Targeting ribosomal protein to impair cell division and growth of the malaria parasite *Plasmodium falciparum*

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Malaria parasites reside inside erythrocytes and the disease manifestations are linked to the growth inside infected erythrocytes (IE). We have recently shown an involvement of a *Plasmodium falciparum* 60S stalk ribosomal protein P2 (PfP2), which gets exported to the IE surface for 6-8 hours during early schizogony, concomitant with functional amyloid-like SDS-resistant oligomerization. Treatment with anti-PfP2 monoclonal arrested *Plasmodium* at the onset of cell division. Here we report structure-function studies on purified recombinant PfP2-tetramer. NMR studies of PfP2-tetramer showed that the N-terminal domain forms a hydrophobic pocket, while the C-terminal stretch of 40 residues remains disordered. How does PfP2 anchor on the infected red cells? NMR studies of PfP2-tetramer in the presence of erythrocytes showed specific protease-sensitive binding of several C-terminal residues of PfP2 with erythrocytes, and no other cell type. Pull-down experiments using intact red blood cells have showed that the N-terminal domain was sufficient to bind to the red cells. Antibodies against P2 protein were found to block lipid uptake, disrupt the parasite-induced tubulovesicule network and restore the cell flexibility. The intriguing question pertains to the role of the IE surface exposed oligomer P2 protein. Does it work as a cell division check-point protein and sense the external milieu for specific serum components? Our results indicate that P2 protein does bind to very specific lipid moieties in an oligomer specific manner. Thus, the unique surface properties of PfP2 ribosomal protein is novel, and given that it is exposed to the immune system, it may be targeted to impair the growth of the parasite.

Biography

Shobhona Sharma has been exploring various aspects of the malaria parasite over several years at the Tata Institute of Fundamental Research, Mumbai, India. One of the major focuses of her lab has been the study of acquired immunity to malaria. Through a differential immunoscreen using sera samples from Eastern India, her group identified several novel protective malarial proteins. Of these, she has studied the structure and novel functions of Plasmodia ribosomal P-proteins extensively. Her metabolic monitoring of disease progression provides understanding of certain biochemical signatures. In collaboration with pharmacologists, her group also explores nanolipid carrier-mediated delivery of antimalarials. Recent results have shown that nano-lipid-carrier mediated delivery of antimalarial drugs and specific antibodies holds great promise in malaria control.

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