There are an estimated 300-500 million cases of malaria and up to 3 million people die from this disease annually. Plasmodium falciparum is the causative agent of the most lethal and sever form of human malaria. Chemotherapy of malaria is available, but is complicated by both adverse effects and widespread resistance to most of the currently available anti-malaria drugs. The malaria parasite depends on de novo synthesis of pyrimidine nucleotides, whereas the human host has the ability to synthesize them by both de novo and salvage pathways. The de novo pathway contains six reaction steps. In the final two steps, uridine 5'-monophosphate (UMP) requires the addition of a ribose phosphate moiety from 5-phosphoribosyl-1-pyrophosphate to orotate by orotate phosphoribosyltransferase (OPRT) to form orotidine 5'-monophosphate (OMP) and pyrophosphate (PPi), and the subsequently decarboxylation of OMP to form UMP, by OMP decarboxylase (OMPDC). Here, we report the X-ray analysis of OMP or UMP-complex forms of OMPDC from Plasmodium falciparum (PfOMPDC) at 2.65 Å resolution. The structural analysis provides the substrate recognition mechanism with dynamic structural changes. And anti-malaria drugs design by using the structure of OMPDC is in progress.

Keywords: malaria, X-ray analysis, structural analysis

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Structural study of enzyme inhibitor complexes of eukaryotic glutamine synthetase from *Zea mays*

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Plants provide nourishment for animals and other heterotrophs as the sole primary producer in the food chain. Glutamine synthetase (GS), one of the essential enzymes for plant autotrophy catalyzes the incorporation of ammonia into glutamate to produce glutamine with concomitant hydrolysis of ATP, and plays a crucial role in the assimilation and re-assimilation of ammonia derived from a wide variety of metabolic processes during plant growth and development. We have determined the crystal structures of maize glutamine synthetase in complexes with three kinds of substrate analogues (J. Biol. Chem., 281, 29287-29296(2006)). From these structures we found a unique decameric structure of the enzyme which is significantly different from the bacterial glutamine synthetase and proposed a phosphate transfer reaction mechanism of ATP. In this study, we aims at gaining insights how the enzyme recognizes the substrate glutamic acid by the methods of mutagenesis and X-ray crystal structure analysis and we prepared several mutant enzymes. We determined new two crystal structures. One structure (WT/PPT/AMPPNP) is a wild type (WT) enzyme in complex with phosphinothricin (PPT) and AMPPNP (ATP analog). The other (H249A/MetSox-P/ADP) is an H249A mutant enzyme in complex with methionine sulfoximine phosphate (MetSox-P) and ADP. Crystal structures of the two complexes were determined at 3.06 and 2.97Å resolutions, respectively. In comparison to the previously reported structures, PPT in the WT/PPT/AMPPNP complex is closer to the γ-phosphate group than MetSox in the WT/MetSox/AMPPNP complex. It is expected that the phosphotransfer energy to PPT is smaller than that of MetSox. It was confirmed that the H249A/MetSox-P/ADP complex contains three manganese ions.

Keywords: plants, enzyme mechanics, ATP dependent reactions

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H/D-exchange and water structure in diisopropyl -fluorophosphatase as reveald by neutron diffraction

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The calcium-dependent phosphotriesterase Diisopropylfluorophosphatase (DFPase) from the squid Loligo vulgaris is an enzyme capable to detoxify a range of highly toxic organophosphorus compounds including DFP ad the nerve agents Tabun (GA), Sarin (GB), Soman (GD) and Cyclosarin (GF). In addition to an already existing atomic-resolution X-ray structure (0.85 Å, PDB: 1PJX) neutron diffraction was employed to reveal the protonation states and indentity of a catalytically important water molecule in the DFPase active site. Additional information was gained on the extend and distribution of H/D-exchange in the protein leading a detailed picture of structural rigidity in the hightly symetrical β-propeller structure of DFPase. Also we were able to determine the positions and oritentations of water molecules in the central tunnel of DFPase with high accuracy. Based on these finding we employed Molecular Dynamics (MD) simulation to investigate the dynamics of these internal water molecules that form an extended network connecting both metall ions in the protein. The results of several simulation runs of 30 ns each obtained using the OPLS all-atom force field and both TIP4P and SPC water models suggest a highly odered and correlated movement of water molecules in the tunnel. As DFPase is currently the protein structure with the largest extended network of internal water molecules characterized by neutron difraction, it might serve as a valuable model for other water filled narrow tunnel and channel like structural moieties. We show that information obtained from neutron diffraction and computational simulations is complementary to other currently employed exterimental methods for investigating internal water dynamics like NMR-spectroscopy.

Keywords: neutron crystallography, molecular dynamics simulations, protein dynamics

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Structural study of putative aminotransferase from *Thermus thermophilus* HB8

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Amiontransferase (AT) is one of pyridoxal 5'-phosphate (PLP) -dependent enzyme and plays an important role in amino acid