Structural studies of human antibody responses against leading malaria vaccine antigen PfCSP

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Malaria is a complex, mosquito-borne disease estimated to cause over 300,000 childhood deaths annually. *Plasmodium falciparum* (*Pf*), the major parasite causative of malaria, accounts for approximately 88% of malaria mortality, and demonstrates considerable resistance to current drug therapies. It is therefore imperative to develop a vaccine to *Pf* to reduce malaria morbidity and mortality. Reverse vaccinology holds promise to design effective immunogens for the development of malaria vaccines. This concept is based on interrogating the B cell repertoire of infected or vaccinated subjects to identify inhibiting antibodies that will guide immunogen design. The circumsporozoite protein (CSP) is the major surface antigen of Pf sporozoites and a leading malaria vaccine antigen. Here, we structurally and functionally characterized protective and non-protective antibodies to PfCSP from four healthy adults living in the malaria-endemic area of Lambaréné, Gabon, and from eight vaccinated European donors who underwent immunizations with aseptic, purified, cryopreserved Pf sporozoites (PfSPZ Challenge) under chloroquine prophylaxis (PfSPZ-CVac), which resulted in protection against controlled human malaria infection. Our structural delineation of protective and non-protective epitopes highlights key differences of B cell responses during natural exposure and vaccination. In addition, we provide the molecular mechanism underlying clonal selection and affinity maturation of human B cells expressing protective antibodies. Collectively, this data provides the blueprints to engineer optimized antigens that can be tested as pre-erythrocytic subunit vaccines.