Institutionen för Medicin, Solna

Naturally Acquired Immunity to *Plasmodium falciparum* Malaria: Antibody Responses and Immunological Memory

AKADEMISK AVHANDLING

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ABSTRACT

Plasmodium falciparum malaria is a significant public health concern particularly in Sub-Saharan Africa. Effective malaria vaccines will contribute significantly towards controlling the disease but their development is hampered by the incomplete understanding of immunity to malaria. Whereas naturally acquired immunity is known to have an important antibody mediated component, the targets and functional correlates as well longevity of these responses are largely unknown and merit further understanding. The studies presented in this thesis, investigate several aspects of naturally acquired immunity to some of the major merozoite vaccine candidate antigens.

In longitudinally monitored children in Tanzania, antibody responses against seven merozoite surface antigens were investigated in relation to the genetic diversity of *P. falciparum* infections, as determined by genotyping of one of the merozoite surface protein genes. The breadth of anti-merozoite antibody responses was positively correlated with the number of concurrent *P. falciparum* clones in asymptomatic children. Further, broad antibody responses and genetically diverse infections, in combination, were more strongly associated with protection against malaria than they were individually suggesting that multicomponent malaria vaccines mimicking naturally acquired immunity should ideally induce antibody responses that can be boosted by natural infections.

The inhibitory activity of naturally acquired antibodies on the *in vitro* growth of *P. falciparum* in relation to merozoite invasion phenotype was investigated in a case-control study in Tanzanian children. The growth-inhibitory activities (GIA) of plasma were different when tested on different parasite lines. The association between GIA and protection against clinical malaria was also parasite line-dependent thus emphasizing the importance of invasion phenotypes as well as the need to consider the choice of parasite lines in the use of GIA as a correlate of protection against clinical malaria in epidemiological and vaccine studies.

Within a longitudinally monitored population in Kenya, temporal dynamics of anti-merozoite antibody responses were investigated in children with different susceptibilities to malaria. Overall, antibody levels were similar in children experiencing multiple episodes or only single episodes suggesting that differences in disease susceptibility are not attributable to differences in the acquisition of anti-merozoite antibody responses, and may be explained by other factors, such as differences in the intensity of exposure to the parasite in this setting of low-moderate malaria transmission.

To investigate the longevity of immune responses induced by natural *P. falciparum* infections, circulating merozoite antigen-specific antibodies and memory B-cells (MBCs) were studied in travelers who had been diagnosed and treated for malaria in Stockholm 1-16 years previously. *P. falciparum*-specific MBCs, but not antibodies, were found to have been maintained for up to 16 years without re-exposure to the parasite.

In conclusion, single natural *P. falciparum* infections induce long-lived memory-B cell responses to merozoite antigens, however, broad and protective antibody responses require repeated exposure and preferably persistent genetically diverse infections to confer clinical immunity to malaria. Taken together, these studies advance the understanding of naturally acquired immunity to malaria and have important implications for the development of malaria vaccines.

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