

## **Genomic Enzymatic Approach to Understand Mechanism of Orotidine 5'-Monophosphate Decarboxylase**

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Orotidine 5'-monophosphate decarboxylase (OMPDC) catalyzes the decarboxylation of orotidine 5'-monophosphate (OMP) to uridine 5'-monophosphate (UMP) in the last step of uridine biosynthesis. Unlike other enzymatic decarboxylation reactions, OMPDC does not utilize a metal co-factor. The rate acceleration of OMPDC from the non-catalyzed reaction is at an amazing  $10^{17}$  fold, and the proficiency is  $2.0 \times 10^{23}$ . This astonishing rate acceleration makes this enzyme the most proficient enzymatic reaction known today. Without an electron sink like other enzymatic decarboxylases, the orotidine base has no obvious resonance structure to delocalize the charge of the carbanion transition state that develops upon the release of  $\text{CO}_2$ . The question as to how OMPDC effectively stabilize the intermediate has stirred up many controversies within the scientific community. Extensive studies in many different areas have tried to explain this phenomenon. Protonation of O2, protonation of O4, nucleophilic attack of C5 and electrophilic displacement of C6 have all been suggested, but each proposed mechanism is inconsistent with other evidence. Our group utilizes genomic enzymology as an approach to systematically revise and investigate mechanism of OMPDC. Herein, I present current mutagenesis and deuterium isotope experimental results of the *Methanobacterium thermoautotrophicum* OMPDC.