Structural vaccinology for malaria: Host-pathogen interactions, broadly-neutralizing antibodies and immunogen design

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Plasmodium parasites use a diverse range of proteins to engage host-cell receptors and host-cell membranes during malaria infection. These proteins are targets for antibody neutralization, and neutralization is associated with naturally acquired immunity. Three features have hampered the progression of malaria antigens as vaccine candidates: 1) the polymorphic nature of parasite antigens induce strain-specific immune responses; 2) the epitopes of broadly-neutralizing versus non-protective antibodies within malaria antigens are not known; and 3) the structures of parasite antigens bound to host-cell components are poorly defined. We will present structural, mechanistic and functional studies of parasite antigens from both *P. falciparum* and *P. vivax* in association with receptors and antibodies. These studies demonstrate that multimeric assembly of receptor-antigen interactions is crucial for host-cell invasion, and highlight critical functional regions that can be exploited for targeted disruption. We found that potently neutralizing antibodies target the assembly interfaces and receptor-binding residues of antigens, while non-neutralizing antibodies target decoy epitopes far removed from functional regions of antigens. This work highlights new approaches to target the molecular mechanisms of parasite-host interactions and lays the foundation for improved malaria vaccine design through structural vaccinology.