Altered Structure and Function of a Beta-retroviral dUTPase

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dUTPase prevents uracil incorporation into DNA and contributes to dTTP biosynthesis. It is indispensable for keeping the appropriate high dTTP/dUTP ratio, essential for cell survival. Its vital character makes it a promising anticancer and antiviral drug target. The protein forms homotrimers with three identical active sites located between two monomers and closed by a flexible C-terminal arm reaching over from the distant third monomer[1].

The economic beta-retroviruses however encode for a shortened dUTPase with compromised catalytic efficiency[2]. Sequence alignments revealed that the gaps accumulate at the beginning of the C-terminal segment, suggesting serious difficulties in reaching the targeted active site. To explain how the enzyme preserves its catalytic ability for dUTP hydrolysis, we combined structural analysis with enzyme kinetics, mutational techniques and modeling approach. Crystal structures of wild type and a truncated mutant dUTPase have been determined in unliganded form, and substrate analogue and product complexes. Structure-based molecular modeling predicted the catalytically relevant conformation of the C-terminal arm. Results propose localization of the C-terminal catalytic residues to the active site formed by the same subunit, and offer insights into the role of the C-terminal arm in catalysis.

[1] Barabas O., et al., *J. Biol. Chem*., 2004, **279**, 42907. [2] Barabas O., et al., *J. Biol. Chem*., 2003, **278**, 38803.

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