Computational Modeling of Sulfurylase Activity of Human 3'-Phosphoadenosine 5'-Phosphosulfate Synthase

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Introduction

The sulfur nucleotide PAPS (3'-phosphoadenosine 5'-phosphosulfate) is the universal sulfuryl donor of the cell. In mammals 3'-phosphoadenosine 5'-phosphosulfate Synthase (PAPSS), using ATP, converts biochemically inert inorganic sulfate to the sulfuryl donor of the cell. In mammals 3'-phosphoadenosine 5'-phosphosulfate Synthase: Biochemistry, Molecular Biology, Vol. 28, No. 2, pp. 374-388.

Methods

Since crystal structures of human PAPSS have been resolved by X-ray diffraction and structural comparison of several residues in the reported increased enzymatic activity in vitro experiments and in alternative conformation of N426K mutation, trigonal planar intermediate. However, this result might be the artifact of the area of constrained search and needs to be confirmed with a novel Eigenvalue analysis.

Objectives

1. Understanding the reaction mechanism of ATP sulfurylase reaction by finding the theoretical transition structure.
2. Elucidate the roles of critical residues within the active site.
3. Creating a potential energy profile for the reaction coordinate.

QM/MM region for QSite calculation and approximate transition structures

Comparison of Secondary structure prediction in alternative conformation of N426K mutant simulations

Alternative Conformation of N426K in Sulfurylase Domain

Conclusions

1. In QM/MM calculation Molecular scan followed by step-wise QMM calculation minimization revealed a S1 type mechanism with trigonal planar intermediate. However, this result might be the artifact of the area of constrained search and needs to be confirmed with a novel Eigenvalue analysis.

2. Alternative conformations of both N426K mutant simulation keep similar secondary structure throughout the simulation.

3. Binding energies correlate with the experimental results obtained. While both histidine residues are contacting ATP and point mutations do affect substrate binding directly, the effect of point mutations in 426 (G to A) and 427 (N to K) is rather indirect as those residues do not contact ATP. Altered protein dynamics as a result of the mutations propagate into the active site and result in a lower binding affinity for Q427A. Interestingly, a higher binding affinity is observed for N426K, correlating well with the reported increased enzymatic activity in vitro experiments and in alternative conformation of Lysine 426 increases the affinity significantly.

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