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Egress and Invasion Machinery of Malaria: An In-depth Look into The Structural and Functional Features of The Flap Dynamics of Plasmepsin IX and X

Plasmepsins, a family of aspartic proteases expressed by Plasmodium falciparum parasite, have been identified as key mediators in the onset of lethal malaria. Precedence has been placed on this family of enzymes due their essential role in the virulence of the parasite, thus highlighting their importance as novel drug targets. A previously published study by our group proposed a set of parameters used to define the flap motion of aspartic proteases. These parameters were used in the study of Plm I–V and focused on the flap flexibility as well as structural dynamics. Recent studies have highlighted the essential role played by Plm IX and X in egress and invasion of the malarial parasite. This study aims to close the gap on the latter family, investigating the flap dynamics of Plms IX and X. Integrating Molecular dynamic simulations coupled with other advanced bio-computational tools we were able to reveal an "open and close" mechanism at the region of the catalytic site. Further computation of the dihedral angles implemented with the use of the CPPTRAJ module in the AMBER 14 package revealed tractability of the catalytic domain specifically at the flap tip and flexible loop. This structural versatility enhances the interaction of variant ligand sizes, in comparison to other Plm family members. The results obtained from this study signify the essential role of structural flap dynamics and its resultant effect on the binding landscapes of Plm IX and X. We believe that this unique structural mechanism may be integrated in the design and development of effective anti-malarial drugs.

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