter- and intra-ethnic comparisons to characterize critical determinants of malaria immunity in natural settings may prove useful in malaria control efforts. However, we are far from a clear understanding of the mechanisms underlying ethnic differences in resistance/susceptibility to malaria. Many basic aspects of *P. falciparum* infection biology remain poorly understood, which limit our comprehension of the mechanisms involved in the acquisition of protective immunity to malaria. In this mini-review we attempt to summarize immuno-epidemiological studies that have focused on ethnic differences in susceptibility to malaria.

2. Clinical and parasitological evidence of interethnic differences in susceptibility to malaria

Epidemiological studies have clearly shown that a high degree of variation in malaria susceptibility exists between ethnic groups in Africa (Bryceson et al., 1976; Greenwood et al., 1987) including parasite load, disease incidence and severity (Greenwood et al., 1991). In particular, studies in West Africa have demonstrated that the Fulani are less susceptible to malaria compared to ethnic groups living in sympatry under the same malaria transmission and exposure conditions (Modiano et al., 1995a, 1996a; Dolo et al., 2005a). These fascinating observations have stimulated much research to dissect the environmental and genetic factors underlying the difference in susceptibility to malaria between ethnic groups.

The Fulani people are traditionally nomadic pastoral people who live across West Africa and often settle in close proximity to other ethnic groups. Several studies have demonstrated that the Fulani are less parasitized, have a higher incidence of spleen enlargement (Bereczky et al., 2006) and are less affected by malaria sickness, despite the fact that people in these areas are exposed to malaria at the same level. Moreover, it has been observed that the pyrogenic threshold of parasitemia was 1,000 parasites/μl of blood in the Dogon and 5,000 parasites/μl of blood in the Fulani (Dolo et al., 2012b) and that the Fulani present more often with symptoms of anemia than the Dogon, despite their lower susceptibility to malaria (Dolo et al., 2012c). However, the etiology of anemia in the Fulani remains unclear and needs to be explored.

3. Identification of the immune mechanisms of resistance to malaria in sympatric ethnic groups

Several studies have been conducted in Burkina Faso, Mali and Sudan to investigate the immunological basis of ethnic differences in malaria susceptibility. The higher incidence of spleen enlargement in the Fulani might reflect a hyper immune reactivity of this secondary lymphoid organ (Bereczky et al., 2006; Vafa et al., 2009a; Alkadarou et al., 2013), a hypothesis supported by several studies which consistently show that the Fulani mount a more robust humoral immune response, as reflected by increased titers of anti-plasmodial antibodies (Modiano et al., 1998, 1999; Bolad et al., 2005; Farouk et al., 2005a; Vafa et al., 2009a). The levels of malaria blood-stage antibodies anti-AMA1 and anti-MSP1 were significantly increased in Fulani, suggesting the higher specific humoral responses against AMA1 and MSP1 in this ethnic group (Dolo et al., 2012a). In addition, phenotypic analysis of the B-cell compartment by flow cytometry has shown that the malaria-resistant Fulani tend to have a higher percentage of activated memory B cells (MBCs) compared to the Dogon, and that *P. falciparum* infection in the Fulani is associated with a higher percentage of circulating plasma cells compared to the Dogon (Portugal et al., 2012).

Other studies have investigated inter-ethnic differences in cellular immune responses to malaria. It is well established that the Th1/Th2 balance (i.e. inflammatory versus anti-inflammatory) plays a crucial role in controlling parasitemia and disease during *P. falciparum* infection. Mononuclear cells obtained from Fulani showed a markedly stronger interferon-γ (IFN-γ) response to *in vitro* stimulation with *P. falciparum* infected red blood cells and this response was strongly associated with lower parasitemia (McCall et al., 2010). Additionally, the Fulani had increased numbers of specific IL-4- and IFN-γ-producing cells compared to the sympatric Dogon ethnic group (Farouk et al., 2005b). The results of studies performed in Burkina Faso also suggest that the relative resistance to malaria in the Fulani could be due in part to a functional deficit in T-regulatory cells. Specifically, the Fulani showed lower serum levels of TGF-β and higher concentrations of the proinflammatory chemokines CXCL10 and CCL22 compared to the Mossi, and moreover, the proliferative response of Fulani to malaria antigens was not affected by the depletion of $CD25^+$ regulatory cells whereas the response of the Mossi was significantly increased (Torcia et al., 2008). This functional deficit of T-regulatory cells observed in Fulani suggests that the suppressive immune response may not be controlled. This may result to an immune hyper reactivity that can often lead to immunological disorders.

Studies aiming to identify which T cells phenotypes might be involved in the proinflammatory responses have found that $CD3^+\gamma\delta^+$ T-cell subpopulations are increased in the Fulani compared to the Mossi ethnic group during the low transmission season as well as the peak of malaria transmission (Sanou et al., 2012). However, these studies did not investigate if the $CD3^+\gamma\delta^+$ T-cell subpopulations were induced by *P. falciparum* infection.

Antigen presenting-cells (APCs), through their release of specific cytokines and chemokines, can influence the development of functionally distinct T-cell responses and participate in the recruitment and activation of other effector cells, such as NK cells, monocytes, and B cells. APCs express pattern recognition receptors (PRRs) such as the toll-like receptors (TLR) that directly recognize microbial conserved products; termed pathogen-associated molecular patterns (PAMP). These PRRs recognize conserved motifs of *P. falciparum* such as glycosylphosphatidylinositol (GPI) anchors (Krishnegowda et al., 2005) hemozoin (Shio et al., 2009), CpG-containing DNA motifs bound to hemozoin (Parroche et al., 2007) and AT-rich DNA motifs (Sharma et al., 2011). Recognition of parasite PAMPs through their corresponding PRRs activates APCs and subsequently stimulates indirectly the adaptive immune response. In further studies performed in Mali, interethnic differences were observed in dendritic cell (DC) activation status upon malaria infections, and that other APCs in the blood were more matured in the Fulani than in the Dogon (Arama et al., 2011). These findings suggest that the activation of the DC subsets may trigger their migration to the spleen and other lymphoid organs and thereby account for the lower frequency of plasmacytoid (p) pDCs, and myeloid (m) DC expressing the blood-derived cell antigen (BDCA)-3+ observed in the peripheral blood of infected Fulani. The specific activation of these DC subsets observed in the Fulani, but not in the Dogon, during *P. falciparum* infection may contribute to