Plasmodium falciparum and the human erythrocyte membrane protein 4.1: to bind or not to bind

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Malaria remains one of the most lethal parasitic diseases afflicting humanity. The development of *Plasmodium falciparum* within human erythrocytes induces significant modifications to the structure and function of the host membrane. This study has focused on the identification of new protein-protein interactions between the parasite and membrane protein 4.1 (4.1R). A novel application of *in vitro* display technology was used whereby *P. falciparum* phage display libraries were created and biopanned against purified human 4.1R. Parasite cDNA inserts were sequenced and bioinformatic analyses identified interacting and in-frame amino acid sequences. Eight proteins displaying strong binding specificity towards 4.1R were identified, including five hypothetical proteins, a putative serine/threonine protein kinase and two parasite invasion proteins, namely erythrocyte binding antigen 175 (EBA-175) and EBA-181. A common binding motif displaying homology to muscle myosin and neurofilament sequences was also identified in four of the eight proteins. The hypothetical proteins and putative kinase are potentially involved in the invasion and/or release of merozoites from the human erythrocyte, and may also be involved in the growth and survival of malaria parasites during intra-erythrocytic development. The N-terminal Duffy-binding-like domains of EBA-175 and EBA-181 mediate invasion by binding specific receptors on the erythrocyte surface. Our findings suggest a new role for EBA-175 and EBA-181. The C-terminal domains of these parasite proteins bind 4.1R, which destabilises the erythrocyte skeleton thus facilitating parasite entry. The characterisation of novel protein interactions will enhance our understanding of *P. falciparum* biology, an important requirement for developing new strategies for malaria control.