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Molecular basis of cyclic peptide antibiotics targeting the bacterial ribosome

Tanakarn Monshupanee[1], Albert E. Dahlberg[2], Shanna K. Johansen[3] and Stephen Douthwaite[3]
[1]Bangkok University, Thailand
[2]Brown University, Rhode Island
[3]University of Southern Denmark, Denmark

Cyclic peptide antibiotics capreomycin and viomycin bind to both subunits of the bacterial ribosome and inhibit the cellular protein synthesis. Here, we described several single nucleotide mutations in either the decoding center of 16S rRNA helix 44 or in the conserved 23S rRNA helix 69 that conferred highly resistant level to capreomycin and viomycin. In consistent, chemical footprinting analysis indicated that the two drugs interact to the ribosome at both the helixe 44 and the helix 69. We also found that a loss of TlyA methyltransferase- directed 2′-O-methylations at both nucleotide C1409 of the helix 44, and at C1920 of the helix 69, caused bacterial cells to exhibit a low-level resistance to the two drugs. Growing a pair of bacterial variant strains (the wild type and a tlyA mutant), different in the level of TlyA-directed methylation shown that even minor alterations in the level of rRNA methylation caused significant growth differences at sub-inhibitory concentrations of capreomycin. The results revealed that TlyA-directed methylations at both C1409 and C1920 facilitate the drug inhibition to the ribosome. Structure-function relationships in how rRNA mutations/methylations confer different levels of the drug resistance and how these cyclic-peptide drugs inhibit the bacterial protein synthesis will be discussed.

tanakarn.m@chula.ac.th