Structures of 5-methylthioribose Kinase: Catalytic Mechanism and Drug Design

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The essential amino acid methionine plays critical roles in a variety of cellular functions but is energetically costly to synthesize. As a consequence, pathways to salvage methionine have evolved in almost all organisms. 5-methylthioribose (MTR) kinase is a key enzyme in this pathway in microorganisms and certain plants, and the absence of a mammalian homolog suggests that the enzyme is a good target for the design of novel antibiotics against MTR kinase containing pathogens and selective herbicides. Recombinant *B. subtilis* MTR kinase has been expressed, purified and crystallized with the detergent CHAPS, and structures of the apo enzyme, ADP, ATP and ATP-MTR complexes have been determined. The first structure was determined by MAD technique using holmium in complex with ADP as the phasing derivative. The structure of MTR kinase has a eukaryotic protein kinase fold, and is similar to 3',5'-aminoglycoside phosphotransferase and choline kinase. Structures of MTR kinase with and without its substrate reveal local conformational flexibility and illuminate a detailed catalytic mechanism of the enzyme. These structures also provide a blueprint for future structure or mechanism based drug design.

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