

Maria del Pilar Quintana

High-throughput isolation of cross-reactive monoclonal antibodies against the placental malaria protein VAR2CSA during natural infection and subunit vaccination

Plasmodium falciparum placental malaria (PM) is a severe complication of pregnancy in areas with stable parasite transmission. It is caused by the adhesion of infected erythrocytes (IEs) to chondroitin sulfate A (CSA), which is exclusively expressed in the placenta and is mediated by the parasite antigen VAR2CSA. PM mainly affects first-time mothers, as naturally acquired immunity (NAI) develops with subsequent pregnancies. This immunity has been associated with antibodies targeting VAR2CSA and inhibiting its binding to CSA. This evidence has provided the rationale for two VAR2CSA-based subunit vaccines, which, disappointingly, induce only variant-specific responses. It remains unclear whether NAI is mediated by broadly cross-reactive monoclonal antibodies (mAbs) or by a repertoire of variant-specific mAbs. Furthermore, the VAR2CSA regions targeted by protective immunity remain poorly defined and the mAb response induced by subunit vaccination has not been studied.

To address these gaps, seven VAR2CSA variants were used to isolate antigen-specific B cells from Ghanaian pregnant women with NAI and from vaccinated donors. LIBRA-seq (linking B cell receptor sequences to antigen specificity through sequencing) was then performed on these cells, enabling the determination of the sequences of hundreds of VAR2CSA-specific mAbs, together with their antigen specificity and cross-reactivity. This talk will present the characterization of a subset of these mAbs, revealing the antigenic landscape of VAR2CSA during natural infection and highlighting the key challenges in developing broadly protective vaccines or prophylactic antibodies against PM.