Immunological responses to malaria

Our immune system is comprised of many specialised components, which work collectively to defend the body from harmful foreign bodies. Knowledge of the immune response elicited during malarial infections mainly comes from research using small animal models such as rodents; Plasmodium berghei and Plasmodium yoelii are species of rodent malaria commonly used in studies. Although an immune response is elicited against malaria, in many individuals the parasite is not effectively eliminated, allowing the parasite to multiply and induce clinical symptoms. Due to the morphological transformations occurring, a different group of immune components will be stimulated at different stages of the life cycle.

Pre-erythrocytic stage

Following immunisation of irradiated sporozoites, sterile protective immunity against malaria can be induced in all models studied, including humans (Nussenzweig et al., 1967; Edelman et al., 1993; Doolan & Hoffman, 2000). Rodent models have implicated antibodies as mediators of this protective immunity; Potocnjak et al. found that monoclonal antibodies against plasmodium berghei sporozoite proteins neutralised the parasite, blocking hepatocyte invasion and protecting mice from subsequent infection (Potocnjak et al., 1980). However, as discussed by Good & Doolan, parasite elimination in humans by antibodies is unlikely, as high levels of pre-circulating specific antibody would be required at sporozoite inoculation to prevent hepatocyte infection (Good & Doolan, 1999). In addition, studies have demonstrated that antibodies do not mediate protection and instead cell mediated responses are involved (Belnoue et al., 2004).

Schofield et al. highlighted the significance of a group of T lymphocytes called cytotoxic CD8+ T cells and the cytokine interferon-gamma (IFN-Î³). Mice immunised with attenuated sporozoites were not protected from malarial infection when depleted of CD8+ T cells, and when IFN-Î³ was neutralised mice were no longer immune (Schofield et al, 1987). Other studies have reported similar conclusions, suggesting CD8+ T cells and IFN-Î³ are important mediators of an immune response against pre-erythrocytic stages, as reviewed by Doolan & Martinez-Alier (Doolan & Martinez-Alier, 2006). However little is known of the activation or mechanism of CD8+ T cells in malarial infection. Rodent models have suggested naïve CD8+ T cells in the lymph nodes near the site of inoculation or in the liver become activated through coming into contact with antigen presenting cells called dendritic cells (DCs), which prime CD8+ T cells through cross presenting sporozoite antigens such as CSP. DCs internalise, process and present antigens in association with MHC class I molecules to CD8+ T cells. After specific interaction and co-stimulatory molecule signals, CD8+ T cells become activated and migrate to, or stay in the liver, where they can eliminate parasitised hepatocytes (Jung et al, 2002; Amino et al., 2006). Usually CD8+ T cells kill via cytotoxic mechanisms; however immunity to P. berghei sporozoites in mice was found to be independent of cytotoxicity molecules fas and perforin, which suggests the cytokine secretion of CD8+ T cells, eliminates parasites (Renglli et al., 1997). Evidence also indicates IL-12 and natural killer (NK) cells are important for CD8+ T cells to carry out effector functions (Doolan & Hoffman, 1999).

CD4+ T cells are essential for CD8+ T cell effector responses and optimal functioning; IL-4 secreting CD4+ T cells are crucial (Carvalho et al., 2002; Doolan & Martinez-Alier, 2006). Furthermore, CD4+ T cells have anti-parasitic functions; CD4+ T cells clones derived from mice immunised with irradiated sporozoites, provided protection against sporozoite infection in malaria-naïve mice (Tsuji et al., 1990). Belnoue et al. proved both CD4+ T cells and CD8+ T cells were important to eliminate pre-erythrocytic P. yoelii in mice; protection was mediated by IFN-Î³ production and dependent upon nitric oxide (NO) (Belnoue et al., 2004). The toxic effects of NO, suggest it is a critical mediator of effectively eliminating malaria.

The mechanisms remain undefined; studies have implicated many different immune components, which can singularly or collectively confer protection in rodent models, with parallel studies identifying different critical mediators.

Erythrocytic stage

Passive transfer studies provide evidence that antibodies are important in eliminating parasites; antibodies from malaria-immune individuals successfully treat individuals with malaria (Cohen S et al, 1961). Furthermore immunity in individuals living in malaria endemic areas may be mediated by high concentrations of antibody specific for a variety of erythrocyte stage parasitic antigens (Osier et al, 2008). As reviewed by Beeson et al., antibodies play a role and are likely to target merozoite proteins, such as MSP-1, to prevent erythrocyte invasion. Antibodies may also target parasitic ligands on the surface of PRBCs such as PfEMP-1. Antibody mechanisms may include inhibition of parasitic development or assist cell mediated

destruction of PRBCs or merozoites through opsonisation or via the complement system (Beeson et al., 2008).

As discussed by Engwerda, the spleen is a primary site of cell mediated immune responses against erythrocytic parasites (Engwerda et al., 2005). Murine models have highlighted the significance of CD4+ T cells in eliminating malaria and suggest they are important for gamma-delta T cell (Î³Î´ T cell) expansion in the spleen during infection (van der Heyde et al., 1993). Research suggests that DCs internalise parasites, mature and migrate to the spleen, where they can present parasitic antigens in association with MHC class I molecules to naïve CD4+ T cells. The subsequent differentiation of CD4+ T cells, through IL-12 secretion from DCs, mediates protective immunity against erythrocytic malarial parasites. Th1 cells activate macrophages through the secretion of IFN-Î³ and Th2 cells assist B cell maturation for the production of antibodies through IL-4, IL-6 and IL-10 secretion (Taylor-Robinson, 1998; Good & Doolan 2010). The production of IL-12 is also believed to activate natural killer (NK) cells, which secrete IFN-Î³. Cytokine secretions from activated cells simulate a positive feedback loop, amplifying the immune response.

Using mice, Couper et al. demonstrated that monocytes/macrophages are crucial to eliminate malaria; the infection got worse in mice depleted of these cells. Evidence suggested there are other pathways of activating macrophages other than T cells and IFN-Î³ (Couper et al., 2007).

Activated macrophages secrete TNF-Î±, a mediator of inflammation, which is believed to participate in the pathogenesis of malaria. Macrophages destroy

some PRBCs through phagocytosis and by the release of toxic free radicals such as NO (Good & Doolan, 2010).

Therefore antibodies, T cells, cytokines, macrophages and free radicals are likely to all play a role in the immune response against the symptomatic stage of the malaria life cycle.