antibodies (Perlmann et al., 1994; Helmby and Troye-Blomberg, 2000). It reflects an underlying switch in regulatory T-cell activities from Th1 to Th2, controlled by both environmental and genetic factors. The importance of the latter is demonstrated by comparison of mono- and dizygotic twins living in malarious areas of Africa (Perlmann et al., 1999). Furthermore, the IgE levels in patients with severe forms of *P. falciparum* malaria are significantly higher than those in patients with uncomplicated disease, suggesting a role of IgE in pathogenesis. An important pathogenic factor in malaria is TNF. Sera from malaria patients have been found to induce an IgE-dependent release of TNF from monocytes *in vitro* by cross-linking of the Fcε receptor II (CD23) (Perlmann et al., 1997). *In vivo*, this may lead to local overproduction of TNF in the microvessels of, for example, the brain, where the parasites accumulate in cerebral malaria.

By varying their antigens, the parasites may escape the neutralizing effects of the host's antibodies. This can be demonstrated *in vitro*, for instance by antibody-mediated inhibition of erythrocyte invasion by merozoites. Here, autologous antibodies are less inhibitory for parasites from the same donor than for those from other donors (Wåhlin et al., 1997). Similarly, prolonged *in vitro* culture of parasites in the presence of sub-optimal concentrations of antibodies against a defined blood stage antigen made them less suceptible to growth inhibition by these antibodies than when they had been cultured without antibodies (Iqbal et al., 1997).

The most important (but not the only) parasite-encoded antigen seen by opsonizing antibodies on the surface of infected erythrocytes is called PfEMP-1 (*P. falciparum* erythrocyte membrane antigen 1) (Celada et al., 1982). It is a large (200–350 kD) and highly variant protein, which has several binding sites mediating adhesion to the vascular endothelium of capillaries and postcapillary venules. This "cytoadherence" protects the parasite from destruction in the spleen. However, it is also pathogenic for the infected host by obstructing blood flow and giving rise to inflammatory reactions in the affected vessels.

The structures mediating endothelial binding of PfEMP-1 vary greatly in sequence and binding specificity, a variation which helps the parasite to evade the host's immune response (Newbold, 1999). Stimulation of the immune system by PfEMP-1 from a parasite causing an infection gives rise to variant-specific antibodies, which will inhibit cytoadherence by that parasite but will not affect risk of infection by parasites expressing different PfEMP-1 variants (Giha et al., 2000).

Cell-mediated immunity

Malaria-induced cell-mediated immune responses may protect against both extra- and intra-erythrocytic stages of the parasite. Direct destruction of infected cells by cytotoxic T cells is major histocompatibility complex (MHC) restricted. As erythrocytes do not have the MHC molecules necessary to stimulate T cells, a direct cytolytic effect of T cells on erythrocytes is unlikely. However, the effector role in malaria immunity of T cells, particularly of the $CD8^+$ type, has been known for some time. One example is the HLA-B53-restricted $CD8^+$ T-cell dependent protection against severe malaria found in West Africa (Hill et al., 1991; Aidoo and Udhayakumar, 2000).

T cells are essential for the acquisition and maintenance of protective immunity against the asexual blood stages of the parasite in both murine and human malarias (Weidanz and Long, 1988; Langhorne, 1989). The evidence for this includes adoptive transfer of protection by $CD4^+$ T-cell lines and clones (Brake et al., 1986; Cavacini et al., 1986; Süss et al., 1988; Meding and Langhorne, 1991; Taylor-Robinson et al., 1993), the inability of mice depleted of $CD4^+$ T cells to suppress their parasitaemia (Kumar et al., 19; Langhorne et al., 1990; Podoba and Stevenson, 1991) and the findings that nude or SCID mice cannot resolve their infections (Meding and Langhorne, 1991). The mechanism by which $CD4^+$ T cells mediate protection has been the subject of many investigations. In general, $CD4^+$ T cells of the Th1 type activate macrophages and other cells to produce TNF, nitric oxide (NO), reactive oxygen species (ROS) and other mediators through the release of inflammatory cytokines, while $CD4^+$ cells of the Th2 type function in humoral immunity as helper cells for B cells (Abbas et al., 1996). Both Th1 and Th2 cells have been implicated in the control of blood-stage parasites. Although antibodies and B cells appear to be crucial for the final elimination of parasites in certain murine models, in others the control of parasitaemias operates through T-dependent but antibody-independent mechanisms (Langhorne, 1989; Stevenson and Tam, 1993; Taylor-Robinson and Phillips, 1993; Perlmann et al., 1995; Helmby and Troye-Blomberg, 2000).

In order to initiate a Th1 response, precursor cells must be given the appropriate signals by IL-12 and co-stimulatory molecules (Trinchieri, 1993). The Th1-promoting cytokine, IL-12, has been found as early as 2 days post infection in certain murine infections (Sam and Stevenson, 1999). Here, resistant mice produced significantly more IL-12 than susceptible mice, and treatment of susceptible mice with recombinant IL-12 resulted in parasite clearance (Stevenson et al., 1995). Depletion of IFN-γ exacerbates acute *P. chabaudi* infections, and IFN-γ receptor-deficient mice infected with these or other murine parasites show higher and prolonged acute-phase parasitaemias as well as greater mortality, supporting an important role of IFN-γ in controlling murine malaria infections (Meding et al., 1990; Stevenson et al., 1990; Favre et al., 1997; Cross and Langhorne, 1998; Li et al., 1999). Administration of rIL-12 before inoculation of mice or rhesus monkeys with parasites provides 100%

protection in both models through IFN-γ-dependent (and perhaps NO-dependent) antiplasmodial mechanisms (Sedegah et al., 1994; Hoffman et al., 1997). Taken together, these studies suggest that protective immunity in experimental malaria is mediated by a cascade of events involving IL-12-induced production of IFN-γ, TNF and NO.

The existence of functionally distinct $CD4^+$ T cells in humans is indicated by results of *in vitro* experiments with peripheral blood mononuclear cells from naturally *P. falciparum*-exposed donors (Troye-Blomberg et al., 1999a). Although the exact role of Th1 and Th2 cytokines in regulating immune responses in human *P. falciparum* infection is not entirely clear, the balance between Th1 and Th2 cytokines appears to be important. Thus, while elevated plasma concentrations of TNF and IL-10 are characteristic of children with malaria anaemia and high-density parasitaemia (Shaffer et al., 1991; Othoro et al., 1999), a low IL-10 : TNF ratio may be specifically associated with malarial anaemia (Kwiatkowski et al., 1990; Mordmüller et al., 1997; Othoro et al., 1999). Winkler et al. (1998) have shown that a more pronounced Th2-driven response, defined as a lower IFN-γ to IL-4 ratio, during acute untreated *P. falciparum* malaria is followed by a shift towards a Th1-biased response, paralleling clearance of parasitaemia. Such results emphasize the role of IFN-γ as a key molecule in the early host defence against *P. falciparum* malaria. However, a role of Th2 responses is supported by the findings in some immune donors of a correlation between IL-4-producing T cells and serum levels of IgE (ElGhazali et al., 1997).

T cells expressing the γδ T-cell receptor (TCR) are expanded during acute and convalescent phases in both human and murine malaria infections (Roussilhon et al., 1990; Chang et al., 1992; Langhorne et al., 1993; Ho et al., 1994; Roussilhon et al., 1994; Hviid et al., 1996; Rzepczyk et al., 1996; Worku et al., 1997; Helmby et al., 2000), suggesting that they contribute to controlling the early stages of infection. This is also supported by the fact that γδ T cells but not αß T cells from naive donors efficiently inhibit parasite replication *in vitro* (Elloso et al., 1996; Troye-Blomberg et al., 1999b). Malaria antigen-activated γδ T cells produce primarily Th1 but occasionally also Th2 cytokines indicative of a T1/T2 dichotomy. This has also been suggested for non-malarial systems (Horner et al., 1995).

Other cell types which are potent producers of proinflammatory cytokines are NKT cells. In line with what has been reported by Orago and Facer (1991), we have recently observed that cytolytic NKT cells are also potent inhibitors of parasite replication *in vitro* (Farouk et al., in preparation). Other potent producers of regulatory cytokines are $Fc\varepsilon RI^+$ non-B, non-T (NBNT) cells, which are expanded in the spleen and peripheral blood during primary murine *P. chabaudi* infection (Helmby et al., 1998). These cells produce IL-4 and IL-6 *in vitro* in response to IL-3 and/or to cross-linking of high affinity Fcε receptors (Brunner et al., 1993). IL-4 produced by these cells may play a role in providing a Th2 milieu in the spleen and therefore favour a switch of $CD4^+$ T cells to a dominant Th2 response. NBNT cells are believed to be of mast cell or basophil origin (Seder et al., 1991). In this context we have recently shown that IgE-containing malaria sera induce IL-4 in highly enriched basophil preparations, probably through the cross-linking of the high-affinity FcεRI, since basophils are devoid of the low-affinity IgE receptors (CD23) (El Ghazali et al., in preparation). Thus, apart from its established role in inducing inflammatory mediators, IgE in malaria may play an immunoregulatory role by amplifying a secondary Th2 type of response.

Malaria and pregnancy

Besides children under five years of age, pregnant women are also highly susceptible to *P. falciparum* infections. Increased risk of malaria varies during the course of pregnancy. Prevalence of infection and parasite density are highest in the first half of pregnancy and decrease progressively until delivery (Menedex, 1995). There is a transient depression of cell-mediated immunity, the mechanism of which is not completely understood. A shift in the Th1/Th2 balance with a polarization towards Th2 occurs in both human and rodent placentas (Wegman et al., 1993; Krishnan et al., 1996; Raghapathy, 1997). Although the immunological changes in pregnancy may be useful for the foetus, the consequence of weakened cellular immunity during pregnancy is increased susceptibility to diseases caused by intracellular pathogens including viruses, malaria and other parasitic infections (Wegman et al., 1993; Clerici and Shearer, 1994; Krishnan et al., 1996).

The placenta is a preferential site for sequestration of infected red blood cells (RBC). Sequestration reflects the binding of infected RBC to the endothelial lining of capillaries and post-capillary venules. During the past several years it has been demonstrated that several specific receptors expressed on the endothelial surfaces of the vascular system support this binding of the infected RBC. These receptors include intracellular cell adhesion molecule-1 (ICAM-1), CD36, vascular adhesion molecule-1 (VCAM-1), E-selectin, P-selectin, thrombospondin and chondroitin sulphate A (Chaiyaroj et al., 1996; Fried and Duffy, 1996; Newbold et al., 1997; Gowder and Ockenhouse, 1999). CD36 and thrombospondins can bind all parasite isolates, but other adhesion molecules may select sub-populations. Chondroitin sulphate A (Fried and Duffy, 1996) and hyaluronic acid (Beeson et al., 2000) are the major if not exclusive receptors for infected erythrocytes in human placenta. Anti-adhesion antibodies that limit this adhesion and accumulation of the parasites in the placenta have been found in multigravidae from Africa and Asia but not in primigravidae or males (Fried and Duffy, 1998). These observations suggest that this anti-adhesion activity is an acquired humoral