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Identification of protein-protein interactions between plasmodium falciparum and the human erythrocyte membrane protein 4.1

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Abstract

Malaria is one of the most debilitating parasitic infections to have afflicted humanity and remains an expanding health risk for many countries. This is attributed largely to the complexity of the parasite's life cycle and refined ability to evade host immunity. During development within the erythrocyte, *Plasmodium falciparum* induces a wide array of changes to the ultrastructure, function and antigenic properties of the host membrane. Numerous proteins encoded by the parasite associate with the erythrocyte skeleton and appear to be essential for *P. falciparum* survival. The elucidation of new protein-protein interactions has therefore formed a key area of malaria research.

To circumvent the difficulties provided by conventional protein techniques, a novel application of phage display technology was used in this research. *P. falciparum* phage display libraries were created and biopanned against human erythrocyte skeletal protein 4.1 (4.1R). DNA sequencing and bioinformatic investigations uncovered a number of parasite proteins with binding specificity toward 4.1R. They included five hypothetical proteins, two invasion proteins, namely erythrocyte binding antigen-175 (EBA-175) and EBA-181, two predicted protein kinases and a putative aminopeptidase. A common binding motif displaying homology to muscle myosin and neurofilament sequences was also identified in four of the ten proteins.

The interaction between EBA-181 and 4.1R was characterised further by mapping the domain in 4.1R responsible for binding to the parasite protein. Recombinant proteins were used in blot-overlay and pull-down experiments, which revealed specific interaction between the highly conserved 10kDa domain and the 4.1R binding region in EBA-181. Binding was concentration dependent, as well as saturable and was abolished by heat denaturation of 4.1R.

Functions of the 4.1R-specific parasite proteins remain to be determined, however, they are potentially involved in parasite growth and survival during intra-erythrocytic development. Furthermore, these proteins may also participate in the entry and/or exit of parasites from the human erythrocyte. The interaction of EBA-181 with the

10kDa domain of 4.1R provides new insight into the molecular mechanisms utilised by *P. falciparum* during erythrocyte entry. It also highlights the multifunctional role of malaria invasion proteins, which may contribute to the success of the pathogenic stage of the parasite's life cycle.