MINI-REVIEW

Polymorphism of the Fcγ receptor IIA and malaria morbidity

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ABSTRACT

Fc receptors (FcRs) are expressed on the surface of all types of cells of the immune system. They bind the Fc portion of immunoglobulin (Ig), thereby bridging specific antigen recognition by antibodies with cellular effector mechanisms. FcγRIIA, one of the three receptors for human IgG, is a low-affinity receptor for monomeric IgG, but binds IgG immune complexes efficiently. FcγRIIA is believed to play a major role in eliciting monocyte- and macrophage-mediated effector responses against blood-stage malaria parasites. A G → A single nucleotide polymorphism, which causes an arginine (R) to be replaced with histidine (H) at position 131, defines two allotypes which differ in their avidity for complexed human IgG2 and IgG3. Because FcγRIIA-H131 is the only FcγR allotype which interacts efficiently with human IgG2, this polymorphism may determine whether parasite-specific IgG2 may or may not elicit cooperation with cellular immune responses during blood-stage malaria infection. Here, we review data from four published case-control studies describing associations between FcγRIIA R/H131 polymorphism and malaria-related outcomes and discuss possible reasons for some incongruities found in these available results.

KEYWORDS: Malaria, Fc receptors, polymorphism, IgG subclasses, case-control studies

INTRODUCTION

Fc receptors (FcRs) belong to the family of immunoreceptors, which includes T-cell receptors, B-cell receptors and natural killer (NK) receptors. These glycoproteins are expressed on the surface of all types of cells of the immune system; they bind the Fc portion of immunoglobulin (Ig), thereby bridging specific antigen recognition by antibodies with cellular effector mechanisms. The FcRs are essential molecules in the host defense against infection. Interaction between antibodies of a given class and the corresponding FcR elicits a variety of cellular responses, such as phagocytosis and endocytosis, antibody-dependent cell-mediated cytotoxicity (ADCC), generation of superoxide radicals and release of pro-inflammatory cytokines (Fleisch and Neppert, 2000). Specific FcRs are known for each class of human Ig, but FcγRI (CD64), FcγRII (CD32), FcγRIII (CD16) and FcεRI form a subset of more closely related molecules within the immunoglobulin superfamily (Kinet, 1999; Ravetch and Bolland, 2001; Monteiro and van der Winckel, 2003).

The three classes of human FcγRs comprise several isoforms (FcγRIA, -B and -C; FcγRIIA, -B and -C, and FcγRIIIA and -B), which differ in their binding affinity to different human IgG subclasses and levels of expression on different cell types. The low-affinity isoforms (FcγRIIA, -IIB, -IIC, -IIIA and -IIIB) co-localize to a region on chromosome 1q23 which includes the genes coding for C-reactive protein, a family of FcR homologues and the Duffy blood group (Su et al, 2002). Members of the FcγRII class differ from those of other FcγR classes in
that they comprise either activitory (ITAM) or inhibitory (ITIM) signaling motifs within their respective ligand-binding chains (Gessner et al, 1998). FcγRIIA is a low-affinity receptor for monomeric IgG (K<sub>A</sub> < 10<sup>-7</sup>M), but binds IgG immune complexes efficiently. It is the most widely distributed FcγR isofrom, being expressed on the surface of virtually all myeloid cells, including mononuclear phagocytes, neutrophils and platelets. This receptor plays critical roles in the removal of immune complexes, activation of inflammatory cells and phagocytosis of antibody-coated microorganisms (Ravetch and Bolland, 2001).

**FcγRIIA polymorphism**

FcγRIIA displays a functionally relevant G → A single nucleotide polymorphism in the region encoding its ligand-binding domain, which causes an arginine (R) to be replaced with histidine (H) at position 131 of its extracellular domain. Both allotypes avidly bind complexed human IgG<sub>2</sub> and IgG<sub>4</sub>, but the FcγRIIA-H131 allotype displays a higher affinity for human IgG<sub>2</sub> and IgG<sub>4</sub> than the FcγRIIA-R131 allotype; none of them bind IgG<sub>1</sub> efficiently. Because FcγRIIA-H131 is the only FcγR which interacts efficiently with human IgG<sub>2</sub> and IgG<sub>4</sub>, this allotype is essential for the clearance of IgG<sub>2</sub>-containing immune complexes (Salmon et al, 1996) and phagocytosis of IgG<sub>2</sub>-opsonised microorganisms (Sanders et al, 1995). As a consequence, the FcγRIIA-R/H131 polymorphism is associated with predisposition to autoimmune diseases such as systemic lupus erythematosus and antiphospholipid syndrome, which may be mediated by the deposition of IgG<sub>2</sub>-containing immune complexes (Karassa et al, 2004), and infections caused by encapsulated bacteria, whose clearance largely depends on IgG<sub>2</sub>-mediated phagocytosis (Rodriguez et al, 1999; Jansen et al, 1999). A second polymorphic site has been described in FcγRIIA: a CA → GA mutation results in glutamine or tryptophan in its membrane-distal Ig-like domain. This amino acid replacement, however, does not affect the receptor avidity for IgG (Warmerdam et al, 1990).

The distribution of the FcγRIIA-H131 and -R131 allotypes vary widely among ethnic groups. H131/H131 homozygotes are more frequent among Eastern Asians than Caucasians (Lehrnbecher et al, 1999), being rare in Amazonian Amerindians (Kuwan et al, 2000). Differences in allotype frequencies of FcγRIIA-H131 and other linked genes are believed to account for the variation in the prevalence of some autoimmune and infectious diseases among ethnic groups.

**IgG subclasses and naturally acquired immunity to malaria**

Malaria parasites are major human pathogens associated with 300-500 million clinical cases worldwide and 0.5-3 million deaths each year, mostly among children under the age of five years living in sub-Saharan Africa (Guerin et al, 2002). Human malaria is caused by four species of parasitic protozoa of the genus *Plasmodium*: *P. falciparum*, *P. vivax*, *P. malariae* and *P. ovale*. The natural history of infection with *P. falciparum*, that causes most severe infections and nearly all malaria-related deaths, has been well characterised in areas of high endemicity in Africa (Day and Marsh, 1991). Infants have a primary malaria attack during their first year of life, while most toddlers and juveniles have already developed tolerance against severe disease, but still experience a few clinical episodes. African adolescents and adults, in contrast, are often clinically immune; they remain free of malaria symptoms despite continuous exposure to the parasite, but maintain low-grade infections throughout the transmission season. Clinical immunity is usually lost during pregnancy, especially among primigravidae, or after migration to non-endemic areas. Life-long exposure to malaria parasites rarely leads to sterile immunity; blood-stage infections remain detectable by sensitive methods in all age groups.

The acquisition of immunity to blood-stage malaria parasites, after several years of continuous exposure to intense transmission, depends on both antibody- and cell-mediated mechanisms. The gradual switch towards Igs of both IgG<sub>1</sub> and IgG<sub>3</sub> subclasses, which bind efficiently to all classes and isoforms of FcγR present on the surface of effector cells such as monocytes, macrophages and neutrophils, is believed to play a key role in this process. The binding of cytophilic antibodies to effector cells triggers parasite-killing effector responses, such as opsonisation and phagocytosis of extracellular parasites or parasitised red blood cells (pRBC) (Ferrante et al, 1990; Groux and Gysin, 1990) and the ADCC-like mechanism known as antibody-dependent cellular inhibition (ADCI) of intracellular parasites (Bouharoun-Tayoun et al, 1990) (Figure 1). Since both ADCI and the opsonising effect of cytophilic antibodies are competitively inhibited, *in vitro*, by non-cytophilic IgG<sub>1</sub> and IgG<sub>4</sub> antibodies with the same specificities (Groux and Gysin, 1990; Bouharoun-Tayoun and Druilhe, 1992), the subclass balance may be a decisive factor in naturally acquired immunity to malaria: protected and unprotected subjects could be differentiated by the relative levels of cytophilic antibodies recognising parasite antigens (Bouharoun-Tayoun and Druilhe, 1992; Ferreira et al, 1996).

Because ADCI is known to be mediated by FcγRII (but not FcγRI) on the surface of monocytes (Bouharoun-Tayoun et al, 1995), FcγRII polymorphisms that alter the affinity of this receptor for some IgG subclasses are expected to modulate the efficiency of monocyte-mediated parasite killing. Non-immune or partially immune subjects, for example, tend to produce predominantly IgG antibodies of the IgG<sub>2</sub> subclass during acute malaria infections (Wahlgren et al, 1983; Ferreira et al, 1996), and this subclass bias has been associated with poor clinical immunity (Bouharoun-Tayoun and Druilhe, 1992). Although often regarded as blocking antibodies (Groux and Gysin, 1990; Bouharoun-Tayoun and Druilhe, 1992), these specific IgG<sub>2</sub> antibodies might elicit both ADCI and phagocytosis by engaging effector cells carrying the FcγRIIA-H131 allotype (Aucan et al, 2000).
Figure 1. Antibody-dependent cellular mechanisms involved in Plasmodium falciparum blood stage killing. (A) Classical phagocytosis of parasitised red blood cells (pRBC). (B) Antibody-dependent cellular inhibition (ADCI). ADCI is an ADCC-like effect which inhibits the growth of young asexual blood stages within erythrocytes through the release of soluble factors (such as tumour necrosis factor [TNF]-α and interferon [IFN]-γ) by monocytes (MN). This mechanism is triggered by the recognition of merozoite surface antigens by IgG, which interacts with MN via their FcγRIIA receptors. Panel B adapted from Druilhe and Pérignon (1997).

More than 70% of the African-American subjects so far typed are either homozygous or heterozygous for the H131 allele (Lehrnbecher et al., 1999); quite similar H131 allele frequencies have been found in malaria-exposed African populations (Aucan et al., 2000; Shi et al., 2001; Cooke et al., 2003; Brouwer et al., 2004). An FcγRIIA with increased affinity for human IgG₂ and IgG₃, in subjects carrying the H131 allele, implies that FcγRIIA-dependent parasite-killing responses might be more efficiently elicited by specific antibodies of these subclasses. Accordingly, FcγRIIA-mediated phagocytosis in vitro, following pRBC opsonisation with IgG₂, is more efficient in human monocytes of the H131 allotype than in those of the R131 allotype (Tebo et al., 2002). Even more evident differences between FcγRIIA allotypes are expected in relation to IgG₂-mediated protection. In fact, IgG₂ antibodies to surface malarial antigens confer significant protection against blood-stage infection and clinical disease in subjects carrying the H131 allele, but not in R131/R131 homozygotes (Aucan et al., 2000). If H131 allele carriers acquire IgG₂-mediated protection from blood-stage infection before the exposure-dependent switch to specific
antibodies of the IgG\textsubscript{1} and IgG\textsubscript{3} subclasses takes place, the Fc\textgamma RI	extsubscript{IA}-H131 allotype may be associated with a faster development of clinical immunity leading to reduced malaria morbidity in these subjects.

Accordingly, in a recent cross-sectional survey in Brazil we found higher levels of IgG\textsubscript{2} subclass antibodies to locally prevalent variants of the major malaria-vaccine candidate antigen, merozoite surface protein-2 (MSP-2), among asymptomatic carriers of \textit{P. falciparum} than in subjects with symptomatic malaria episodes due to the same species. Antibodies of all other IgG subclasses were found in similar concentrations in both clinical groups. Because of the high H131 allele frequency in the local population (83%), IgG\textsubscript{2} antibodies to surface malaria antigens may help in triggering cell-mediated immunity to blood-stage parasites, via the Fc\textgamma RI	extsubscript{IA}-H131 allotype, in the majority of these subjects (Scopel KKG and Braga EM, in preparation).

**Fc\textgamma RI	extsubscript{IA}-H131 allotype and malaria morbidity**

Four published case-control studies have examined the association between H/R131 Fc\textgamma RI	extsubscript{A} polymorphism and malaria morbidity in African and East-Asian populations (Table 1). Since different malaria-related outcomes were evaluated (high-density \textit{P. falciparum} parasitaemia, severe malaria in children or adolescents and adults and placental malaria) in different ethnic and age groups, these studies are not strictly comparable. Significantly, however, none of them reported an association between Fc\textgamma RI	extsubscript{IA}-H131 allotype carriage and protection from malaria morbidity, as it could be expected on the basis of a putative IgG\textsubscript{2}-mediated protection against blood-stage parasites (Aucan et al, 2000). In contrast, R131/R131 homozygosity was associated with protection against high-density parasitaemia in one study (Shi et al, 2001) and H131/H131 homozygosity was associated with increased risk of either severe/cerebral malaria or placental malaria in three studies (Omi et al, 2002; Cooke et al, 2003; Brouwer et al, 2004).

| Country | Comparison groups | Main findings | Reference |
|---------|------------------|---------------|-----------|
| Kenya   | High-risk\textsuperscript{a} (n = 97) and low-risk\textsuperscript{b} (n = 85) infants aged 1 year | Significant excess of R131/R131 homozygotes in the low risk group, when compared to H131/R131 heterozygotes; similar proportions of H131/H131 homozygotes in both groups | Shi et al, 2001 |
| Thailand| Patients aged > 13 years (mean, 25 years) with either cerebral malaria (n = 107), non cerebral severe malaria (n = 157) or mild malaria (n = 202) | Significant excess of H131/H131 homozygotes carrying the Fc\textgamma RI	extsubscript{IB}-NA2 allotype\textsuperscript{c} among cerebral malaria patients, when compared to mild malaria controls | Omi et al, 2002 |
| Gambia  | Children aged 0-10 years with either severe (n = 524) or mild malaria (n = 333) and non-infected controls (n = 558) | Significant excess of H131/H131 homozygotes among severe malaria patients, when compared to non-infected controls | Cooke et al, 2003 |
| Kenya   | Pregnant women, either HIV-1 positive (n = 658) or not (n = 245), with (n = 285) or without (n = 618) placental malaria\textsuperscript{d} at delivery | Significant excess of H131/H131 homozygotes among HIV-1-positive women (but not among HIV-1-negative women) with placental malaria; similar proportions of R131/R131 homozygotes in both groups | Brouwer et al, 2004 |

\textsuperscript{a}High-risk infants had \textgeq 30\% of routine monthly blood smears positive for \textit{Plasmodium falciparum} (parasite counts \textgeq 5000 parasites per microlitre) over their first year of life.

\textsuperscript{b}Low-risk infants had \textleq 8\% of routine monthly blood smears positive for \textit{Plasmodium falciparum} (parasite counts \textgeq 5000 parasites per microlitre) over their first year of life.

\textsuperscript{c}The Fc\textgamma RI	extsubscript{IB}-NA2 allotype reduces the capacity for phagocytosis in neutrophils, when compared to the Fc\textgamma RI	extsubscript{IB}-NA1 allotype (Salmon et al, 1990). The authors report no significant independent association between Fc\textgamma RI	extsubscript{A} or Fc\textgamma RI	extsubscript{IB} allotypes and cerebral malaria; a significant association only emerged when the simultaneous carriage of H131 and NA2 alleles was considered.

\textsuperscript{d}Placental malaria was defined as the presence of malaria parasites in blood samples obtained, at delivery, from a shallow incision on the maternal side of the placenta.

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Therefore, H131/H131 homozygosity emerged as a risk factor for malaria morbidity in three different populations, and R131/R131 homozygosity was associated with protection from high-density parasitaemia in one population. These unexpected findings could be tentatively explained as a consequence of an increased activation of the immune system, due to the engagement of FcγRIIA-H131 by a broader repertoire of IgG subclasses, leading to the release of large amounts of pro-inflammatory cytokines and therefore to immunopathology and disease (Cooke et al, 2003). High frequencies of the H131 allele could have been maintained in malaria-exposed African populations as a result of a delicate balance between negative selection (due to the increased risk of severe malaria) and positive selection (due to reduced morbidity and mortality from infections with encapsulated bacteria) (Cooke et al, 2003). Alternatively, this may represent a spurious causal association resulting from linkage disequilibrium between the FcγRIIA-H131 allotype and other genetic determinants of malaria morbidity.

Further speculations are limited by the lack of more appropriate data. No longitudinal study, for example, has so far examined the combined effects of H/R131 FcγRIIA polymorphism and levels of IgG subclasses, leading to the release of large amounts of pro-inflammatory cytokines and therefore to immunopathology and disease (Cooke et al, 2003). High frequencies of the H131 allele could have been maintained in malaria-exposed African populations as a result of a delicate balance between negative selection (due to the increased risk of severe malaria) and positive selection (due to reduced morbidity and mortality from infections with encapsulated bacteria) (Cooke et al, 2003). Alternatively, this may represent a spurious causal association resulting from linkage disequilibrium between the FcγRIIA-H131 allotype and other genetic determinants of malaria morbidity.

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STATEMENT OF COMPETING INTERESTS

The authors declared no competing interests.

LIST OF ABBREVIATIONS

ADCC: antibody-dependent cell-mediated cytotoxicity
ADCI: antibody-dependent cellular inhibition
FcR: Fc receptor
FcE: receptor for immunoglobulin E Fc
FcγR: receptor for immunoglobulin G Fc
H: histidine
Ig: immunoglobulin
NK: natural killer
pRBC: parasitised red blood cells
R: arginine

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