

# Molecular basis of catalytic promiscuity of the bi-substrate enzyme Phosphoribosyl Isomerase A from *M. tuberculosis*

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The  $(\beta/\alpha)_8$ -barrel fold is the most dominant class of protein folds and the vast majority of enzymes acting in the metabolic pathways are of this fold. Classical examples of such can be seen in the histidine and the tryptophan biosynthesis pathways where at least two reactions in the histidine biosynthesis and three reactions in the tryptophan biosynthesis are catalyzed by  $(\beta/\alpha)_8$ -barrel enzymes [1,2]. The prevailing hypothesis regarding the evolution of these enzymes suggests that they have evolved from a single common ancestor through gene duplication and divergence [1,3,4]. Two of the  $(\beta/\alpha)_8$ -barrel enzymes in the histidine and the tryptophan biosynthesis pathway, ProFAR isomerase (HisA) and PRA isomerase (TrpF), catalyze similar Amadori rearrangements and are believed to be evolutionary related [5,6].

Recently, it was observed that two of the microorganisms belonging to the actinobacteria phylum, *M. tuberculosis* and *S. coelicolor*, do not have an identifiable *trpF* gene [7]. When investigating the *hisA*-homolog gene it was seen that its gene product aside from HisA activity also exhibited TrpF activity [7,8]. This protein was named Phosphoribosyl Isomerase A (PriA) due to its dual specificity towards phosphoribosylated HisA and TrpF substrates. The discovery of PriA supports the proposed hypothesis that HisA and TrpF have evolved from a HisA/TrpF-like enzyme.

As PriA is one of the few contemporary generalized enzyme intermediates it offers the opportunity to study the structural and functional mechanisms that lies behind enzyme evolution and enzyme promiscuity. The presented work will show a detailed structural and biochemical analysis of PriA from *M. tuberculosis* unraveling the molecular principles of its bi-substrate specificity.

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