Mario A Bianchet et al., J Drug Metab Toxicol 2015, 6:4
http://dx.doi.org/10.4172/2157-7609.C1.002

OMICS International
conferenceseries.com

Mycobacterium tuberculosis cell-wall biosynthesis as target of carbapenems

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Transpeptidases play essential roles in the bacterial cell-wall biosynthesis. Inter-stems cross-links made for these enzymes assemble the peptidoglycan mesh that confer mechanic stability to the bacteria. β-lactam antibiotics, penincillin, inactivates (4-3) DD-transpeptidases. These transpeptidases also called penincillin-binding proteins, cross-linked-centers of the fourth residue main-chain with that of the third residue side-chain of adjacent peptidoglycan stems. Most bacteria utilize(4-3) crosslinks to build their peptidoglycan layer. However, the *Mycobacterium* genus and some penicillin-resistant bacteria—involved in nosocomial infections—majoritarily utilize the (3,3)-crosslinks carried out by (3,3) LD-transpeptidases. This (3,3)-crosslink joins the L-center of the third residue main-chain and the D-center of the another third residue main-chain of an adjacent stem. The use of this crosslink and the presence of a potent β-lactamase (BlaC) confers to mycobacteria resistance to penicillin and other antibiotics that mimic the D-Ala^{4}-D-Alanyl^{5} terminal region of the pentapeptide donor stem recognized by DD-transpeptidases. LD-transpeptidases are resilient to this type of inhibition because they exclusively recognize a tetrapeptidedonor stem lacking the D-alanyl terminal. Carbapenems are β-lactam antibiotics that have a carbon atom replacing the sulphur atom at position1 of the penicillin core. This class of antibiotics inactivate LD-transpeptidases by a quasi-irreversible acylation of the enzyme catalytic cysteine, resulting in a effective agent to treat these penicillin-resistant bacteria. We are going to discuss our recent structural, biophysical, and biochemical characterization of members of this family of enzymes and their complexes with a series of carbapenemsin medical use.

Biography

Mario A Bianchet has completed his PhD from The University of La Plata, Argentine, and performed Postdoctoral studies at Johns Hopkins University School of Medicine, where he is now a Assistant Professor of Neurology since 2011. He has published 65 papers in reputed journals. As structural enzymologist and expert in ligand recognition, he has participated in several seminal structural and mechanistic studies of macromolecules and ligand/macromolecule interactions of biomedical interest. He has important contributions to different fields, including bioenergetics: F1-ATPase, xenobiotic-response: NADPH:Quinone oxidoreductases, DNA-repair: Uracyl-Glycosylase/inhibitors, carbohydrate-recognition: animal lectins, and late stage cell-wall biosynthesis: LD-transpeptidases and their complexes with substrates and carbapenems.

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