Abstract

*Plasmodium falciparum* is a deadliest *Plasmodium* species responsible for human malaria. Plasmepsin X (PMX) from *Plasmodium falciparum* is a pepsin-like aspartic protease that plays essential role in the invasion and egress of the parasite (1,2). Invasion and egress processes involve a cascade of events and are essential for the survival and dissemination of infection in the parasite life cycle. Plasmepsin X is an upstream protease in this cascade of events and hence, is an attractive drug target (3). We have reported the first crystal structure of *Plasmodium falciparum* Plasmepsin X (PfPMX) zymogen, with a novel prosegment fold (4). The zymogen structure has five disulfide bonds with a unique disulfide bond formed by two adjacent cysteine residues (C447-C448). The twisted loop from prosegment occupies the active site forming several hydrophobic interactions with mature enzyme, and arginine 244 from the initial mature region forms the salt bridge interactions with catalytic aspartates inactivating the PfPMX zymogen. Such an inactivation mechanism has not been observed previously for any other pepsin-like aspartic proteases. Sequence and structural alignment studies also showed that such a unique zymogen inactivation mechanism could be applicable to other PMX-like proteases from other apicomplexan parasites. The biochemical data suggest the conversion of zymogen to mature enzyme occurs through cleavage of the prosegment at multiple cleavage sites. The structural features of PfPMX presented would aid in developing potent inhibitors of this enzyme and similar proteases from apicomplexan parasites in efforts to combat malaria and other apicomplexan diseases.

References

Structure of PfPMX zymogen