REGIONAL CENTRE FOR BIOTECHNOLOGY
Seminar series

Malaria: Insight into the mechanism of Invasion and Cytoadherance

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Malaria is responsible for killing millions of humans in tropical countries. This situation is alarming as malarial parasite has continuously been developing resistance to known drugs and due to unavailability of vaccine.

In the life cycle of parasite, blood stage is responsible for all clinical manifestations and is an important target for development of vaccines and drugs. Invasion of erythrocyte, an important step for survival of parasite, is mediated by various receptor-ligand interactions. Apical membrane antigen 1(AMA1) is one such molecule involved in invasion process. Blocking of these interactions would lead to the prevention of invasion of erythrocytes. We used phage display technology to isolate single chain variable fragments (scFv) to target AMA1. We demonstrated that it was possible to isolate scFv from the phage display library prepared from peripheral blood lymphocytes (PBL) of immune individuals. Apart from known molecules involved in invasion of erythrocytes, there could be many more "unknown" molecules that could be targeted. We identified many such potential molecules using bioinformatic approaches. One such molecule is apical sushi protein (ASP) and we showed that although ASP is not important for invasion, but it could play an important role in the host complement regulation.

Another complexity in malaria arises due to cytoadherance of infected erythrocytes to endothelial linings of host, leading to severe forms of malaria, such as placental malaria. Parasite ligand known for pregnancy associated malaria (PAM) is var2CSA. Var2CSA, a 350 kDa protein, comprises six duffy binding like domains (DBLs). We were able to express and homogenously purify recombinant full extracellular domain (300 kDa) of DBL and showed that it possesses high affinity and specificity for its ligand (CSA). Using small angle x-ray scattering (SAXS) we showed that this protein possesses a much more compact organization than thought previously. Antibodies raised against this protein cross-react with various field and lab isolates. We further showed that minimal binding pocket lies in N-terminal half, comprising first three DBL domains of the protein. Presently we have been working in the direction of mapping the residue(s) important for interaction of Var2CSA with its ligand and developing vaccine against minimal region important for PAM.