Malaria Liver Stage Immunity

Michael R. HOLLINGDALE

Department of Biology, University of Leeds, Leeds, UK

Malaria genome sequencing projects will completely change our approaches to malaria drug discovery and vaccine development. It is likely that the entire genome will be sequenced within 5 years. However, the major challenge, as with other microorganisms, will be to understand the stage specific expression and function of individual malaria genes. Integral to this will be our ability to culture parasites, and even nearly a century after the discovery of malaria, these techniques remain difficult, especially in the case of the liver stage of *Plasmodium falciparum*. This stage is important as it is a major target of protective immunity, particularly that elicited by irradiated sporozoites. Much less is known about immunity to liver stages elicited by natural transmission.

P. falciparum LSA-1 is a 230 kDa secreted protein expressed only in the vacuole surrounding the liver stage parasite. Anti-LSA-1 antibodies are extensively found in endemic populations suggesting that most individuals develop an immune response. Our current understanding of the immune mechanisms elicited by irradiated sporozoites suggest that immune CD4 and particularly CD8 T cells play an important role, probably by gamma-interferon mediate parasite cytotoxicity. Volunteers immunized with irradiated sporozoites develop proliferative T-cell responses to LSA-1 epitopes whereas similarly immunized non-protected volunteers do not. Recently, we have identified 3 T-epitopes in LSA-1. Our studies in Papua New Guinea suggest that CD8 gamma-interferon responses to one LSA-1 epitope correlated with resistance to infection. This response was genetically-restricted by an HLA haplotype that is 40% frequent in this population. We are now using genetically modified live vectors as candidate vaccines designed to elicit these responses. Since the malaria genome is large, it is probable that immune reponses to other antigens are also involved in immunity to liver stages. Therefore, we are interested in applying modern molecular biology techniques to construct liver stage expression libraries to take advantage of geneome sequencing for the identification of other candidate protective antigens.

Michael R. HOLLINGDALE, Department of Biology, University of Leeds, Leeds LS2, 9JT. United Kingdom