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EDITORIAL

The Development of Immunity to Malaria

(A CLINICAL VIEW)

Parasites have evolved an ingenious array of mechanisms to avoid host-defence mechanisms and establish infections. The malaria parasites are no exception, although their strategy differs somewhat between species. The feeding female anopheline mosquito injects sporozoites into the blood and lymphatic circulations. These rapidly target hepatic parenchymal cells and cannot be detected in the circulation after 45 minutes following inoculation.[1] The host has very little time to intervene and, although both humoral and cellular immune responses to sporozoites are detectable in immune individuals-their role in the natural acquisition of immunity is uncertain. Epidemiological studies indicate that sporozoite immune responses, reflected by antibodies to the circumsporozoite protein (CSP), develop poorly under natural conditions[2] and that sustained high levels occur well after the acquisition of immunity to disease. This may be explained by MHC restriction of the T-cell mediated immune response and a paucity of T-cell epitopes in the CSP.[3] Nevertheless, the sporozoite and its antigenic repertoire are the subject of considerable interest as candidates for a malaria vaccine.

The pre-erythrocytic stage of development is also vulnerable to immune attack as evidenced by the recent finding of cytotoxic T-cells which recognise liver stage antigens[4]-but again the importance of this in the development of natural immunity is uncertain. After hepatic schizogony, merozoites are released into the blood and these rapidly invade passing erythrocytes. Once hidden inside the red cell the parasite progressively consumes the erythrocyte's haemoglobin and begins to alter its membrane. There are modifications to the major anion transporter, band 3 (senescent antigen), and increased expression of phosphatidylserine residues (analogous to accelerated "ageing" of the erytrhocyte).[5] Both of these promote phagocytosis. In *P. falciparum* a variant adhesive protein is expressed on the surface of the red cell after some 24-26 hours of development, but the extent to which other proteins are expressed externally is less certain.[6] Nevertheless, immune responses to a variety of asexual stage parasite antigens have been detected in man-despite the lack of HLA molecules on red cells (and thus an inability to mount HLA restricted T-cell responses). These parasite specific responses compliment the non-specific immune responses to the altered red cell membrane. But in natural infections, all these responses are relatively ineffective. Multiplication efficiency in the growth phase of natural infections is high. Untreated infections with malaria last for weeks or months, or in the case of *P. malariae* for years. The host is usually able to control the infection, but the process of eradicating it is very slow. Various mechanisms are responsible for the poor development of immunity to the asexual stage; malaria parasites appear to induce a broad array of non-specific immune responses with widespread cellular activation (through mitogens and superantigens) which probably interfere with the orderly sequence of immune responses that should lead to effective immunity. This has been termed "an immunological smokescreen".[7] The specific antibodies that are produced often include a predominance of non-cytophilic immunoglobin (IgG_2 IgM) which cannot cooperate effectively with immune effector cells.[8] There

is also an antigen-specific depression of cellular responses to malaria antigens.[9] Furthermore, like other protozoal parasites, the plasmodia exhibit surface antigenic variation even within cloned lines.[6] Natural parasite populations are remarkably diverse and there is very little cross-strain protection. The net result is that natural immunity develops very slowly despite considerable immune stimulation.

In areas of intense transmission, young babies are bitten repeatedly by infected mosquitoes and by the age of one year nearly all have been, or are infected. Severe malaria is very unusual in the first six to nine months, but between one and three years of age the mortality from falciparum malaria is significant. In holoendemic areas severe disease usually manifests as severe anaemia, and cerebral malaria is unusual. As the child gets older, the severity of the infections lessens, until by the second decade malaria is a mild infection at worst, and by adulthood it is largely asymptomatic. In these areas of intense transmission everyone is infected most of the time. Where transmission of malaria is less intense, or very seasonal then the age spectrum of disease shifts to older children and cerebral malaria becomes a more prominent manifestation. Severe malaria now occurs in older children, the case specific mortality is higher, and severe anaemia is less prominent.[10] With even less transmission, or where malaria is intensely focal or seasonal then severe disease may occur at any age and the clinical spectrum of disease in adults is different to that seen in children. Acute renal failure, jaundice and acute pulmonary oedema are prominent manifestations of severe malaria in adults, whereas they are rare in children.[11]

Immunity is reduced in pregnancy - and malaria tends to be more severe, and the response to treatment worse. Even in areas of intense transmission where adults have asymptomatic infections, malaria reduces birthweight in primigravidae and is associated with maternal anaemia. Where mothers are partially or non-immune then falciparum malaria in pregnancy is associated with a high maternal and foetal mortality.

One of the problems confronting immunologists and the development of a malaria vaccine is the lack of a good *in-vitro* correlate of immunity. There is simply no single test that will predict an individual's immune status and response to malaria infection. Indeed the term immunity is a misnomer as in malaria this usually refers to protection from disease rather than protection from infection. The majority of "immune adults" in endemic areas are infected - but they have no symptoms. This state is usually referred to as premunition. It reflects two processes; an increased ability to control parasite expansion and to clear circulating infected erythrocytes, and an increased threshold for symptoms i.e. the subject can tolerate a parasite burden which would cause adverse symptoms in a non-immune individual. This latter phenomenon is also called anti-toxic or anti-disease immunity.[12]

How are these diverse observations relevant to clinical practice and to the development of vaccines? With regard to clinical practice, non-immune individuals are more vulnerable to severe disease. Partial immunity reduces the chances that a lethal complication will develop, and hastens the therapeutic response to antimalarial treatment. But even partial immunity requires repeated infection, and each infection carries the risk of severe disease. Premunition or asymptomatic infection with *P. falciparum* is achieved at the cost of considerable mortality in childhood. Malaria vaccines are going to have to do better than "nature" if they are going to prevent severe malaria and death. Although solid strain specific immunity was demonstrated clearly in the artificial infections of malaria therapy,[13] asexual stage vaccines will have to deal with a considerable natural diversity of parasites. It is now generally accepted that vaccines will not be 100% effective, and cannot be relied upon as the sole antimalaria measure. Finally whereas vaccines may have a large impact on malaria transmission and the overall toll of disease where malaria is already unstable (i.e. of low endemicity), the possibility that a reduction in malaria an area of very high stable transmission could be harmful should be considered. If intense stable transmission is associated with severe anaemia only in very young children, whereas less intense transmission is associated with cerebral malaria over a larger age range, and a higher case-specific mortality, then a reduction in malaria transmission could conceivably increase mortality. In The Gambia, West Africa, a reduction in transmission associated with the Sub-Sahelian drought may have been associated with an increase in mortality. The apparent protection from fatal malaria in holoendemic malarious areas could be explained by repeated boosting ("immunization") in early infancy from frequent infections, under the cover of passive maternal antibody and innate erythrocyte protection. This would result in less severe disease overall and more rapid development of immunity than infrequent infection in early childhood. A partially effective vaccine might reduce transmission, but increase mortality. This is a theoretical possibility - but one that should be considered before implementing vaccine programmes.

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