Genomic Studies of the Cytidine Deaminase Superfamily: From Mononucleotide to RNA (DNA)-Editing Deaminases

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In the previous years, we have solved crystal structures of four members of the cytidine deaminase superfamily: yeast cytosine deaminase, a nucleotide deaminase from the archaeal *Methanosarcina mazei*, *Bacillus subtilis* guanine deaminase and RibG.

Bacterial RibG is a potent target for antimicrobial agents because it catalyzes the two consecutive deamination and reduction steps in the riboflavin biosynthesis. The crystal structure of *Bacillus subtilis* RibG displayed a tetrameric ring-like structure (1). The N-terminal deaminase domain belongs to the cytidine deaminase superfamily. A structure-based sequence alignment of a variety of nucleotide deaminases reveals not only the unique signatures in each family member for gene annotation, but also putative substrate-interacting residues for RNA-editing deaminases. The C-terminal reductase is the only protein to date to share high structure homology to the pharmaceutically important dihydrofolate reductase..

The complex structures reveals distinct interaction networks of the product/substrate with the deminase and reductase domains, and hence may be useful in guiding drug design. Upon the product binding to the deaminase domain, significant conformational changes were induced in two loops moving toward for interaction with the ribosyl and phosphate moieties, respectively (Fig. 1). The phosphate forms hydrogen bonds with Asn^{23}, His^{49}, His^{76}, Lys^{79}, and Thr^{80}, while the ribose contacts with Asp^{101} and Asn^{103}. Mutational analyses reveal that Glu^{51} and Lys^{79} are essential for deaminase activity. Unexpectedly, the electron density map demonstrates a ribitylimino intermediate bound at the reductase domain. Both the pyrimidine ring and phosphate form extensive interactions with Lys^{151}, Ser^{167}, Ile^{170} and Thr^{171}, and Arg^{183}, Ser^{202}, Leu^{203}, and Arg^{206}, respectively, while the ribityl group with Asp^{199} and Glu^{290}. Lys^{151} has been evolved to ensure specific recognition of the deaminase product rather than the substrate, through its amino group interacting with the carbonyl moiety, but repelling the amino of the substrate.

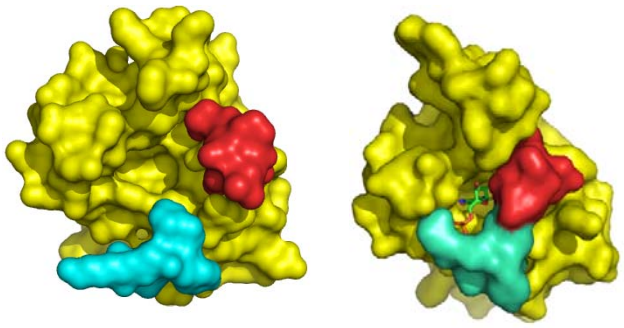

Figure 1. Molecular surfaces of the D domain with or without the product binding. The two loops with alternative conformations are shown in red and cyan.

1. Chen *et al.*, J. Biol. Chem. **281**, 7605 (2006).
2. Chen *et al.*, Manuscript in preparation.