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Structural-functional studies of mosquito-larvicidal BinAB receptor (Cqm1) protein

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Glycoside hydrolase 13 (GH13) family represents a large and diverse enzyme family. Cqm1, an amylomaltase of *Culex* mosquito, belongs to the GH13 family and subfamily 17 (GH13_17) [1]. Cqm1 is localized at the midgut membrane and is attached to lipid rafts via GPI anchor. It serves as the receptor for mosquito-larvicidal BinAB proteins [2], which are used world-over for control of mosquito borne diseases. Interaction of Cqm1 with BinAB proteins is essential for intracellular toxicity of larvicidal BinAB toxin and mutation in *cqm1* gene leads to resistance development in mosquitoes. Solution studies showed that Cqm1 exists as dimer, binds with high affinity to BinAB proteins, and chelation of Ca(II) ion from the protein with EGTA abrogates enzymatic activity and reduces thermal stability [1]. The oligomeric status of Cqm1 is thought to be critical for its stability and presentation on the lipid rafts. The Cqm1 protein was crystallized in the presence of a mixture of divalent metal ions [3]. Cqm1 crystal structure was solved using the MRSAD method using Cd(II) anomalous at 1.9Å wavelength and the structure was refined against 1.8Å synchrotron data [4]. The diffraction intensity data were acquired at PX beamline, INDUS-2 synchrotron. One tightly bound Ca(II) ion in each of the monomer is observed. Extensive sequence analysis reveals this site may be unique to the GH13_17 family. Molecular dynamics simulations provide clues for the functional role of Ca(II) ion. An energy-optimized substrate (maltotriose) bound structure of the complex has been constructed based on which 'retaining-type' mechanism can be predicted reliably. It reveals large conformational change in aromatic residues situated at active-site entrance. A Cd(II) ion is observed overlapping with the substrate-binding site. Kinetics data suggests non-competitive inhibition of Cqm1 by Cd(II). This is the first structure from the GH13_17 family and provides template for constructing reliable models for other members.

1. Sharma *et al.*, *Insect BiochemMol Biol.* 2018, **93**, 37-46.
2. Colletier *et al.*, *Nature.* 2016, **539**, 43-47.
3. Sharma *et al.*, *ActaCrystallogr F StructBiolCommun.* 2018, **74**, 571-577.
4. Sharma and Kumar, *Int J BiolMacromol.* 2019, *In press.*

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