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Structural insight into mechanisms of inactivation of L, D transpeptidases by carbapenems

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Carbapenems are among the most potent antimicrobial β-lactams available today. Emerging evidence indicates that, unlike other subclasses of β-lactams, carbapenems inhibit non-classical transpeptidases (L, D-transpeptidases) that generate 3→3 linkages in the bacterial peptidoglycan. Five different L, D-transpeptidases form part of the cell-wall biosynthesis machinery in *Mycobacterium tuberculosis (Mtb)*, being LdtMt2 the most consequential for mycobacteria survival. Homologous enzymes have been found in ESKAPE pathogens. Evidences show that the peptidoglycan structure produced by these enzymes confers antibiotic-resistant to strains of Enterococcus Faecium and Clostridium difficile. Biapenem, tebipenem and panipenem exhibit therapeutically valuable potencies against drug resistant pathogens. These three different carbapenems inactivate these enzymes by forming adducts with their catalytic cysteine and two other carbapenems, imipenem and meropenem docks to one of the two (inner and outer) cavities that access the catalytic site. The complexes of biapenem, tebipenem and panipenem with LdtMt2 provide evidence that the dock to the outer cavity as a preferred binding mode. Unexpectedly, biapenem and tebipenem result in the same adduct resulted by an enzyme-catalyzed decomposition of the carbapenem resembling the S-conjugate elimination by β lyases. This elimination could be used to our advantage to the targeted delivery and release of the additional antimicrobial compounds. The binding mode and adduct stability are important factors to be considered in any antibiotic design based on the carbapenem scaffold. The potential correlations between these factors and carbapenems affectivity as antibiotics will be reviewed under the light of the structures of complexes of these carbapenems with LdtMt2.

Biography

Mario Antonio Bianchet has completed his PhD from The University of La Plata, Argentine and Postdoctoral training at Johns Hopkins University School of Medicine where he joined as an Assistant Professor of Neurology in 2011. He is a structural Enzymologist. He has participated in several seminal structural and mechanistic studies of macromolecular systems of biomedical interest including cell-wall biosynthesis: L, D-transpeptidases and their complexes with antibiotics. In addition, he has given valuable contributions to diverse fields, including bioenergetics: F1-ATPase, xenobiotic-response: NADPH: Quinone oxidoreductases, DNA-repair: Uracyl-Glycosylase/inhibitors, carbohydrate-recognition: Animal lectins, which resulted in 65 publications in reputed journals.

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