Poster Presentation

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Study of 2'-macrolide phosphotransferase selectivity for different substrates

J. Blanchet[1,2], D. Fong[1,2], A. Berghuis[1,2,3]

[1]McGill University, Department of Biochemistry, Montreal, Canada, [2]Groupe de Recherche Axé sur la Structure des Protéines (GRASP), [3]McGill University, Department of Microbiology & Immunology, Montreal, Canada

Macrolides are antibiotics that have been in use since the late 1950s to treat a wide range of bacterial infections (e.g. upper respiratory infections, skin and soft-tissue infections, stomach ulcers and some venereal diseases). The structure of these antibiotics contains a lactone ring of either 14, 15, or 16 members, with a variety of sugar moieties attached. Resistance to this class of antibiotics may result from the reaction carried out by macrolide phosphotransferases [MPHs]. MPHs belong to the family of antibiotic kinases which catalyzes the transfer of a phosphate group from a nucleoside triphosphate to a specific hydroxyl on the antibiotic. However, unlike most antibiotic kinases, MPHs utilize GTP as the phosphate donor. Specifically, 2'-macrolide phosphotransferase type I [MPH(2')-I] transfers the gamma-phosphate from GTP to the 2'-hydroxyl of 14- and 15-membered ring macrolides. Crystal structure of the ternary complexes of MPH(2')-I with both 14- and 15-membered lactone macrolides have been determined. To study the basis of substrate selectivity, we have generated mutations of several amino acid residues in the macrolide-binding pocket and examined the catalytic activities of these mutants on the different classes of macrolides, including those containing a 16-membered lactone. Furthermore, we will present kinetic studies of MPH(2')-I containing mutations in the nucleoside-binding pocket in order to study the mechanism for the enzyme's preference for GTP.

Keywords: Kinase, Antibiotic resistance, Macrolides