Crystal Structure of Inhibitor-bound Mouse Cytidine Deaminase at 1.5 Å

Teh Aik Hong[a], Masaki Yamamoto[b], Makoto Kimura[b], Isamu Yamaguchi[b], Nobuo Tanaka[a], Takashi Kumasaka[a], [a]*Department of Life Science, Tokyo Institute of Technology.* [b]*RIKEN, Japan.* E-mail: ahongteh@bio.titech.ac.jp

Cytidine deaminase (CDA) catalyses the deamination of cytidine and deoxycytidine to uridine and deoxyuridine. Two types of CDA, dimeric and tetrameric CDAs, have been classified [1,2]. The dimeric CDA has two cysteine and one histidine residues liganding a zinc ion at the active site, whereas the three residues are all cysteine in the tetrameric CDA. Arg56 of the tetrameric CDA from *Bacillus subtilis* partly neutralises the negative charge of the cysteine [2,3].

The inhibitor-bound structure of the tetrameric mouse CDA has, surprisingly, revealed the corresponding residue, Arg68, in two alternate conformations. While in the first conformation Arg68 forms hydrogen bonds with two of the zinc-binding cysteine residues, in the second conformation these hydrogen bonds are abolished. Although hydrogen bonds are important for maintaining zinc reactivity [3], the absence of it in the second conformation, conversely, can facilitate product dissociation by increasing negative charge donation from cysteine to the zinc ion, hence weakening the zinc–product interaction. Furthermore, the nearby Gln72 dyad, formed by Gln72 from two adjacent subunits, interacts with Arg68 in the second conformation, suggesting an allosteric cooperativity between the two subunits.

[1] Betts L., Xiang S., Short S.A., Wolfenden R., Carter C.W.J., *J. Mol. Biol.*, 1994, **235**, 635. [2] Johansson E., Mejlhede N., Neuhard J., Larsen S., *Biochemistry*, 2002, **41**, 2563. [3] Johansson E., Neuhard J., Willemoës M., Larsen S., 2004, **43**, 6020.

Keywords: cytidine deaminase, alternate conformation, product dissociation