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PHENOTYPE AND ACTIVATION LEVELS OF DENDRITIC CELLS (DC) AND MONOCYTES IN PREGNANCY-ASSOCIATED MALARIA DURING A FOLLOW-UP IN BENIN

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Dendritic cells (DC) are important both in amplifying the innate immune response, and in initiating adaptive immunity and shaping the type of T helper (Th) response. Although the role of DC in immune responses to many intracellular pathogens has been delineated and research is underway to identify the mechanisms involved, relatively little is known concerning the role of DC in immunity to malaria. We evaluated the immunophenotype of antigen presenting cells (APC) in peripheral blood of pregnant Beninois women from the area of Come, southwestern Benin, where we are conducting a longitudinal prospective study of 1000 mothers. Pregnant women are enrolled ≤ 24 weeks of pregnancy and followed at each ante-natal visit until delivery. Cellular immunological assessments have been performed with samples from a subgroup of 149 women at enrolment and 106 at delivery, with or without active *Plasmodium falciparum* infection detected by a rapid diagnostic test. Immunophenotyping of APC and their level of activation (HLA-DR, CD86 expression) are being evaluated using flow cytometry. *P. falciparum* infection was associated with DC altered maturation in pregnant women, as reflected by lower frequencies of MDC and PDC and their downregulated expression of HLA-DR but not CD86, whether in early pregnancy or at delivery. DC of pregnant women with anaemia were present at low frequency during pregnancy. In conclusion, HLA class II expression on DC is fundamental for presenting antigens to T cells and inducing their activation. Therefore, impaired DC activation upon malaria infection in pregnant women may result in a deficient and delayed adaptive immune response to the parasite and/or to other pathogens. Therefore, through an inhibitory effect on DC, *P. falciparum* may impair cell mediated immunity in pregnant women leading to a reduce response against the parasite itself and possibly rendering pregnant women more susceptible to other infections.

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INHIBITORY HUMORAL RESPONSES TO THE PLASMODIUM FALCIPARUM VACCINE CANDIDATE EBA-175 ARE LINKED TO ERYTHROCYTE RECEPTOR USAGE

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Plasmodium falciparum utilizes multiple ligand-receptor interactions for invasion. The invasion ligand EBA-175 is being developed as a major blood-stage vaccine candidate. It is located in the apical micronemes

of merozoites and mediates parasite invasion of host erythrocytes in a sialic acid dependent manner. In this study, we seek to address the ability of naturally acquired antibodies raised against the EBA-175 RII erythrocyte binding domain to inhibit parasite invasion, in relationship to its sialic acid dependence. To address this hypothesis, we have taken two primary approaches. We have determined the presence of antibodies to the PfEBA-175 RII domain by ELISA in individuals from malaria endemic areas of Senegal with high or low transmission. We have tested the plasma of those individuals for their specific EBA-175 inhibitory potential by performing invasion assays using *P. falciparum* EBA-175 KO transgenic parasites. We have also affinity purified antibodies to the EBA-175 RII domain from pooled patient serum for the invasion inhibition of uncultured Senegalese parasite isolates in *ex vivo* assays. Our results suggest that naturally acquired anti-EBA-175 RII antibodies significantly inhibit invasion of Senegalese parasites and this inhibition is dependent on the sialic acid dependence of the parasite strain. This work has implications for vaccine design based on EBA-175 in the context of alternative invasion pathways.

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IMPACT OF MATERNAL CYTOKINE GENE POLYMORPHISMS ON MOTHER AND FETUS BIOLOGICAL AND IMMUNOLOGICAL PARAMETERS IN THE CONTEXT OF PLACENTAL MALARIA

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Some single mutations in cytokines genes are related to modifications of the protein production. For cytokines involved in the regulation of the antibody production, particular gene polymorphisms influence the antibody levels. We investigated the consequences of some cytokine gene polymorphisms on the antibody levels of mothers at delivery, and on fetal immunity, in the context of *P. falciparum* placental malaria infection. We hypothesized that if some maternal cytokine gene polymorphisms lead to an increased production of maternal specific antibodies, they could help to lower the *in utero* sensitization of the fetus to plasmodial antigens, and contribute to delay the occurrence of the first malaria attack in early life. Six-hundred pairs of mothers and children were recruited in south-west Benin, where malaria is endemic. At delivery, peripheral blood was drawn from mothers, as well as corresponding cord blood. Eleven percent of mothers had a placenta infected with *P. falciparum*. From the maternal genomic DNA, 5 mutations occurring in genes coding for IL-4, IL-10 and IL-13 were genotyped by quantitative PCR. High frequencies were observed for genotypes IL-4-590 TT (61.8%), IL-4 +33 CT (50.5%), IL-10-1082 AA (52.5%), IL-10-592 AC (51.3%) and IL-13-1055 CT (51.0%). We evaluated the influence of these mutations on the ability of maternal mononuclear cells to produce the cytokines of interest, following stimulation by mitogens. Finally, we determined maternal and fetal plasmatic levels of IgM, IgG and cytophilic isotypes IgG1 and IgG3 directed against recombinant proteins from the MSP1, MSP2, MSP3, AMA1 and / or GLURP antigens, which are candidates for inclusion into a multivalent vaccine against malaria. The analysis of the relationships between i) maternal cytokine gene polymorphisms, ii) maternal cytokine and related antibody production, and iii) fetal specific antibody production, may help to understand the strength of the mother and child immunological interactions during pregnancy, depending on the presence or not of a plasmodial placental infection.