ANTIBODY-INDEPENDENT MECHANISMS IN THE DEVELOPMENT OF ACQUIRED IMMUNITY TO MALARIA

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The plasmodia are hemoprotozoan parasites which cause malaria in a variety of animal species, including man. Infection with these parasites stimulates acquired immune responses which are directed primarily against blood stages and, when successful, bring about a reduction in the number of circulating plasmodia and/or protect the host against reinfection with homologous parasites (1,2). While the actual mechanisms of resistance are ill-defined, it appears that immunity to malaria requires the participation of both T and B lymphocyte systems.

Antibodies reactive with plasmodia are readily demonstrated in the sera of hosts which have recovered from acute disease. Certain of these antibodies have been shown to have neutralizing activity against merozoites, thus preventing the infection of new target cells (3). The same or other antibodies may serve to agglutinate merozoites and/or to opsonize them as well as parasitized erythrocytes for eventual clearance by phagocytic mechanisms (4-7). Several reports have indicated that plasmodia or parasitized erythrocytes may be destroyed by antibody-dependent cell cytotoxicity mechanisms (8,9). Further support for the protective role of antibody in malaria comes from numerous passive transfer studies in which infection could be delayed, prevented, or cured following the injection of immune globulin or hyperimmune serum (reviewed in reference 10). Also, experimental animals rendered B-cell deficient prior to infection routinely died when injected with avirulent strains of plasmodia (11-13). While similar results were observed when T-cell deprived hosts were infected with the same parasites, it was reasoned that the absence of T-helper cells prevented these animals from making antibodies (14).
It should be noted that the mere presence of serum antibodies reactive with plasmodia does not insure that the host will resist infection with the homologous parasites. While monkeys immunized with P. knowlesi merozoites in complete Freund's adjuvant produced neutralizing antibodies and were immune to challenge infection, monkeys immunized with merozoites in other adjuvants produced comparable titers of neutralizing antibodies but remained susceptible to challenge infection (15). Also, Miller et al. (16) observed that there was no correlation between functional immunity in malaria and serum levels of merozoite neutralizing antibody.

Other findings suggest that mechanisms in addition to those mediated by antibody may have a protective role in malaria. For example, Cox (17) observed that a considerable degree of "heterologous immunity" existed among hemoprotozoan parasites; i.e., infection with one species of murine plasmodia subsequently protected the host against infection by heterologous species of plasmodia or babesia. The strength of the immunity induced far exceeded that which would be explained by levels of cross-reacting antibodies in the serum of the resistant host (18). More recently, Allison, Clark, and colleagues achieved a considerable degree of resistance against various hemoprotozoa by stimulating mice with assorted immunomodulators prior to challenge infection (19,20). The resistance displayed by the treated mice could not be attributed to antibodies. While it cannot be denied that the use of immunomodulators may induce nonspecific immunity, the fact that such treated mice appear to destroy hemoprotozoan parasites by nonantibody-mediated mechanisms is quite interesting. The same or similar mechanisms of resistance may be functional during natural infection in conjunction with or apart from antibody-dependent mechanisms.

Additional evidence suggesting that antibody-independent mechanisms contribute to acquired immunity in malaria has been obtained from experiments in which immunity to assorted plasmodia was induced in B-cell deficient hosts. Initially, chickens were rendered B-cell deficient by means of combined chemical bursectomy (21). When subsequently infected with P. gallinaceum, treated chickens uniformly died, whereas their immunologically intact hatchmates spontaneously resolved their acute infections and were immune to subsequent challenge infections (12). However, when acute P. gallinaceum infections in B-cell deficient chickens were controlled with subcurative chemotherapy, the birds developed chronic low-grade infections and resisted challenge infection with homologous parasites. These data suggest that drug-controlled acute malarial infections in B-cell deficient hosts activated a nonantibody-mediated mechanisms of immunity which was capable of limiting the numbers of parasites within the blood but which was not sufficient to sterilize the infection. Further, they suggest that whereas a B-cell product, presumably antibody, was essential