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Polyphosphate Kinase 1 Active Site Characterization for the Identification of Novel Antimicrobial Targets

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Abstract : Inorganic polyphosphate (poly P) is present in all living forms tested to date, from each of the three kingdoms of life. Studied mainly in prokaryotes, poly P and its associated enzymes are vital in diverse basic metabolism, in at least some structural functions and, notably, in stress responses. These plentiful and unrelated roles for poly P are probably the consequence of its presence in life-forms early in evolution. The genomes of many bacterial species, including pathogens, encode a homologue of a major poly P synthetic enzyme, poly P kinase 1 (PPK1). Genetic deletion of ppk1 results in reduced poly P levels and loss of pathogens virulence towards protozoa and animals. Thus far, no PPK1 homologue has been identified in higher-order eukaryotes and, therefore, PPK1 represents a novel target for chemotherapy. The idea of the current study is to purify the PPK1 from Escherichia coli to homogeneity in order to study the effect of active site point mutations on PPK1 catalysis via the application of site-directed mutagenesis strategy. The knowledge obtained about the active site of PPK1 will be utilized to characterize the catalytic and kinetic mechanism of PPK1 with model substrates. Comprehensive understanding of the enzyme kinetic mechanism and catalysis will be used to design and screen a library of synthetic compounds for potential discovery of selective PPK1-inhibitors.

Keywords : antimicobial, Escherichia coli, inorganic polyphosphate, PPK1-inhibitors
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