राष्ट्रीय प्रतिरक्षाविज्ञान संस्थान
जैव प्रौद्योगिकी विभाग, विज्ञान और प्रौद्योगिकी मंत्रालय, भारत सरकार का स्वायत्त अनुसंधान संस्थान
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Polyamines are essential for cell growth and proliferation. In plants and many bacteria, including *Helicobacter pylori*, the parent polyamine putrescine is only produced through the metabolism of N-carbamoylputrescine by N-carbamoylputrescine amidase (CPA). Thus, CPA is a crucial intermediate enzyme. Moreover, the absence of CPA in humans makes its presence in *H. pylori* a potential target for the development of new therapeutics against this pathogen. Despite this enzyme's presence in plants and bacteria, its structure-function is not completely explored. Using structure-guided biochemical and biophysical studies on *H. pylori* CPA, an aromatic cluster containing four conserved tryptophans near the catalytic site was discovered and its role was elucidated. Mutational studies revealed that they are individually vital to enzyme function. Unlike wild-type, which forms a hexamer, the Trp to Ala mutants only formed dimers. Interestingly, two other conserved residues, Gln155 and Asp278 interact with the tryptophan cluster and perform similar roles. Our results indicate that aromatic-aromatic and H-bonding contacts between the residues (Trp156-Trp273, Trp196-Gln155 and Trp153-Asp278) play a crucial role in stimulating activity through hexamer formation. Additionally, Trp156 is essential to generating a catalytically efficient hexamer. These results suggest dual roles for the tryptophans; in hexamer formation and in generating its functionally active form, thereby providing a mechanistic understanding into the role of the cluster. The catalytic roles of Glu43, Lys115 and Cys152, which are present at the active site, were also elucidated. Using the structure of catalytic site and its surrounding region, a new inhibitor of the *H. pylori* enzyme was identified. Thus, our findings not only highlight, for the first time, the importance of a tryptophan cluster in *H. pylori* CPA function, but also offer an opportunity to design therapeutic inhibitors with greater efficacy.

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