Crystallographic analysis of orotidine 5'-monophosphate decarboxylase ~ distortion of C6-group ~

オロチジンーリン酸脱炭酸酵素の結晶学的研究～C6 置換基の歪曲～

黒田新悟[1], 藤橋雅宏[1], Lakshmi, P. Kotra[2-4], Emil F. Pai[2,5], 三木邦夫[1]
[1]京大・院理・化学, [2]トロント総合研, [3]トロント大・薬,
[4]ノースカロライナ大グリーンスボロ校・化、生化,
[5]トロント大・生化、医学生物物理、分子遺伝

Orotidine 5’-monophosphate decarboxylase (ODCase) catalyzes the conversion of orotidine 5’-monophospate (OMP) to uridine 5’-monophosphate (UMP). This enzyme is known as one of the most proficient enzymes, accelerating the reaction by 17 orders of magnitude when compared to the spontaneous reaction. Although numerous crystal structures and biochemical analyses have been reported, the reaction mechanism of this enzyme is still open to dispute.

A characteristic electrostatic network (Lys42-Asp70-Lys72-Asp75: numbering as ODCase from *Methanobacterium thermoautotrophicum*) is conserved in all known ODCases. One of these residues, Lys72, is the essential residue for catalysis. Mutation of this residue generates a non-reactive mutant. The amino head of the lysine contacts to the C6 atom and its substituent of the substrate analogues. We have determined the crystal structures of wild-type and Lys72Ala mutant ODCase from *M. thermoautotrophicum* with several sets of substrate analogues at 1.2-1.5 Å resolution in order to understand the role of this residue in detail.

A series of determined structures indicates the systematic difference between the ligand-binding positions of wild-type and Lys72Ala mutant enzymes. The pyrimidine rings of all ligand sets in the wild-type are moved approximately 0.5 Å towards the opposite side of Lys72 compared to the positions of those in Lys72Ala mutant. This observation suggests that Lys72 pushes down the C6 atom and substituents of the ligands.