

Theoretical research on the substrate specificity of uridine-cytidine kinase

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Uridine-cytidine kinase (UCK) catalyzes phosphorylation of uridine and cytidine. This reaction is important in the salvage pathway of pyrimidine-nucleotides as sources of energy and materials for biosynthesis of DNA/RNA. UCK from *Thermus thermophilus* HB8 (ttCK) has substrate specificity toward only cytidine. The replacement of the Tyr93 by histidine endows ttCK with activity toward uridine. It suggests that the specificity derives from Tyr93 [1]. However, the molecular mechanism of substrate specificity in UCK has not yet been elucidated.

In this study, the mechanism of substrate specificity of UCK was investigated by using molecular dynamics (MD) simulations and free energy analyses. MM-PBSA method is used to evaluate the substrate binding free energy. We have succeeded to reproduce the weak ttCK WT-uridine binding and the strong ttCK Y93H-cytidine binding. Furthermore, possibilities of different protonation states in the ttCK WT uridine interactions are investigated by using the mixed quantum mechanics / molecular mechanics (QM/MM) method.

[1] Tomoike, F. et al. (2011) *Biochemistry* 50, 4597-4607