# 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-nucleosides as sources of energy and materials for biosynthesis of DNA/RNA. Because cells take in some agents through this pathway, UCK is the target of some anticancer drugs. UCK from *Thermus thermophilus* HB8 (ttCK) has specificity to only cytidine, and this character depends on only a single amino-acid residue (Y93)[1]. The molecular mechanism of substrate specificity in ttCK 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. Molecular Mechanics - Poisson Boltzmann Surface Area (MM-PBSA) method is used to evaluate the substrate binding free energy. We have succeeded to reproduce the strong interaction between ttCK and cytidine and weak interaction between ttCK and uridine (Fig.1). On the other hand, a sufficient binding free energy is not calculated for Y93H mutant-uridine interaction. Thus, possibilities for other protonation states are investigated. Mixed quantum mechanics / molecular mechanics (QM/MM) calculations are also used.

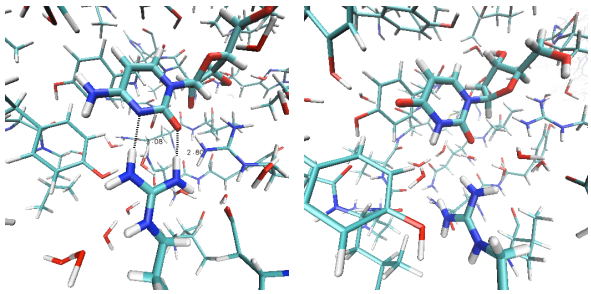

Fig.1 : The interaction between ttCK and cytidine (left) and between ttCK and uridine (right)

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