Poster Presentation

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Determinants of nucleoside specificity of a macrolide phosphotransferase

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2'-macrolide phosphotransferase type I [MPH(2')-I] is an antibiotic kinase that renders many macrolides, such as erythromycin, inactive by catalyzing the transfer of a phosphate group from a nucleoside triphosphate to the hydroxyl at the 2'-position of the antibiotic. MPH(2')-I is functionally and structurally analogous to the aminoglycoside kinases (APHs). However, it is distinct from most APHs in that it utilizes GTP exclusively as its phosphate donor. We will present the crystal structure of MPH(2')-I in its apo and ternary complex forms with guanosine nucleotide and different macrolide substrates. We will compare its nucleoside-binding pocket to that of the 2''-aminoglycoside phosphotransferases [APH(2'')], a subclass of aminoglycoside kinases that are capable of utilizing GTP as a phosphate donor. To further decipher the structural basis of the nucleoside specificity of MPH(2')-I, mutations of amino acid resides in the nucleoside-binding pocket have been carried out and their effects on the binding affinity of purine nucleotides were examined by isothermal titration calorimetry. Our preliminary results show that the "gatekeeper" residue plays a role in governing the nucleoside selectivity.

Keywords: kinase, antibiotic resistance, macrolide