Structural Comparison and Analysis of the Substrate Specificities of Purine Nucleoside Phosphorylases

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The reversible phosphorolysis of purine and pyrimidine nucleosides is an important reaction in the salvage pathway, where cleavage of glycosidic bond yields a free base and ribose-1-phosphate. Structural studies reveal that only two folds exist, which provides the basis to classify the nucleoside phosphorylases into two families: nucleoside phosphorylase-I and nucleoside phosphorylase-II. Nucleoside phosphorylase-I enzymes share a common single-domain subunit, have either a homotrimeric or a homohexameric quaternary structure, and accept both purine and pyrimidine substrates. Nucleoside phosphorylase-II enzymes share a common two-domain subunit fold with a dimeric quaternary structure, and are specific for pyrimidine nucleosides [1]. Purine nucleoside phosphorylases (PNPs) belong to the nucleoside phosphorylase-I family. Typically, homohexameric PNPs cleave inosine, guanosine and adenosine, while homotrimeric PNPs cleave guanosine and inosine but not adenosine; however, exceptions have been observed.

Fifteen known structures of homohexameric and homotrimeric PNPs from bacterial and mammalian species are analyzed based on sequence alignment, phylogenetic analysis and substrate specificity. While conservation of key active site residues is observed in both bacterial and mammalian PNPs, there is significant sequence divergence between the two classes of PNP. Comparison of the active sites from known structures of the trimeric and hexameric PNP family members provides insight to the structural basis of substrate specificity.

[1] Pugmire M., Ealick S.E., *Biochem. J*, 2002, **361**, 1.

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