response associated with reduced prevalence and density of infection in multigravidae. Conversely, the increased malaria susceptibility in primigravidae may be related to a lack of anti-adhesion antibodies.

Genetic control of malaria immunity/pathogenesis

There is accumulating evidence for the role of genetic control of malaria infection in both rodent and human malaria. Murine parasite variants may give rise to lethal infections in some strains of mice but not others (Stevenson et al., 1982; Cross and Langhorne, 1998). Mortality in the susceptible strains is highest in male mice and appears not to be related to the H-2 system, while parasite clearance in resistant mice may be H-2 linked (Burt et al., 1999).

In humans, case-control studies have detected associations between MHC-encoded genes and cerebral and severe malaria (Hill et al., 1991). A pronounced effect of MHC genes on the risk of complicated malaria has been reported (Jepson et al., 1997a). In a large twin study conducted in Gambia, the contribution of non-MHC genes to resistance to malaria exceeded that of MHC-encoded genes (Jepson et al., 1997b). Others have described genetic regulation of blood infection levels (Abel et al., 1992; Garcia et al., 1998; Rihet et al., 1998) and of anti-malarial immune responses (Troye-Blomberg et al., 1991; Sjöberg et al., 1992; Jepson et al., 1997b).

Alternative approaches to study the genetics of malaria in humans are segregation and linkage analysis. In one segregation analysis, a predominant recessive gene controlling blood infection levels was detected (Abel et al., 1992). More recent segregation analyses showed the existence of complex genetic factors controlling blood infections (Garcia et al., 1998; Rihet et al., 1998). These studies revealed a strong interaction between genetic factors and age; the younger the children the more prominent the genetically related differences. In a recent candidate-region approach, a sib-pair linkage between chromosome regions 5q31-q33 and *P. falciparum* blood infection levels was seen. This chromosome region contains numerous candidate genes encoding immunologically important molecules such as cytokines, growth factors and growth factor receptors, all involved in the control of immunity to *P. falciparum* blood-stage infections (Troye-Blomberg et al., 1999a). The region is also linked to plasma IgE levels (Marsh et al., 1994; Meyers et al., 1994), bronchial hyperresponsiveness (Postma et al., 1995) and schistosomiasis infection (Marquet et al, 1996; Müller-Myhsok et al., 1997).

In recent years, population-based association studies have highlighted the potential importance of a number of candidate gene regions. TNF and NO synthase promoter genes have attracted great interest because of the dual role of their gene products in host defence and in the pathogenesis of cerebral and severe malaria. Homozygosity of the TNF$\alpha^{*}2$ allele has been shown to be associated with greater risk of severe disease, cerebral malaria and death due to malaria infection (McGuire et al., 1994; Wattavidanage et al., 1999). Three different TNF promoter polymorphisms appear to be independently associated with different forms of severe malaria (McGuire et al., 1994; Knight et al., 1999; Kwiatkowski, 2000). In Gabon, a single nucleotide polymorphism of the inducible NO promoter gene has been associated with protection from severe malarial anaemia. In Gambia a NO synthase promoter polymorphism has been found to be associated with susceptibility to fatal malaria (Burgner et al., 1998; Kun et al., 1998). Neither of these associations were found in Tanzania (Levesque et al., 1999).

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