

## Malaria in pregnancy: getting to grips with a sticky problem

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### SUMMARY

**In malaria-endemic areas, by young adulthood people have developed functional immunity to malaria. However, during pregnancy this immunity is breached and infection occurs, leading to increased risks for mother and child. In the past this effect has been attributed to nonspecific immunosuppression, but recent research has revealed a specific pathogenic mechanism, involving the adherence of rare parasite variants to the placenta. This commentary explores the current state of research in this area and proposes a model of immune evasion and placental colonization. This model points the way to the development of future therapeutic interventions.**

### Introduction

Each year, tens of millions of women are exposed to the risk of maternal malaria, an infection that leads to intrauterine growth restriction, low birthweight and high levels of infant mortality (1). In the coastal areas of Papua New Guinea (PNG), year-round exposure to malaria leads to the acquisition of functional immunity, and women of childbearing age rarely exhibit symptomatic disease. However, during pregnancy their immunity appears to be compromised and malaria is common. Though severe disease in the mother is rare (2), up to 40% of low-birthweight babies in malaria-endemic areas in PNG can be attributed to malaria infection (3).

A characteristic feature of malaria in pregnancy is the accumulation of *Plasmodium falciparum*-infected erythrocytes in the placenta (4). The local parasite density can reach high levels, even in the absence of peripheral parasitaemia, and the parasites are typically mature forms (5). Previously the immunological explanation for the reversion to a disease-susceptible state was nonspecific local immunosuppression (6). But while immune changes undoubtedly take place (7), this is a rather vague and unsatisfactory explanation and fails to properly account for the reduction of infection in the second and subsequent pregnancies (8). In addition to

consideration of host factors, there is clearly a need to explain the targeting of the placenta by the parasite and relate this to immune evasion and immunity. Studies on the adherence of *P. falciparum* have begun to cast some light on this problem.

### Cytoadherence of *Plasmodium falciparum* in the placenta

Mature parasites are hardly ever seen in the peripheral circulation during *P. falciparum* infection. Characteristically, the parasites adhere to the endothelium of postcapillary venules and sequester in deep tissues as a normal part of the replication cycle. Although cytoadherence presumably evolved as a mechanism of immune evasion, to avoid splenic clearance, the same mechanism also confers potential pathogenicity on the parasite. Many different adhesion ligands have been identified for *P. falciparum*-infected cells and the ability of the parasite to utilize diverse ligands in the host must extend its ability to avoid clearance. Unfortunately, this versatility also extends its spectrum of pathogenicity and sequestration in the brain is a common correlate with death from cerebral malaria (9).

The syncytiotrophoblast cell layer that lines the blood spaces of the placenta represents a large area of contact between the fetus and the maternal circulation. Histological examination

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of *P. falciparum*-infected placentae show parasites to be adherent to these cells (10). On this layer there is a prominent coat of glycosaminoglycans (GAGs), including a previously recognized parasite receptor chondroitin sulphate A (CSA) (11). Field studies in western Kenya (12) discovered that placental parasite isolates frequently bound to CSA. In contrast, peripheral isolates from these women, and from non-pregnant controls, rarely bound to this receptor. The importance of CSA as a placental receptor was confirmed in further studies in Malawi (13), but these studies also identified a significant number of parasites in the placenta which did not adhere to CSA. Follow-up of this observation led to the discovery of a second important GAG receptor in the placenta, hyaluronic acid (HA) (14).

Recently, the parasite ligand that mediates adhesion to CSA has been identified as *Plasmodium falciparum* erythrocyte membrane protein 1 (PfEMP1) (15). This is a high molecular weight, highly variable, parasite-derived protein that is associated with knob-like structures at the erythrocyte surface (16). Forms of this protein had already been associated with adherence to CD36 and ICAM-1 (17), so this discovery was not entirely surprising, but the relationship of PfEMP1 to acquired immunity starts to offer an explanation for the connection between the parasite's specificity for placental GAGs and its ability to evade the pregnant woman's immune response.

### **Immune evasion and immunity to malaria in pregnancy**

Antibodies which target PfEMP1 and can cause in vitro agglutination of infected erythrocytes show a strong correlation with protection from symptomatic malaria (18). To evade this immune response the parasite has evolved a mechanism of clonal antigenic variation (19) and every generation a small number (2-3%) of variant antigenic types are produced that may not be recognized by the primary antibodies. The result is a large number of variant antigenic types in the natural parasite population (20).

It is now a generally accepted paradigm that acquisition of immunity is associated with

repeated infection and development of a wide repertoire of strain-specific agglutinating antibodies (21). This explains the frequent symptomatic infections of childhood that diminish over the first ten years of life as immunity slowly builds up. The theory was most conclusively proven in a study of Kenyan children, where it also became obvious that parasites isolated during clinical disease corresponded to gaps in each child's developing repertoire of anti-PfEMP1 antibodies (22).

Why, then, do these gaps reappear in pregnancy? A number of important observations about antibody responses arose in the Malawian studies on malaria in pregnancy (13). Firstly, there was no reduction in the pregnant woman's ability to recognize the same range of parasites as adult men, so immunosuppression was not a factor. Secondly, the serum of multigravid women agglutinated placental isolates, whereas serum from primigravidae or men did not, suggesting that a rare, pregnancy-specific, parasite variant was responsible for infection. A major study in Kenya (23) showed that not only did the agglutinating antibodies associated with protection from maternal malaria block adhesion to CSA, but that sera from multigravidae from a range of countries could block the adhesion of African parasites. This infers that the antigenic types capable of infecting the placenta are quite limited, even on a global scale.

The final piece of this puzzle is the knowledge that adherence type and antigenic type are comodulated (24), as PfEMP1 changes form. Therefore, selection for cytoadherence to a specific receptor selects for a limited range of PfEMP1 and a restricted group of antigenic types. If only a very small number of PfEMP1 types are capable of adhering to a particular receptor than there is a functional restriction on the antigenic types related to this phenotype. With this piece in place it is now possible to construct a feasible molecular model of placental infection and maternal malaria.

### **A model of the pathogenesis of malaria in pregnancy**

By childbearing age a woman in a malaria-endemic area will have been exposed to many

antigenic variants of *P. falciparum* and, whilst still susceptible to being infected, her broad range of anti-PfEMP1 antibodies will keep clinical malaria at bay. In the delicate balance of infection and its control by antibody, variants will occasionally be produced which can potentially adhere to GAGs such as CSA or HA, but as these receptors are not present in high levels the parasites will fail to get established and not induce an antibody response. When the woman first gets pregnant CSA/HA will be present in the body in large amounts, in the placenta. Now, when the rare variant is produced it will have two huge selective advantages: firstly, a receptor that it can adhere to and avoid the spleen and secondly, a novel antigenic type, which represents a chink in the armour of the antibody response. It is not surprising that such a parasite strain can establish a symptomatic infection and disturb placental function.

The immune system quickly responds to this challenge and after 2 or 3 pregnancies the gap in the antibody repertoire has been filled and the woman is not at risk in subsequent pregnancies. The speed of this response, compared to the slow accumulation of protection during childhood, gives hope that the adhesive interaction between PfEMP1 and the GAG receptors might be a good target for therapeutic intervention. As the ability to adhere to GAGs is a rare property of PfEMP1 and the functional restriction of the antigenic types is obviously quite tight, then it is possible that despite the variable nature of the protein ligand, the actual binding site might have conserved elements that could be specifically targeted in order to block adhesion. Current research is exploring the nature of the binding interaction and will hopefully confirm the feasibility of this approach in the very near future.

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