Poster Presentation

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Structural and Functional study of Mevalonate Diphosphate Decarboxylase

C. Chen[1], C. Stauffacher[1]

[1]*Purdue University, Department of Biological Sciences, West Lafayette, Indiana, USA*

Mevalonate diphosphate decarboxylases (MDD) (EC 4.1.1.33) catalyze the Mg2+-dependent decarboxylation of mevalonate 5-diphosphate (MVAPP) by hydrolyzing adenosine triphosphate (ATP) and producing isopentenyl diphosphate (IPP) in the final step of mevalonate pathway. This enzyme is essential in Enterococcus faecalis and other Gram (+) bacteria; therefore, MDD protein is an ideal drug target for the treatment of bacterial infections. We have studied the enzyme kinetics and structures of MDD from Enterococcus faecalis (MDDEF) which causes clinical enterorococcal infections. In the crystal structure of the MDDEF bound with ATP, the catalytically unfavored orientation of the γ-phosphate of ATP implies that conformational changes of MDDEF might occur in order to accommodate the binding of ATP when the MVAPP binds to the active site in advance. A 10-fold decrease of the dissociation constrant (Kd) value of ATPγS has been observed using isothermal titration calorimetry (ITC) when MDDEF is pre-bound with MVAPP. The increase of binding affinity of ATPγS suggests that cooperative binding of ATP to MDDEF can be achieved by the prerequisite binding of MVAPP. Indeed, the crystal structure of MDDEF soaked with the MVAPP shows that one flexible loop that eventually should bind ATP becomes non-flexible and bends toward the active site of MDDEF. Thus, we hypothesize that the binding of the MVAPP to the active site triggers conformational changes of MDDEF which induces the binding of the other substrate, ATP, in its catalytically favored position. Further experiments will be performed for investigating a substrate-binding mechanism for MDDEF and these will serve as platforms for specific drug development in the near future.

[1] *C.A. Arias, B.E. Murray(2012). Nature Reviews Microbiology, 2012, 10, 266-278,* ***[2]*** *M.L. Barta, W.J. McWhorter, H.M. Miziorko, et al, Biochemistry, 2012, 51, 5611-5621*

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