Structural Studies of an Antibiotic Resistance Factor

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The number of multidrug resistant microorganisms has increased in clinical settings and the danger of new pathogenic bacterial strains spreading has placed emphasis on understanding the biochemical basis of resistance. One class of unique last resort antimicrobials is the streptogramins which consist of naturally occurring macrocyclic lactone ring compounds. This family is comprised of Group A and Group B compounds which independently are bacteriostatic against Gram-positive bacteria acting to decrease protein production. However, in combination they exhibit synergistic bactericidal effects due to the permanent inhibition of peptide bond formation in the 50S ribosomal peptidyl transferase centre of prokaryotes.

Resistance to the Group B streptogramins can be conferred enzymatically by cleaving the ring structure of these small peptide drugs. The enzyme responsible is found both on chromosomal DNA and on bacterial plasmids allowing for potential quick dissemination of resistance. Recently, selenomethionine crystals were obtained for this enzyme by hanging drop diffusions method. Diffraction data were collected at the NSLS (Upton, NY) to 1.6Å resolution. Difficulties in solving the structure were encountered as a result of heavy atoms falling close to special positions and extensive internal symmetry of the protein structure. Neither MAD nor molecular replacement on their own were sufficient in obtaining phasing information thus the two techniques were employed in combination to solve the structure. Here we present the high resolution three dimensional structure of streptogramin B linearizing enzyme using X-ray crystallographic techniques and place it in a biological context.

Keywords: antibiotic resistance, enzyme, crystal structure