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Two-domain aminopeptidase of M1 family: Structural features for substrate specificity and gating in absence of C-terminal domain

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ABSTRACT : Zinc metallopeptidases of the M1 family (M1 peptidases) with unique metal binding motif HEXXH(X)$_{18}$E regulate many important biological processes such as tumor growth, angiogenesis, hormone regulation, and immune cell development. Typically, these enzymes exist in three-domain or four-domain format in which N-domain and catalytic domain are more conserved. The C-domain plays important roles in substrate binding and gating. In this study we report the first structure of a two-domain (N-domain and catalytic domain) M1 peptidase at 2.05 Å resolution. Despite the lack of C-domain, the enzyme is active and prefers peptide substrates with large hydrophobic N-terminal residues. Its substrate-bound structure was determined at 1.9 Å resolution. Structural analyses supported by site directed mutagenesis and molecular dynamics simulations reveal structural features that could compensate for the lack of C-domain. A unique loop insertion in the N-domain has important roles in gating and desolvation of active site. Three Arg residues of the catalytic domain are involved in substrate-binding roles typically played by positively charged residues of C-domain in other M1 peptidases. Further, its unique exopeptidase sequence motif, LALET, creates a more hydrophobic environment at the S1 subsite than the more common GXMEN motif in the family. This leads to high affinity for large hydrophobic residues in the S1 subsite, which contributes towards efficient substrate binding in absence of C-domain.



Biography: Richa Agrawal has completed her Master's at the age of 23 years from Jiwaji University and persuing PhD from Indian Institute of technology Indore in the field of structural studies of peptidases. She has published 2 papers in reputed journals and One paper in under review related to her PhD work. She is further interested to do post doctoral research in cryoelectron microscopy

Publication:1. Structural basis for the unusual substrate specificity of unique two-domain M1 metallopeptidase
Crystal structures of pyrrolidone-carboxylate peptidase I from
2.Deinococcus radiodurans reveal the mechanism of L -pyroglutamate recognition
3.Crystal structures of pyrrolidone-carboxylate peptidase I from Deinococcus radiodurans reveal the mechanism of L-pyroglutamate recognition
4.Crystal structures of pyrrolidone-carboxylate peptidase I from Deinococcus radiodurans reveal the mechanism of L-pyroglutamate recognition
5.Two-domain aminopeptidase of M1 family: Structural features for substrate binding

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