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Evolutionary trace analysis of the a-D-phosphohexomutase superfamily

Pseudomonas aeruginosa is an opportunistic human pathogen and a leading cause of hospital-acquired infections. It is a common cause of infections in cystic fibrosis, immunocompromised, and burn patients. Adding to its pathogenicity, P. aeruginosa produces multiple virulence factors, including lipopolysaccharide, rhamnolipid, and alginate. These exoproducts render the bacterium resistant to antibiotic treatment and the host immune response, and proteins involved in their biosynthesis are thus attractive candidates for inhibitor design. One enzyme in particular, phosphomannomutase/phosphoglucomutase (PMM/PGM), is required for the production of all three exoproducts, and has been characterized both structurally and mechanistically. PMM/PGM is a member of the phosphohexomutase superfamily, which encompasses four groups of enzymes: PMM/PGM, phosphoglucomutase, phosphoglucosaminemutase, and phosphoacetylglucosaminemutase. These proteins catalyze a reversible, intramolecular phosphoryl transfer for a variety of phosphosugar substrates in bacteria, eukaryotes, and archae. Recently, we have used the evolutionary trace analysis to examine sixty-nine members of the phosphohexomutase superfamily. This method uses sequence-sequence and sequence-structure comparisons to identify residues that are evolutionarily conserved and therefore presumably of structural and/or functional importance. According to this analysis, many active site residues important for the generic phosphoryl transfer mechanism are conserved throughout the enzyme family. Also, some important regions show class-specific differences in sequence that appear to be correlated with differences in substrate specificity exhibited by subgroups of the family. The results from this research provide new insight into enzyme mechanism and substrate recognition by the phosphohexomutase family.

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